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REVIEW CRANIOFACIAL/MAXILLOFACIAL

Oral and Maxillofacial Autologous Fat Transplantation: History, Clinical Application Status and Research Progress

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Abstract After more than a century of development, autologous fat transplantation (AFT), a repair method for soft tissue defects and deformities, has the advantages of being simple, rapid, effective and safe, and it is increasingly favoured by plastic surgeons. This article reviews the developmental history of AFT, analyses its clinical application status in the oral and maxillofacial regions, and provides a preliminary summary and discussion of the research progress related to AFT. The hope is that that this technique could be widely applied for oral and maxillofacial diseases as well as facial rejuvenation indications.

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Keywords Autologous fat transplantation · Oral and maxillofacial region · Soft tissue defect repair

Abbreviations

AFT	Autologous fat transplantation
ADSCs	Adipose-derived stem cells
SVF	Stromal vascular fraction
PRF	Platelet-rich fibrin
CAL	Cell-assisted lipotransfer
BMI	Body mass index

Introduction

Autologous fat transplantation (AFT) has been widely used in soft tissue reconstruction for nearly a century. Because this technique is minimally invasive, safe, effective, and economical, it is increasingly favoured by clinicians. Statistics show that approximately 80% of plastic surgeons use AFT as a common treatment in their daily work [1]. As an effective supplement to conventional surgical methods, AFT has a wide range of applications for soft tissue defects and deformities that occur in various parts of the body, especially in the maxillofacial region. In recent years, people have paid increasing attention to facial rejuvenation, which has further expanded the fields of application for AFT [2]. This paper will discuss AFT history, clinical application and scientific issues in the fields of oral and maxillofacial surgery.

The History of Autologous Fat Transplantation

In 1893, the German surgeon Gustav Neuber used arm fat to correct orbital soft tissue deformities [3]. This was the first case report of fat transplant surgery in history. In the early decades of the 19th century, some scholars injected paraffin or a mixture of paraffin and fat into the affected area to treat pathological defects, such as saddle nose deformity caused by syphilis [4]. However, a problem caused by the injection of paraffin soon surfaced, where many patients were affected by infections, swelling, pain, "paraffin tumours" and other complications, following allogeneic injections; this procedure was gradually abandoned, and AFT was accepted by an increasing number of doctors. In 1919, the German craniofacial plastic surgeon Lexer [5] published on die freien transplantation (free transplantation), in which the indications and treatment for AFT were introduced for various soft tissue diseases, such as scar depression, craniofacial deformities, breast reconstruction, and off-section ankylosis. In 1926, American plastic surgeon Miller [6] obtained fat from the abdomen to correct nasolabial folds, crow's feet and saddle nose deformities. As the number of treated cases has accumulated, severe absorption has been found to occur often after fat transplantation. In the 1950s, Lyndon A Peer published an article confirming that 1 year after transplantation, there is a loss of adipose tissue volume and weight of up to 45% or more [7]. He proposed the theory of blood supply establishment and tissue replacement that was believed to cause precursor fat cells to become mature fat cells. In the following 100 years, clinicians and researchers engaged in many attempts to improve fat survival rates after AFT. In the 1980s, Fournier [8] and Illouz [9] invented the liposuction technique. Pierre used a minimally invasive aspiration syringe, and Illouz used a negative-pressure suction pump in fat transplantation operations [8, 9]. In the 1990s, Coleman [10] standardized the steps of fat transplantation through a series of studies and clinical practices, significantly improving volume maintenance after fat transplantation. He proposed "using the blunt needle connected to a syringe for fat suction", "centrifuge for fat purifying", and "multi-level, multi-tunnel fat injection". This principle has been widely accepted by plastic surgeons. In 2004, his publication "Structural Fat Transplantation" laid the foundation for modern AFT. Since the Coleman series of outstanding contributions, indications for the AFT technique continue to expand, and the safety continues to improve, leading to the popularity of AFT worldwide. Recently, a series of important discoveries appeared in the field of AFT, deepening the understanding of this technique. For example, in 2001, Zuk et al. [11, 12] found a large number of mesenchymal stem cells (adipose-derived stem cells, ADSCs) in human adipose tissue, and these cells are believed to have applications in the medical treatment of regenerative diseases [13]. In 2006, Yoshimura [14] proposed the cell-assisted lipotransfer (CAL) technique, which is used to enhance long-term volume retention after fat transplantation. In 2007, Rohrich and Pessa [15] proposed the fat compartment concept in the head and neck region, providing an anatomical basis for maxillofacial AFT. In 2013, Tonnard et al. [16] proposed the concept of nano-fat and applied it in facial rejuvenation.

After 100 years of development, the AFT technique has matured, although some problems remain to be solved. However, it is undeniable that AFT has become important in the field of plastic surgery. The history of fat transplantation is shown in Fig. 1.

Clinical Application of Autologous Fat Transplantation in the Maxillofacial Region

Indications for AFT in Maxillofacial Diseases

AFT refers to obtaining autologous fat and injecting it into the receiving area through a minimally invasive method to correct various soft tissue deformities and to improve local functions and skin texture. Maxillofacial AFT is mainly used for treating various types of diseases caused by the insufficient capacity of soft tissue, such as hemifacial atrophy [17], soft tissue trauma, infection malformations, tumours after radiotherapy and local soft tissue function disorders [13]. It may also be used to improve the texture of the facial skin to achieve facial rejuvenation [10]. In addition, it can also be used to treat all kinds of scars, oral mucosal diseases [18] and velopharyngeal insufficiencies.

Autologous fat Transplantation Clinical Treatment Process

Modern AFT is based on the Coleman fat grafting system and is further optimized for the clinical treatment process. It can be divided into three parts: fat acquisition, fat processing and fat injections.

Fat acquisition In fat acquisition, three factors need to be considered: donor sites and tumescent and suction methods.

Common donor sites for autologous fat include the abdomen, thighs, buttocks, and inner knees. Although some scholars have compared volume retention between different donor sites [19], the decision is mainly at the surgeon's discretion in practice. For example, for patients who need autologous cartilage transplantation for rhinoplasty and facial fat filling simultaneously, we often choose the abdomen as the donor site based on the "principle of proximity". If the patient's body mass index (BMI) is too

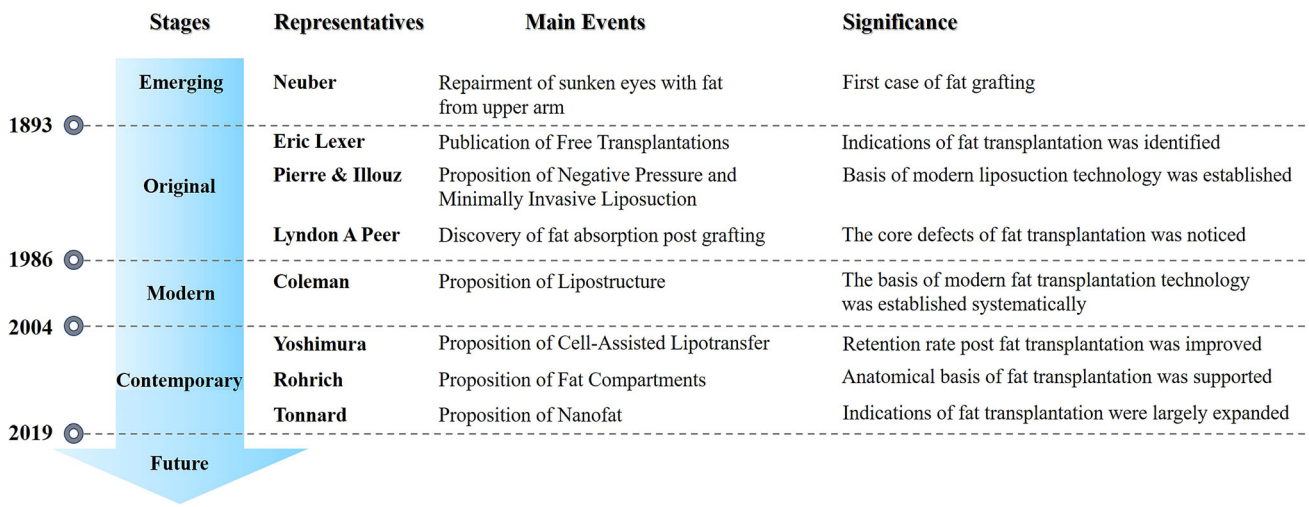

Fig. 1 A brief summary of autologous fat transplantation history.

low, to obtain enough fat, the "abdomen + thigh" dual donor site may be considered.

Before liposuction, tumescent will be injected into the fat tissue layer in donor sites to disperse adipose cells in order to facilitate vacuum suction. This approach will reduce local pain and bleeding. The ingredients of tumescent are saline, lidocaine, epinephrine, sodium bicarbonate, etc., wherein lidocaine, epinephrine and other ingredients can significantly reduce local pain and bleeding. Some studies have shown no obvious effect on adipose cell viability, including proliferation and differentiation [20, 21]. The clinical tumescent formula commonly used by our group is as follows: 500 ml saline + 10 ml lidocaine (10 ml:0.1 g) + 0.5 ml epinephrine (1 ml:1 mg) + 5 ml sodium bicarbonate (250 ml:12.5 g). After the injection of tumescent, there is a mild reaction on a patient's donor site without adverse complications, which is worth mentioning.

After tumescent takes effect, fat can be obtained through liposuction technology. The basic principle is to extract fat from the donor site after being "humidified" by means of negative pressure. According to different mechanical principles, liposuction technology is divided into manual suction, negative pressure-assisted suction, laser-assisted liposuction, etc. Rohrich et al. [22] compared different methods of fat suction and showed few differences. Shiffman and Mirrafati [23] found that when the negative pressure exceeded 700 mmHg, the result was cell damage. In recent years, commercial liposuction systems have been on the market, such as the LipiVage system (Genesis Biosystems, Lewisville, Texas) [24] and Viafill system (Lipose Corp., Maitland, Fla.) [25]. For maxillofacial autologous fat filling, due to the low overall fat requirement, conventional manual suction can meet the need of facilitating flexible control of negative pressure values, and it is more economical.

The diameter of the liposuction tube is an important factor influencing the fat survival rate, and the aperture of the side opening determines the type of fat obtained. Studies have shown that when suction tubes are thicker rather than thinner, the activity of fat cells is better, and the long-term volume retention rate is also relatively high. Erdim et al. [26] found that using a 6 mm tube diameter to acquire fat resulted in more cell activity than using a 4 mm or 2 mm tube diameter. Kirkham et al. [27] also found that fat acquired using a 5 mm diameter suction tube had better volume retention than fat acquired using a 3 mm diameter suction tube. A possible reason is that a thicker suction tube causes smaller shear forces and less damage to fat tissue [27]. In fact, the most commonly used suction tube diameter for maxillofacial fat filling is 5 mm. The opening aperture on the side of the anterior section of the suction tube determines the type of fat obtained. Generally, the fat particles obtained when the pore diameter is larger than 2 mm are called macro-fat. This type of fat particle has a better supportive performance and is more suitable for structural fat filling. The fat particles obtained when the pore diameter is less than 2 mm are called micro-fat. This type of fat particle is smaller; more conducive to vascular ingrowth; and more suitable for eyelids, lacrimal grooves, and nasolabial folds [28]. There is another type of fat called nano-fat. Tonnard proposed this concept in 2013. Nano-fat obtained from micro-fat was passed back and forth 30 times through 2 connected syringes. The nano-fat was intradermally injected via a 27 G needle, mainly for facial rejuvenation or scar treatment [16]. The preparation processes for autologous fat (macrofat, microfat and nanofat), platelet-rich fibrin (PRF) and the stromal vascular fraction (SVF) are described in Fig. 2.

Fat processing Fat processing removes tumescent and other useless ingredients via centrifugation or other

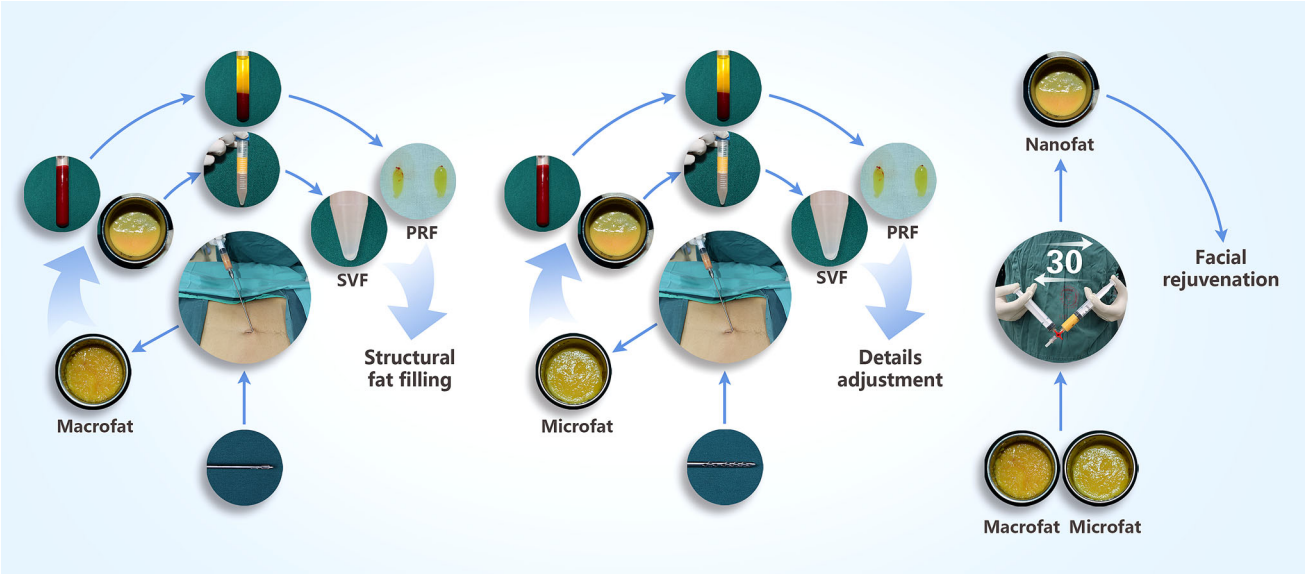

Fig. 2 Preparation processes for autologous fat (macrofat, microfat and nanofat), platelet-rich fibrin (PRF) and stromal vascular fraction (SVF).

methods, maintaining the activity of fat cells, to obtain fat particles suitable for injection. Many clinical studies have shown that fat injection via centrifugation (or other methods) has better transplantation effects than untreated conditions [29, 30]. The mainstream centrifuge parameters are based on the Coleman fat grafting system: 3000 rpm, 3 min. Ferraro et al. [31] compared three fat processing parameters (3000 rpm, 3 min; 1300 rpm, 5 min; and the precipitation method), resulting in fat absorption rates of 50% and 20% and an even higher rate for the precipitation method. Rohrich et al. [19] compared the effects of centrifugation and non-centrifugation on the fat volume retention rate after fat transplantation, showing no significant difference. Ramon et al. [32] compared centrifugation (1500 rpm, 5 min) and cotton filtration for fat grafting, also showing no significant difference in volume retention. Yi et al. [33] divided the centrifuged fat (3000 rpm, 3 min) into three equal parts, upper, middle and lower, and found that the volume maintenance rate of the lower part in fat transplantation was significantly higher than that of the other two groups. Kim et al. [20] evaluated the effects of different centrifugation parameters on the activity of adipocytes and found that irreversible fat cell destruction could occur after 5 min at more than 5000 rpm. The recommended maximum centrifuge speed was 3000 rpm. In summary, most scholars support the method of processing fat by centrifugation, which is more economical and effective than other methods. However, at the same time, it is necessary to control the centrifugation speed to avoid fat cell damage and to increase the maintenance of graft volume after fat transplantation.

Fat injection The main purpose of AFT is to transplant the obtained fat particles into the recipient sites by ”injection“ to treat soft tissue defects and deformities. Fat injection must follow the following principles: the surgical aseptic principle, blunt needle injection, multi-level and multi-tunnel injections, needle withdrawal injection, and a small number of multiple injections. The purpose is to increase the survival rate of fat transplantation as much as possible and to reduce the number of complications such as postoperative infection and embolism.

Injection layers, especially for facial rejuvenation or lifting injections, are usually based on the anatomic facial fat compartments proposed by Dr Rohrich in 2007 [15]. Rohrich [15] proposed that maxillofacial fat is not a continuous layer but is divided into several compartments by muscles, fascia, blood vessels, nerves, glands, bones and other structures. The maxillofacial fat compartment can be divided into the superficial fat compartment and deep fat compartment. The superficial fat compartment can be divided into the nasolabial fat compartment, cheek fat compartment, forehead and temporal fat compartment, periorbital fat compartment and mandibular fat compartment. The deep fat compartment can be divided into the suborbicularis and iris fat compartments, buccal fat pad, deep medial cheek fat compartment and lateral medial cheek fat compartment. The concept of fat compartments not only provides a deeper understanding of the distribution of maxillofacial fat but also provides guidance for maxillofacial fat filling (Fig. 3 and Table 1).

For fat injection into the maxillofacial region, 1.2 mm or thicker diameter needles with straight, curved planes or needle-shaped grease needles (for macro-fat or micro-fat)

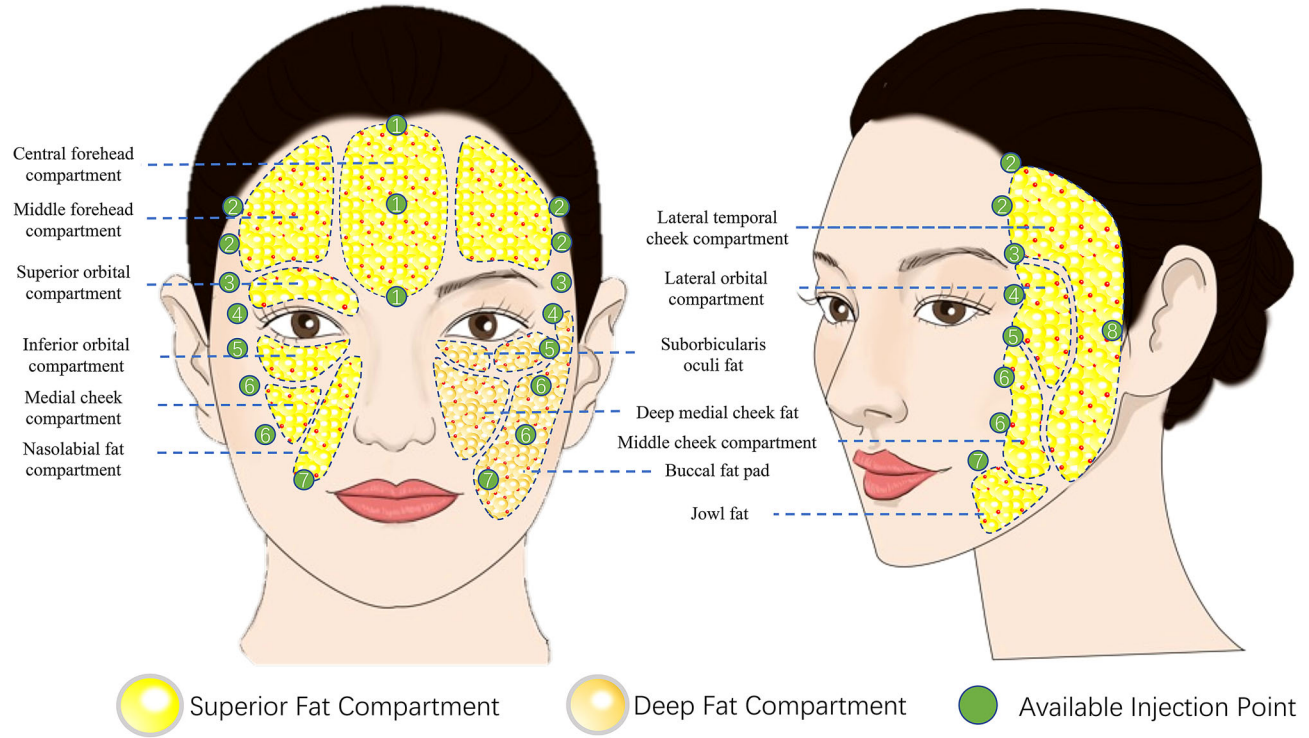

Fig. 3 Fat compartments in the maxillofacial region and schematic diagram of injection points.

Table 1 Overview of autologous fat transplantation technique

Areas	Fat compartments	Types of fat particle	Injection point	Fat needed	Critical anatomical structure
Forehead	Central and middle forehead compartment	Macro and micro fat	1, 2, 3	Total<7 ml	Supratrochlear artery and vein Supraorbital artery and vein
Tempus	Lateral temporal cheek compartment	Macro and micro fat	2, 3, 8	Unilateral<5 ml	Superficial temporal artery and vein
Peri-orbit	Superior orbital compartment	Micro and nano fat	3, 4, 5	Unilateral superciliary arch<2 ml	Supratrochlear artery
	Inferior orbital compartment			Unilateral lacrimal sulcus<0.5 ml	Supraorbital artery
	Lateral orbital compartment Suborbicularis oculi fat			Unilateral dark under-eye circles<1 ml	Infraorbital artery
Nasolabial Folds	Nasolabial fat compartment Deep medial cheek fat	Macro and micro fat	6, 7	Unilateral<4 ml	Angular artery and vein
Lips	None	Micro and nano fat	7	Total<2 ml	Arteria labialis superior Arteria labialis inferior

are generally selected. The main reason for choosing a thicker fat injection needle is the lower pressure needed for fat injection with this diameter, which greatly reduces the possibility of vascular embolism. However, the temporal and periorbital regions are still high-risk areas for fat injection, requiring the surgeon to be familiar with the anatomy and to operate in a standard manner.

The general principles of maxillofacial fat injection are to apply a small amount, many times, in multiple layers, with low pressure, while gradually withdrawing the needle. The most commonly used method is to connect a 1 ml syringe for injection. The small amount means that the amount of fat in each injection should be as small as possible, and large fat masses cannot be formed, resulting

in necrosis and liquefaction of the centre. Many times and multiple layers indicate that for 1 ml of fat injection, fat should be injected several times into different layers, the objective of which is to increase the contact area, improve fat survival, and reduce absorption postoperatively. Low pressure indicates gentle and backward injection simultaneously to avoid injection into blood vessels, causing serious complications. The effects of treatment are demonstrated in Figs. 4, 5, 6 and 7.

Scientific Issues Behind Autologous Fat Transplantation

There are a large number of scientific problems behind AFT that need to be solved by clinicians and basic science researchers. First, the technology is widely used in clinical practice, and further research is needed to improve the absorption rate after fat transplantation, for example, by adding active cytokines (from platelet-rich fibrin (PRF) and other sources) and strengthening graft vascularization. Second, adipose tissue is the main storage location of mesenchymal stem cells in the human body. By extracting vascular matrix components (SVF, mainly ADSCs), a therapeutic quantity of stem cells can be obtained during

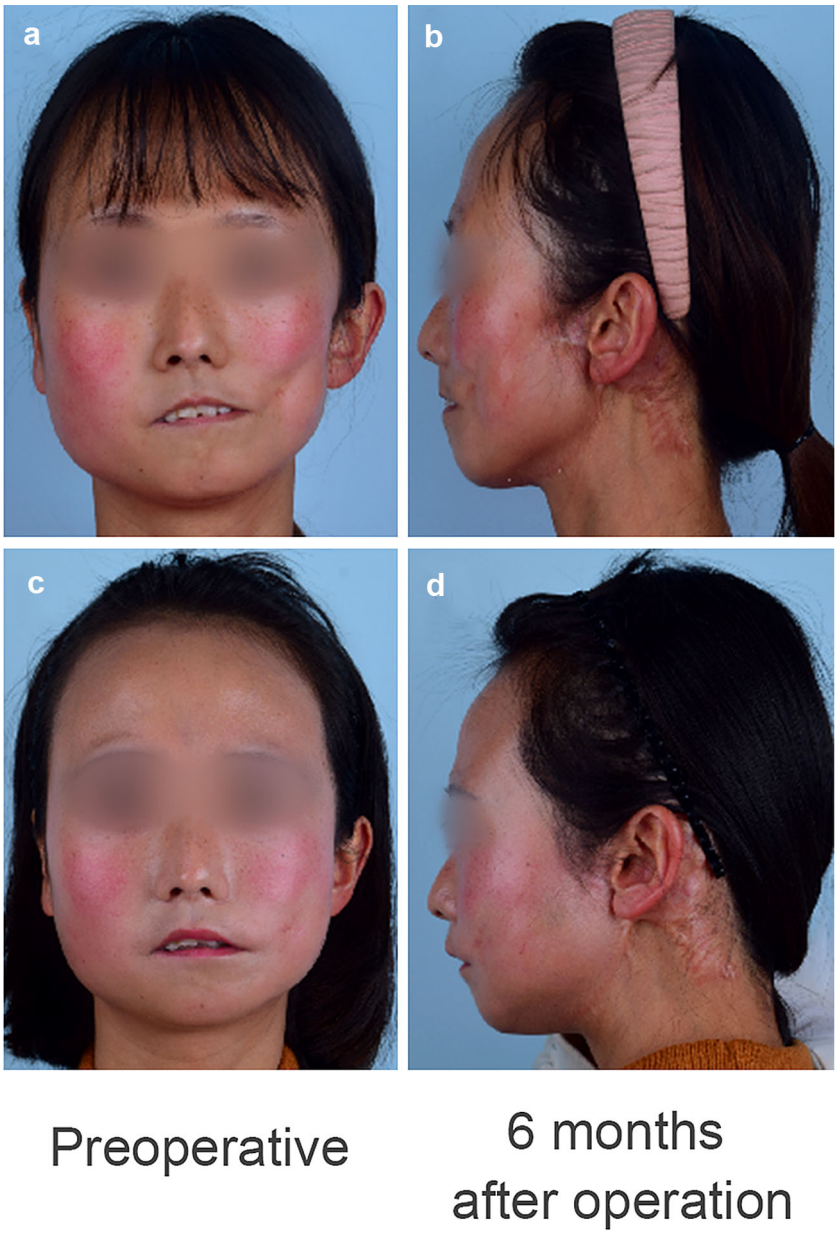

Fig. 4 Patients with left facial atrophy, before injection (**a**, **b**) and 6 months after the operation (**c**, **d**). Summary of injection method: deep medial cheek fat, buccal fat pad (macrofat+PRF+SVF), lateral temporal cheek compartment, lateral orbital compartment, medial cheek compartment, nasolabial fat compartment (microfat+PRF+SVF).

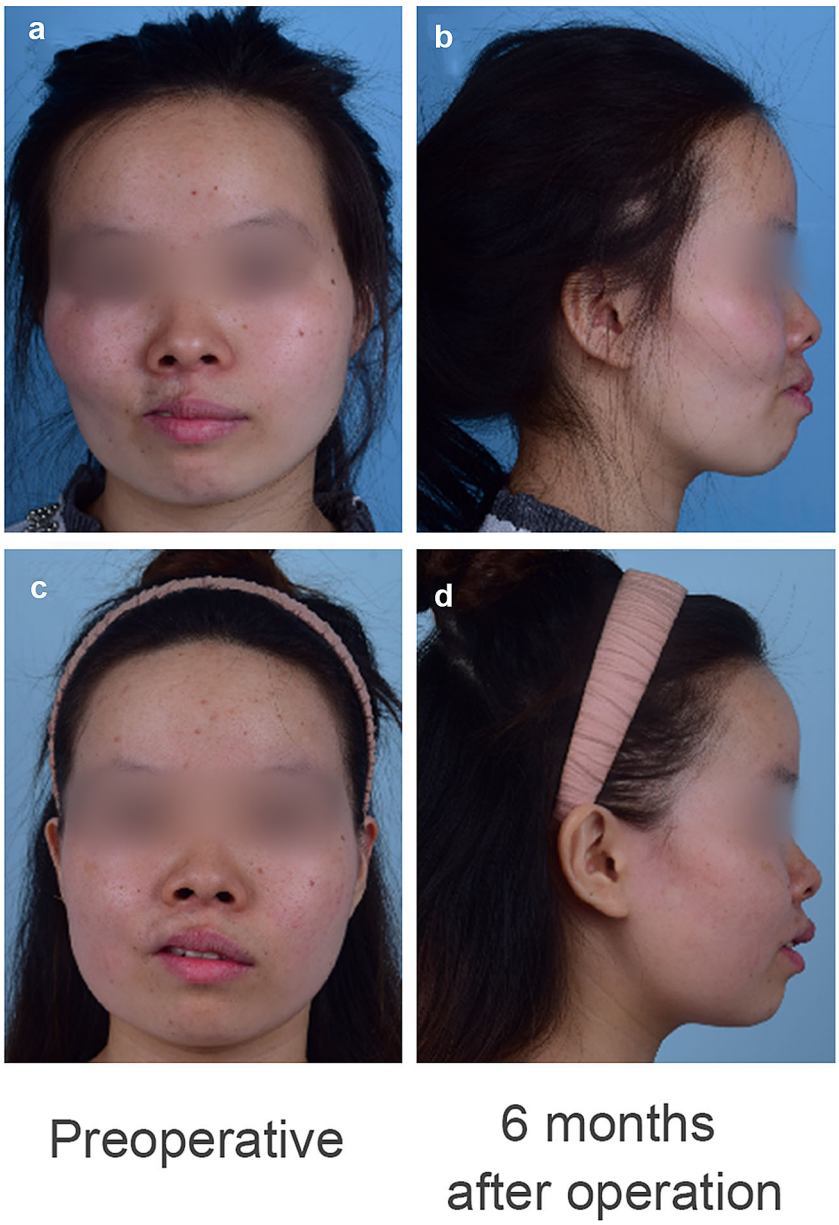

Fig. 5 Patients with right facial atrophy, before injection (**a**, **b**) and 6 months after the operation (**c**, **d**). Summary of injection method: deep medial cheek fat, buccal fat pad (macrofat+PRF+SVF), lateral temporal cheek compartment, lateral orbital compartment, medial cheek compartment, nasolabial fat compartment (microfat+PRF+SVF).

surgery, making fat transplantation technology an indication far beyond the scope of volume filling. This technique has potential scientific and clinical application value in facial rejuvenation, scar treatment, skin damage repair after radiotherapy, etc. Finally, based on ADSCs, AFT can even be extended to the fields of bone, cartilage, and nerve regeneration.

To reduce the absorption rate after AFT, in addition to clinicians' research to improve operation skills, such as fat acquisition and treatment and injection methods, Yoshimura proposed CAL technology in 2006 to reduce the fat absorption rate after transplantation. This technology processes fat by enzymatic digestion, collects SVF in adipose tissue, expands in vitro, and mixes with transplanted fat for subcutaneous implantation in nude mice, and it has been found that fat absorption is greatly reduced after AFT [14]. Due to the need for expanding ADSCs in vitro, this method has ethical limitations in clinical application. Some scholars use mechanical methods (such as emulsification, vibration, and centrifugation) to extract the SVF in order to improve volume retention. The author's team compared the quantity and quality of the extracted SVF between the enzyme digestion method, emulsification method, centrifugation method and vibration method, resulting in more advantages with the vibration method than with the other three methods in terms of volume retention. At the same time, the addition of the SVF also increases the graft vascularization rate, which further explains why absorption

Fig. 6 Patients with nasolabial deformity, comparison photos before injection (**a**, **b**) and 6 months after operation (**c**, **d**). Summary of injection method: Deep medial cheek fat (Macrofat+ PRF + SVF), Medial cheek compartment, Nasolabial fat compartment (Microfat+PRF+SVF)

can be reduced after transplantation [34]. Some scholars also found a reduced absorption rate after fat transplantation by adding platelet grafts. For example, Bin compared the absorption rate between the AG+NS, AG+SVF, AG+PRF, and AG+SVF+PRF groups and found that PRF could effectively reduce fat absorption after transplantation [35].

The production process of nano-fat is actually the SVF extraction process based on the emulsification method. By injecting nano-fat into the dermis, scars can be well treated, wrinkles can be reduced, local pigmentation can be reduced, and skin quality can be improved [36–38]. By adhering to the SVF culture, purified ADSCs can be obtained, which can then be used in the regeneration of bone, cartilage, nerves and other tissues. There are more than 112 clinical trials based on ADSCs in the clinical trial database, covering facial rejuvenation, diabetic foot disease, Crohn's disease, myocardial infarction, spinal nerve injury, etc. [39].

In recent years, with the development of society, the majority of patients have greater requirements for the repair of facial contour problems caused by various maxillofacial diseases. As a method of treating soft tissue defects and deformities, compared with traditional surgery, AFT has the characteristics of less damage, lower risks, simple operation, cost-effectiveness, and great potential for future treatment. AFT is very worthy of clinical promotion. At the same time, fat-related research can be quickly

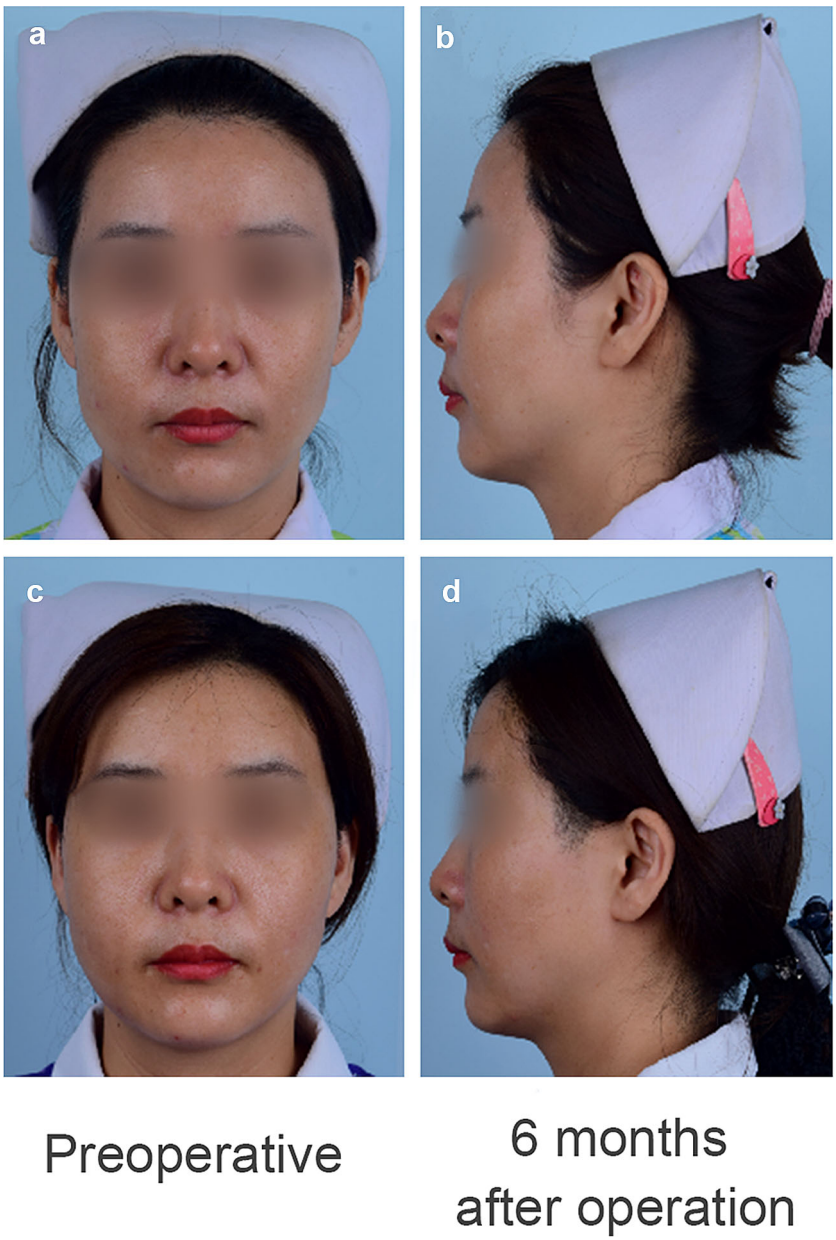

Fig. 7 Facial rejuvenation patients, comparison photos before injection (**a**, **b**) and 6 months after operation (**c**, **d**): Summary of injection method: Central forehead compartment, Middle forehead compartment, Lateral temporal cheek compartment (Microfat +PRF+SVF), facial wrinkle nano fat filling

transformed into clinical applications through the SVF, which also represents one of the important developmental directions of stem cell-based therapy in the future.

Regarding future expectations, the first step should be to strengthen research on the revascularization of transplanted fat. Revascularization is essential for the survival of transplanted fat. Severe ischemia and hypoxia can lead to degeneration of transplanted fat. In recent years, there have been many studies suggesting that exosomes could promote angiogenesis in the recipient tissue. The newly formed blood vessels provide nutrition for the transplanted fat tissue [40]. Second, in addition to research efforts aiming to reduce the absorption of grafted fat, further attention should also be paid to the regeneration of fat in the host area. Some studies have indicated that fat regeneration after autologous fat transplantation includes not only the survival of graft fat but also the regeneration of fat in the host area. Fat regeneration in the host area is another direction that improves the volume maintenance rate after fat transplantation [41]. Third, the emergence of fat cryopreservation technology has reduced the patient discomfort and surgical costs caused by multiple fat injections, as well as the problem of insufficient fat in the donor area in thinner patients, but due to its lack of safety and effectiveness, its clinical application has been limited; the improvement of its safety and effectiveness will be a breakthrough in fat transplantation technology [42, 43].

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Authors' Contributions Junrui Zhang and Bin Lu designed of the work. Kai Zhang and Zhiye Li made the table and organized the pictures, Huan Chen collected data, Yunpeng Li and Qiang Niu wrote the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Publish The patients provided informed consent to publish all presented case reports.

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