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*SURG INNOV* published online 29 January 2014  
DOI: 10.1177/1553350613518846

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# Autologous Fat Grafting: In Search of the Optimal Technique

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## Abstract

**Objective.** Recent advances in adipose cellular biology have repopularized autologous fat grafting as a method widely used in both reconstructive and aesthetic surgery. This review aims to summarize our current knowledge on autologous fat grafting emphasizing harvesting techniques and processing methods as well as current trends and approaches. **Methods.** A thorough search of earlier and recent literature until October 2013 was conducted using the terms *autologous fat grafting*, *autologous fat transfer*, *lipoaspirate*, *lipoinjection*, *fat harvest*, and *lipotransfer* in PubMed and ClinicalTrials.gov databases, and relevant English- and German-language articles were included. **Results.** Findings were categorized in a step-by-step approach of the fat grafting procedure into indications, selection of donor site, techniques for harvesting, processing, and reimplantation of autologous fat. **Conclusions.** Further in-depth knowledge will provide definite answers on fat graft survival; demonstrate safe methods to increase cell viability, grafting outcome predictability; and reliability; enhance safety; and strengthen the scientific and clinical establishment of this increasingly promising method.

## Keywords

breast surgery, evidence-based medicine/surgery, maxillofacial surgery, pediatric surgery, tissue engineering, liposuction, autologous fat grafting

## Introduction

Recent insights into and advances in adipose cellular biology have rekindled the interest in fat grafting. Scientific and clinical research aims to explore the expansion of indications in parallel with investigating the efficacy and safety of the use of adipose tissue and deriving cells. Adipose tissue is used for aesthetic and reconstructive surgery such as fat transfer but also in regenerative medicine and translational research for adipose-derived stem cells (ADSCs). This review is focused solely on autologous fat transfer, also known as autologous fat grafting.

Because data from experimental and animal studies cannot be automatically translated to humans and, to date, even well-conducted clinical studies on fat grafting lack standardized methodology, more questions than answers are raised by controversial and often confusing results. In fact, many techniques in the various steps of the fat-transfer procedure are not at all evidence based, despite fat grafting being a well-established method, important in most fields of surgery. The principal aim of this overview is to summarize our current knowledge about fat grafting, emphasizing techniques, processing methods, and current approaches. Given the substantial differences described in the literature regarding the art and science of fat grafting, practical difficulties in

designing and conducting prospective clinical studies on this topic are recognized. It is hoped that information presented in this review article will be used by surgeons to scientifically approach fat grafting and choose indications and techniques based on objective findings.

## Methods

The authors conducted a comprehensive review on autologous fat grafting involving a thorough search of PubMed and ClinicalTrials.gov until October 2013 using the search terms *autologous fat grafting*, *autologous fat transfer*, *lipoaspirate*, *lipoinjection*, *fat harvest*, and *lipotransfer*. Search was limited to English- and German-language articles indexed as studies, clinical trials, randomized controlled trials, systematic reviews, case series, or case reports.

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Findings were summarized step by step, and the entire basic fat grafting procedure was divided into indications, donor site selection, harvesting, processing, delivery, and graft viability enhancement.

## What Is Fat Grafting and How Is It Different From ADSC Therapy

Autologous fat grafting is the removal of fat from one area of the patient's body and reinsertion into the desired recipient location. Also termed as *fat transfer*, *lipoinjection*, *liposculpture*, or *autologous adipocyte transfer*, it is a method of soft-tissue enhancement for mild to moderate defects.<sup>1</sup>

Harvested fat contains mature adipocytes, extracellular matrix, ADSCs or adipose-derived stromal cells, endothelial cells, pericytes, and vascular smooth muscle cells. After enzymatic processing, the nonbuoyant cellular component contains ADSCs, vascular progenitor cells, pericytes, and endothelial cells and is termed the *stromal vascular fraction*.<sup>2</sup>

ADSCs isolated from the vascular stromal fraction of harvested fat tissue are adherent, cultured, multipotent cells that can be used in regenerative therapy for irradiated, scarred skin or chronic wounds.<sup>2</sup>

The 2 methods exploit the adipose tissue potentials in different ways and may be combined by means of cell-assisted lipotransfer (CAL), but have distinct indications; harvesting, processing, and application techniques; outcomes; risks; and complications.<sup>2</sup> Standard fat grafting procedures that transfer some stem cells naturally present within the tissue should be described as fat grafting procedures, not stem cell therapy.

Although fat grafting was first introduced by Neuber in 1893,<sup>3</sup> the method was popularized after 1980 when the evolution of liposuction allowed the retrieval of generous amounts of fat that could be transferred as grafts.<sup>4</sup> Fat grafting is a reconstructive and cosmetic procedure for patients with volume loss or contour deformities caused by disease, trauma, congenital defects, tumor extirpation, or the natural aging process.<sup>5,6</sup> Actually fat is the closest to the ideal filler because it is readily available; easily obtainable, with low donor-site morbidity; repeatable; inexpensive; versatile; and biocompatible. Therefore, it is the standard against which all other fillers are compared.<sup>6</sup>

Despite ongoing concerns about survival and longevity of fat grafts after implantation and unpredictability of long-term outcome, fat has been successfully used as a filler in facial hemiatrophy and lipodystrophy,<sup>6,7</sup> in recontouring and rejuvenation of the aging face<sup>8-13</sup> and the hands,<sup>14</sup> in the treatment of depressed scars,<sup>15,16</sup> in breast augmentation and reconstruction,<sup>17-21</sup> and in volume and contour deformities of the trunk<sup>19</sup> and lower limbs.<sup>22</sup> It has also been successfully used in cleft lip and palate surgery,<sup>23,24</sup> in

orbital reconstruction after tumor extirpation,<sup>25</sup> in the treatment of painful extremity neuromas,<sup>26</sup> and in nailbed contour deformities.<sup>27</sup> It has been useful in temporomandibular joint surgery for treatment of ankylosis and prevention of fibrosis and heterotopic ossification around total joint prosthesis.<sup>28</sup>

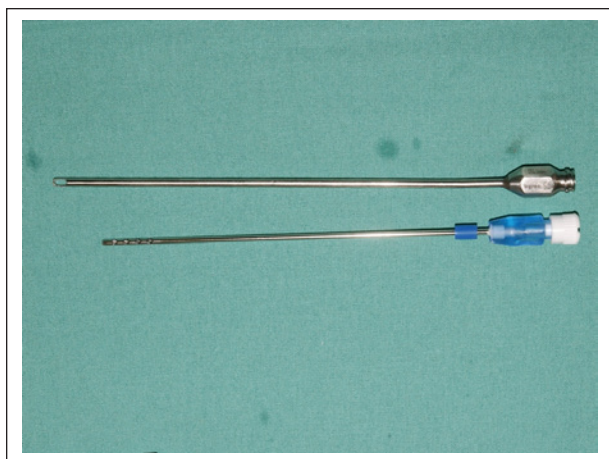
Fat grafts have long been used in neurosurgery for spine and skull base surgeries to treat or prevent cerebrospinal fluid leaks<sup>29</sup> as well as in otolaryngology for obliteration of ear<sup>30</sup> and frontal sinus cavities<sup>31</sup> and for vocal cord augmentation.<sup>32</sup> Recently fat grafting has been used in the successful treatment of chronic anal fissures and fistulas<sup>33</sup> as well as in endoscopic management of vesicorenal reflux in children.<sup>34</sup>

## Preferable Donor Site for Fat Retrieval

The most common fat harvest sites include the abdominal wall, thighs, hips, flank, inner knee, upper extremity, and dorsocervical fat pad. The presacral region has been reported to be associated with minimal donor-site morbidity.<sup>11</sup> Greater cell size and adipogenic activity has been demonstrated in fat tissue from the femoral and gluteal area compared with abdominal fat, whereas smaller adipocytes with almost no adipogenic activity were found in facial fat.<sup>35</sup>

The recipient site may also determine the choice of the donor site. Trepsat<sup>12(p246)</sup> suggested the inner part of the knee as the most suitable fat donor site for the lower palpebral area because the fat was "less fibrous, more supple and provided smaller individual tissue particles." In our experience, for buttocks enhancement, the back, flank, and gluteal donor sites are preferred so as to achieve a better contour of the surrounding area by liposuction as well. In a study conducted by Rohrich et al,<sup>36</sup> no differences in adipocyte viability were demonstrated among abdominal, thigh, flank, or knee fat donor sites, with fat that was immediately removed and untreated.

In a more recent study, however, Padoin et al<sup>37</sup> investigated the influence of donor sites on cell concentrations of the lipoaspirate and found that the lower abdomen and the inner thigh have a higher processed lipoaspirated cell concentration. Fat grafts obtained from these sites might theoretically be of better quality because they naturally contain more stem cells; however, the method used in this study for measurement of stem cells was the C-kit expression, which is known to also measure lymphocytes. Therefore, conclusive evidence to support superiority of a specific fat harvest site in terms of improved adipose cell count and viability does not exist.<sup>38-40</sup> In our clinical praxis, abdominal, gluteal, and flank harvest sites are the most frequently used because of their ease of access and tissue availability.



**Figure 1.** Coleman 2-hole (top) and Magalon 2-hole (bottom) cannulas for fat retrieval.

## Methods for Fat Harvest

Numerous studies have demonstrated that fat graft loss depends highly on the methods of harvesting, processing, and reimplanting. It is widely accepted that less-traumatic methods result in increased viability of adipocytes and graft survival.<sup>41</sup>

Several techniques have been proposed for fat harvesting, and there is an ongoing debate in the literature as to which method produces more viable and functional adipocytes. The main techniques are vacuum aspiration, syringe aspiration, and surgical excision.

Recent experimental as well as some clinical studies support direct fat excision over aspiration. Fagrell et al<sup>42</sup> introduced a technique called “fat cylinder graft,” in which fat is drilled out in cores by a punching device, whereas Qin et al<sup>43</sup> recommended the core graft for en block grafting because it keeps the structure and viability of harvested fat tissue by avoiding damage of adipocytes. Pu et al<sup>44</sup> found significantly impaired adipocyte cellular function in conventional liposuction aspirates compared with fresh fatty tissue samples and syringe-aspirated fat.

Low negative-pressure lipoaspiration may yield fat faster than syringe aspiration and can be used when a large volume of fat is required, as in breast surgery. High vacuum pressures of conventional liposuction may cause disruption of cellular structures in up to 90% of adipocytes.<sup>41</sup>

Erdim et al<sup>45</sup> reported increased graft viability in fat harvested by liposuction using a 6-mm cannula compared with grafts obtained by 4-mm and 2-mm cannulas.<sup>45</sup> Coleman<sup>8</sup> described a technique for fat harvest that minimized trauma to the adipocytes. Using a 3-mm blunt edge, 2-hole cannula connected to a 10-cc syringe, fat is suctioned manually by withdrawing the plunger (Figure 1).

Rubin and Hoefflin<sup>46</sup> described a similar technique but used a 4-mm blunt edge cannula with large, multiple openings for aspiration. Nordstrom<sup>47</sup> also used a 3-mm curetting cannula and described the “spaghetti” technique.

In 1993, Carpaneda and Ribeiro<sup>48</sup> demonstrated that graft thickness and its geometrical shape were inversely proportional to survival if the diameter of the graft exceeds 3 mm, thus rendering any previous techniques that delivered larger aliquots of fat of historic interest. Furthermore, smaller cannula sizes are thought to be more atraumatic and allow for removal of smaller-sized lobules of fat, thus improving graft flow and reducing trauma during transplantation. Karacalar and Ozcan<sup>49</sup> used a curved, semiblunted 14-gauge microcannula with a tip that separated the subcutaneous tissue without cutting it, attached to a 10-cc syringe as an ideal instrument for harvesting fat.

An important consideration, besides cannula size, is cannula hole size and the number of holes. Trepsat<sup>12</sup> described a technique of harvesting fat for periorbital rejuvenation using a thin, multiperforated 1.5-mm cannula connected to a 10-cc syringe, allowing tiny particles of fatty tissue to be aspirated with minimal negative pressure. Recently, Nguyen et al<sup>50</sup> introduced the use of a multiperforated cannula with holes 1 mm in size for atraumatic fat harvesting. In our experience, the 2-mm blunt tip cannula with four 600- $\mu$ m gauge holes (Figure 1) designed by Magalon for microlipografting (St’rim, Thiebaud Biomedical Devices, Margencel, France) provides increased graft viability and survival of innate stromal cells,<sup>51</sup> whereas for larger volume deficiencies, we prefer the Coleman 3-mm cannula for fat harvesting.

According to a national survey in the United States, most surgeons use the Coleman cannula for routine fat harvesting,<sup>40</sup> and since the 2009 National Consensus Meeting in Germany, fat harvesting using low vacuum settings has been advised.<sup>52</sup>

Infiltration of the donor area has been another subject for debate in the literature. The term *dry technique* implies liposuction performed without infiltration solution, under general anesthesia or regional blocks. It was introduced in 1983 by Fournier and Otteni,<sup>53</sup> who reported advantages of the technique such as rapid execution and less tissue distortion but also disadvantages such as the requirement for volume resuscitation in large-volume liposuction.

In 1993, Klein<sup>54</sup> showed that the so-called tumescent or “wet” technique, injecting the donor site with fluid solution, improves the safety of large-volume liposuction because it eliminates the need for general anesthesia and reduces surgical hemorrhage. Illouz and de Villers<sup>4</sup> also highlighted the fact that the technique causes hydrodissection and enlarges the target fat layer, thus facilitating the subsequent aspiration with decreased pain and ecchymosis.



Performing histomorphometric analysis and assessing cell viability of harvested adipocyte samples, Agostini et al<sup>55</sup> found no differences between the dry and the wet technique. Karacalar and Ozcan<sup>49</sup> reported fat harvest under tourniquet control to provide a bloodless field and avoid the need for lidocaine or epinephrine.

In their *in vitro* study, Keck et al<sup>56</sup> reported that different local anesthetics caused different preadipocyte viability and that this effect could explain the different results obtained in the autologous fat transfer. In contrast, Livaoglu et al<sup>57</sup> in an experimental study reported that there is no negative effect of lidocaine plus epinephrine or prilocaine on microangiogenesis and the survival of fat grafts. Similarly, according to Shoshani et al,<sup>58</sup> a local anesthesia solution, consisting of lidocaine and epinephrine, does not alter the uptake of fat grafts and has no influence on the viability of adipocytes.

Most clinicians routinely inject the donor site with local anesthetic. Coleman<sup>8</sup> recommended using 0.5% lidocaine with epinephrine (1:200 000), whereas Nordstrom<sup>47</sup> suggested infiltration of the donor area with 0.5% lidocaine and epinephrine (1:80 000). Tzikas<sup>10</sup> used a mixture of 50 mL of 2% lidocaine, 1 mL of epinephrine (1:1000), and 12.5 mL of sodium bicarbonate in 1 L of lactated Ringer's solution.<sup>10</sup>

Water-assisted liposuction is an evolution in liposuction devices utilizing a dual-purpose cannula that emits pulsating, fan-shaped jets of tumescent solution and simultaneously suctions fatty tissue and the instilled fluid through a separate channel within the cannula into an integrated suction unit.<sup>59,60</sup> Continuous irrigation with tumescent solution during the aspiration facilitates fat harvest through small cannula holes in spite of the low vacuum. The fat is then separated from superfluous water. The method is fast, there is minimal loss of blood, and no general anesthesia is required for moderate liposuctions, and in breast lipofilling, fat graft survival has been recently found to be equal to that of cell-enriched graft.

## Processing of Fat Grafts Before Delivery

After aspiration of the fatty tissue, it is important that nonviable components of the aspirate, such as oil, blood, and local anesthetics are removed and, at the same time, the quality, integrity, and viability of the adipocytes and the inherent mesenchymal stem cells in the aspirate be maintained. Processing techniques are sedimentation, filtering, washing, and centrifugation. There is no consensus as to the optimal method of fat graft preparation.

Condé-Green et al,<sup>61</sup> comparing different processing methods, found that decanted lipoaspirates contained more viable adipocytes, whereas washed lipoaspirates

were richer in mesenchymal stem cells compared with centrifuged tissue. But eventually, it was the pellet collected at the bottom of the centrifuged samples that showed the highest concentration of stromal cells. Rose et al<sup>62</sup> in a histological comparison of autologous fat processing methods suggested that sedimentation appears to yield a higher proportion of viable adipocytes than does washing or centrifuging. On the other hand, washing harvested fat eliminates inflammatory mediators, reduces immune response at the recipient site, and enhances overall graft survival.

As already mentioned, the superdry fat harvesting technique has been used to eliminate the need for further graft processing.<sup>49</sup> Rohrich et al<sup>36</sup> found no quantitative difference in adipose viability between centrifuged and noncentrifuged fat.

Recently, commercially available lipofiltration systems that streamline the graft preparation process by selectively washing lipoaspirate while draining superfluous tumescent fluid, free lipids, and debris have been developed. The BEAULI method using body-jet and a LipoCollector (Humanmed Ag, Germany)<sup>63</sup> is a tissue-friendly, water-assisted liposuction technique that can deliver quickly large amounts of washed and sterile fat graft that does not require centrifugation. This is an increasingly popular method, especially for breast lipofilling because harvested fat can be easily reinjected because of the high percentage of fluid it contains (30%), and minimal processing also eliminates some of the risks that may result from "fueling" of cancer cells by potent stem cells. Puregraft 250 (Cytosol Therapeutics, San Diego, CA) is another system that can prepare in the operating theater large amounts of purified and concentrated graft in a closed, sterile environment.<sup>64</sup>

Filtering the aspirate through open cotton gauze or drying it rolled in Telfa gauze are also techniques proposed that are preferred to centrifuging in terms of fat graft viability, but none of them has been confirmed by any other study.<sup>65,66</sup> In a clinical trial on facial fat grafting, Botti et al<sup>67</sup> found no difference between fat that was filtered and washed and centrifuged fat. In contrast, Rubin and Hoefflin<sup>46</sup> believed that fat purification with centrifugation was a selective process to isolate only the fittest adipose cells and that a graded density of adipose tissue is achieved with this process. High-density fat contains more vasculogenic cytokines and progenitor cells and yields longer graft survival than low-density fat. Moreover, it has to be highlighted that centrifugation is an important step of process in CAL, when stromal cells are to be isolated and concomitantly used to enrich the fat graft.

Coleman suggested a processing method that has gained popularity and has been since integrated in many fat-transfer clinical protocols.<sup>6,40,41</sup> Aspirated fat in



**Figure 2.** Centrifuged fat retrieved by the Coleman method. The aspirate is separated into a top oil layer from ruptured lipocytes, a middle layer of usable fat tissue, and a bottom layer of blood and tumescent solution.

syringes was spun at 3000 rpm for 3 minutes to isolate the fat (Figure 2).<sup>6,8</sup> In our clinical routine, the Coleman method is more frequently used because we have found it to constantly produce grafts of good quality.

More aggressive processing with centrifugation has been used to dispose of fat cell debris, free triglycerides, ruptured membranes, and fragile fat cells, but Ferraro et al<sup>68</sup> reported better graft viability with low centrifugal forces at 1300 rpm (250g) for 5 minutes. Fine-tuning aspiration using low *g*-forces similarly produced good cell viability results.<sup>69</sup>

To challenge the significance of the acceleration forces in cell viability, Pulsfort et al<sup>70</sup> examined the vitality of adipocytes in lipoaspirates after centrifugation by 8 different accelerations up to 20 000g, immediately as well as 4 days later, and found no significant histological alterations in the viability of differently centrifuged adipocytes and no apoptotic changes.

## Fat Graft Delivery

Despite a long history of clinical use and evolution of techniques for fat transfer, no consensus exists to date on the best technique and the longevity of results; yet the principles of fat reimplantation are based on optimal recipient site vascularity for increased fat survival.<sup>3,6,9,71</sup>

When volume increase is the goal and large amounts of fat have to be transferred, the main consideration of techniques is the size and the hole size of injecting cannulas.<sup>19-21</sup> Small-gauge cannulas are thought to reduce trauma to the recipient site, thus reducing the risks of bleeding, hematoma, and poor graft oxygen diffusion. The hole size of the injection cannula should match closely the hole size of the aspiration cannula. By

matching hole sizes, harvested fat lobules flow easily through the injection cannula without resistance.<sup>72</sup>

For breast augmentation and reconstruction, when more than 100 mL of fat is required, the BRAVA technique has been developed for preexpansion of the recipient breast.<sup>73</sup> The breast is externally expanded by the application of vacuum via a specially designed bra (BRAVA LCC, Miami, FL) for 3 weeks before fat injection; thus, a natural, well-vascularized scaffold is created to receive the grafted fat. The name of the technique derives from an acronym of its properties and advantages:

- Bigger potential spaces available for overall volume of graft
- Reduces demand on adipocytes to act as internal expanders
- Augments tension on scar tissue, improving breast shape
- Variables like time-consuming processing become less demanding
- Angiogenesis effect may increase recipient site oxygen tension and graft take<sup>73,74</sup>

It is generally believed that fat within 2 mm of an arterial supply will survive, but fat placed beyond that distance will undergo necrosis and replacement by fibrous tissue.<sup>52,71,72</sup> Therefore, in an attempt to increase the surface-to-volume ratio of the graft to the recipient vascularized tissue, many authors prefer microinjection of fat by the lipostructure technique or the Coleman technique.<sup>6,8,41</sup> Through multiple access sites, multiple tunnels are created on insertion, but fat is injected only during withdrawal of the cannula in a “fanning-out”



**Figure 3.** Rigotomy of a breast scar; preparing the recipient site for fat transfer.

pattern. Fat grafts are distributed in small aliquots and fan out into various soft tissue depths to avoid excessive interstitial pressure in the recipient site and overcrowding of transplanted adipocytes.<sup>8</sup>

When fat is to be transferred to scarred tissues, scars have to be released prior to graft transfer. This technique was first described by Rigotti<sup>16</sup> (who used a pickle fork to release a heavily scarred radiated recipient site) and is used to release subcutaneous bands and scars. A large-bore needle or a Toledo cannula can be used for the same purpose. This technique is called 3-dimensional ligamentous band release or “Rigotomy” and, like meshing a 2-dimensional skin graft, releases contour deformities of subcutaneous fibrotic tissue (Figure 3).<sup>16,72</sup> Grafted fat acts not only as a filler, improving contour, but also as a spacer keeping distance between the transected scar and preventing re-formation.

Regarding the cannula size, several authors use different caliber cannulas for fat injection, and the nature of the recipient site is the major determinant in the choice of the injecting cannula size. Coleman described the use of a 17-gauge blunt cannula connected to a 1-mL syringe to prevent the formation of a hematoma.<sup>6</sup> For periorbital injection, Trepsat<sup>12</sup> used specific pointed malleable cannulas blunter than a needle. He used a 0.3-mm cannula attached to a 1-mL Luer Lock syringe for the upper eyelid, injecting fat from the deep layer near the bone to a superficial layer just under the orbicularis oculi muscle. For fat grafting in the lower eyelid, he suggested a fine, 19-gauge cannula on a 1-mL syringe to inject fat in a multipass, pretunneled area of the suborbicularis oculi fat. Nordstrom<sup>47</sup> described a “spaghetti” fat grafting technique in which 3-mm grafts were laid down in tunnels not touching each other. Tzikas<sup>10</sup> designed 16-gauge, bullet-tipped, one-hole cannulas attached to 1-mL

syringes. Erdim et al<sup>45</sup> found no differences in the viability of fat grafts injected through 14, 16, and 20-gauge needles.

Studies on fat graft maintenance have demonstrated that mobile areas of the face, such as the glabella and lips, are less amenable to correction compared with less-mobile areas, such as the malar and lateral cheek areas. To minimize graft desorption, the fat autograft muscle injection method was developed to deliver fat directly into the intrinsic facial muscles by using blunt-tipped cannulas. Butterwick and Lack<sup>75</sup> reintroduced this technique for large-volume fat injection and believed that it causes less facial edema. In breast augmentation, we prefer to distribute the fat graft, so that about two-thirds is placed in the subcutaneous fat area and one-third intrapectorally using 2.5-mm cannulas connected to 10-mL syringes.

For superficial or subdermal refinements of volume and contour, Nguyen et al<sup>50</sup> modified the microinjection technique for liposculpture and managed to successfully transfer fat through 25-gauge cannulas. For microlipografting, we use the st’rim system, with 20-, 23-, and 25-gauge (Thiebaud Biomedical Devices, Margencel, France) fat-injecting cannulas designed by Guy Magalon. Microinjection techniques allow for superficial grafting and precision in graft delivery, which is especially useful in facial lipotransfer, orbital rejuvenation, and correction of liposuction deformities and further increases the surface to volume ratio of the graft, resulting in enhanced graft survival.<sup>51</sup>

## Methods for Improving Viability of Fat Grafts

Many clinicians do not advocate the addition of bioenhancers to harvested fat. Coleman opposed the addition of chemicals, hormones, drugs, or any foreign substances in general and emphasized the importance of preventing chemical or mechanical damage to the sensitive adipose tissue.<sup>6,8</sup>

Based on the hypothesis that fat graft desorption is the result of ischemia and lack of neoangiogenesis,<sup>71,76</sup> several studies have been conducted in to find ways to increase the viability of the transplanted tissue. The use of growth media and nutrients as part of the processing procedure has been reported to improve fat survival and enhance cell growth. Unfortunately, many of the recent reports vary widely in methodology and use a combination of agents that make it difficult to determine clinical applicability.<sup>38,72,77</sup> Preprocessing of harvested human fat with Cariel, a medium enriched with vitamins, amino acids, anabolic hormones such as thyroxine, insulin, growth hormone, and sodium selenite, has been reported to increase graft uptake, weight, and longevity.<sup>78</sup>



Yuksel et al,<sup>79</sup> in an animal study, used poly(lactic-co-glycolic acid)-polyethylene glycol microspheres to deliver continuous doses of insulin, Insulin-like Growth Factor (IGF 1), basic fibroblast growth factor, or combinations to inguinal fat grafts and found that all the growth factors increased fat graft weight and volume in comparison with control blank microspheres. The efficacy and safety of bioenhancers will likely be determined by the results of ongoing investigations related to tissue engineering.

The beneficial effect of fat graft suspension has also been investigated. Palma et al<sup>80</sup> injected autologous fat with purified type I collagen gel in the preauricular area of 30 New Zealand rabbits and found reduced local inflammatory reaction and improved graft survival. Piasecki et al<sup>81</sup> reported improved survival when fat grafts were suspended in matrigel. Shoshani et al<sup>82</sup> evaluated hyperbaric oxygenation and found that administration of 100% oxygen at 2 atm for 90 minutes per day beyond 5 days of treatment had a negative association with fat survival. To date, there are no studies evaluating the use of hyperbaric oxygen to improve autologous fat transfer in humans. Baek et al<sup>83</sup> suggested the injection of fat in conjunction with botulinum toxin A to reduce fat desorption.

CAL is a promising method used to enrich the fat graft with ADSCs before transplantation.<sup>84,85</sup> There are also closed systems such as Celution (Cytosol, Therapeutics, San Diego, CA) that can prepare cell-enriched lipograft in the operating room in approximately 1 hour, and this has gained approval in some countries.<sup>86</sup> In an attempt to engineer a regulatory compliant form of CAL in the United States, autologous fat transfer with in situ mediation of injected collagenase has been recently developed as a method of fat graft enrichment by the stromal cells released,<sup>87</sup> but apparently, it can only be used for small fat transfers, as in scar revision. CAL aims to improve fat graft uptake and survival and produce more predictable and longer-lasting results than mere lipofilling. Nevertheless, because potent stem cells can also stimulate oncogenesis, the safety of this method has yet to be determined.

## Conclusion

Despite the growing literature on regenerative and translational potentials of cells, evidence-based clinical studies on fat grafting are sparse. Standardization of methods of fat harvesting, processing, and delivering; assessment of graft survival; and evaluation of outcomes will increase the safety and reliability of fat grafting. The Coleman procedure for harvesting, processing, and delivering fat grafts is a standardized method preferred by many surgeons.

Unpredictable graft desorption is an area that needs further improvement in fat grafting, which is otherwise a safe and versatile method in reconstructive and aesthetic surgery. The future of fat transplantation is in elucidating the mechanisms and interactions underlying every procedural step of fat grafting, rather than in the development of new techniques, instruments, and devices.<sup>5,40</sup> The optimal growth and angiogenic factors as well as bioengineered matrices for maximal enhancement of adipocyte viability have to be determined. Further in-depth knowledge and proof-of-concept clinical trials are essential to increase the reliability, enhance the safety, and strengthen the scientific and clinical establishment of this increasingly popular and promising method and its possible combination with stem cell therapy.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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