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REVIEW

Fat Grafting Versus Adipose-Derived Stem Cell Therapy: Distinguishing Indications, Techniques, and Outcomes

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Abstract With adipose-derived stem cells (ASCs) at the forefront of research and potential clinical applications, it is important that clinicians be able to distinguish them from the fat grafting currently used clinically and to understand how the two approaches relate to one another. At times, there has been confusion in clinically considering the two therapies to be the same. This report is aimed at distinguishing clearly between fat grafting and ASC therapy with regard to the indications, harvesting, processing, application techniques, outcomes, and complications. Findings have shown that autologous fat transfer, a widely used procedure for soft tissue augmentation, is beneficial for reconstructive and cosmetic procedures used to treat patients with volume loss due to disease, trauma, congenital defects, or the natural process of aging. On the other hand, ASCs have been identified as an ideal source of cells for regenerative medicine, with the potential to serve as soft tissue therapy for irradiated, scarred, or chronic wounds. Recent advances in tissue engineering suggest that the supplementation of fat grafts with ASCs isolated in the stromal vascular fraction may increase the longevity and quality of the fat graft. Research suggests that ASC supplementation may be a great clinical tool in the future, but more data should be acquired before clinical applications.

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Autologous fat grafting is a technique shown to be beneficial as a reconstructive and cosmetic procedure for patients with volume loss due to disease, trauma, congenital defects, or the natural process of aging. Adipose-derived stem cells (ASCs) have been identified as an ideal source of cells for regenerative medicine with the potential to serve as soft tissue therapy for irradiated, scarred, or chronic wounds. For a clinician, there are important distinctions between fat grafting and ASCs.

Fat grafting has been well studied, but less is known about therapy with ASCs or multipotent stromal-derived cells. At times, there has been confusion clinically, with the two therapies considered one and the same [1]. Surgeons have even begun to market "stem cell face-lifts" when in fact the procedure involves merely facial fat injections without a rhytidectomy [2, 3].

Because ASC therapy is an emerging field, it is critical to separate data from anecdote. Evidence-based, well-controlled clinical trials are crucial for differentiating fact from fiction, much better than anecdotal before-and-after photos presented at national meetings. This report aims to distinguish clearly between fat grafting and ASC therapy with regard to the indications, harvesting, processing, application techniques, outcomes, and complications.

The authors conducted a thorough review of the current literature on autologous fat grafting and ASC therapy. This review involved a comprehensive search of PubMed and ClinicalTrials.gov to identify and evaluate current literature using the search terms "autologous fat grafting," "lipoinjection," "autologous fat transfer," "adipose-derived stem cells," "fat harvest," "stem cell therapy," "lipoaspirate,"

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and "lipotransfer." Search limits restricted results to English-language articles indexed as human studies, clinical trials, randomized controlled trials, systematic reviews, case series, or case reports.

Definition

Fat grafting, fat transfer, lipoinjection, and liposculpture refer to a soft tissue enhancement procedure for mild to moderate defects (Table 1). Fat grafting is considered minimally invasive with low associated morbidity. Because it is autologous and noncarcinogenic, it lacks an immune host response. It uses a readily available donor source and has minimally detectable scarring at the recipient site. Findings have shown that it results in good to excellent short-term patient satisfaction. It may be used instead of alternative soft tissue-volume corrective procedures such as dermal fat grafts, local flaps, free tissue transfer, alloplastic implants, and injectable fillers. However, fat graft resorption is considered variable or unpredictable and may require repeat grafting or recontouring procedures [4].

In regenerative laboratories and clinical settings, ASC therapy is being studied as a way to treat difficult wound beds with poor blood supply, to heal radiation injury, or to enhance fat grafting take and predictability. In addition,

Table 1 Fat grafting versus adipose-derived stem cell therapy

	Autologous fat transfer	ASC therapy
Definition	Autologous adipocyte transfer	Multipotent cells isolated from the vascular stromal component of lipoaspirate
Indications/therapeutic targets	Volume deficiency due to aging, infection, trauma, Parry-Romberg syndrome, scleroderma, hemifacial microsomia	Enhancement of fat grafting, wound healing, and tissue-engineering applications
Harvesting	Atraumatic syringe aspiration (Coleman technique) from abdomen, thigh, flank, or gluteal region	Tumescent liposuction with liposuction cannulas from similar donor sites
Processing	Centrifugation for separation of blood, supernatant, and cells	Washing of aspirate with PBS to remove blood, saline, and local anesthetics
	Removal of supernatant and blood (soaked up by cottonoids)	Digestion using collagenase to isolate ASCs from adipose cells
		Centrifugation to isolate cell pellet containing the ASCs
	Transfer to 1-ml syringes for injection	Removal of supernatant and resuspension of cell pellet in 10% FBS
		After 15 min of incubation for cell adherence, the sample is ready for injection
Implantation	Blunt cannula injection of small aliquots into different depths from different access sites to correct preoperatively marked defect	For ASC-supplemented fat grafts, mix for 15 min then perform injection technique similar to fat grafting
		For wound healing, inject in multiple depths in and around periphery of wound
		For tissue engineering, seed ASCs onto scaffold matrix, then implant
Outcome	Good results, but long-term resorption may occur with outcome variability (30–70%)	CAL may enhance angiogenesis, maintain volume, and improve survival of grafts
		Reports from Europe and Asia indicate that ASCs may promote healing of problematic wounds
		In tissue engineering, early studies have shown a capacity for differentiation of ASCs within dermal matrix and collagen scaffolding for soft- and hard-tissue defect healing. In other fields such as gastroenterology, neurology, cardiology, and orthopedics, ASCs also have shown the potential for diverse clinical applications
Complication	Cellulitis, contour irregularity, lumpiness, prolonged ecchymosis, asymmetry from unpredictability of "take"	Complications similar to those for fat grafting; theoretical risk for cell transformation
Future	Improved processing and grafting techniques for predictable "take"	Soft tissue repair, regenerative cell therapy, improved biologic scaffolds for ASCs

ASC adipose-derived stem cell, *PBS* phosphate-buffered saline, *FBS* fetal bovine serum, *CAL* cell-assisted lipofilling

Details may vary among clinicians

other disciplines are investigating the use of ASC therapy for regeneration of injured cardiac muscle, fabrication of neobladders, vascular intimal grafts, and bone tissue engineering [5–8].

Adipose-derived stem cells (formerly termed adipose-derived stromal cells or adipose-derived regenerative cells) are isolated from the vascular stromal component of lipoaspirate. A standard raw lipoaspirate is composed of mature adipocytes, extracellular matrix, ASCs, endothelial cells, and mural cells (pericytes and vascular smooth muscle cells). When enzymatically digested, the non-buoyant cellular fraction forms the stromal vascular fraction (SVF) and contains ASCs, vascular progenitor cells, pericytes, and endothelial cells [9].

Although ASCs are of mesodermal origin, they have the potential, under the appropriate conditions, to differentiate into multiple lineages of adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, and neurogenic cells [10, 11]. Recent studies also show that ASCs are able to differentate into tissues of ecto- and endodermal lineages such as neural cells, hepatocytes, pancreatic islet cells, endothelial cells, and epithelial cells [11, 12]. An attractive advantage of these adult stem cells is that lipoaspirate provides an easily obtainable source of ASCs at a frequency of 1:100 to 1:1500 cells. This greatly exceeds the frequency of other multipotent cells such as mesenchymal stem cells (MSCs) from bone marrow 500-fold, with 1 g of adipose tissue yielding nearly 5,000 ASCs [13].

History

Fat grafting or autologous fat transfer is a method whereby fat from the patient is removed from one area of the body and reinserted into the desired recipient location. It was first introduced by Neuber [14] in 1893 and then modified by Bruning in 1911 [15] as an injectable procedure. In 1912, Eugene Hollander achieved natural-appearing results for correction of lipoatrophy of the face [16], and by 1926, Charles Conrad Miller had applied fat grafting to cicatricial contraction of the face and neck in 36 cases [17].

In the 1980s, liposuction allowed for the collection of fat that could be applied as fat grafts. The first trials reported from Illouz [18] described great success when fat grafting was applied to iatrogenic liposuction deformities and facial lipodystrophies, but later studies showed a poor survival rate for the grafted fat similar to that of injected collagen [18].

Because learning to handle the lipoaspirate fat graft was still novel, it took time for clinicians to realize that traumatic processing would decrease its longevity [19]. By the early 1990s, more positive reports of fat grafting were published, including an improvement in skin quality, tissue quality, and scar revision, in addition to volume improvement, although its longevity still is in question [20].

The physiology of fat graft take has been studied experimentally. Fat grafts initially require nutritional diffusion until vascularization from the recipient bed occurs. Insufficient vascularity to central areas of the graft during the first 6 months leads to apoptosis and cell death. Long-term volume depletion has been histologically confirmed by loss of adipocytes and some conversion to fibrous tissue and cysts [21].

To minimize fat graft loss, studies have shown benefits offered by less traumatic methods of harvesting, processing, and injecting. Microinjection of fat via the "lipostructure technique" or the Coleman technique has been adopted by many plastic surgeons. This technique distributes fat grafts in small aliquots by meticulous injection through multiple access sites, from which the graft fans out into various soft tissue depths. Despite laboratory studies and a long history of clinical use, no consensus exists to date on the best technique and the longevity of results [22].

Isolated from human lipoaspirate, ASCs were shown to be multipotent in 1998 and first published in 2001 [10]. As early as 2004, Garcia-Olmo et al. [23] had applied ASCs clinically. In a prospective phase 1 clinical trial in Madrid, Spain, nine fistulas were treated successfully in five patients with Crohn's disease using ASCs in fibrin glue, and a phase 3 trial for the treatment of complex perianal fistulas currently is underway. By 2006, fat grafts were supplemented with ASCs and experimentally found to increase weight, volume, and quality after 6 months in rats and humans during trials in Europe and Asia [21]. The use of fat grafts supplemented with ASCs was based on studies that showed improved angiogenesis and minimal inflammatory responses thought to be detrimental to fat graft survival [24]. In the United States, supplementation of fat grafts with ASCs currently is experimental but seems to be a promising therapy for improving fat-grafting predictability.

Indications

Fat grafting is indicated for any volume loss due to aging, infection (e.g., facial lipoatrophy from human immunodeficiency virus [HIV] infection), trauma, Parry-Romberg syndrome, schleroderma, hemifacial microsomia or other causes of soft tissue deficiency resulting in asymmetry or contour irregularity [22, 25]. Some clinicians have used larger volumes of fat grafts for cosmetic breast augmentation [26, 27]. Although more controversial, fat grafting is being used for correction of breast lumpectomy defects and for breast reconstruction after cancer ablation [28, 29].

More recently, fat grafting has been used for the treatment of radiation damage, breast capsular contracture, damaged vocal cords, and chronic ulceration [20, 30]. In 2007, the American Society of Plastic Surgeons Fat Graft Task Force conducted an assessment regarding the safety and efficacy of autologous fat grafting and concluded that the current recommendation grade for fat grafting is level B for breast augmentation and correction of defects associated with medical conditions and previous breast [31, 32]. Other indications including facial augmentation and correction of defects, gluteal and lip augmentation, and hand rejuvenation all received a level 1 grade in the same assessment, meaning that the Task Force was unable to conclude in making a recommendation. Clinical trials for fat grafting are necessary for increasing our scientific understanding and improving the level of recommendation of these procedures.

Adipose-derived stem cells have the potential for use in regenerative medicine and for the enhancement of fat grafting. In the United States, ASC-enriched transplantation still is used primarily for research and tissue engineering because it is believed that more evidence-based medicine is needed to support its use. In particular, the biology of ASCs as a therapy for wound healing still is being studied. Abroad, it has been used clinically in human patients to fill large soft tissue defects and for patients with radiation damage or facial lipoatrophy [33], for cosmetic breast augmentation [34], and for treatment of perianal fistulas [35–37]. In vivo studies show the potential use of ASCs in rat myocardial infarction models via increased neovascularization, improved wall thickness, and cardiac remodeling [38–40]. In mice, ASC-supplemented fat grafts at 6 months had a greater survival (by wet weight) than autologous fat tissue alone [41]. In addition, ASCs show potential for restoring degenerative discs and may prove effective in the treatment of intervertebral disc degeneration by restoration of collagen type 2 and aggregans in a rat model [42].

In a recent 3-year case study of 30 patients, ASC-enriched fat grafts were performed for a breadth of cases including polio infection sequel, Parry Romberg disease, breast reconstruction, scarring, gluteal soft tissue defect, pectus excavatus, and dermatofibromatosis [43]. Other indications under study in preclinical animal studies include critical sized craniofacial and long-bone defects, spinal fusion, stroke, spinal cord trauma, multiple sclerosis, Crohn's disease, bone marrow transplantation, osteoarthritis, liver regeneration, type 1 diabetes, acute ischemia, wound healing, burns, and tendonitis [44, 45].

Because ASCs are progenitor cells, patients with a history of tumor formation may be contraindicated. In one study, ASCs co-injected with human prostate cancer cells in mice increased the rate of tumor progression [46]. However, another study with a breast cancer model found that ASCs enhance the growth of active but not resting tumor cells. This suggests that ASC-enhanced therapies should be conducted only when there is no evidence of active disease [47]. We must be aware that many of these studies are anecdotal, and more controlled human trials are required before these ASC therapy indications are asserted. It also is important to note that according to the Oxford Centre for Evidence-Based Medicine, the current level recommended for use of ASCs would be considered level D because current scientific evidence is inconclusive for assessing the balance of the risk versus the benefit [48].

Harvesting

Fat grafts typically are harvested via the syringe aspiration technique with a long atraumatic cannula (Fig. 1). Usual fat depot sites include the lower abdomen, flanks, inner or outer thighs, and flanks, but other regions including gluteal and submental sites have been used. Tumescent injection is not universally used (we use 0.5% lidocaine-1:200,000 epinephrine injected through a 22-gauge spinal needle before aspiration). The Coleman microcannula technique is a method whereby a light negative pressure container is created by withdrawing the plunger of a 10-ml syringe connected to a 3-mm cannula when introduced in the subcutaneous space through a small incision. The cannula is moved through the adipose compartment mechanically, loosening the fat tissue and drawing it into the syringe. Individual clinicians may modify or use alternative harvesting, processing, and implantation methods, and an optimal protocol has not yet been established from randomized controlled trials.

Also, ASCs typically are harvested via liposuction cannula and vacuum (Fig. 1). Large volumes achieved with tumescent liposuction (compared with syringe aspiration) are needed to obtain enough ASCs in the operating room without the need for laboratory expansion. Donor-site and age variability also are factors to be optimized.

In a recent study in December 2010, Faustini et al. [49] showed that the highest-yield collection site in males was the abdomen, whereas in females, the biopsy region did not create a statistically significant difference in yield. Although the harvesting technique may vary, a standard liposuction blunt-tipped cannula typically is used. With this technique, the suction generates a high negative pressure for vacuum extraction. Although this technique is not ideal for fat grafting because it may result in up to 90% adipocyte rupture, findings have shown it to be appropriate for ASC harvesting [10].

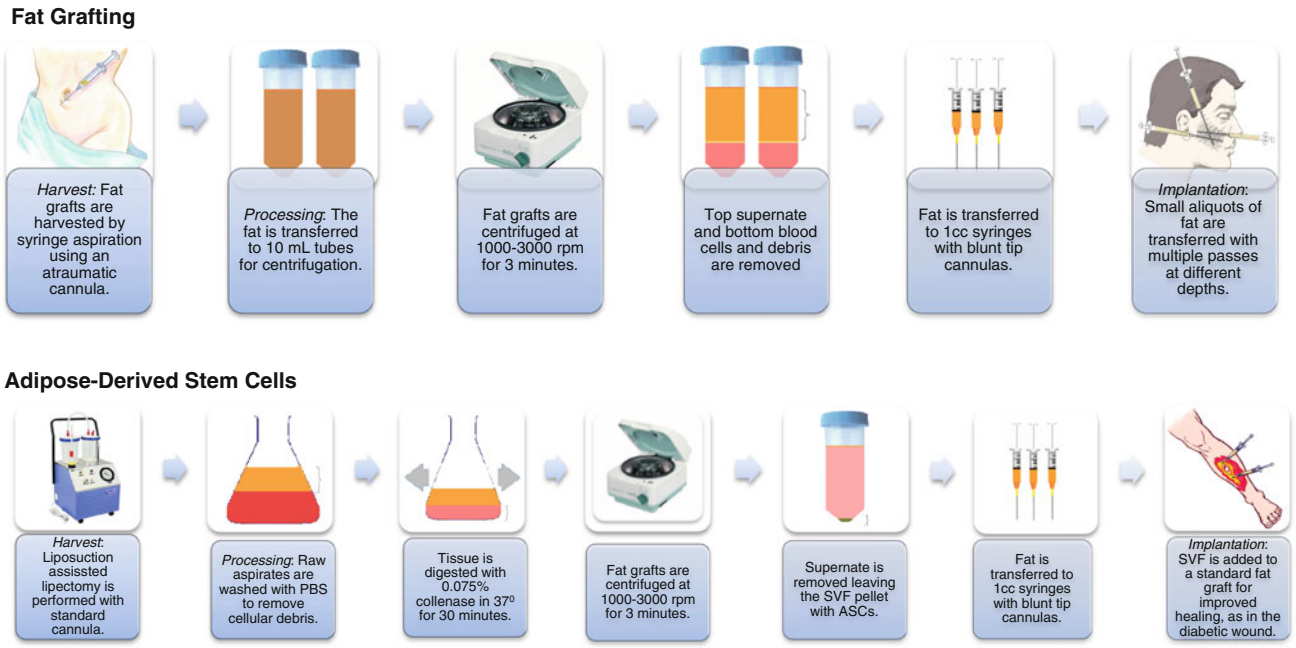

Fig. 1 Harvesting, processing, and implantation techniques. **a** Fat grafting. Fat grafts are harvested using an atraumatic cannula from a donor site such as the abdomen, processed with centrifugation and removal of supernate, and ultimately injected into the recipient site of the same patient. **b** Adipose-derived stem cells (ASCs). Unlike fat grafts, ASCs can be harvested using a standard liposuction cannula, then processed with washing, digestion (collagenase), and centrifugation for the ASC pellet. Finally, ASCs are ready for direct implantation (for wounds), augmentation of fat grafts, or tissue-engineering (for wounds)

Processing

Fat grafts may be prepared from the syringe suction harvest by separating the blood, supernatant, and cells via centrifugation. Although 3,000 rpm for 3 min is standard, there is some evidence from level 2 controlled studies that slower centrifugation (e.g., 1,200 rpm) may reduce adipocyte rupture [50]. It also is important to note that a larger centrifuge generates a much larger gravitational force at the same rpm.

After spinning, a top layer of oil from ruptured adipocytes, a middle layer of viable cells, and a bottom layer of blood and cellular debris are noted. The infranatant is discarded by draining, and the supernatant can be soaked up by absorbent cottonoids from above. Modifications of this procedure include fat washings with saline or no preparation of the aspirate at all. Exposure to cold may or may not lead to adipocyte inflammation or necrosis [51].

In fat graft preparation, the choice of anesthetic may have a role in preadipocyte viability and survival of the fat graft [52]. Additionally, time between harvest and injection, as well as air exposure, is minimized as tissue undergoes cytoplasmic lysis at air exposure. The fat obtained by this procedure does contain ASCs but not in clinically significant numbers and is termed ASC-poor aspirated fat. Once processed, the fat is transferred into 1-ml syringes for injection (see Implantation).

Adipose-derived stem cells harvested in raw aspirate are processed by extensive washing with sterile phosphate-buffered saline (PBS) to remove the blood cells, saline, and local anesthetics. A minimum starting lipoaspirate volume of 250 ml is required for a sufficient yield of ASCs because 250 ml of lipoaspirate is expected to yield 1×10^7 to 1×10^8 ASCs in the SVF. For ASCs to be separated from adipose tissue, the cells must be digested with 0.075% collagenase at 37°C for at least 30 min. The study of Faustini et al. [49] optimized SVF generation with a 0.2% collagenase concentration and a digestion time of 1 h [49].

Collagenase then is inactivated by the addition of an equal volume of Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin (Gibco, Carlsbad, CA, USA). The digest is centrifuged at 1,500 rpm for 5 min. The supernatant is removed, and the cell pellet, termed the SVF, is left. The SVF, containing ASCs, is resuspended in 10% FBS. This portion may be recentrifuged and repeat filtered through a 100-μm nylon filter for further removal of debris [53] (commercially available processors are being tested to ease this process) (Cytori, San Diego, CA, USA). To improve cell adherence, 15 min of incubation are used.

If an insufficient quantity of ASCs is obtained or if ASCs are needed for research purposes, the cells may be expanded in culture by the following methods. After filtration, the cells can be plated in standard tissue culture

plates at 1×10^6 cells per plate. The cells are passaged two or three times and maintained in 37°C/5% carbon dioxide (CO_2) at a confluency no greater than 80% to prevent spontaneous differentiation [10, 13, 54]. The culture medium contains 0.5 mmol/l of isobutyl-methylxanthine (IBMX), 1 μmol/l of dexamethason, 10 μmol/l of insulin, 200 μmol/l of indomethacin 1%, and antibiotic/antimycotic, and should be replaced every 3 days [53]. The ASCs should not be passaged for more than 4 months because malignant transformation was noted by Rubio et al. [13], and overgrowth of fibroblasts or other components of the SVF may occur because it is a heterogeneous collection of cells.

Implantation

Fat-grafting injection techniques are aimed at filling preoperatively marked deficiencies with adipocytes that will survive and become incorporated into the recipient bed. An accepted principle of fat grafting is that adipocytes survive only when within 2 mm of an arterial blood supply. Fat cells outside this boundary may undergo necrosis leading to scar tissue [20, 55].

Successful fat application is performed using a blunt cannula that creates a tunnel at insertion, with fat injected in very small amounts during withdrawal. Multiple passes are used to fan across the deficient region. Fat is grafted at various depths of the defect and through several access sites around the defect. Due to the unpredictable nature of fat take, most physicians overcorrect a volume deficiency by an average of 20–30% [22]. Excess fat can be frozen up to 6 months for later application, but the quality of the fat is dubious, as mentioned previously, due to cold exposure [56]. Most popular sites of facial injection include the nasolabial folds, lips, nasojugal region, malar eminence, chin, forehead, lower eyelids, and upper eyelids.

Techniques of ASC implantation depend on the operative goal. Optimal techniques still are being sought for newer procedures. For implantation in and around problematic wounds, techniques similar to fat grafting currently are being used that apply small aliquots of cells in multiple layers from different port sites. Fat grafts supplemented with ASCs combine the isolated adipose SVF with the aspirated fat.

After moderate mixing and a wait of 10–15 min to allow for ASC cell adherence to the aspirated fat, the ASC-supplemented fat is put into an injection syringe [33]. Again, grafting is performed similar to the method described earlier, with insertion in both the subcutaneous fatty layer and the muscle layer using various directions to achieve proper distribution. Implantation for tissue-engineering techniques of cell seeding onto dermal matrices or collagen gel matrices will vary [57]. Other types of bioreactors or intraoperative tissue-engineering methods require different implantation techniques as well.

Outcomes

Fat grafting, as reported, typically yields good results (Fig. 2). However, outcomes are not always predictable, especially in the long term. Early reports of autologous fat grafts showed an average retained weight of only 45% a year after transplantation [58]. Recent studies, which vary in levels of evidence from 2 to 3, vary in reported resorption from 30 to 70% [22, 50].

Results of fat-grafting procedures typically are assessed by observation, examination with palpation, and photographs. More objective methods currently are used to

Fig. 2 Facial lipoatrophy corrected by autologous fat transfer. **a** A patient displaying facial lipoatrophy on the right side underwent autologous fat transfer. **b** A 6-month follow-up assessment showed improved symmetry restored to the face

assess outcomes including laser scanners, three-dimensional photography, and magnetic resonance imaging (MRI) studies [22, 59].

Several mechanisms may contribute to the variability of outcomes for fat-grafting procedures. The harvesting process is traumatic to adipocytes, which can lead to apoptosis. Additionally, results for recipient wound beds with different degrees of blood supply and fluctuations in oxygen delivery may range from adequate revascularization and good "take" to insufficient revascularization and ischemia, apoptosis, and dedifferentiation of central adipocytes. Outcomes also may be influenced by other factors including differences in the centrifugation speeds [50]. Other considerations that have been investigated include age of the donor, motion to the recipient site, scarring, radiation, and preparation methods [22, 60]. National Institutes of Health (NIH)-registered clinical trials studying outcomes also are currently underway, including a level 1, phases 1 and 2 study of autologous fat transfer for scar prevention and remodeling (NCT01119326) [61].

Outcome studies of ASCs are ongoing. The results are promising but have not yet been scientifically borne out. There is a need for a controlled randomized level 1 study, but currently, none exist. In small case series, ASCs have been shown to promote healing of problematic wounds and to improve radiation fibrosis (Fig. 3) [59, 62]. Additionally, in a level 3 case-control study, ASC-supplemented fat grafts in cell-assisted lipofilling (CAL) were suggested to improve on some of the weaknesses in standard autologous fat transfer [33]. The use of ASCs may enhance angiogenesis, improve the survival of grafts, and thus reduce atrophy. Yoshimura used this CAL technique to treat facial lipoatrophy in human trials. He based this trial on positive results from a rat model used by Matsumoto et al. [63] in which CAL fat survived 35% better than non-CAL fat and showed that stromal vascular fraction cells differentiated into vascular endothelial cells. In addition, Yoshimura used CAL for cosmetic breast enhancement and showed good maintenance of volume after 5 years [34].

Other examples of clinical trials using ASCs include filling of large soft tissue defects, patients with radiation damage or facial lipoatrophy [33], cosmetic breast augmentation [34], and treatment of perianal fistulas [35]. Currently, NIH-registered clinical trials enrolling patients include autologous ASC transplantation in patients with lipodystrophy (NCT00715546), safety and efficacy study of ASCs for the Crohn's fistula (NCT00992485), ASCs for critical limb ischemia in diabetic patients (NCT01257776), and development of bone grafts using ASC and different scaffolds (NCT01218945) [64]. In addition, Cytori Therapeutics currently is sponsoring the following clinical trials in Europe: APOLLO-01 (NCT00442806) using ASCs as a treatment for heart attack patients, PRECISE-01 (NCT00426868) evaluating injection of ASCs in chronic ischemia patients, and RESTORE-02 (NCT00616135) studying ASC-enriched breast reconstruction patients [65]. Trials are ongoing, and as results are reported, it will be crucial to evaluate the long-term outcome of such procedures continuously. These studies will offer level 1 or 2 evidence-based medicine. Future modifications to our understanding will be anticipated as data are collected.

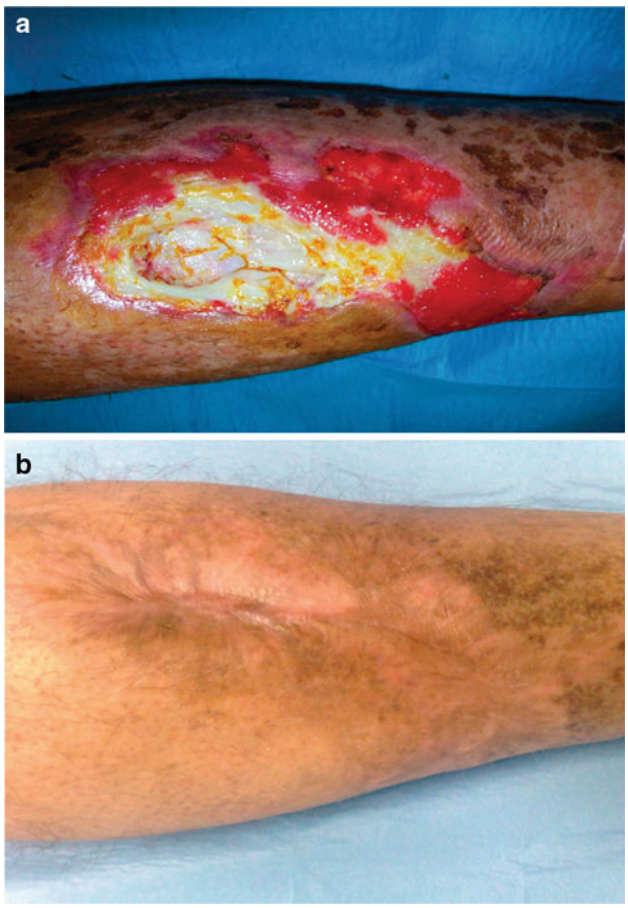

Fig. 3 Wound healing with adipose-derived stem cell therapy. **a** A posttraumatic wound with bone and soft tissue exposure before treatment. **b** After treatment with adipose-derived stem cells and platelet-rich plasma, the wound was completely healed by week 6. Courtesy of Cervelli V et al. [62]

Complications

Fat grafting may be associated with complications. Common side effects include swelling, redness, loss of volume to some extent, tingling, and moderate bruising. Less common complications include hematoma, cellulitis responsive to antibiotics, fibrosis, oil cysts, and calcification [66]. Rarer and more serious complications depending

on the injection site such as the upper third of the face include fat emboli in the retinal or cerebral arteries, hemiparesis, aphasia, and loss of vision. Over time, hypertrophy of the graft is possible. This hypertrophy may be unwanted because fat maintains its donor-site characteristics. This unwanted result is seen when abdominal fat grafted to the face (still acting as abdominal fat) increases in size when abdominal fat increases.

Clinical use of ASCs is new, and all of the complications are unknown. There likely will be some complications similar to those for fat grafting listed earlier. In some clinical trials, ASC-supplemented fat grafts have been reported to develop subcutaneous bleeding as well as postoperative swelling lasting up to 4 weeks [33]. In addition, multipotent cells may pose a risk for cellular transformation if implanted in a field known to be at risk for tumorigenesis.

Although ASCs may benefit autologous fat transfers for postmastectomy breast reconstruction in the formation of new vasculature and promotion of graft retention [21, 66], studies have indicated that ASCs may augment the growth of active tumor cells but not resting cancer cells [47]. Therefore, caution should be invoked when ASCs are used for breast reconstructive therapy until it can be ensured that residual cancer cells are dormant. Clinicians should consider this a current limitation for the use of ASC therapy. Due to limited clinical trials and procedures performed to date, more research must be conducted to identify other potential complications that may arise from ASC-supplemented fat grafts.

Future Applications of ASCs

Findings have shown ASCs to be an easily accessible and reproducible cell source with great promise for soft tissue repair and regenerative cell therapies. Although successful clinical trials and case reports on the use of ASC therapies for soft tissue, orthopedic, and immune indications have been published in Europe and Asia, clinical translational applications still are under regulatory review by agencies such as the Food and Drug Administration in the United States and still remain an area of research [21, 44]. Further study of ASCs in both basic science and clinical settings is necessary to ensure that ASC-supplemented fat transfers are performed in a safe and effective manner. In addition, long-term studies of outcomes measures such as predictability of results, graft survival, ease of procedures, costs, and aesthetic outcomes compared with traditional treatment options (including fat grafts) are necessary before ASCs can serve as a viable treatment option with a strong grade of recommendation. Nonetheless, the ASC potential has far-reaching application, not only in the realm of soft tissue cosmetic and reconstructive surgery but also in other fields including gastroenterology, neurology, and orthopedics.

Therapies using ASCs seeded onto biologic scaffolds are a promising application for the future of soft tissue repair. Because ASCs are stromal cells, they can be grown on a biologic scaffold, a framework that allows cell attachment, proliferation, and differentiation. Some scaffolds that have been investigated include polylactic-co-gylocalic acid, a type 1 collagen sponge, and fibrin glue. These scaffolds have been found to promote the growth of local blood vessels and chemotaxis [13, 54].

Current research is investigating new and optimum scaffolds for use as larger volume fillers [21]. Research findings suggest that ASC supplementation and other such therapies may be great clinical tools in the future, but more data must first be acquired before clinical applications. Only through well-controlled, evidence-based clinical trials will we be able to distinguish fact from fiction. In the meantime, it is important to clarify current misconceptions in the realm of stem cell therapies and fat grafting.

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