ID Design 2012/DOOEL Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2017 Jul 25; 5(4):403-408.
**Special Issue: Global Dermatology**
https://doi.org/10.3889/oamjms.2017.117
eISSN: 1857-9655
***Clinical Science***

# Fillers and Facial Fat Pads

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**Citation:** Wollina U, Goldman A, Tchernev G. Fillers and Facial Fat Pads. Open Access Maced J Med Sci. 2017 Jul 25; 5(4):403-408. https://doi.org/10.3889/oamjms.2017.117

**Keywords:** Fillers; aesthetic medicine; facial anatomy; fat pads.

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Received: 13-Apr-2017; Revised: 11-May-2017; Accepted: 12-May-2017; Online first: 18-Jul-2017



**Funding:** This research did not receive any financial support.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abstract**

Fillers are used for facial sculpturing and anti-ageing treatments with increasing popularity. The optimal outcome of any filler treatment depends upon different factors: exact indication, known limitations, filler product, and filler placement. For volumizing effect and longevity of procedures, however, the interaction of fillers and facial fat pads seems to be crucial. Here, we will review the optimum filler injections for facial applications in relationship to new data and concepts concerning facial fat pads anatomy and physiology. Such a view will us enable to provide optimum results in aesthetic procedures.

## Introduction

The facial ageing process is characterised loss of volume and ptosis. This is particularly visible in the two lower thirds of the face. Here, bone ligamentous structures, muscles, facial fat pads and skin contribute to the triangular frontal shape that characterises an aged face [1].

The current concept in facial rejuvenation is to gain a natural youthful appearance by three-dimensional sculpturing with a minimally invasive approach [2, 3]. The major biophysical qualities of “dermal” fillers are viscosity, elasticity and cohesivity. However, once placed into human tissue, fillers remain not inert but interact with cells and tissues [4].

## Anatomy of facial fat pads

Facial fat pads can be divided into superficial and deep fat pads [5]. Recently another, the third compartment has been identified – the deepest facial fat compartment including buccal and temporal deep fat pads [6].

The superficial, subcutaneous adipose layer is separated by fibrous septae and consists of dermal white adipocytes (dWAT). In the medial and lateral face as well as parts of the periorbital region, temple and forehead the adherence to the skin are loose (Type 1 dWAT). Due to the rich, three-dimensional septal network, it can be classified as structural WAT [6-8].

The type 2 WAT is localised to eyebrows, perinasal and perioral region. Here, a tighter connection to the skin is realised by direct insertion of facial muscles and fibrous septae into the skin. The fibrous WAT is sharply demarcated from structural WAT in nasolabial, labiomandibular and submental sulci [6-8].

dWAT is a dynamic structure that is involved in the innate immune system, thermoregulation, wound healing, and hair follicle cycling. These adipocytes have been shown to transdifferentiate into myofibroblasts under certain circumstances [9].

Deep fat compartments contain subcutaneous white adipose tissue (sWAT) separated by the

superficial musculoaponeurotic system (SMAS) in the midface and the superficial temporal fascia in the temple. Boundaries of these deep fat pads are created by facial muscles and retaining ligaments. The deep fat pads are slowly renewing with an average turnover time of about ten years [10].

In some parts of the face, another deeper fat pad compartment can be found. The most prominent are the buccal fat pad localised in the Bucco temporal space and serve a metabolic function [11].

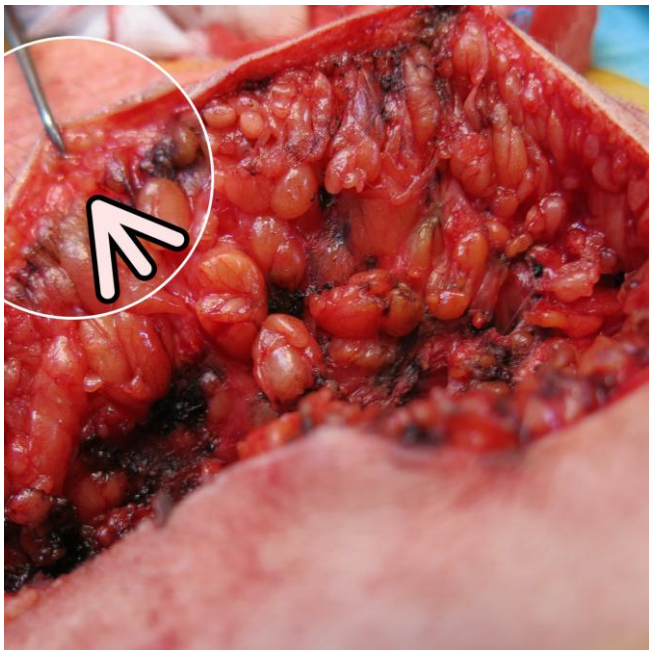

*Figure 1: Abdominal subcutaneous fat with small adipocytes in the superficial layer and large adipocytes in the deep layer separated by a delicate membrane (Arrow)*

Adipocytes are not uniform by size and functionality (Fig. 1). The release of chemokines from adipocytes [12] and macrophage infiltration [13] are directly related to the size of the adipocytes. Hypertrophic (large) adipocytes exhibit increased expression and secretion of pro-inflammatory cytokines, including tumour necrosis factor α (TNFα), interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) [14]. This elevation of pro-inflammatory cytokines leads to serine phosphorylation of insulin receptor substrate-1 via nuclear factor κB and Jun N-terminal kinase signalling, resulting in the development of insulin resistance [15].

A theoretical model suggests in the development of obesity, adipocyte hypertrophy and macrophage recruitment becomes a vicious cycle, that finally blocks preadipocyte recruitment and overall adipose tissue functioning and health [16]. There is also some evidence linking adipocyte size and weight loss regain [17, 18]. Additionally, Dankel et al. (2014) showed that some molecular mechanisms were significantly different in small from large adipocytes in abdominal fatty tissue. And, this difference allows the assumption that small adipocytes are the main source for endotrophin and thus control the adipose tissue development and expandability [19]. There is a strong correlation between BMP4 levels and adipocyte size, as well as insulin sensitivity in humans [20].

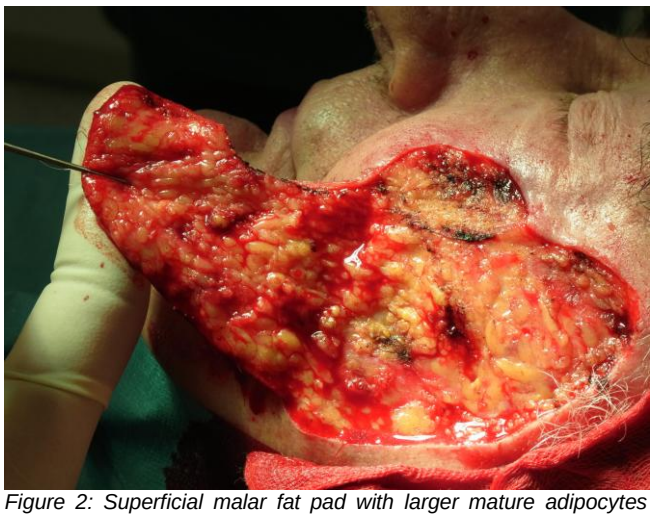

*Figure 2: Superficial malar fat pad with larger mature adipocytes embedded in a fibrous network representing type 1 sWAT, also known as structural facial fat*

Adipose tissue consists not only of adipocytes but extracellular matrix as well. There is an interplay between adipocytes and high-molecular weight hyaluronic acid (HA; 2000 kDa) of the extracellular matrix. HA is responsible for extracellular water binding capacity of adipose tissue. Higher water content prevents lipolysis by reduction of aquaporin-7 channels in adipocytes. The application of hyaluronidase, on the other side, can reduce fat masses and adipocyte size significantly [21, 22].

Medium molecular weight HA (50 kDa) inhibited differentiation of pre-adipocytes via major adipogenic transcription factors PPAR-γ and C/EBP-α. Also, FAS and ap2 – two target genes of PPAR-γ were also suppressed [23].

Bertossi et al. (2015) classified facial fat using transmission and scanning electron microscopy:

- Malar fat pad with large adipocytes by loose and thin collagen fibres (Type 1) (Fig. 2).
- Labial and nasal fat pads with mature adipocytes associated with a dense three-dimensional extracellular matrix (Type 2) (Fig. 3).
- Periorbital fat pads with pronounced lobules and dense basket-like extracellular matrix.
- Buccal fat pad with large mature adipocytes not completely covered by extracellular matrix fibres [8].

Mechanical stiffness of adipose tissue is inversely correlated with the average size of

adipocytes. The fibrous WAT develops the highest stiffness values. During the facial ageing process, prominent changes can be macroscopically noted in structural WAT. This leads to deformations like ptosis, wrinkles and jowls [24].

## Facial fat pads and filler placement

It was Owsley and Fiala (1997) who suggested moving the malar fat pad craniolaterally to improve nasolabial folds [25]. However, surgery often is not necessary since soft tissue filler injections the malar fat pad can volumize this compartment resulting in smoothed nasolabial folds and younger appearance [26, 27].

The most versatile and popular filler nowadays is HA. Since native HA becomes rapidly decomposed by endogenous hyaluronidase, HA filler uses various cross-linking technologies to increase durability. HA fillers are of high-molecular weight [28]. Histologic investigations demonstrated filler deposits mainly within the subcutaneous tissue. Thus the term „dermal filler“ is a misnomer [29]. Activation of dermal fibroblasts has been claimed for HA fillers. Recently, this has been questioned [30]. Instead, a spatial modification of facial fat tissue and activation of adipose tissue derived stem cells has been suggested [31].

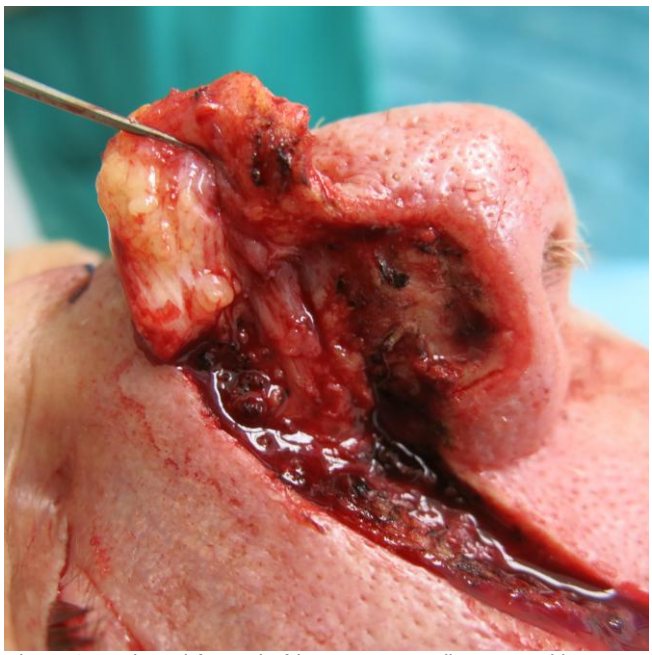

*Figure 3: Perinasal fat pad of large mature adipocytes with a more densely connective tissue network representing type 2 sWAT or fibrous type fat pad*

By detailed investigations – both with imaging techniques and cadaveric studies – of deep midfacial fat pads, it became evident that for volumizing one should specifically target these structures. Deep medial cheek fat pads and sup-orbicularis oculi fat pads of layer 4 of soft facial tissue are crucial in midfacial rejuvenation and are used to correct the cheek sagging which is a major aggravating factor for deep nasolabial folds [11, 24].

De Maio addressed this point and added two structural support depots of the lateral midface, i.e. zygomatic arch and zygomatic prominence, for optimal cheek rejuvenation [11].

For longevity of filler effects, however, the deep midfacial fat pads are of outmost importance (Fig. 4).

Cadaveric studies from Wan et al. (2014) argue for differences in superficial and deep facial fat pads. Indeed, they observed that the average adipocyte size of deep medial cheek fat was significantly smaller than that of nasolabial fat ($p < 0.0001$) [32]. Small adipocytes have a diameter of about 40 µm. The Smaller size is connected to alterations of fatty acid composition [33].

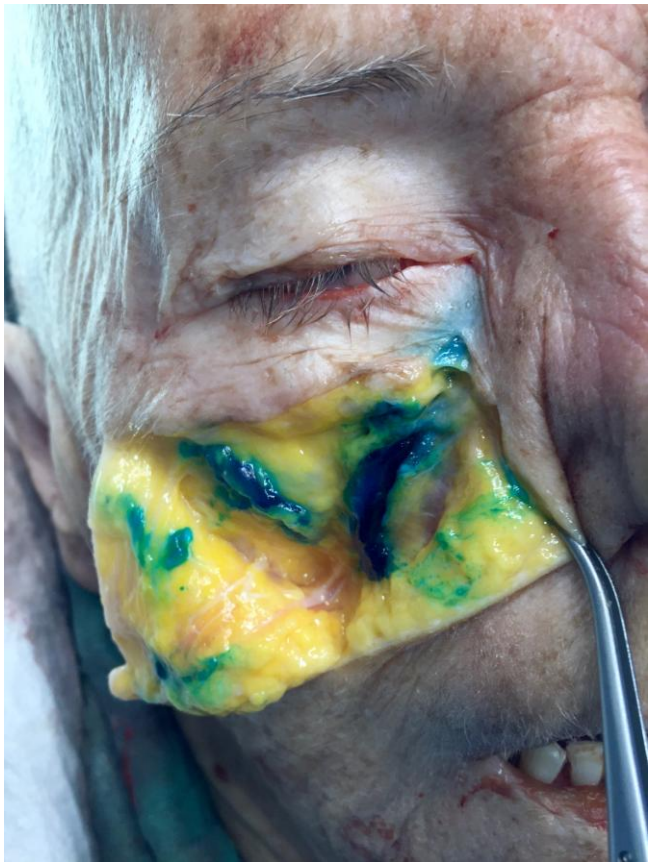

*Figure 4: Filler deposition (blueish) along the suborbicularis oculi fat (SOOF) and in the deep medial fat pad*

Collagen VI is one of the most abundant collagens in adipose tissue and consists of three isoforms. *COL6A3* isoform has previously been implicated in fibrosis [34]. COL6A3 mRNA expression is 2.8-fold higher in small compared to large adipocytes ($P = 0.004$) [35]. Low-molecular HA cannot only stimulate fibrosis but support assembly of

collagen IV [6]. Both factors may contribute to an improved mechanical stiffness after HA filler injections.

## Hyaluronic acid and adipose tissue-derived stem cells

There is evidence that HA may support human adipose tissue derived stem cells (ASCs).

Using the in vivo model of nude mice, HA gel containing ASCs was subcutaneously injected into the subcutaneous pocket in the back. Eight weeks after injection, ASCs were well attached to and proliferated on the HA gel. By this time new adipose tissue developed. Analysis of neo-adipose tissues by PCR revealed the presence of the *Alu* gene, repetitive elements of the human genome [36].

In a vocal fold injury model of Sprague-Dawley rates, local injection of ASC (ASC group) was as effective as bone marrow-derived stem cells (BMSC group). Histological examination showed significantly increased hyaluronic acid (HA) and decreased dense collagen deposition. Real-time PCR revealed that hyaluronan synthase 1 (Has1) and Has2 were upregulated in the ASC group. Fibroblast growth factor 2 (basic), hepatocyte growth factor and Has3 were upregulated in both cell transplantation groups [37]. Interestingly, smaller scaffolds (diameter about 40 μm) produced more ADSs cells than larger ones [38].

ASCs express the HA receptor CD44 [39-41]. Proliferation among ADSs occurs almost exclusively in those who express CD44 [42].

These findings might have a consequence for facial rejuvenation with HA fillers. Injection of HA fillers deep in the facial fat pads could be a stimulator of ASC expansion and differentiation leading to adipose tissue hyperplasia. When the injected fillers become degraded, low-molecular weight HA may support the 3D-connective tissue network. Adipose tissue hyperplasia is more important for volumizing whereas stimulated extracellular connective fibre network can contribute to mechanical stiffness [6, 43].

Such a view might explain the clinical observation, which HA fillers provide a significantly longer durability in improving nasolabial folds compared to collagen fillers [44-48].

HA filler injection in more superficial fat compartments - as in lip enhancement or for perioral rejuvenation - has a more limited effect on mechanical properties, volume preservation and durability [49, 50]. The less intense stimulation of deep seated ADS may be an important underlying factor.

In conclusion, the findings discussed argue for HA fillers as stimulators of ADCs with a pronounced effect and considerable duration of beautification when injected into the deep midfacial fat pads [31]. Future direction in filler development should aim to specifically induce and control expansion and differentiation of ADCs in deep dermal fat pads, thereby aiming a durability obtained today only in case of successful adipose tissue transfer [51, 52].

## Acknowledgements

Anatomical picture Fig. 4 was possible by courtesy of Prof. S. Cotofana (DGBT Anatomical Course) and prepared by the author. All figures were taken by U. Wollina.

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