https://doi.org/10.48047/AFJBS.6.14.2024.10429-10440

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview on Autologous Nano fat transfer

Raafat Abdel latif Anany, Yehia Zakaria Awad Ibrahim, Mohamed Ali Mustafa Nassr, Mohamed Ibrahem Mohamed El-Anwar

Department of plastic surgery, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Mohamed Ibrahem Mohamed El-Anwar,

E-mail: ebrahemm478@gmail.com

Volume 6, Issue 12, July 2024

Received: 07 July 2024

Accepted: 22 June 2024

Published: 15 Aug 2025

doi:10.48047/AFJBS.6.14.2024.10429-10440

Background:

Fat is a filler with ideal properties: it naturally integrates into tissues, is autologous, and is 100% biocompatible. However, this is not the only function of lipofilling; fat is an active and dynamic tissue composed of several different cell types, including adipocytes, fibroblasts, smooth muscle cells, endothelial cells, and adipogenic progenitor cells called "preadipocytes"**[1].**

Adipose-derived stem cells (ASCs) have a differentiation potential similar to that of other mesenchymal stem cells as well as a higher yield upon isolation and a greater proliferative rate in culture when compared to bone marrow–derived stem cells. Because of these properties and because these cells can be easily harvested in great amounts with minimal donor-site morbidity, ASCs have proved to be particularly promising for regenerative therapies **[2].**

Fat harvesting:

The use of the excisional method and fat harvesting with large-bore cannulas reduce the occurrence of cellular rupture and preserve the native tissue architecture. With a 3-mm, blunt-edged, 2-hole cannula connected to a 10-mL syringe, fat is suctioned manually by withdrawing the plunger. The cannula is pushed through the harvest site, as the surgeon uses digital manipulation to pull back on the plunger of the syringe and create a gentle negative pressure **[2].**

A combination of slight negative pressure and the curetting action of the cannula through the tissues allows parcels of fat to move through the cannula and Luer-Lok aperture into the barrel of the syringe. When filled, the syringe is disconnected from the cannula, which is replaced with a plug that seals the Luer-Lok end of the syringe. The plunger is removed from the syringe before it is placed into a centrifuge **[3].**

There are different natural fat deposits in the body; surgeons should identify the most suitable area after an accurate examination of the patient. The abdomen is the most common site of fat harvesting; the second is the trochanteric region (saddlebags) and the inside of the thighs and knees. The harvesting of fat grafts can be performed via a "wet" method or a "dry" method **(fig.1) [4].**

Fig. (1): Micro fat harvested from abdomen.

Micro- and nanofat grafts, typically harvested with cannulas as small as 0.7 mm in diameter, can be used to treat delicate areas of the face such as the eyelids and lips. Microfat particles are harvested from the abdomen using a cannula with a 1-mm diameter. An amount of the microfat is sheared into finer particles using a Leur-to-Leur connector with two 10-mL syringes **[5].**

The nanoparticles are then filtered and collected. Macrofat particles could also be harvested using a standard 3-mm cannula to serve as controls. The nanofat grafts are devoid of adipocytes, and the native architecture is disrupted. However, the nanografts retained a rich supply of ASCs, which were similar to the ASCs in the macro- and microfat samples in terms of proliferation and differentiation **[6].**

In several clinical cases, the use of nanofat grafts has resulted in improved skin quality by 6 months postoperatively. Therefore, many authors suggest that while nanografts do not contain viable adipocytes, the high content of stem cells in these grafts may be clinically useful for skin rejuvenation **[7].**

Fat Processing:

The most commonly used methods to prepare fat grafts are sedimentation, filtering, washing, and centrifugation. Fat processing is necessary because lipoaspirate contains not only adipocytes but also collagen fibres, blood, and debris. These elements can cause inflammation at the recipient site, which can be detrimental for the fat graft **(fig.2)[1].**

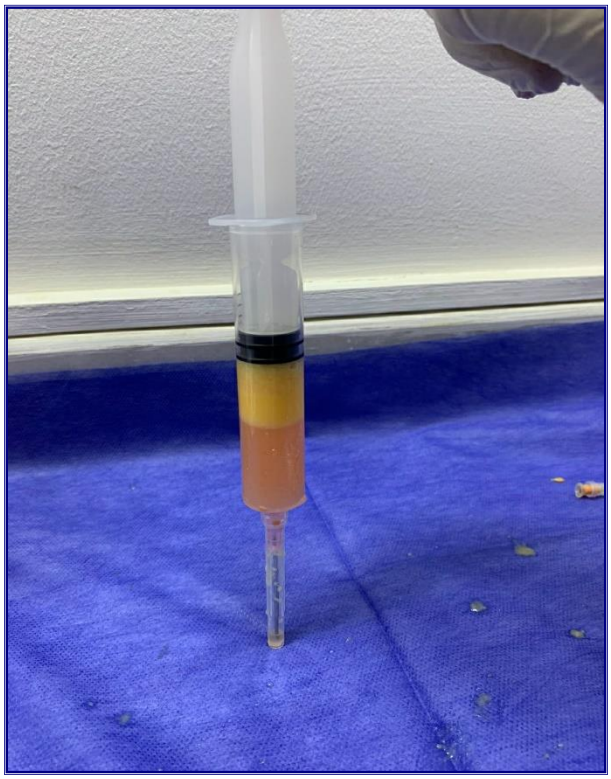

Fig. (2): Preparation of fat by sedimentation and washing**.**

Blood must be extracted because blood accelerates the degradation of the transplanted fat. Moreover, the injection of debris gives an erroneous impression of the volume of correction because the debris will be absorbed after a few hours **[7].**

Applications:

Autologous fat is used for a variety of medical applications, including volume augmentation, facial contouring, and tissue rejuvenation. Apart from the lipofilling property of

adipocytes, advances in fat preparation and processing have been promoted as a means of more anti-aging properties. This new era in fat use began in 2001 when Nilforoushzadeh et al. discussed the multipotent progenitor cells known as adipose-derived stem cells (ADSCs) **[8].**

Recently, the utilization of adipose tissue and ADSCs in regenerative medicine is becoming more common in all parts of medicine. Loss of hair and thickness of the scalp subcutaneous fat have been linked, as the decrease in scalp thickness and loss of its fat was found to be associated with hair loss. In addition, research on the effect of ADSCs on hair growth has shown that adipose tissue is an important element of the normal hair cycle **[9].**

Scars:

Patients with retractile and painful scars compromising the normal daily activity/mobility of the joint involved can take advantage of lipofilling treatment. In fact, fat transplantation can be used not only to fill atrophic scars but also to reduce scar contracture as a regenerative alternative to other surgical techniques **[2].**

Burns:

Burn injury is a devastating trauma with systemic consequences. Although survival rates are increasing, burn injury remains a great challenge in the field of cutaneous wound healing. Major burns patients lack enough skin to cover their burns, and the currently used cutaneous substitutes and cultured epithelial autografts are still neither efficient nor effective solutions **[10].**

Nanofat:

Nanofat is an emerging technique for fat grafting that is gaining popularity in the fields of regenerative medicine, aesthetics, and translational research. The power of mesenchymal stromal cells (MSC) has been known since the 1970s and recent studies have shown that MSCs are present in multiple tissues such as adipose tissue **[11].**

Indeed, adipose tissue is a major reservoir of MSCs and accessible via liposuction techniques daily used in plastic surgery. Hence it has become increasingly evident that MSCs used by adipose tissue transfer have a considerable interest for regenerative surgery. This treatment became known as fat grafting, lipofilling, and lipomodelling **[12].**

In fact, by producing appropriate support MSCs promoted neo-angiogenesis and reduced tissue inflammation. This technique is based on the use of autologous fat and represents a new concept in the field of lipofilling. In this technique, fat is harvested from the patient and

transformed into nanofat, which is composed of small fat particles (less than 0.1 mm in diameter) containing a high concentration of stem cells and growth factors **(fig.3) [13].**

Nanofat grafting has a wide range of clinical applications, including scar repair, alopecia treatment, breast tissue regeneration, and tissue regeneration in general. This technique is particularly useful for lipomodelling as it contains many stem cells that can differentiate into various cell types, such as adipocytes, osteoblasts, and chondrocytes **[14].**

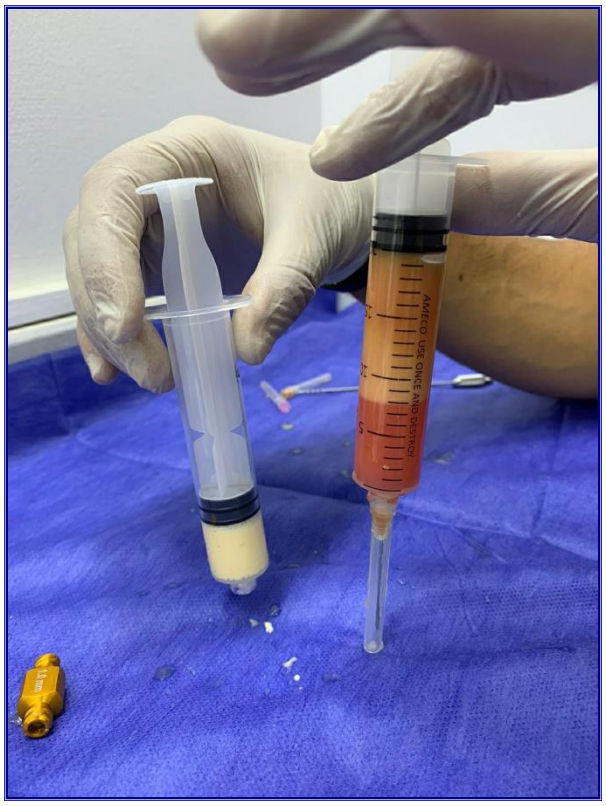

Fig. (3): This picture shows how adipose tissue is mechanically emulsified to obtain nanofat.

Fat is a well-organized and compact tissue that contains a heterogeneous population of cells and is often referred to as a "stem cell depot" due to its abundance of stem cells. Researchers typically identify nanofat using electron microscopy, either transmission electron microscopy (TEM) or scanning electron microscopy (SEM) **[15].**

The first method involves passing a beam of electrons through an ultra-thin sample of nanofat and provides high-resolution images that can reveal the internal structure of the nanofat particles. The second involves scanning a focused beam of electrons across the surface of a sample **[16].**

As the electrons interact with the sample, various signals are generated, and these signals are then used to create a detailed 3D image of the surface topography of the nanofat particles. TEM allows researchers to observe the size, shape, and arrangement of lipid droplets, cell fragments, and other components within nanofat **[11].**

SEM is particularly useful for examining the surface morphology and texture of nanofat. By employing electron microscopy techniques, researchers can gain insights into the ultrastructure and composition of nanofat, allowing for a better understanding of its properties

and potential mechanisms of action. This information can help optimize the preparation and application of nanofat in various medical and cosmetic procedures **[17].**

Nanofat is composed of vascular stromal cells, including mesenchymal stromal cells (MSCs), along with a mixture of lipids, growth factors, and cytokines, with a high expression of CD34 and CD49d. It has been established that nanofat contains adipose-derived stem/stromal cells (ASCs), and its potential application in regenerative medicine has been the subject of numerous studies **[12].**

Concept of Nanofat:

In 2013, Tonnard introduced the nanofat technique for skin rejuvenation. The technique can involve injecting nanofat grafts into various areas, including breast cleavage, glabellar skin, and perioral skin, as well as to treat dark lower eyelids, scars, and other conditions **[11].**

A 27-gauge needle is used for superficial intradermal and subdermal injection, and injection continued until a yellowish tint appeared. Discoloration typically resolves within a few hours after injection, and clinical outcomes improve progressively over time, peaking between 4 and 6 months after surgery **[17].**

No significant complications, granulomas, infections, fat cysts, or other adverse effects are reported in this series, although brief erythema lasting 1.5 to 2 days occurs when larger areas, such as the face or décolletage, are injected **[15].**

The Three Phases of Nanofat:

The most common method for obtaining nanofat involves shuffling lipoaspirate between syringes and filtering it to produce the nanofat product. The process of obtaining nanofat can be divided into three phases. The first phase is the fat harvesting procedure, which involves collecting fat from the lateral side of the thigh (preferably in females) (micro-nanofat), the medial side of the thigh, and the abdomen (the most reliable collection site in males) **[13].**

The collection site is treated by infiltrating a solution of 1% lidocaine and 1:1,000,000 adrenaline. The fat is collected using a liposuction cannula with 1 mm side ports, taking approximately 40–50 mL of aspirate. The second phase involves the emulsification of the fat, which is achieved by shifting the fat between two 10-cc syringes connected to each other **(fig.4) [16].**

Once the emulsification and filtering phase is complete, the resulting product is a translucent liquid that is rich in high-quality mesenchymal stem cells but devoid of any viable adipocytes. The final phase involves the injection of the nanofat product into the desired areas of the patient **[12].**

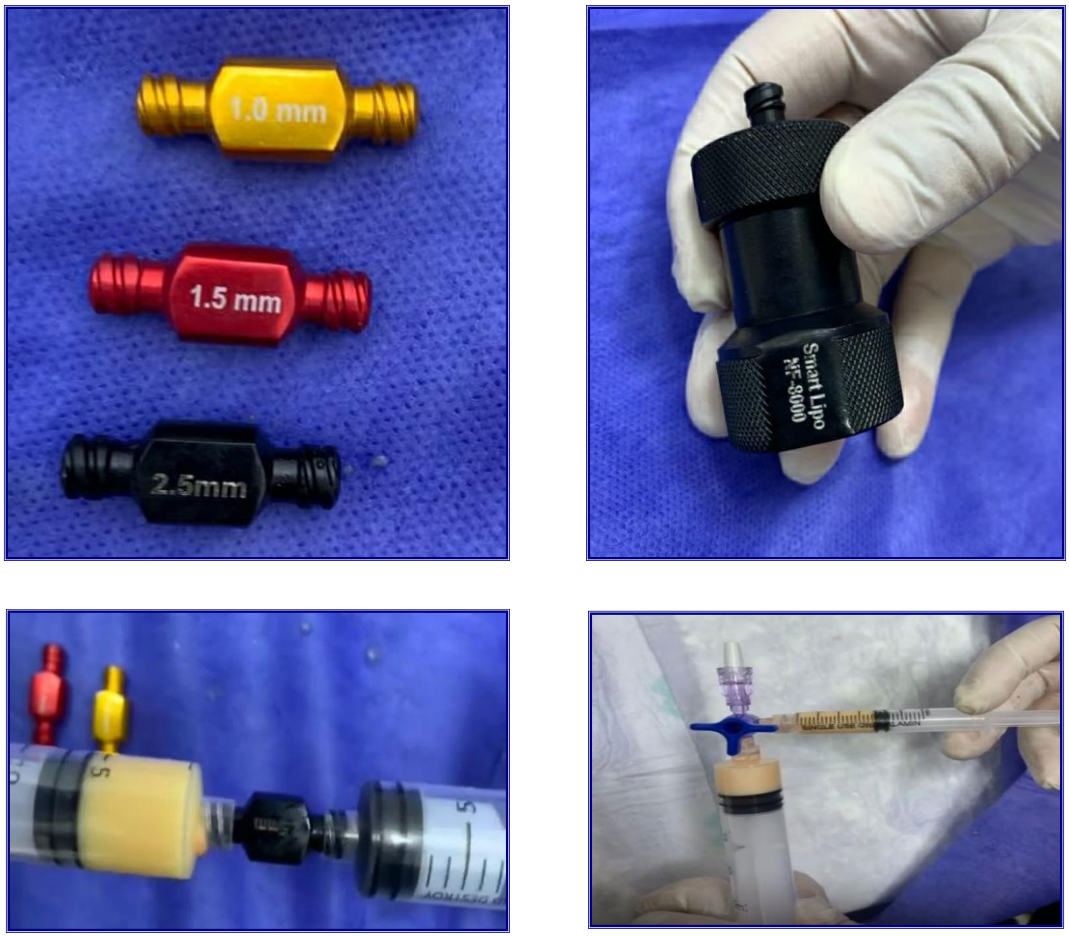

Fig. (4): Schematic representation of the method for obtaining nanofat using the Tulip system. Adipose tissue is harvested using a cannula with a 1 mm hole attached to a Luer-lock syringe (a). The adipose tissue is then passed back and forth 30 times between two 10 cc syringes connected by a Luer-lock connector, with diameters of 2.5 mm and 1.5 mm, respectively (b,c). Finally, a single pass is made through a nanofilter (d). The resulting emulsion can be infiltrated using 30-gauge needles.

Mechanism of Nanofat:

Adipocytes represent only 25% of the total number of cells in fat tissue, despite accounting for 80% to 90% of its volume. The remaining 75% of the sample, known as the stromal vascular fraction (SVF), is rich in adipose-derived stem cells (ADSCs), endothelial cells, granulocytes, monocytes, macrophages, and lymphocytes **[18].**

Recent studies suggest that the many cell types in the SVF may work together to create a microenvironment that promotes the regenerative capacity of both stem cells and tissues. Mechanical shear stress applied to fat during nanofat production has been shown to activate

signalling pathways that enhance the ability of multipotent and pluripotent stem cells to regenerate **[11].**

Reports indicate that these intricate intercellular crosstalk events can lead to increased collagen deposition, improved skin suppleness, development of new blood vessels, tissue remodelling, dermal thickening, and downregulation of melanogenic activity. Nanofat also appears to reduce inflammation and stimulate angiogenesis **[17].**

The positive effects of ASCs on wound healing are linked to their ability to promote vascular regeneration. ASCs have the capacity to differentiate into endothelial vascular cells, and when co-cultured with endothelial cells they can promote the formation of a vascular network. In comparison to bone-marrow-derived stromal cells, ASC co-cultures develop more junctions and higher network density, indicating their effectiveness in promoting vascular stability **[14].**

ASCs exhibit features of pericytes and can enhance neovascularization through expression of various growth factors, including VEGFA and insulin-like growth factor-1. The paracrine function of ASCs plays a significant role in their regenerative effects, and their secretome contains a wide variety of factors, including leptin, VEGF, HGF, b-FGF, TGF-β, IL-8, PDGF, PlGF, and SDF-1, which are involved in different stages of angiogenesis **[18].**

ASCs can form capillary-like tubes, increase endothelial cell growth, and reduce endothelial cell apoptosis through secretion of VEGF, HGF, and TGF-β. The expression of FGF and VEGF can stimulate ASC proliferation, migration, attachment, and endothelial differentiation, and can have a co-stimulatory effect on ASC endotheliogenesis **[12].**

Nanofat stem cells (NSCs) possess strong immunomodulatory effects on both the innate and adaptive immune systems. As shown by Tonnard, the nanofat technique preserves stem cells and shows a marked proliferation capability. They can partially suppress the proliferation of lymphocytes and inhibit the proliferation and differentiation of B-lymphocytes into plasmocytic cells **[15].**

Treatment with stromal vascular fraction (SVF) cells or ASCs greatly reduces the activities of T-helper 1 and T-helper 17 cells, along with their associated proinflammatory cytokines. The secretome of ASCs is also important for their immunomodulatory and angiogenic properties **[11].**

However, the characteristics of ASCs may vary depending on patient age, sex, body mass index (BMI), or metabolic state. For example, ASCs derived from patients with type 2 diabetes have been shown to exhibit increased expression of inflammatory markers and reduced immunosuppressive activities **[17].**

This type of therapy shows promise for the treatment of autoimmune diseases as well. NSCs can modify the behaviour of surrounding cells and remodel the extracellular matrix (ECM) in the dermis. ASCs promote the proliferation and migration of dermal fibroblasts and epidermal keratinocytes, both through direct cell-to-cell contact and through the secretion of factors that activate these cells in a paracrine manner **[16].**

Additionally, ASCs enhance the secretion of ECM proteins, such as collagens and fibronectin, and regulate the synthesis of collagen and matrix metalloproteinases (MMPs) and their inhibitors. ASCs can modulate the homeostasis of MMPs and their endogenous inhibitors, leading to improved collagen organization and decreased expression of α-smooth muscle actin, which are markers of dermal fibrosis improvement **[13].**

Moreover, ASCs can inhibit the expression of profibrotic factors such as transforming growth factor (TGF)-β1 or IL-6 and increase the expression of the antifibrotic factor TGF-β3. The antifibrotic effect of ASCs is also mediated by their paracrine activity through the secretion of basic fibroblast growth factor (b-FGF), hepatocyte growth factor (HGF), and interleukin-10 (IL-10), which decrease TGF-β1 expression, prevent fibroblast-to-myofibroblast differentiation, and induce myofibroblast apoptosis **[15].**

This explains the potential benefits of using nanofat as regenerative approach for anti-aging strategies. Nanofat injection is seen as a shift towards a more proactive prevention and maintenance approach, and not only to slow down the aging of facial skin,. It is compared to taking care of a house by periodically replacing carpet or applying more paint to prevent the need for a total renovation **[11].**

Additionally, the passage mentions injectable tissue replacement and regeneration (ITR) as an innovative approach that combines anatomical fat replacement with regenerative ingredients tailored to the specific needs of the patient. This approach utilizes different types of fat grafting, such as millifat, microfat and nanofat, to replicate the characteristics of fat cells lost with aging and improve the condition of aging skin **[14].**

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