

Lipofilling in plastic surgery

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**UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE**

Savion Knafo

Lipofilling in plastic surgery

GRADUATE THESIS



Zagreb, 2024

This graduation thesis was made at the Department of surgery division of Plastic-Reconstructive and Breast Surgery, University Hospital Centre Zagreb, School of Medicine University of Zagreb.

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Abbreviations:

ADSC- Adipose stem cells

LIOR- Lateral inferior orbital rim

LLD- Left lateral decubitus

MIOR- Medial inferior orbital rim

MSD- Malar septal depression

NJG- Nasojugal groove

PJS- Prejowl sulcus

SOR- Superior orbital rim

SVF- Stromal vascular fraction

Summary

Lipofilling in plastic surgery

Savion Knafo

Lipofilling, also known as fat grafting, stands as a cornerstone in modern plastic and reconstructive surgery, offering a versatile array of applications across various medical specialties. This thesis explores the development and diverse applications of lipofilling, focusing on its use in facial augmentation and volume restoration. The history of fat grafting dates back to the late 1800s and includes the groundbreaking work of Gustav Neuber and Viktor Czerny. These pioneers set the stage for later developments in surgical methods, most notably the standardized methods advocated by Sydney Coleman. These innovations have propelled the popularity of fat grafting and broadened its clinical applications, marking it as a preferred technique for many reconstructive and aesthetics challenges.

The rationale for selecting fat as a grafting material is rooted in its autologous source, abundant availability, natural appearance, and versatile applications. Notably, fat grafting offers several advantages, including minimally invasive harvesting, long-lasting results, and a reduced risk of immunogenicity. Understanding the indications for lipofilling is paramount, given its ability to address a wide range of aesthetic and functional concerns in plastic surgery. Common indications encompass breast reconstruction, treatment for postmastectomy pain syndrome, treatment for capsular contracture, management of radiation therapy effects, lymphedema treatment, and correction of contour deformities. This thesis delves into the intricate techniques involved in fat grafting, spanning from donor site selection and anesthesia to fat harvesting, processing, usage of stem cells and injection.

Through an examination of the background, principles, applications, and methods of lipofilling, this thesis seeks to provide a thorough understanding of the critical role that fat grafting plays in modern plastic surgery. Fat grafting is a field that is constantly developing, and more study and improvement in this area should increase its effectiveness and expand its uses in the field of plastic and reconstructive surgery.

Keywords: Lipofilling, facial augmentation, volume restoration, contour deformities, stem cells

SAŽETAK

Lipofilling u plastičnoj kirurgiji

Savion Knafo

Lipofilling, poznat i kao presađivanje masnog tkiva, stoji kao temelj suvremene plastične i rekonstruktivne kirurgije, nudeći raznolik niz primjena u različitim medicinskim specijalnostima. Ova teza istražuje razvoj i različite primjene lipofilinga, usredotočujući se na njegovu upotrebu u povećanju lica i obnavljanju volumena. Povijest presađivanja masnog tkiva seže u kasne 1800-e i uključuje revolucionarni rad Gustava Neuberera i Viktora Czernyja. Ti pioniri postavili su temelje za kasnije razvoje u kirurškim metodama, posebno standardizirane metode koje zagovara Sydney Coleman. Ove inovacije su potakle popularnost presađivanja masnog tkiva i proširile njegove kliničke primjene, označavajući ga kao preferiranu tehniku za mnoge rekonstruktivne i estetske izazove.

Razlog za odabir masti kao materijala za presađivanje leži u njezinom autolognom izvoru, obilnoj dostupnosti, prirodnom izgledu i raznovrsnim primjenama. Treba istaknuti da presađivanje masnog tkiva nudi nekoliko prednosti, uključujući minimalno invazivno uzimanje, dugotrajne rezultate i smanjeni rizik od imunogenosti. Razumijevanje indikacija za lipofiling je ključno, s obzirom na njegovu sposobnost rješavanja širokog spektra estetskih i funkcionalnih problema u plastičnoj kirurgiji. Uobičajene indikacije obuhvaćaju rekonstrukciju dojke, liječenje sindroma postmastektomne boli, liječenje kapsularne kontrakture, upravljanje učincima radioterapije, liječenje limfedema i ispravljanje deformacija kontura. Tema istražuje složene tehnike uključene u presađivanje masnog tkiva, obuhvaćajući odabir donorskog mjesta i anesteziju do uzimanja masnog tkiva, obrade, korištenje matičnih stanica i injekcije.

Proučavanjem pozadine, načela, primjena i metoda lipofilinga, ova teza ima za cilj pružiti temeljno razumijevanje ključne uloge koju presađivanje masnog tkiva igra u suvremenoj plastičnoj kirurgiji. Presađivanje masnog tkiva je područje koje se stalno razvija, a daljnje studije i poboljšanja u ovom području trebala bi povećati njegovu učinkovitost i proširiti njegove primjene u području plastične i rekonstruktivne kirurgije.

Ključne riječi: Lipofilling, povećanje lica, obnova volumena, deformacije kontura, matične stanice

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1. Introduction

Autologous fat grafting has gained popularity in recent years due to its numerous new reconstructive applications for the face and breasts, burn and post-radiation injuries, and congenital anomalies, in addition to its many aesthetic uses in body contouring, breast augmentation, facial contouring, and other areas.

Due to the intrinsic biocompatible qualities of autologous grafting, general soft tissue augmentation and volume replacement can be successfully treated with minimal patient morbidity.

An institutional review board–approved retrospective study of patients undergoing fat grafting procedures from January 2015 to July 2018 was performed. Records were reviewed for fat graft recipient site, donor site, amount grafted, and complications. Their study found that lipofilling can be safely performed for a variety of indications. Analysis of the study revealed a 5.01% major complication rate with no reports of death or fat embolism. Most complications were minor asymmetries(1)(2).

Today lipofilling is the preferred technique for many reconstructive and cosmetic challenges due to its low cost, easy accessibility, and lack of immunogenicity(3). Numerous methods for preparing donor and recipient sites, harvesting fat, and processing it have been developed as a result of widespread use. Determining the optimal donor site based on recipient site volume requirements, healing implications, and patient characteristics is frequently challenging(4). Furthermore, there hasn't been much proof up until recently showing how effective different harvesting and processing methods like centrifugation, cotton gauze filtering, and sedimentation are. This thesis will elaborate on the extensive history of autologous fat grafting, provide a thorough explanation of the theory and science underlying autologous adipocyte transplantation, and discuss the methods that are frequently employed, with a focus on lipofilling techniques in facial augmentation and volume restoration. These consist of engraftment, processing, harvesting, recipient and donor site preparation.

2. History of the procedure

The first 'fat grafting' procedure dates to the late 19th century, 1889, report by Meulen et al. In this study, omental fat was grafted between the liver and diaphragm to help treat a diaphragmatic hernia(5). However, the more relevant fat transfer was performed by a German plastic surgeon, Gustav Neuber (1850-1932) transferred fat from the arm to the orbital region to correct depressed scars formed from osteomyelitis.

Only two years later, 1895, Dr. Viktor Czerny (1842-1916) excised and grafted a lipoma into the breast to establish symmetry following removal of nodules for fibrocystic mastitis.

In 1911, Brunning et al demonstrated the first use of a needle and syringe to transplant fat. He was the first to inject the autologous fat graft into the subcutaneous space to correct the aesthetic result of a rhinoplasty procedure.

However, fat grafting had trouble gaining acceptance during the next 100 years due to the many complications that routinely accompanied the procedure. Modern liposuction techniques had not yet been developed or standardized and the extracted fat was generally of inconsistent quality, which yielded poor results.

In the 1990's, Dr. Sydney Coleman, a New York City Plastic Surgeon, began publishing papers describing standardized techniques for fat extraction, processing, and injection. Since that point in time, the procedure's popularity has only increased along with a wider variety of clinical applications(6). This was later supplemented by the technique of preparing the harvest site with a tumescent solution as proposed by the dermatologist Dr. Klein in 1993. The study detailing this technique proposed that this would further minimize adipocyte trauma and maximize harvesting of fat, while providing adequate hemostasis and local anesthesia(7).

3. Rationale for choosing fat as grafting material

The rationale for choosing fat as a grafting material in various medical procedures, such as autologous fat transfer or lipofilling, is based on several key factors:

- **Autologous Source:** Fat grafting uses the patient's own adipose tissue, which reduces the risk of allergic reactions, rejection, or compatibility issues. This autologous source ensures that the graft is well-tolerated by the recipient's body, minimizing the potential for immune system responses(3).
- **Abundant and Accessible:** Fat tissue is readily available in most individuals. It can be harvested from areas with excess fat deposits, such as the abdomen, thighs, or buttocks, making it a convenient and accessible grafting material.
- **Natural Appearance and Feel:** Fat grafting provides a natural look and feel, which is particularly important in cosmetic and reconstructive procedures. When properly harvested, processed, and injected, fat can closely mimic the texture and appearance of surrounding tissues.
- **Versatile Applications:** Fat can be used in a wide range of applications, including facial rejuvenation, body contouring, breast augmentation, and reconstructive procedures. Its versatility allows plastic surgeons to address various aesthetic and functional concerns(5).
- **Minimally Invasive:** Harvesting fat for grafting can be performed through minimally invasive techniques, such as liposuction. This reduces scarring and the need for large surgical incisions, making it an attractive option for patients seeking less invasive procedures.
- **Long-Lasting Results:** Properly harvested and placed fat grafts can offer long-lasting results. Although some reabsorption may occur, fat is a stable grafting material that can persist for years, making it an enduring solution for patients.
- **Dual Benefit:** Liposuction to harvest fat provides the added benefit of body contouring, allowing patients to achieve a more sculpted appearance in conjunction with their primary grafting goals.

- **Minimal Risk of Disease Transmission:** Because the graft is derived from the patient's own body, the risk of disease transmission, such as infections or viral transmission, is significantly reduced compared to the use of allografts or synthetic materials.
- **Customizable and Precise:** Fat grafting allows for precise and customizable shaping of grafts, enabling plastic surgeons to address specific patient needs and create natural, harmonious results.
- **Reduction of Donor Site Morbidity:** When performed by experienced surgeons, fat harvesting through liposuction is generally well-tolerated, with limited post-operative discomfort and a relatively quick recovery period(2) .

These reasons collectively make fat an appealing grafting material for a wide range of plastic surgery applications, ensuring safety, natural results, and a high degree of patient satisfaction. However, it's important to note that the success of fat grafting depends on proper harvesting, processing, and injection techniques, as well as the skills and experience of the surgeon.

4. Indications for Lipofilling

Lipofilling, also known as fat grafting, has emerged as a versatile and increasingly popular technique in modern plastic and reconstructive surgery.

Over the years, lipofilling has evolved from a simple technique to a sophisticated method with diverse applications across different medical specialties. Although this thesis will focus on volume restoration and facial augmentation using lipofilling, in this thesis, there will be mentioned some of the most common indications and uses of lipofilling in plastic surgery.

Fat grafting in breast reconstruction

Fat may be used to improve volume in autologous-based breast reconstructions in thin patients desiring larger reconstruction without the use of prosthetic devices. Fat grafting is also useful to ease the contour of the transition between tissue flaps and the native chest wall(8).

Fat grafting as treatment for postmastectomy pain syndrome

Postmastectomy pain syndrome is characterized by chronic pain that is neuropathic in character, located in the axilla, shoulder, or chest wall ipsilateral to the patient's operation, and occurs continuously or intermittently beyond the normal healing period of 3 months. Multiple studies have reported that autologous fat grafting is an effective treatment for postmastectomy pain syndrome due to scar remodeling by the adipose tissue. Fat grafting to the scarred area is proposed to prevent nerve entrapment that leads to persistent pain experienced by patients(9).

Fat grafting usage in capsular contracture

A study by Papadopoulos et al found that fat grafting can provide pain relief and reduce the grade of capsular contracture from grade 4 to grade 3.

It has also been suggested that fat grafting not only relieves pain associated with capsular contracture but also improves skin quality and sensation of the breast(10).

Fat grafting in radiation therapy

Effects of radiation include fibroblast injury, excessive scarring, and decreased microcirculation in targeted areas. These injuries have been linked to poor aesthetic outcomes, patients frustration and increased risk for capsular contracture.

The pluripotent stem cells in grafted fat are postulated to improve angiogenesis through paracrine signaling and endothelial cell recruitment, thus fat grafting come in hand by improving healing in patients that have undergone radiation therapy(11).

Fat grafting as treatment for lymphedema

In the Western world, lymphedema most commonly occurs following treatment of cancer. Up to 38% develop lymphedema of the arm following mastectomy, standard axillary node dissection, and postoperative irradiation. Some patients with long-standing pronounced lymphedema do not respond to these conservative treatments because slow or absent lymph flow causes the formation of excess subcutaneous adipose tissue. Liposuction removes the hypertrophied adipose tissue and is a prerequisite to achieve complete reduction(12).

Fat grafting usage in correcting contour deformities.

Lipofilling is widely used for correcting contour deformities and seen as one of the major breakthroughs in reconstructive plastic surgery. Its applications in facial reconstructive surgery have been of particular interest owing to the prospect of achieving autologous reconstruction by a minimally invasive approach(13).

5. Stem cells and fat grafting

The use of stem cells in fat grafting procedures which involve moving fat from one area of the body to another in order to increase volume or improve contours has been widely investigated for possible advantages. The source of these stem cells is the adipose tissue which has been viewed in the past as an endocrine organ, a soft tissue filler, an organ of energy storage, and a tissue that should be removed cosmetically through liposuction. Today it is known that adipose tissue contains a large number of progenitor cells, some of which can differentiate into different lineages. Thus it is now considered to be a promising source of adult stem cells(14).

Adipose stem cells can be largely extracted from subcutaneous human adult adipose tissue. A large number of studies show that adipose tissue contains a biologically and clinically interesting heterogeneous cell population (Figure 1) called stromal vascular fraction (SVF). The SVF may be employed directly or cultured for selection and expansion of an adherent population, so called adipose-derived stem cells(15).

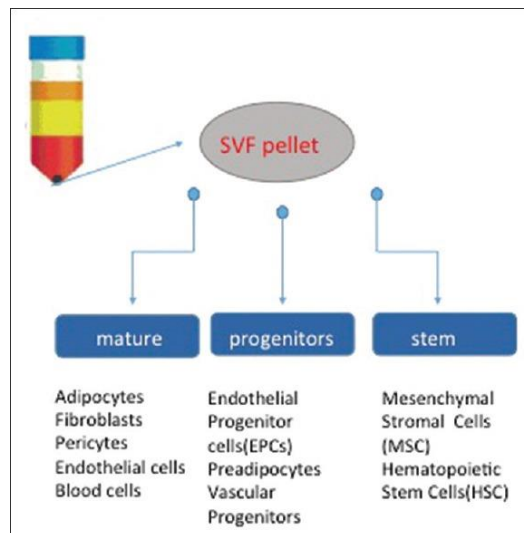


Figure 1. components of stromal vascular fraction. Modified from Role of adipose-derived stem cells in fat grafting and reconstructive surgery, Shaun s Tan (2016).

The main goals of using adipose-derived stem cells in fat grafting are to increase the quality of the finished product and the transplanted fat's survival rate.

In addition, the ability ADSCs to differentiate into other types of cells, such as endothelial cells, vascular smooth muscle cells, or cardiomyocytes, is used in tissue engineering in order to stimulate the process of angiogenesis and tissue regeneration(16). Recent articles presume that poor microvascular circulation conditions also contributes to angiogenesis and regeneration by triggering ASCs to induce angiogenic growth factors like VEGF (17)(18).

One of the challenges in fat grafting is the potential for a portion of the transplanted fat to be reabsorbed by the body over time. Stem cells may help reduce this resorption rate, leading to longer-lasting results. A technique utilizing stem cells called cell assisted-lipoaspirate was developed by yoshimura *et al.* to address this challenge. In cell assisted lipoaspirate the fat graft is augmented with SVF, which contains ASCs, CD45+ myeloid-derived cells, endothelial (progenitor) cells and pericytes. Studies on this technique showed better fat survival in enriched fat grafts compared to animals controls(19) and human(20)(21) especially in the field of breast augmentation and facial ageing(22). These results further indicate that ASCs appear to play an important role in fat grafting.

In conclusion with the advent of ASC therapy, autologous fat transfer holds much promise for the future, especially in the realm of soft tissue reconstruction and aesthetic surgery.

6. Fat grafting techniques

To date, a variety of different techniques have been presented, whereas no clear consensus on a gold standard has been achieved yet(23). The reason for this could be the lack of clear results on a number of procedural variables that could have an impact on the quality of the fat grafting process and thus the outcome(24).

Despite the mentioned above, the standard surgical steps for performing fat grafting can be divided into several steps which include:

1. Selection of donor site
2. Donor-site anesthesia
3. Recipient- site anesthesia
4. Fat harvesting
5. Fat processing
6. Fat injection

Instruments for donor-site anesthesia:

1. 20-cc Luer-Lok syringes
2. 22- gauge spinal needles
3. 1% lidocaine with 1:100,000 epinephrine
4. Normal saline

Instruments for recipient-site anesthesia:

1. 5-cc and 10-cc syringes
2. 1/2 "30-gauge needles
3. 1-1/4" 27- gauge needles
4. 18-gauge needle

5. Straight infiltration cannula
6. 1% lidocaine with 1:100,000 epinephrine

Instruments for donor-site fat harvesting:

1. 10-cc Luer-Lok syringes
2. 25% Albumin (Baxter)
3. 3 mm bullet-tip harvesting cannula (15 cm length)
4. 16-gauge Nokor needle or No. 11 Bard-Parker blade

Instruments for fat processing:

1. Syringe plugs and caps
2. Centrifuge with sterile sleeves
3. Test tube rack
4. 4 X 4 cotton gauze or Codman neuropaddies
5. 20-cc Luer-Lok syringes (quantity: 1)
6. Transfer hub

Instruments for fat injection:

1. 1-cc Luer-Lok syringes (quantity: 4)
2. Straight, blunt infiltration cannula
3. 1.2 mm 6 cm spoon-tip cannula
4. 0.9 mm 4 cm spoon-tip cannula

6.1 Selection of donor site

What is the best donor site?

Knees, abdomen, flanks and thighs are the most commonly used harvest sites(25). According to study conducted by Li et al. which compared fat tissue grafts harvested from 6 women and different donor-sites (flank, upper and lower abdomen, lateral and inner thigh). The adipose tissue was implanted subcutaneously into nude mice and grafts were harvested and analyzed at 12 weeks. Authors found no significant differences among grafts from distinct donor sites regarding weight, volume, and histological features(25). In contrast, Tsekouras et al., in a study involving 40 donor women, reported the outer thigh adipose tissue to have significantly higher SVF cell count in comparison to any other sites such as inner thigh, abdomen, waist and inner knee. Also, inner, and outer thigh were associated with a significantly higher number of ADSCs when compared to abdominal, waist, and inner knee lipoaspirates(26). Due to conflicting results in many studies, there is no clear answer regarding the best harvesting site. However, in a study by Geissler et al, an age- related difference in adipose viability was observed with higher viability of adipocytes in the lower abdomen compared to the flanks in younger population, while this different was not observed in older population(27). On the other hand, adipose cells harvested from the flanks showed a higher viability in older population while not different was observed in the inner thighs(27). Therefore, depending on the patients age, harvesting from a specific site can yield better results, but further clinical trials are necessary to confirm this assumption.

Nonetheless, selection of an ideal donor site is still considered a crucial step to achieve maximal results with minimum adverse effects. It requires taking into consideration several important aspects:

For instance, since women and men have different distribution and percentage of body fat, the selection of the ideal donor site will be different.

Table 3-1. Shows the order of preference for donor-site fat harvesting based on gender and is divided into rank order of preferred sites for the trunk and extremities. The lower abdomen and inner thigh are preferred areas for harvesting in the female patient, primarily to avoid repositioning, the inner thigh is the preferred area under local anesthesia. Modified from Complementary fat grafting (2015), p.36.

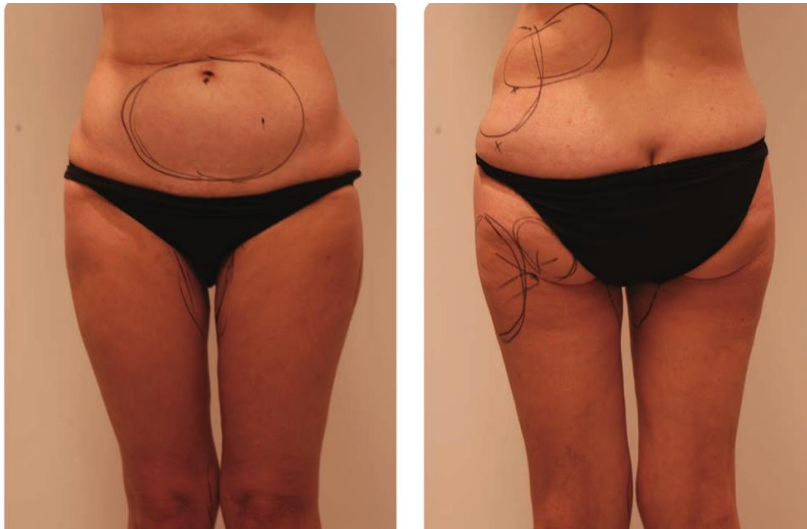
TABLE 3-1 Selection of Donor Site in Women	
TRUNK	EXTREMITY
1. Lower Abdomen	1. Inner Thigh
2. Hip	2. Outer Thigh
3. Waist	3. Buttock
	4. Anterior Thigh
	5. Triceps
	6. Inner Knee

Table 3-2. Shows the preference for donor-site harvesting in men. The hip is generally the preferred area for harvesting in the male patient. The lower extremity is typically not an area for harvesting in men. Modified from Complementary fat grafting (2015), p.36.

TABLE 3-2 Selection of Donor Site in Men	
TRUNK	LOWER EXTREMITY
1. Hip	N/A
2. Lower Abdomen	

Another aspect that needs to be taken into consideration is patients who have undergone abdominal surgery. These patients must undergo evaluation for the type of incisions they have and for the existence of any obvious or occult ventral hernias that would endanger safe abdominal fat harvesting. Ventral hernia can be assessed by placing the patient in a supine position and by instructing him to perform a valsalva maneuver. Even after evaluation and recognition of such a condition, preparation should always be done for any complication that might arise. For example, a case report that was published shows a case of a 69 y.o. woman who underwent abdominal contouring surgery consisting in flank pseudohernia correction, liposuction and short scar abdominoplasty, which was complicated by intestinal perforation(28).

Another obstacle can arise for example when facing thin, athletic individuals. A thin, athletic individual should be evaluated for the presence of adequate donor fat. If on examination limited donor fat is found to be available, the patient may need to be prepared for the possible use of alloplastic implants to obtain the desired result(29). Similarly, patients who have undergone extensive body lipocontouring may have limited fat deposits from which to harvest, and it is always easier to harvest from virgin areas that have not been subjected to prior body liposuctioning. Although fat can be harvested from areas of prior liposuctioning, the amount may be more limited and the area generally more fibrotic. This issue can be solved by harvesting from overlooked areas such as the waist roll that descends along the lower back, the triceps, and the inner knee(29) (Picture 1)



Picture 1. Shows marking of lower abdomen, waist roll and inner thigh for harvesting, Modified from Complementary fat grafting (2015), p.35.

6.2 Anesthesia

Any degree of anesthesia, from simple local infiltration to general anesthesia, can be used for fat transplantation. Given the degree of local anesthetic infiltration, the patient may experience some discomfort during local anesthesia. Most of the time, general anesthesia is not necessary. If body repositioning is required for fat harvesting, level II conscious sedation, also referred to as moderate sedation is preferred, which offers sufficient patient comfort and cooperation. General anesthesia will be the method of choice in cases where a combined procedure is planned.

Anesthesia can be divided into two parts, in the first part a donor-site anesthesia is performed, similarly in the second part a recipient-site anesthesia is performed.

6.2.1 Donor-site anesthesia

Addressing the points of entry for fat harvesting is the first step in the infiltration of local anesthesia. The site where the local anesthetic will be injected and later where the harvesting cannula will be inserted is treated with a tiny bleb of local anesthetic made of 1% lidocaine and 1:100,000 epinephrine. A study by Agostini et al. demonstrated that exposure to tumescent solution enhanced the adipocyte viability in adipose tissue compared with cells isolated by means of dry technique(30)

After a skin bleb has been anesthetized, the local anesthetic is injected into the donor site. Whether the patient is receiving intravenous sedation, general anesthesia, an oral sedative, or no sedation at all will determine the type and quantity of local anesthetic used (Table 3-4). When general anesthesia is the method of choice, a 20-cc Luer-Lok syringe with a mixture of 15 cc of normal saline and 5 cc of 1% lidocaine with 1:100,000 epinephrine is infiltrated into the donor site using a 22-gauge spinal needle in a fanlike distribution. Half of the mixture is injected along the deep aspect of the fat pad and the other half is injected in the immediate subcutaneous plane, totaling 20 cc per donor site (per side of the patient). Because it primarily penetrates the fat pad's deeper and superficial layers, the middle level of the fat pad doesn't contain as much anesthetic, allowing for cleaner harvesting. The most sensitive area, the superficial layer, is injected first by using the nondominant hand to pull the skin taut. In order to inject the anesthetic

into the deeper part of the fat pad, it is necessary to grasp the fat pad with the nondominant hand. A larger percentage of lidocaine is used during surgery if oral sedation or just local anesthetic is being used. Equal amounts of saline and lidocaine-10 cc of regular saline and 10 cc of 1% lidocaine with 1:100,000 epinephrine are loaded into the 20-cc Luer-Lok syringe. The above-discussed injection technique is applicable.

Table 3-4. Demonstrates how the type of anesthesia the patient will receive, oral or without sedation versus intravenous or general anesthesia determines the local anesthetic mixture for the donor site. Modified from Complementary fat grafting (2015), p.38.

TABLE 3-4 Local Anesthesia Preparations		
	FOR PATIENTS UNDER ORAL OR NO SEDATION	FOR PATIENTS UNDER INTRAVENOUS OR GENERAL ANESTHESIA
<i>Mixture</i>	10 cc of normal saline and 10 cc of 1% lidocaine with 1:100,000 epinephrine	15 cc of normal saline and 5 cc of 1% lidocaine with 1:100,000 epinephrine
<i>Amount</i>	Total 20 cc into each donor site (per side), 10-cc deep to the fat pad and 10-cc superficial to the fat pad	Total 20 cc into each donor site (per side), 10-cc deep to the fat pad and 10-cc superficial to the fat pad

6.2.2 Recipient-site anesthesia

The two main phases of recipient-site anesthesia are: **phase a-** injection of specific points and areas using a sharp needle and **phase b-** injection of broad areas using a blunt infiltrating cannula. Phase b is carried out to prevent the formation of hematomas and ecchymosis that could result from piercing vascular structures with a sharp needle, which could negatively affect the outcome: extended recovery and morbidity periods for the patient, challenges for the surgeon in precisely assessing the volumes and contours of fat, and potentially decreased viability of fat cells (29).

Phase A

To reduce the discomfort associated with a broad injection of anesthesia, it is essential to start by injecting specific points along the face that correlate with sensitive neurovascular structures. A short 1/2 30-gauge needle connected to a 5-cc syringe is used to infiltrate the first seven points in Figure 1 percutaneously with 1% lidocaine and 1:100,000 epinephrine. The final two areas are injected using a fanning technique with the same 1% lidocaine:1:100,000 epinephrine mixture using a 1-1/4 27-gauge needle connected to a 5-cc syringe. Roughly 5 cc of local anesthetic are used for each side of the face. Phase a is carried out on one side of the face, followed by the same technique on the contralateral side before repeating this sequence for Phase b.

Although the chronologic order of injection is not crucial, the order has been demonstrated to facilitate memorization and promote a systematic approach. The anesthesia of the zygomaticofacial nerve, which runs along the inferolateral orbital rim of the maxillary branch of the trigeminal nerve, corresponds to the first injection site (Fig. 2, Point 1). The second point (Fig. 2, Point 2) is situated 2–3 cm lateral to the lateral canthus and correlates with fat infiltration entry site B. Next, the zygomaticotemporal branch of the of the trigeminal nerve, located along the superolateral aspect of the orbital rim, is anesthetized (Fig. 2, Point 3). Proceeding medially, the supraorbital bundle of the trigeminal nerve's ophthalmic branch becomes infiltrated (Fig. 2, Point 4). Next, to reduce the discomfort caused by fat infiltration in this sensitive area, the fifth injection site is positioned halfway along the lateral nasal wall (Fig. 2, Point 5). The entry site A:5 for fat infiltration is represented by the sixth point. On a horizontal axis that extends from the base of the nasal ala, it is situated inferolaterally to the malar depression (Fig. 2, Point 6). The seventh point, which corresponds to the fat infiltration entry site C (Fig. 2, Point 7), is located 2 cm behind the prejowl sulcus, which normally occurs about halfway along the length of the mandibular body. The maxillary face's infraorbital nerve corresponds to the eighth injection site (Fig. 2, Point 8). The 1-1/4 27-gauge needle is injected into the nerve from an entry site at the precanine fossa, directed toward the bony face of the maxilla superolaterally, in order to properly anesthetize the nerve. Lastly, from what will be entry site D for fat infiltration,

the marionette line and labiomental sulcus are infiltrated in the subcutaneous plane (Fig. 2, Point 9). This region is anesthetized using a wide, fanning technique using the same 1-1/4 27-gauge needle. (Alternatively, a blunt cannula can be used to infiltrate every site.)

RECIPIENT SITE ANESTHESIA (SHARP NEEDLE PLACEMENT)

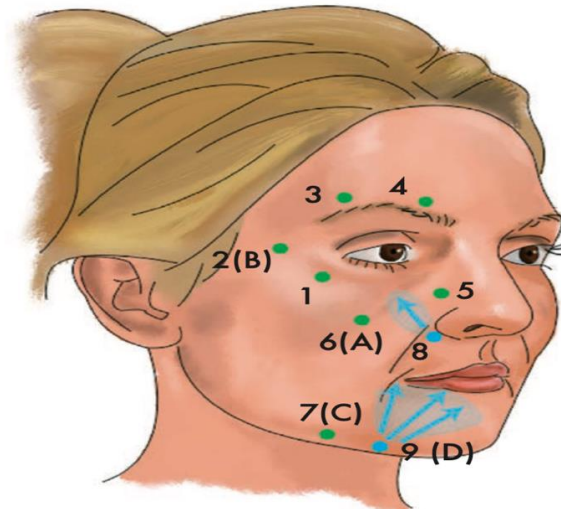


Figure 2. Demonstrates sites of anesthesia injection. Modified from Complementary fat grafting (2015), p.40.

Phase B

The injection is performed with a 10-cc syringe fitted with a blunt, spoon-tip cannula 1.2 mm or 0.9 mm (Tulip Medical Inc., San Diego, CA) and 1% lidocaine with 1:100,000 epinephrine. All blunt-cannula anesthesia infiltrations will use this infiltration cannula. For cannula entry, the skin is punctured at sites A, B, C, and D using a standard 18-gauge needle. Beginning superiorly, local anesthetic is infused into the brow and temple in a fanning pattern, distributing into a deep supraperiosteal plane in the lateral superior orbital rim and a subcutaneous plane in the temple, both of which correlate with the placement of fat (Fig. 3, Point 12). The inferior orbital rim is then completely anesthetized beginning at entry site A (Fig. 3, Point 13). The inferior orbital rim's supraperiosteal plane is anaesthetized at the level where fat infiltration is expected to occur. It should be about 2 cc for the whole inferior orbital rim.

The blunt infiltration cannula is used to anesthetize the nasal sidewall, nasojugal

groove, precanine fossa, and the entire length of the nasolabial fold (Fig. 3, Point 14). Supraperiosteally, there is infiltration of the bony nasojugal groove. From entry site A, the buccal region is infiltrated in a fan-like manner into the deep subcutaneous plane (Fig. 3, Point 15). Point C is the entry point into the prejowl area, which includes the mandibular anterior and inferior borders as well as the areas where fat will be distributed. The various levels of fat infiltration in this region can usually be adequately anesthetized by an intermediate plane of local infiltration (Fig. 3, Point 16).

RECIPIENT SITE ANESTHESIA 2 (BLUNT CANNULA PLACEMENT)

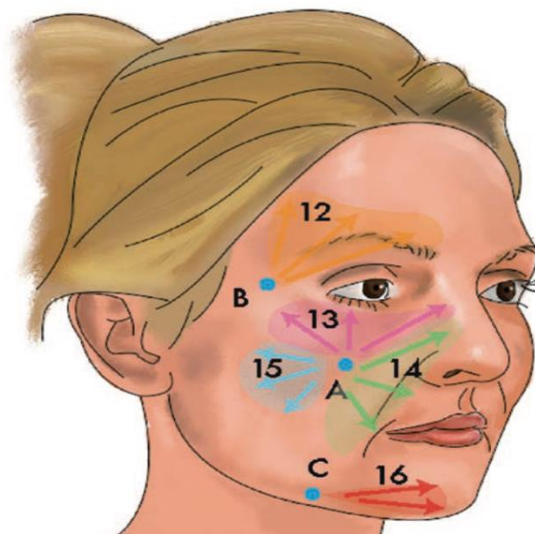


Figure 3. Demonstrates sites of blunt cannula placement as described above. Modified from Complementary fat grafting (2015), p.41.

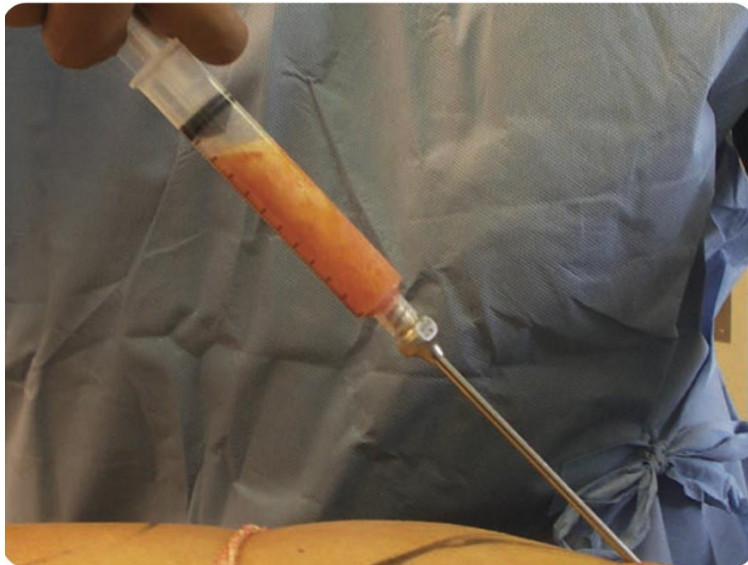
6.3 Fat harvesting

Harvesting of fat can be performed by several methods such as: hand-held syringe aspiration, suction-assisted lipectomy, and ultrasound-assisted lipectomy. In addition, liposuction can also be assisted by a liquid-jet, or laser energy(21,22). Studies investigating the impact of hand-held syringe aspiration, suction-assisted lipectomy, and ultrasound-assisted lipectomy have demonstrated differences in cell viability and adipocyte functionality resulting from these different methods of isolation. Compared with suction-assisted lipectomy, several studies have shown that hand-held syringe lipoaspirates yielded greater adipocyte count and viability(33). However, when

tumescent solution was used to prepare the donor site, no significant difference was observed in cell counts or viability between hand-held syringe aspiration and suction-assisted lipectomy(34).

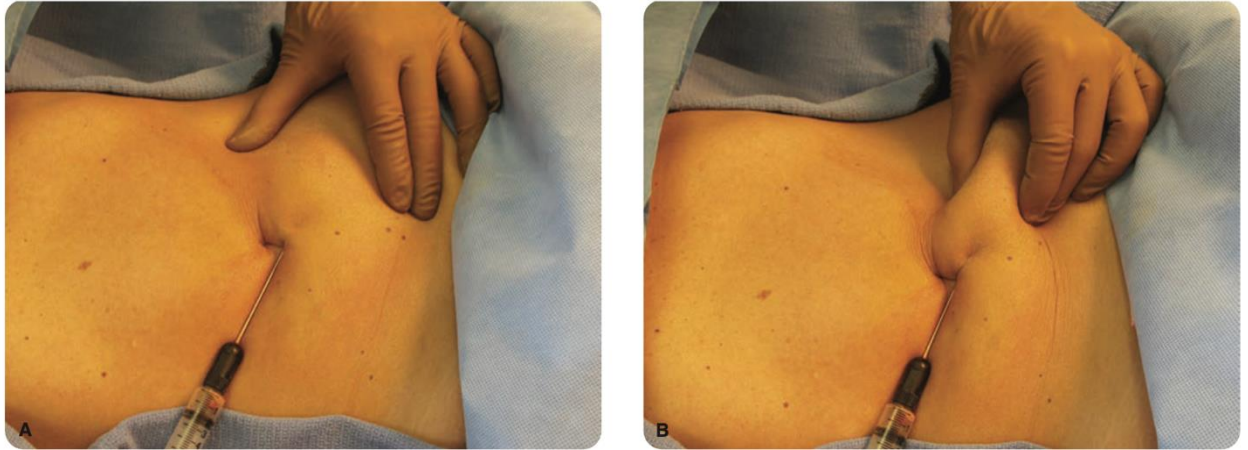
Irrespective of the method or location of the donor site, there are certain fundamentals that must be remembered in order to carry out fat harvesting in a reliable and consistent manner.

- Only 1 to 2 cc of negative pressure should be applied to the syringe during harvesting to avoid the risk that undue pressure will cause lysis of adipocytes (Picture 2)



Picture 2. Demonstrates the correct fat harvesting method. Modified from Complementary fat grafting (2015), p.43.

- The nondominant hand is used to gently pinch surface of the skin in order to stabilize the fat pad. Squeezing the fat pad firmly with the nondominant hand will reduce the ability to fan uniformly across the entire donor site and raise the possibility of contour irregularities in the donor site (Picture 3).



Picture 3. Shows A: proper technique vs B: improper technique and as a result contour irregularity. Modified from Complementary fat grafting (2015), p.45.

- The cannula should be brought nearly to the entry site after three or four passes through the fat, at which point it should be turned and the tip reoriented in a different direction.
- Failure to withdraw the cannula sufficiently before changing directions will give the appearance of harvesting from a new area when in fact the same localized spot is being worked on, this mistake could result in an excessive amount of fat being removed from a single, defined area, which could decrease the amount of fat that is harvested and more importantly will lead to development of contour irregularity at the donor site.
- The entire cannula should be taken out of the entry site and the tip cleaned if it seems to be clogged or if suction is lost. The plunger can be drawn back until the fat is cleared from the cannula.
- Roughly half of the volume in the syringe will be made up of lidocaine, blood, albumin, and lysed fat cells when estimating the total volume of fat that needs to be harvested. Hence, roughly 100 cc (10 full syringes) of fat should be harvested if a total plan of 50 cc of fat is desired. To obtain the same desired amount of fat, a proportionately larger number of syringes may be required if each syringe contains more blood than usual, and vice versa.

- After harvesting, the donor-site stab incision usually doesn't need to be closed.

Site-specific Technique

Harvesting fat from specific sites in the body, such as the abdomen, thighs, or buttocks, is a common procedure in plastic and reconstructive surgery, particularly in procedures like fat grafting. Each site requires a different technique and positioning, with special points to consider to ensure optimal results and minimize risks. For example, harvesting fat from the abdomen involves positioning the patient lying flat on their back while conducting a careful preoperative assessment to identify ventral scars and/or hernias that may limit or prevent harvesting in certain areas(29). However, when harvesting fat from the thighs or buttocks, the patient may need to be positioned differently to access these areas effectively. Additionally, the characteristics of the fat, such as its consistency and viability, may vary depending on the site, requiring adjustments in the harvesting technique(25). Furthermore, considerations such as the patient's anatomy, skin elasticity, and desired outcome play crucial roles in determining the most suitable harvesting site and technique. Overall, a tailored approach to fat harvesting, taking into account the specific characteristics of each site and patient, is essential for achieving satisfactory results in cosmetic and reconstructive procedures.

6.4 Processing the fat

Processing of lipoaspirates is a crucial step because they consist not only of beneficial adipocytes and SVF cells but also debris, blood, and collagen fibers(35). Those components can lead to inflammation and subsequent degradation of the transplanted fat at the recipient site(36)(37). In addition, injection of debris gives a false impression of the volume potentially achieved but is reabsorbed after several hours(37). Thus, the goals of processing the fat are first to ensure that the fat is free from unwanted components, this can be achieved by a variety of techniques such as centrifugation, gravity separation, washing and filtration(38), and second to prepare it for injection.

Centrifugation was first introduced by Coleman et al. in 1987(38) and is now a widely used technique(39). Originally the technique involved the separation of lipoaspirates by

centrifugation at 3000 revolutions per minute(rpm) for 3 minutes, draining tumescent solution and blood from the bottom layer (40) afterwards the oil is decanted and soaked up with a sterile cotton gauze for 3 minutes (41). However, today multiple studies suggest different centrifugation settings(41), a study by Ferraro et al. found the same amount of viable cells in the 500 and 1,300 rpm settings, despite an increase in peripheral damage at higher speed(42). In contrast, several other trials have also shown no effect of different centrifugation settings on the quality and viability of lipoaspirates(43). As a result comparison of these data is difficult due to the lacking standardization of centrifugal speed, force and duration(41).



Picture 4. The fat is shown uncentrifuged (above) and centrifuged (below). The centrifuged fat shows the heavier blood and lidocaine at the bottom (left) and the lysed fat cells at the top (right). Modified from Complementary fat grafting (2015), p.56.

Even though consensus about the ideal settings is still lacking, centrifugation ensures that the harvested fat is properly processed, purified, and later transferred into smaller syringes, ready for use in fat grafting procedures during plastic surgery. The emphasis on sterility, purity, and accurate measurements is crucial for successful fat grafting and patient safety(29).

6.5 Fat injection

Regarding facial augmentation using lipofilling injections, the fundamental idea behind contemporary fat transfer is the blunt insertion of small fat parcels into multiple anatomical layers(38). Damage to underlying neurovascular structures by sharp instrumentation may result in neuropraxia, either temporary or permanent, and/or the formation of hematomas(29). Any resulting ecchymosis and/or frank hematoma can impair the viability of fat overall by impeding nutrition due to reduced contact with surrounding tissue. As a result, for fat infiltration, only blunt instruments should be used(29). Very small fat deposits can infiltrate surrounding tissue more easily and increase the surface-to-volume contact between the deposited fat and surrounding tissue. This increases the nutrition and viability of the fat cells. The avoidance of palpable or visible lumps of fat is the other rationale behind the placement of tiny fat parcels. In general, the three facial planes where fat is infiltrated are the deep-directly above the periosteum, intermediate-inside the muscle, fascia, and deep subcutaneous plane, and superficial -in the medium to superficial subcutaneous plane(Figure 3).

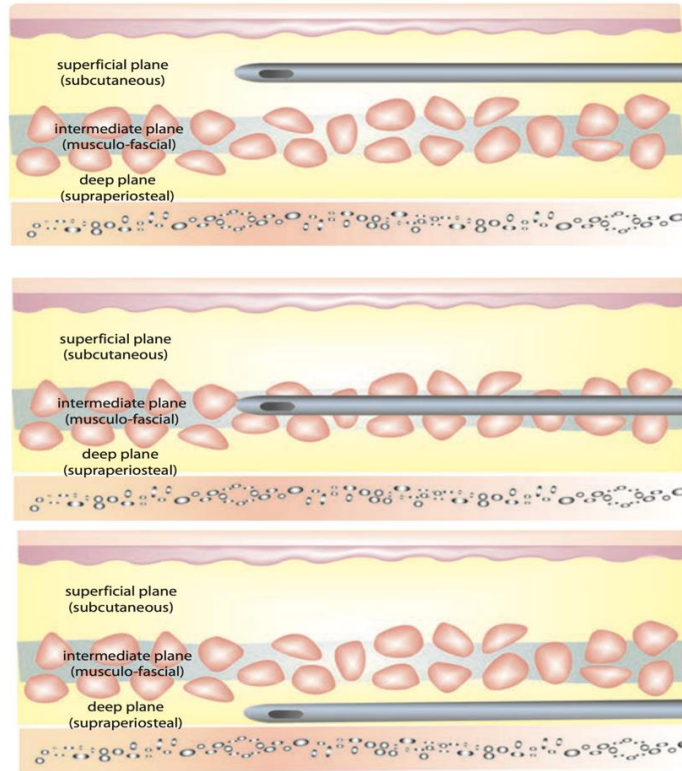


Figure 3. Illustrates the three planes where fat is infiltrated. Modified from Complementary fat grafting (2015), p.61.

Injection of fat should be gradually transitioned from a deeper level within a particular layer toward a more superficial level until the arrival of the next level(29). Therefore, the entire time, the cannula is gradually passing from a greater depth to a more superficial depth without abrupt transitions. This graduated deposition of fat ultimately permits the most uniform distribution. Prior to the emergence of the subsequent level, progression from from a deeper level within a given layer toward a more superficial level is desired. Consequently, there are no sudden changes in depth as the cannula is continuously moving from a deeper to a more superficial level. In the end, the most even distribution is made possible by this graduated fat deposition(38).

Fat injection Technique

Injection technique can be divided into two distinct levels: A) Volumetric foundation and B) Refinements(44).

Part A: Volumetric foundation- describes a standardized and methodical fat infiltration that is beneficial to nearly all patients (Figure 4). Consequently, each patient receives the same quantity and procedure in the same order. The volumetric foundation is placed in a consistent amount and distribution according to empirical recommendations, negating the need for artistic interpretation.

Part B: Refinements refers to additional volume and distribution of fat that a particular patient requires based on individual anatomy.

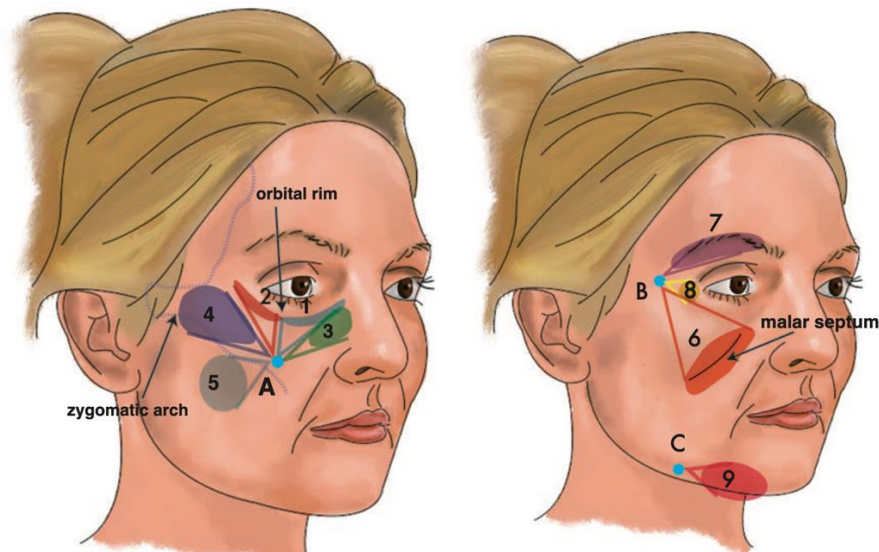


Figure 4. The prescribed areas for augmentation which are numbered according to a recommended chronologic sequence for fat infiltration. **1)** medial inferior orbital rim, **(2)** lateral inferior orbital rim, **(3)** nasojugal groove, **(4)** lateral cheek, **(5)** buccal **(6)** anterior cheek, **(7)** superior orbital rim, **(8)** lateral canthus/lateral inferior orbital rim hollowing. From entry site C, fat can be infiltrated into **(9)** the prejowl sulcus. A, B and C are points of entry. Modified from Complementary fat grafting (2015), p.64.

Site specific technique:

Medial inferior orbital rim

The inferior orbital rim (Figure 4, point 1) is the most challenging area due to potential surface irregularities, thin skin, and lack of soft tissue(29). Initial infiltration should be deep along the orbital rim, followed by another layer placed just superficial to it. To avoid palpable or visible nodules, injections should be performed deep to the orbicularis oculi muscle because the skin of the eyelid is very thin(45). Initial placement of 2 cc of fat while avoiding exceeding a total of 4 cc is usually performed to prevent overcorrection(29)

Lateral inferior orbital rim

The exact same technique, cautions and limitations described above for the MIOR are applied to the LIOR(Figure 4,point 2).

Nasojugal groove

After infiltrating the inferior orbital rim adequately, the next area to infiltrate should be the nasojugal groove(Figure 4,point 3). Infiltration to this area begins with identifying the nasojugal groove as a fan-shaped bony depression, with the medial extent of the inferior orbital rim and the nasal sidewall defining its superior and inferomedial limits, respectively. Using the same entry site as for the IOR, Insertion of fat into the same deep supraperiosteal plane is performed while using tactile feedback with the nondominant hand and ensure the cannula tip abuts bone to guide fat placement. Following identification of the area, infiltration with 0.1 cc of fat per pass of the cannula, for a total of 1cc into the entire NJG is performed(29,45).

Lateral cheek

Due to possible visual impairment brought on by local anesthesia, palpation with the nondominant hand to maintain accuracy when placing fat is crucial(29).

Injection to the lateral cheek is performed by inserting the cannula, initiating with the deep supraperiosteal plane and by passing the cannula from entry site A towards the lateral bony zygoma, filling the region broadly up to the lateral canthus. Placing approximately 0.1 cc of fat can be per pass of the cannula for a total of 3cc. It is essential to continue to march upward from a deeper plane to a more superficial one, crossing gradually across all three soft tissue levels to achieve maximal results(45).

Buccal

The buccal area tends to be a forgiving area for fat enhancement and can oftentimes benefit from a generous amount of transplanted fat(29). Injection to the buccal area begins with inserting a cannula from entry site A (Figure 4). Deposition of fat is performed in the deep subcutaneous plane in a radial manner with a deposition 0.1cc with each pass for a total of 2cc. If necessary, deposition of additional fat can be performed during refinements as needed.

Anterior cheek

In contrast to the lateral cheek, the anterior cheek requires special consideration. To access the medial-inferior extent of the anterior cheek, the cannula must first forcefully breach the tough, fibrous malar septum. The malar septum's physical presence varies; it can be persistent or nearly nonexistent at different times. The sporadic existence of a malar mound is the second noteworthy and distinct feature of the anterior cheek(29,45).

Superior orbital rim

To provide the eye a suitable frame, the SOR should be enhanced while balancing the fat enhancement in the cheek and IOR. In addition, the SOR(Figure 3, point 7) area tends to be forgiving in terms of avoiding contour irregularities from uneven fat infiltration(29). Infiltration of fat begins with insertion of the cannula from entry site B (Figure 4) with deposition of 0.1-0.2cc fat per pass in the deep-medium soft tissue planes starting from the inferior edge of the SOR and by feathering upward toward the superior aspect of the hair-bearing portion of the brow. If any gross asymmetry is visible applying gentle molding and sculpting to redistribute the fat more evenly is necessary(29).

Lateral canthus

The lateral canthus region (Figure 4, point 8) carry risk for complications; thus, it is important to maintain a conservative approach toward enhancement. In addition, the lateral canthus tends to be quite vascular, and hematoma formation is possible, which can in turn obscure the site and reduce fat cell viability(29). Infiltration to this area begins with insertion of 0.9mm blunt cannula from entry point B, with placement fat in the deep, supraperiosteal plane along the lateral extent of the IOR. Placing 0.1cc per pass for a total of three-five passes is usually the standard(29).

Prejowl sulcus

The prejowl sulcus(Figure 4, point 9) should be viewed as a three-dimensional cylindrical hollow that runs along the anterior face of the mandibular body, the inferior aspect of the mandibular body, and the transition zone between these two areas(29). Infiltration begins with insertion of the cannula from entry site C (Figure 4). Injection of 0.1cc of fat per pass for a total of 3cc while distributing 1cc for each of the three zones described above is preferred(29).

7. Postoperative care

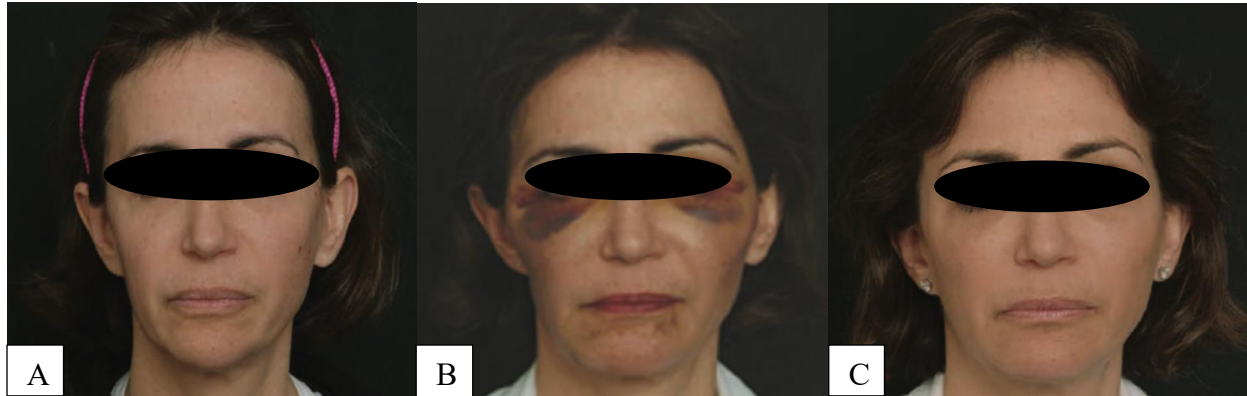
Lipofilling, unlike traditional surgeries does not require extensive management immediately following the surgery, the use of drains or compressive dressings which are commonly used in plastic surgery is unnecessary(38). There are no sutures on the body or face to take care of or remove because there isn't a true incision made. Therefore, there's no need for a particular skin-cleansing routine or topical ointment.

Patient guidance through the projected postoperative course before surgery, will be helpful in establishing realistic recovery times and thereby permits the patient to schedule time off from work and away from important social events. Informing the patient about variability in healing before surgery is necessary. However, as a guideline the patient should be informed that it will require a full 2 weeks off from work to look "socially acceptable." Helping a patient to understand what he or she will look like immediately after surgery and in the ensuing months will relieve anxiety and dispel misconceptions(46).

After the initial period following surgery, patients might experience swelling fluctuations, which could get worse upon waking up or after engaging in more activity. A faster return to baseline can be achieved by instructing the patient to ice the swollen area to counteract the edema. The patient should also be instructed to sleep in semi-upright recliner for the first two nights, ideally for the entire week to minimize facial edema. In addition, the patient should be instructed to avoid household chores that involve bending or straining, as these can worsen edema and delay recovery. Instead, light exercise should be encouraged to facilitate recovery, although vigorous workouts should be modified initially. There's no need for activity restrictions at the donor site, but activities that raise intra-abdominal pressure should be avoided to prevent increased facial edema. Dietary salt restriction can also help minimize postoperative swelling.

Perioperative antibiotics that target skin flora such as cefalexin are prescribed even though infections are uncommon. Regarding pain, patients usually manage their discomfort with acetaminophen or without any medication at all.

At last, regular patient visits should be standard procedure for a surgeon. Depending on the degree of anxiety or care required by the patient, a personalized postoperative plan can be implemented. A less nervous patient who is at ease with the healing process can be asked to follow up one week after surgery and then again four to six weeks later. On the other hand, a patient who is worried about the appearance of swelling can be seen every week for reassurance(29,46).



Picture 5. **A)** Shows preoperative appearance of a 49-year-old female with facial volume loss. **B)** Postoperative appearance at three days following periorbital, perioral, and midface autologous fat transfer with a total of 45 cc of fat demonstrating severe bruising. **C)** Thirty days postoperative view. According to Complementary fat grafting (2015), p.86.

8. Complications

Although complication rate associated with fat grafting is estimated to be only around 5.01%(2), complications are possible with any surgical operation, and autologous fat grafting is not an exception. While using good judgment and appropriate technique is crucial to preventing complications, problems can arise at the donor or recipient site. Since fat retention after fat grafting is never 100%(45), there is always a risk of fat necrosis at the recipient location. The percentage of viable adipocytes after fat grafting varies greatly throughout studies, however it typically ranges from 50% to 70%. The residual fat from injections is usually reabsorbed, but in certain cases, it might result in palpable fat necrosis or oil cysts, which can cause pain or deformity in the patient(47).

As any other surgery, many types of complications can theoretically arise after facial augmentation using lipofilling, this section will address only the commonly encountered complications related to facial augmentation using lipofilling and how to correct them. Complications can be divided into: A) contour irregularities (further divided into the categories of lumps or bulges), B) persistent malar edema, C) overcorrection, D) undercorrection, and E) divoting at the cannula entry site(29,45).

A) Contour irregularities

Lumps

A lump is a tiny, distinct mass of fat that develops from one of two causes: an excessively large fat bolus injected during the procedure, or a bolus injected too near to the skin(29). Because there is little soft tissue covering the orbital rim to act as a buffer and the area surrounding the orbital rim is thin, the periorbital region is particularly vulnerable to this problem. Precautionary fat placement in the periorbital area helps prevent this issue. The first line of treatment is observation to see if the edema resolves; intralesional steroid injections come next; and if necessary, direct excision of the lump which is very effective method(29).

Bulges

Bulge is used to describe a wider area of elevation at the recipient site which can occur either due to fibrosis, persistent edema or secondary to uneven placement of a large bolus of fat. The two common areas for bulge development are along the IOR and along the malar depression(29). The first is treated by limiting fat transfer to less than 4 cc, preferably 2 cc, and administering repeated steroid injections to the palpably thickened tissue, gradually increasing dose and strength cautiously to avoid steroid-related dermal atrophy. The latter, unlike the first type, is not characterized by palpable fibrosis, and the tissue feels soft. Thus, steroid injections are not effective in this case. Treatment involves targeted microliposuction using Klein 18-gauge Capistrano liposuction cannula, aiming to correct the overfilled area while preserving facial harmony(29).

B) Persistent malar edema

Accurately diagnosing this issue is the most crucial and frequently challenging first step toward treatment(29). One of three conditions could be represented by fullness in the malar region: overcorrection, a fat bulge, or persistent malar edema. Each of these conditions demands different treatment and wrong choice of treatment can lead to a worsening and increased morbidity(29). Malar edema presents as boggy, edematous appearance of the malar mound that may fluctuate in severity. The edema is well delineated at its inferior limit by the malar septum. On the other side, overcorrection, which is rare, presents as uniformly diffuse malar enlargement. Treatment of true malar edema involves limiting salt intake and local injections of steroids until resolution. Triamcinolone acetonide (Kenalog) injections should not be given sooner than 2 months after surgery and if possible, waiting at least 4 months before beginning intervention is preferred. Awareness when administering steroid solutions is required due to the risk of dermal and subcutaneous atrophy and the potential for developing telangiectasias. In contrast, if malar edema is associated with a malar mound, then direct excision of the mound may be needed.

C) Overcorrection

When a patient's and/or surgeon's aesthetic preferences dictate that too much fat be transplanted, the condition is known as overcorrection. However, a patient may eventually be happy with the outcome as the edema subsides over a few weeks to months. It is recommended that a minimum of six months of waiting time be extended prior to the rendering of an overcorrection . As previously mentioned, using a Klein 18-gauge Capistrano liposuction cannula for microliposuction is the most efficient and beneficial way to lessen an overcorrected area(29).

D) Undercorrection

When a patient's and/or surgeon's aesthetic preferences dictate that too less fat be transplanted, the condition is known as undercorrection(29). Comparing to other complications discussed in this section, undercorrection is the easiest one to address since additional fat transfer is a simple and straightforward matter. As with overcorrection it is recommended to allow several months for the edema to subside before determining the amount of additional fat that a patient requires to achieve an ideal result.

Divotting at the Cannula Entry Site

Rare complication but not very harmful which can present as skin tethering and depression. skin tethering can be easily corrected with a standard subcision technique using a 20-gauge needle across the scarred dermal attachments(29). The depression may require injection with a filling material to completely correct it.

9. Conclusion

In conclusion, lipofilling also known as “fat grafting” is a well-established technique in plastic surgery that offers various advantages over other methods. Lipofilling can be used in countless applications ranging from aesthetics procedures such as simple correction of volume loss to reconstructive procedures such as breast reconstruction, lipofilling is also effective in treatment of pain caused by radiation scars and capsular contractures. Unlike traditional surgeries lipofilling usually does not require extensive management immediately following the surgery, the use of drains or compressive dressings which are commonly used in plastic surgery is unnecessary. There are no sutures on the body or face to take care of or remove because there isn't a true incision made. Therefore recovery is faster and easier for the patient. Complications can occur as any other surgery, but their rate is low, and management is relatively easier comparing to other surgeries and can be minimized by following accurate measures. Therefore, all mentioned above enables the surgeon to achieve maximal results using lipofilling techniques.

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Savion Knafo

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12. Biography

Savion Knafo was born on the 2 June 1996. He completed his primary and secondary education in Kiryat Atta, Israel, during his secondary education he was chosen to be ambassador of LEAD organization which aims to develop young leadership in Israel. During his time in LEAD, he developed a project to aid children in need in his community. After which, he was recruited to the army where he served as commander and medic in a combat unit. He is an aspiring surgeon, and is proud to have attended the University of Zagreb, Medical School, with the world-class standard and knowledge they provide.