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*Perspective Article*

# From Filling to Function – the Evolution of Dermal Fillers

Uwe Wollina[1,2]

*[1]Former Head of the Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital, Dresden, Germany; [2]Adjuvant International Adjuvant Faculty, Department of Dermatology, Venerology & Leprosy, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research - Premier Deemed to be University, Wardha, Maharashtra, India*

*Corresponding author:*
Prof. Dr. Uwe Wollina, M.D.
Former Head of the Department of Dermatology and Allergology,
Städtisches Klinikum Dresden, Academic Teaching Hospital,
01067 Dresden, Germany;
Adjuvant International Adjuvant Faculty,
Department of Dermatology, Venerology & Leprosy,
Jawaharlal Nehru Medical College,
Datta Meghe Institute of Higher Education & Research
Premier Deemed to be University,
Wardha, Maharashtra, India
e-mail: uwollina@gmail.com

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## ABSTRACT

**Dermal fillers first gained interest in the late 19th century, but their safety and efficacy were inadequate. But the development of fillers continued and is going on. Temporary fillers like cross-linked hyaluronic acid are widely used nowadays. Biostimulatory semi-permanent fillers like poly-L-lactic acid and calcium hydroxylapatite offer an increase in longevity with excellent safety. Newer developments are the hybrid fillers that often combines a temporary and a semi-permanent filler type to obtain better rheological qualities for a natural look. With the development of products on the market, our understanding of fillers has moved from substitution of lost volume to stimulation of autologous cells, such as fibroblasts, endothelial cells, and adipocytes. An improved understanding of tissue regeneration will support the design of a new filler type for specific interaction with the host tissue.**

## INTRODUCTION

Dermal fillers are the most versatile tools in esthetic dermatology to restore lost volume and provide a youthful appearance. The fillers go back to the 19th century when mineral oils like paraffin or oils from animal or plant sources such as lanolin, camphor oil, and cottonseed oil were used. Paraffin and other oils can cause granulomas, sterile abscesses, necrosis, embolization, and lymphangitis. Despite the major adverse events, it has survived the illegal criminal injections in the penis and muscles (1-3).

Liquid medical-grade injectable silicone was introduced in 1962. It was used to correct facial wrinkles and furrows. It became popular in the late 20th century. Orentreich invented the microdroplet injection (4). Later, it was propagated for the correction of HIV-associated facial lipoatrophy (5). Since it is a permanent filler, adverse events can occur years after implantation, such as filler migration, granulomas, induration, edema, ulcerations, and even hypercalcemia (6).

Collagen fillers became FDA approved in the early 80ties of the last century with Zyderm® and Zyplast® (Collagen Corporation, Palo Alto, CA) – two bovine products. Skin tests before injection were recommended to screen for collagen hypersensitivity. Porcine and human collagen products followed. The longevity of the volumizing effect of bovine collagen is usually between 4 to 6 months (1).

The first non-collagen product for wrinkle correction was launched in the 90ties with Profill® (OVI SA, France) and Arteplast® (INTERPLAST, Germany). Arteplast® was a permanent filler composed of polymethyl-methacrylate microspheres in gelatin. Profile® was a mixture of hydroxy-polyethylene and hydroxy-polypropylene. Novabel® (Merz Pharma, Germany) was launched in 2010. It consisted of spheres made of alginate. Profill® and Novabel® were associated with adverse events such as facial lipoatrophy or a higher risk of granulomas, respectively. Therefore, these products were withdrawn from the market. Arteplast® gave granulomas, which led to further modifications of the carrier gel and the microspheres (1). Artefill® became FDA-approved in 2006. Other permanent filler materials include polyethyl-methacrylate, polyacrylamide, and polyalkylimide. Granulomas, migration, sterile abscesses, and soft tissue infections have been reported even years post-procedure (7).

### *Cross-linked Hyaluronic Acid, Poly-L-lactic Acid, and Calcium Hydroxylapatite*

Hyaluronic acid (HA) is a high-molecular-weight glucosaminoglycan. HA has a high affinity for water molecules (Fig. 1). HA fillers (HAFs) are stabilized by cross-linking agents, preventing the rapid degradation of the filler product by endogenous hyaluronidase. Nowadays, HAFs are the most frequently used biodegradable dermal fillers in esthetic and reconstructive medicine (8).

They are generally safe, but procedure- or product-related adverse events can occur. The most common adverse events are mild and temporary, such as swelling, lumps or bumps, and firmness. Vascular complications are the most severe complications. Fortunately, they are rare (9).

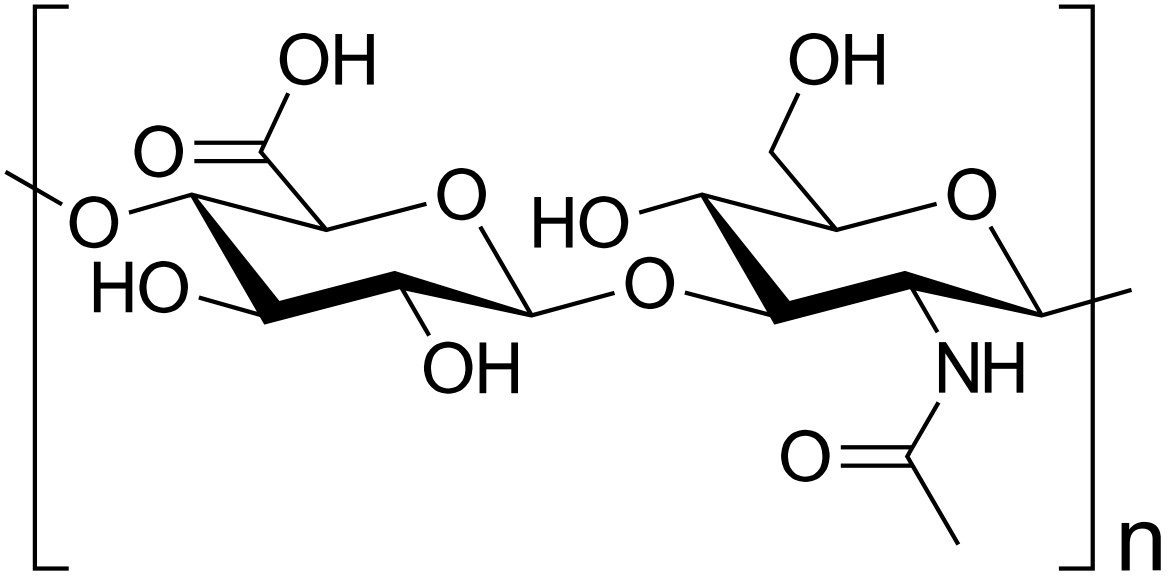


**Fig. 1.** *Hyaluronic acid is a polymer of disaccharides that are composed of D-glucuronic acid and N-acetyl-D-glucosamine, linked via alternating β-(1→4) and β-(1→3) glycosidic bonds (Public domain).*

Semi-permanent and biostimulatory fillers include poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) (Fig. 2, 3). Both are completely biodegradable but offer a longer longevity of ≥24 months. PLLA is injected 2-3 times a month apart. Sculptra® Aesthetics (Galderma, Dallas, TX) consists of 10–200 µm large microparticles and leads to chronic low-intensity inflammation resulting in stimulation of collagen production, volumizing, and skin tightening (10, 11).

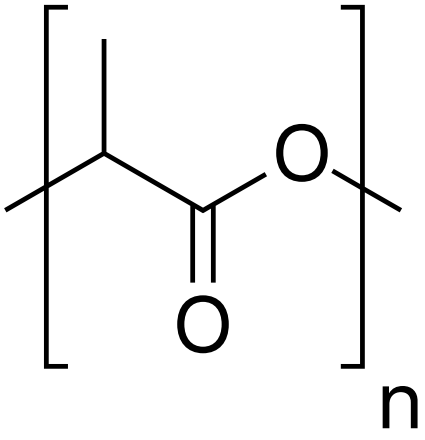


**Fig. 2.** *Polylactic acid (Public domain).*

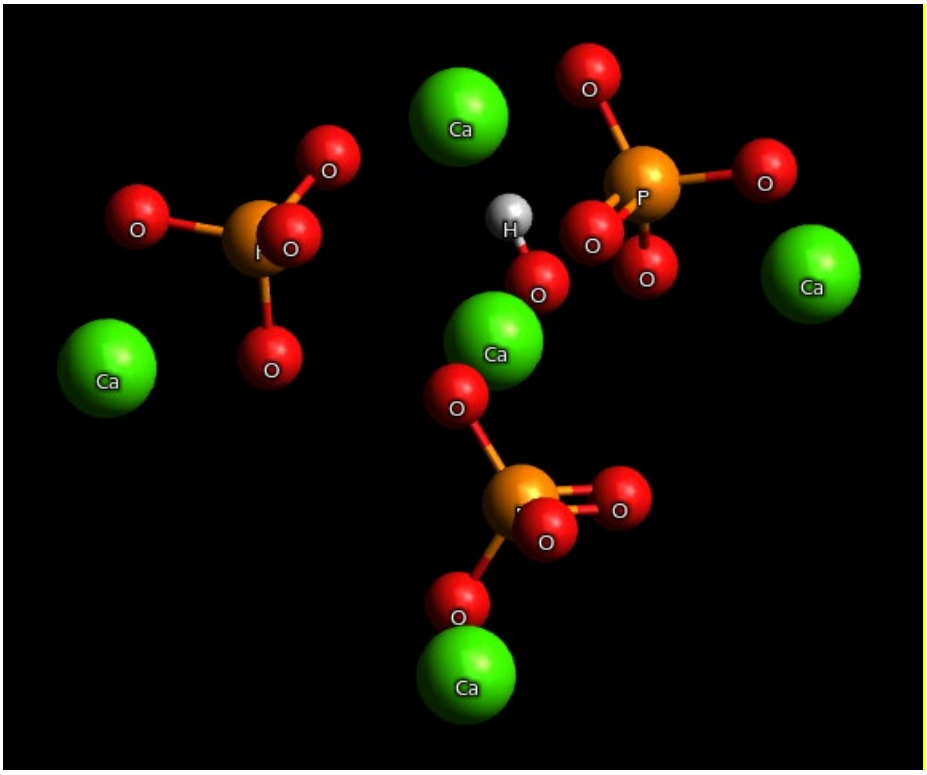


**Fig. 3.** *Hydroxylapatite (Public domain).*

Radiesse® (Merz Pharmaceuticals GmbH, Frankfurt/M.) is a CaHA Filler composed of round 20-45 µm large microspheres in a carboxymethyl-cellulose gel. After implantation, the production of collagen I and III, elastin, and proteoglycans was stimulated, and no inflammatory tissue response was observed (12, 13).

More recently, hybrid fillers have been released on the market. They aim to improve rheological qualities (14-17). Table I provides an overview of hybrid fillers.

**Table I.** *Hybrid fillers.*

| Product | Remarks | Reference |
|---|---|---|
| **Hybrids of high- and low-molecular HA** | | |
| Profhilo® (IBSA Farmaceutici, Italy) | Hybrid complexes of high- (1,100–1,400 kDa) and low-molecular HA (80–100 kDa), 32 mg/mL HA, NAHYCO® technology | (14) |
| Profhilo® Structura (IBSA Farmaceutici, Italy) | Like Profhilo® but 45 mg/mL HA | |
| **Hybrids of HA and CaHA** | | |
| HArmonyCa® (Allergan Aesthetics, an AbbVie Company) | HA (20 mg/mL); CaHA (55.7%) microspheres (25-45 µm), and 0.3% lidocaine | (15) |
| Stimulate® (MatexLab SA, Lugano, Switzerland) | HA (26 mg/mL), CaHA (1%) and amino acids, pegylated HA | (16) |
| Stimulate® Man (MatexLab SA, Lugano, Switzerland) | HA (28 mg/mL), CaHA (1%), and amino acids pegylated HA. | |

| | | |
|---|---|---|
| **Hybrids of PLLA and HA** | | |
| AestheFill® (Regen Bio Global Inc., Seoul, South Korea) | HA (46 mg) and PLLA (154 mg) in a 200 mg vial | (17) |
| Reversal® PLA+HA (Koru Pharma; Seoul, South Korea) | HA (30 mg) and PLLA (170 mg) in a 200 mg vial | |
| Juvelook® Volume (LV Plastic Surgery, Seoul, South Korea) | HA (30 mg) and PLLA (170 mg) in a 200 mg vial | |

### *Adipose Tissue and Fillers*

Adipose tissue in humans consists of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Facial adipose tissue is important in facial aging and rejuvenation (Fig. 4). In adults, it is mostly white adipose tissue (WAT). The facial adipose tissue has subcutaneous WAT (sWAT) and a dermal compartment (dWAT), forming cones around hair follicles and eccrine sweat glands. The facial subcutaneous WAT (sWAT) has been divided into three groups (Table II) (18).

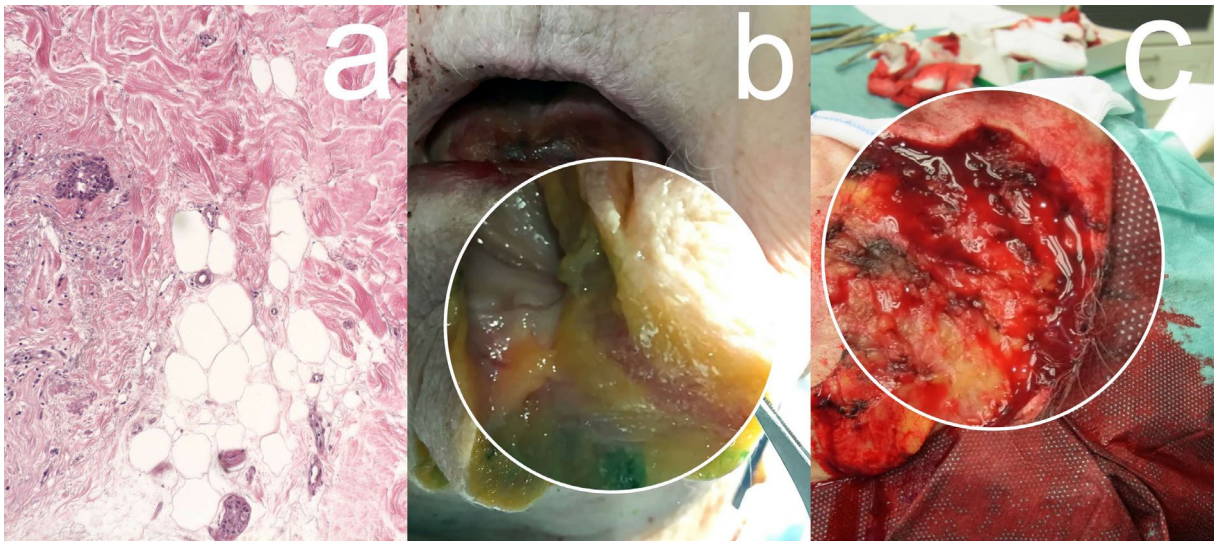


**Fig. 4.** *Facial adipose tissue. (a) Dermal white adipose tissue forming a cone around eccrine sweat glands (hematoxylin-eosin, ×100). (b) Subcutaneous white adipose tissue, fibrous type, of the chin. (c) Subcutaneous white adipose tissue, structural type, of the cheek (From: Wollina U, Goldman A, Abdel-Naser MB, Philipp-Dormston WG. Adipose tissue, fillers, and skin tightening. Dermatol Ther. 2019;32(2):e12626.).*

**Table II.** *Facial subcutaneous white adipose tissue (sWAT).*

| Type | Remarks |
|---|---|
| Metabolic sWAT | large adipocytes and minor extracellular connective tissue network |
| Structural sWAT | large adipocytes with a fibrous network around the cells |
| Fibrous sWAT | smaller adipocytes covered by a thick fibrous shell; lobular or non-lobular |

The adipose tissue is deeply affected by facial aging. sWAT is involved in volume reduction, collagen content modification, and skin mechanical stability (19).

Facial adipose tissue contains human adipose stromal cells (hASCs), a subset of mesenchymal stem cells with numerous regenerative capabilities (20). HA is a key player in cell polarity and hydrodynamic processes. HA modulates the proliferation, migration, morphogenesis, and senescence of ASC (21-23). Huang et al. investigated the effect of hASCs-loaded HA gel in vitro after subcutaneous injection into nude mice. When

the mice were sacrificed at 8 weeks, the investigators detected new deposits of fat tissue (average size 0.6 x 0.5 x 0.3 cm) surrounding the residual gel but no fibrosis or cystic space formation. In the surrounding tissue, neovascularization was noted. The adipocytes were rich in lipid droplets.

HAF injected into facial skin comes in close contact with dWAT and sWAT. HA has various pro-adipogenic effects (24). On the other hand, ASCs can reduce inflammation and accelerate collagen maturation by interacting their exosomes with HA, e.g., pro-inflammatory interleukin -6 becomes down-regulated (25).

In vitro, highly concentrated (45 mg/mL) high/low-molecular-weight HA hybrid complex increased cell viability of adipocytes by about 20% and 16% after 96 h and 7 days of incubation compared to controls. Intracellular lipid accumulation was about 3-fold compared to controls with increased droplet diameters. Adipocytes expressed CD44. By quantitative real-time polymerase chain reaction (qRT-PCR), it could be demonstrated that the gene expression of peroxisome proliferator-activated receptor gamma (PPARγ) was upregulated to about 56-fold vs. controls at day 14. In the same time range, there was an upregulation of adiponectin vs. controls of 1.37-fold. The leptin protein level increased by 2.01 at day 21 (32). These data demonstrate that high-molecular HA is an enhancer of adipocyte differentiation from stem cells (21).

Svolacchia et al. used enriched adipose tissue progenitors obtained by the MilliGraft kit® (Dual Trend srl Corso Torino, Chieri, Italy). These cells were diluted in a commercial HA filler and injected subcutaneously for deep dermal wrinkle correction in 14 adult females. Using a Numeric Rating scale (NRS) 10–0, a modified Vancouver scale, and a Berardesca scale, the patients were investigated for 150 days after the procedure. In addition, patient satisfaction was measured. All parameters significantly improved for the whole follow-up period (23).

During my clinical practice, I observed that deep filler placement in the midface could result in a prolonged sculpturing effect on the face, irrespective of its HA content. This could not be explained by temporary stimulation of fibroblasts, which produce pro-collagen (Fig. 5).

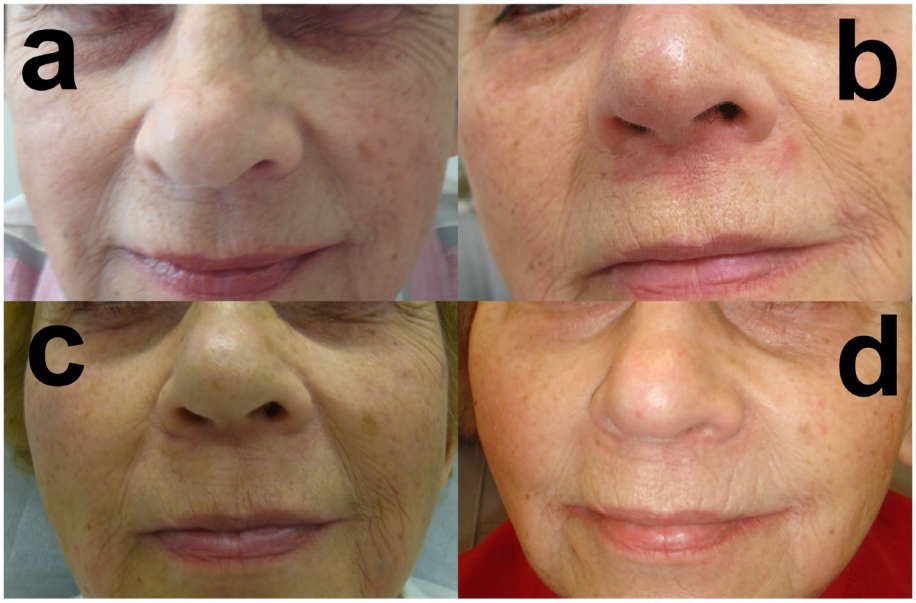


**Fig. 5.** *81-year-old woman before treatment (a) with a regular HA filler treatment. (b) At the age of 82. (c) At the age of 85. (d) At the age of 86. Over the years, subcutaneous and deep HA filler placement has restored volume and shape.*

Mechanical stress exerted by filler injection can induce hASC differentiation and pericellular fibrosis around adipocytes (26). Some of these effects are created by HA binding to CD44 expressed on adipocytes. ASC supports autologous fat graft performance, stimulates angiogenesis, and decreases adipocyte necrosis in a HA scaffold. The effectiveness and longevity of HAF depend not only on the filler product but also on the local content of ADC and its ability to proliferate and differentiate (27).

A study with cross-linked HA, such as in commercial HAF in vitro, has proven this concept. Various cross-linked HA fillers with an HA concentration between 0.02 and 0.3% exerted no cytotoxic effects on preadipocytes (ASC). It was demonstrated that these HAF support adherence and survival and reduce basal and induced lipolysis in fully mature adipocytes. 0.3% cross-linked HA significantly increased the number of cells (+80%) compared to 0.02% HA. Cross-linked HA preserved the adipogenic capacity of preadipocytes (ASC) during prolonged cell culture. 0.3% HA increased lipid accumulation by about 200% vs. control and adiponectin secretion by nearly 500% (28). In a mice model, cross-linked HA enhanced the vascularization of fat grafts by stimulating the expression of CD31 and vascular endothelial growth factor (29). Another study in rats demonstrated histologically that HAF acts as a scaffold for autogenous tissue and angiogenesis, followed by the proliferation of adipocytes. This supports the concept that the injected filler volume is maintained in the long term by replacing HAF partially with autologous tissues (30).

Exogenous hyaluronidase inhibits the differentiation of 3T3L1 adipocytes in vitro. Hyaluronidase transitory stimulates calcium-binding Matrix Gla protein and CD44 expression up to 3-fold. The lipid accumulation is decreased. This demonstrates the role of HA in stem cell differentiation (33).

## CONCLUSIONS AND OUTLOOK

The future of fillers may lay in the specific stimulation of autologous cells, including adipocytes of sWAT and dWAT, to rejuvenate the human face. This needs a better understanding of the factors for the differentiation of hASC into fully mature adipocytes, including molecular weight, composition and crosslinking of HA fillers, supplementary substances, and peculiarities of adipocyte physiology in different compartments of the human face.

Following this concept, it might even be possible to reduce the injected volume and the frequency of injections needed for boosting (31).

**Ethical issue:** Written consent was obtained from the patient.

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