Cell-assisted lipotransfer in the clinical treatment of facial soft tissue deformity

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Cosmetic surgeons have experimented with a variety of substances to improve soft tissue deformities of the face. Autologous fat grafting provides significant advantages over other modalities because it leaves no scar, is easy to use and is well tolerated by most patients. Autologous fat grafting has become one of the most popular techniques in the field of facial plastic surgery. Unfortunately, there are still two major problems affecting survival rate and development: revascularization after transplantion; and cell reservation proliferation and survival. Since Zuk and Yosra developed a technology based on adipose-derived stem cells and cell-assisted lipotrophy, researchers have hoped that this technology would promote the survival and reduce the absorption of grafted fat cells. Autologous adipose-derived stem cells may have great potential in skin repair applications, aged skin rejuvenation and other aging-related skin lesion treatments. Recently, the study of adipose-derived stem cells has gained increased attention. More researchers have started to adopt this technology in the clinical treatment of facial soft tissue deformity. The present article reviews the history of facial soft tissue augmentation and the advent of adipose-derived stem cells in the area of the clinical treatment of facial soft tissue deformity.

Key Words: *Adipose-derived stem cells; Cell-assisted lipotransfer; Facial soft tissue deformity*

Le transfert de graisse cellulaire pour le traitement clinique des malformations des tissus mous de la face

Les plasticiens ont mis diverses substances à l'essai pour corriger les malformations des tissus mous de la face. La greffe de graisse autologue comporte d'importants avantages par rapport aux autres modalités, car elle ne laisse aucune cicatrice, est facile à utiliser et est bien tolérée par la plupart des patients. C'est désormais l'une des techniques les plus populaires en chirurgie plastique de la face. Malheureusement, deux grands problèmes influent encore sur le taux de survie et le développement : la revascularisation après la greffe ainsi que l'inventaire, la prolifération et la survie des cellules. Depuis que Zuk et Yosra ont mis au point une technologie qui repose sur les cellules souches adipeuses et la lipotrophie cellulaire, les chercheurs espèrent que cette technologie permettra de promouvoir la survie et de réduire l'absorption des cellules adipeuses greffées. Les cellules souches adipeuses autologues ont peut-être plus de potentiel pour les applications de réparation cutanée, le rajeunissement de la peau vieillissante et d'autres traitements des lésions cutanées liées au vieillissement. L'étude des cellules souches adipeuses a commencé à susciter l'attention. Plus de chercheurs ont commencé à adopter cette technologie pour le traitement clinique des malformations des tissus mous de la face. L'histoire de l'augmentation des tissus mous de la face et l'utilisation des cellules souches adipeuses pour le traitement clinique des malformations s'y rapportant sont analysées dans le présent article.

Facial soft tissue deformity can include: unilateral or bilateral facial atrophy; poor facial soft tissue development; facial infection; trauma; depressed surgical scars; zygomatic, temporal, frontal, or orbital depression associated with the lower eyelid; lacrimal groove or temporal buccal groove depression; deep nasolabial sulcus; and thin upper lip. Such loss of facial soft tissue volume compounded by tissue laxity leads to the aged appearance of the periorbital, perioral, cheek and mandibular areas (1).

Cosmetic surgeons have experimented with injections of a wide variety of substances to alter human facial soft tissue deformities. However, since Lexer used fat grafting in the treatment of abnormal facial soft tissue depression in 1910, fat particles have been widely applied to alter facial soft tissue deformity due to its natural appearance, abundant sources, ease of collection, durability, lack of rejection and lack of scarring (2). A major problem with fat grafting centres around its absence of reproducibility and inconsistent results, with fat resorption shown to be anywhere from 20% to 90% (3). Although many studies have attempted to improve the various donor site selection methods, such as liposuction (4), harvesting (5), autologous fat processing (6) and reimplantation (7), and optimization of centrifugal conditions (6), the achievements to date have not been promising.

ADIPOSE-DERIVED STEM CELLS AND CELL-ASSISTED LIPOTRANSFER

Adipose-derived stem cells (ASCs) and cell-assisted lipotransfer (CAL) have presented new options for the field of plastic surgery. These technologies are well suited to regenerative medicine due to a capacity for ex vivo expansion and multilineage differentiation (8), which may promote the survival and reduce the absorption of fat cells. Autologous ASCs have great potential in skin repair applications, skin rejuvenation and aging-related skin lesion repair (9). The present article reviews the history of soft tissue augmentation using fat grafting and the advent of the clinical use of ASCs on the human face.

In 2002, Zuk et al (10) discovered a group of fibroblast-like stromal cells in liposuction aspirates. After digestion, centrifugation and washing, ASCs with a cell surface antigen protein phenotype were identified. Enzymatically digested adipose tissue yields a heterogeneous population of many other cell types, including ASCs, endothelial cells, preadipocytes, fibroblasts, hematopoietic-lineage cells, and pericytes, all found in the stromal vascular fraction (SVF) of centrifuged lipoaspirate. Suga et al (11) found that ASCs are the main proliferating cells involved in tissue repair after ischemia-reperfusion injury, and the SVF can secrete growth factors to promote the regeneration of adipose tissue cells and angiogenesis. Since the report of these findings, the study of ASCs has gained increased attention. Numerous studies have demonstrated that ASCs can be differentiated into different cell lines as shown in Table 1 and are involved in other processes through the secretion of paracrine factors. Matsumoto et al (12) first proposed CAL technology based on successful results in animal experiments. An SVF containing ASCs was freshly isolated from one-half of the aspirated fat and recombined with the other half. The SVF or ASCs were supplemented or concentrated within the lipoaspirate before grafting, thereby creating a CAL. The experimental results indicate that CAL increases fat cell viability by 35% compared with

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TABLE 1
Multilineage capacity of adipose-derived stem cells (ASCs)

Differentiation of ASCs	Reference
Fat cells	49
Bone cells	50
Chondrocytes	25
Muscle cells	51
Myocardial cells	52
Nerve cells	53

TABLE 2
Published reports of cell-assisted lipotransfer for facial soft tissue deformity

Indication	n	Follow-up, months	Reference
Facial lipoatrophy	6	1 to 13	Yoshimura (17)
Facial tissue defects	20	18	Sterodimas (18)
Craniofacial microsomia	6	6	Tanikawa (19)
Parry-Romberg syndrome	1	1 to 12	Castro-Govea (20)

non-CAL methods (ie, traditional lipotransfer). Adipocytes die easily under ischemic conditions, whereas ASCs are activated and contribute to adipose tissue repair (13). ASCs can not only significantly improve tissue revascularization, survival and surgical outcomes, but can also reduce fat transplantation fibrosis, cysts and calcification. ASCs also have an ameliorating effect on skin tone (14).

CAL in the clinical treatment of soft tissue deformity

ASCs and the SVF have been applied in the clinical treatment of soft tissue augmentation. Yoshimura et al (15,16) used CAL in 55 patients using a three-dimensional measurement system to evaluate the surviving fat volume. The final clinical results were highly satisfactory. The surviving fat volume of injected fat was promising, the atrophy of injected cells did not change substantially after two months and no major abnormalities were observed after 12 months. This evidence suggests that CAL is a suitable technology for the treatment of soft tissue deformity.

CAL for clinical treatment of facial deformity

ASCs and the SVF have been used for the clinical treatment of facial soft tissue augmentation. Yoshimura et al (17) compared conventional lipoinjection (non-CAL [n=3]) with CAL (n=3) on six patients with facial lipoatrophy due to lupus profundus or Parry-Romberg syndrome. All patients showed improvement in facial contour, but the CAL group had a better clinical improvement score than the non-CAL group; however, the difference did not achieve statistical significance. Adipose necrosis was found in one non-CAL case who took perioperative oral corticosteroids. His results suggested that CAL is effective and safe, and potentially superior to conventional lipoinjection for facial recontouring.

Sterodimas et al (18) compared CAL technology with autologous fat transplantation. In that study, 20 patients with congenital or acquired facial tissue defects were randomly divided into two groups. An analysis of patient satisfaction during the first six months clearly demonstrated better results in the group using CAL. However, there was no significant difference between the two groups in terms of patient satisfaction at the 18-month evaluation. The CAL group produced aesthetically acceptable results without the need to repeat treatment sessions, whereas multiple treatment sessions were necessary for the other group; however, further long-term studies might be required to confirm the favourable results.

Tanikawa et al (19) used CAL for craniofacial microsomia and reported statistically superior volume retention at six months, with 88% of the original graft volume retention in the experimental group and only 54% in the unenhanced control group. In such applications, CAL can achieve satisfactory results but frequently requires multiple follow-up procedures of additional lipotransfer.

Castro-Govea et al (20) also reported one case using CAL to treat patients with mild and moderate Parry-Romberg syndrome using computed tomography with three-dimensional reconstruction. The postoperative evolution of those patients in the short- and long-term (one and 12 months, respectively) was satisfactory. Infiltration with enriched autologous fat containing ASCs reduced the severe depression of the frontotemporal region and provided better volume and symmetry. That study also reported clinical improvement of skin quality, including better moisture, texture, shine and elasticity. Accordingly, CAL is not only advantageous for tissue regeneration but also beneficial for the skin itself. The summary of CAL for the clinical treatment of facial deformity is shown in Table 2.

A summary of CAL: ASCs and SVF accession and processing

The past decade has witnessed an explosion of preclinical data relating to the isolation, characterization (21), cryopreservation, differentiation and transplantation of freshly isolated SVFs and ASCs in vitro and in animal models (22). Despite the ASC acquisition methods that have been reported, controversy remains because of disparities in the techniques, extraction sites and separation methods used, as well as the most appropriate cell doses needed, all of which require further study and discussion.

Padoin et al (23) and Aguena et al (24) considered the lower abdomen to be the site with the highest concentration site of ASCs, whereas Jugens et al (25) suggested the buttocks. Zhu et al (26) suggested that a 1×10^6 cells/mL cell dose can increase the survival of transplanted fat tissue rate, whereas Kakudo et al (27) considered 3×10^5 cells/mL to be the best cell dose when using an automated Celution 800/CRS system (Cytori Therapeutics Inc, USA), to extract ASCs. The cell dose reportedly ranges between two and five times the dose of unenhanced tissue in humans.

Adipose tissue was harvested by conventional liposuction in the procedure modified by Yoshimura et al (15), who used artificial means or the automated Celution 800 system to separate, concentrate and purify the autologous fat. The fat cells were then used to culture ASCs and the SVF. The aspirated fat was washed with phosphate-buffered saline to remove contaminating debris and red blood cells and was digested on a shaker at 37°C in phosphate-buffered saline containing 0.075% collagenase (type I; Sigma-Aldrich, USA) for 30 min. A portion was centrifuged at 1200× *g* for 5 min, and the pellets were resuspended and filtered with a 100 mm mesh. The SVF obtained could be used as a direct source of stem cells or expanded in culture. When the SVF needed to be expanded, the freshly isolated or cultured SVF was plated (30,000 cells/cm^2) on gelatin-coated dishes and cultured at 37°C in an atmosphere of 5% carbon dioxide in humid air. The culture medium contained isobutylmethylxanthine, 1 µM dexamethasone, 10 µM insulin and 200 µM indomethacin 1%. Seven days later, attached cells were passaged by trypsinization and cultured in the same medium, which was replaced every third day. This method has been applied by domestic experts and scholars in facial soft tissue deformity treatments.

Injection of ASCs and SVF into target sites

The centrifuged lipoaspirate is gently mixed with the freshly isolated or cultured ASCs and SVF. The cell-supplemented fat is ready for transplantation after cell adherence to the centrifuged fat occurs (approximately 15 min). Fat grafting with a blunt cannula has been used by plastic surgeons for altering facial contours for 100 years. Fournier (28), Donofrio (29) and others have contributed to our collective understanding of periorbital aging and have appropriately emphasized the importance of volume preservation in our surgical techniques and illustrated the success of volume restoration using fat. Currently, there is a better understanding of the need for the restoration or adjustment of facial volume (30), and that the revascularization of a small graft is

superior to that of a large graft (31). For these reasons, a technique has been developed whereby fat is harvested and injected through a blunt cannula with minimal vacuum to prevent explosion of the cell-supplemented fat.

Importantly, the injection process must take into account multiple radial pathways, points, tunnels and levels, according to the three-dimensional structure of facial fat growth, and that the fat tissue near the zygomatic cheek is divided into two layers, whereas there are three layers near the nasolabial fold. Furthermore, each cell segment is separated from the other by host tissue, which maximizes the host-prosthesis interface and the possibility for the exchange of nutrients (32). Superficial musculoaponeurotic system fascia should be injected at the subcutaneous level, not into the muscles. In the eyelid, lower eyelid, lacrimal groove and nasolabial fold, and for temporal and sunken scars, shallow injections are optimal. Additional cell-supplemented fat is injected into a more superficial plane within the subcutaneous tissue of the lower eyelid with careful attention to avoid bolus deposition and a too superficial injection directly under the lower eyelid skin (33). The need for overcorrection is minimal. In the forehead and the cheek, the cell-supplemented fat should be injected into the muscle layer and in a direction parallel to the direction of the nerves and blood vessels to avoid damaging them. For patients with a flat nasal bridge, the injection should follow the middle of the tunnel along the nasal bone on the dorsum. In short, the injection should ensure the distribution of cell-supplemented fat in each tunnel. The cell-supplemented fat transfer volume ranges between 1 mL and 4 mL per site (34). A summary of CAL procedures is shown in Figure 1, similar to Sterodimas et al (35).

DISCUSSION

After CAL, patients should devote attention to local skin damage and sun exposure to reduce tissue fluid exudation, and should be given antibiotics to prevent infection because a range of activities and local infection ischemia will affect the blood supply.

ASCs may be an ideal type of stem cells, given that they are more readily available, are of autologous tissue origin and are nonimmunogenic (36). Mailey et al (37) reported similar results between CAL and unenhanced cases with regard to symmetry, scarring and deformity; however, they did report a significant increase in skin improvement in patients who underwent CAL. It is well known that volume loss in the upper one-third of the face contributes significantly to the look of aging (38). Traditional surgery has been combined with lipoinjection and has offered the opportunity to produce long-lasting tissue lifting in the face with less risk of complications (39). According to clinical studies, CAL will become an accepted technique widely used in the treatment of facial soft tissue deformity (40).

However, there are also many problems that remain unsolved. The best separation method and the best translated cell doses that do not waste resources remain subjects of debate. ASCs have no specific markers; therefore, the identification and separation after extraction remains a problem (41). Moreover, there are still several problems to be addressed regarding the differentiation potential of ASCs in vivo (42). ASC effects on human tumour growth still need to be researched. (43); ASCs still have potential risks and present ethical issues regarding tumour cell development and, therefore, this is a bottleneck that restricts its clinical development (44). The CAL technology lacks a unified standard. CAL extraction takes 90 min to 100 min, which is time consuming and costly. Furthermore, mamma magnetic resonance imaging volumetry to evaluate the rate of fat survival after autologous lipotransfer should be more widely used (45). It is also not yet clear whether the age, sex or body mass index of the patient affects CAL therapeutic potential (46). Worldwide clinical use of ASCs and CAL has dramatically increased in parallel to questions concerning the safety and efficacy of CAL treatments (47). Well-controlled clinical studies are needed to demonstrate the safety and efficacy of the clinical CAL methods that have been widely used for facial treatments in humans (48). Table 2 shows the published clinical reports and trials that have used CAL for facial soft tissue deformity.

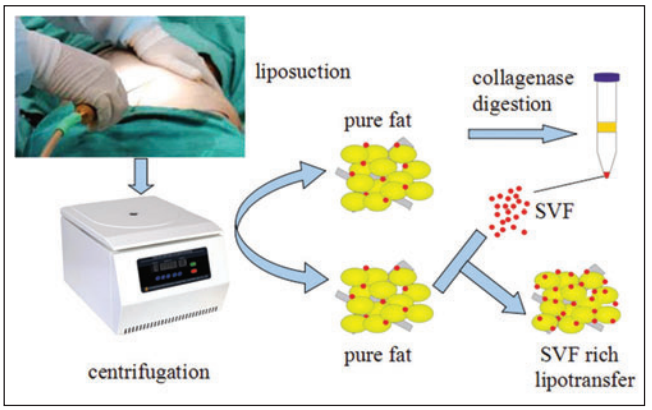

Figure 1) *Summary of cell-assisted lipotransfer procedures. SVF Stromal vascular fraction*

CONCLUSIONS

Although good results have been reported, we still lack a complete set of clinical practice guidelines (ie, a standard surgical procedure) that includes the effect of postoperative evaluation criteria, safety assessments and solutions, with randomized double-blind controlled trial data to evaluate the efficacy of evidence-based medicine. The biological properties of ASCs suggest a potential role in enhancing fat graft retention and facilitating minimally invasive reconstructive treatments, but these properties remain unclear. Moreover, well-designed clinical trials are also warranted to better investigate the safety of CAL procedures in patients. Nevertheless, the novel methods for CAL application in facial tissue deformity as reviewed in the present article are highly promising and may bring us closer to identifying new therapeutic approaches and safely accelerating the transition of basic research findings into clinical advances in the fields of aesthetic surgery and regenerative medicine.

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