## Choosing The Optimum Filler For Volume Lifting

There is definitely no cosmetician today who does not use volumizing fillers. Volume lifting is one of the most popular cosmetic procedures. The variety of volumizing agents available at the market is so huge that a practitioner sometimes even finds it hard to choose. Today, our Success Workshop section is going to tell you about the features of modern volumizing fillers and their effects on the clinical outcomes.

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The history of contour correction comprises two stages. The first one is about filling skin defects (wrinkles, scars, etc.) with various agents in order to even out skin surface. The second one included enhancement of facial soft tissues, possibly compensating for loss of volume with age or due to a trauma, or physiological volume deficiency (1). In case of aging changes in facial soft tissues, the effect of volumizing is not usually limited to gaining volume of the area in question but also consists in true lifting of the tissues related to the area. In this case, lifting is made through shifting the tissues along the vector directed toward the area to be enhanced. The key to successful enhancement and/or volume lifting of facial soft tissues is, first and foremost, the right choice of the agent. So, what should be the filler of choice to perform facial lifting?

### A GLANCE INTO HISTORY

Historically, the first stage of the development of contour correction was not the filling of wrinkles but attempts to restore loss of volume occurring with age. Plastic surgeons of the early 20th century used a variety of substances for that purpose, including latex, gutta-percha, celluloid, gold, silver, ivory, horn, hydrocarbon fillers (paraffin and petroleum jelly). The use of these materials often caused various complication, including filler migration, fistulae, inflammations, abscesses, etc. After 1920, this method was rejected. SMAS lifting was developed and gradually improved instead.

However, late 1980's showed another wave of interest for soft tissue enhancement. Autologous adipose tissue was used as the filler now, through a procedure called lipofiling (4). The purpose was now not only to improve soft tissue volume but also to fill specific skin defects. Later on, inert synthetic fillers and forming implants appeared. Thus, for quite a long time, handling facial tissues volume was the job of plastic surgeons only.

Upon the invention of biodegradable fillers, cospeticians also became able to do contour correction. However, the entire process developed the other way: from

simple filling of separate defects on a dermal level (wrinkles, folds, scars...) to lifting and enhancement of soft tissue volumes (5).

## VOLUMIZING AGENTS

Today, the agents used for contour correction, particularly for volumizing, can be divided into three groups: permanent (non-biodegradable); prolonged-action (partially biodegradable); and temporary (biodegradable). The first group includes autologous adipose tissue (for lipofilling) and agents containing synthetic biopolymers; the second one, compounds of calcium hydroxyapatite, polylactic acid, cross-linked alginate; the third one comprises fillers based on collagen and hyaluronic acid (HA).

Each group has its benefits and its drawbacks; therefore, the choice is to be made based on the balance of each group's pros and contras (Table 1).

Today, lipofilling is used only by plastic surgeons. Cosmeticians are not allowed to do it. Agents containing synthetic polymers can be homogeneous (contain the chemical agent only) or heterogeneous (contain particles of other substances within collagen or HA). The synthetic chemicals suitable for the procedure are liquid silicone, polydimethyl silicone, polyacrylamide, and polymethylmethacrylates. Permanent fillers have the following advantages: they are slowly resorbed; gels can be of various densities and preset shapes; and the procedure is economical. There are also certain drawbacks, like irregularity of contours and lack of homogeneity of soft tissues, areas of hypercorrection, foreign body sensation, and a high risk of late complications (showing up between 2 and 15 years post-treatment).

The late complications of the usage of permanent fillers include:

- acute and/or chronic inflammation of the injection area;
- granulomatous reactions;
- hypervascularization and venous lakes;
- dyschromia (hyper- and hypochromia);
- adenopathy;
- proneness to the formation of fistulous tracts and fibrous formations in soft tissues;
- filler migration;
- soft tissue necrosis around the injection area.

Permanent gels are not compatible with any other agents whatsoever.

Today, liquid silicone is not allowed for use in Europe.

Partly biodegradable fillers are made from materials containing microparticles of polymer microfibers. When the main liquid part of the filler is resorbed, new connective tissue is formed around the microspheres. The particles are usually from 30 to 100 μm large. Their main benefit is the significant durability of the result (compared to temporary fillers): 1.5 to 2 years. Their drawback is the difficulty of reversing hypercorrection, which lasts longer than in case when fully biodegradable fillers are used.

Temporary fillers are of natural origin. They include collagen- and HA-based products. Collagen products were first used to even out wrinkles in 1981. Collagens can be xenogenous (bovine), homologous (extraneous to the body), or autologous

(obtained from the same organism). The filling effect does not last long since collagenases start breaking collagen down straight after the injection. Bovine collagen is economical but often causes hypersensibility reactions, therefore at least two skin allergy tests should be performed before the procedure. Granulation growth is also possible. Human collagen is refined before use, so it is better tolerated.

HA-based fillers have been in use since 1996. HA forms a part of skin, bones, cartilage and connective tissue itself. HA makes up the base of intercellular matrix and has no species specificity. It is synthesized in the body on the surface of the cells and is broken down by hyaluronidase enzymes. Substance used to make the fillers is obtained from avian material (rooster's comb) or made by biosynthesis (in genetically engineered bacterial cultures). Today, fillers are mostly made using biosynthetic HA. To extend the stay of the agent in skin and, accordingly, the filling effect, the method of HA stabilization is used.

A drawback of these agents is the transient nature of the effects of correction (between 4 months and 1.5 years), especially when collagen-based products are used. A significant advantage is the possibility for the injected HA to be dissolved should any adverse effects appear, using the specific enzyme of hyaluronidase. HA-based preparations are the most popular ones for contour correction and filling in particular. This is because they present an optimum combination of quality, price, quality, filling longevity, and low risk of side effects and complications.

The agents' properties are defined based on the characteristics of the HA (stabilization and concentration) and the HA-based gel (phasicity, residual hygroscopicity, elasticity/tension, plasticity and cohesiveness).

**Table 1. Particular features of biodegradable and partly biodegradable preparations used for volumizing.**

| Base for preparation | Onset of action | Duration of volumizing effect | Possibility of allergic reactions | Additional volumizing capacity | Specific antagonist |
|---|---|---|---|---|---|
| Collagen | Right after | 3-4 months | High (preliminary test needed) | No | No |
| Hyaluronic acid | Right after | 6-18 months | Low | Isovolemic biodegradation | Hyaluronidase |
| Calcium hydroxyapatite | Best effect in 6 months | 1.5-2 years | Low | Through potent stimulation of neocollagenesis | No |
| Polylactic acid | Best effect in 6 months | 1.5-2 years | Low | Through potent stimulation of neocollagenesis | No |

## HYALURONIC ACID: STRUCTURE AND STABILIZATION

HA is a heteropolysaccharide, first recovered from the vitreous body of bovine eye in 1934. Later on, HA was found in the tissues of all vertebrates. The structure of HA is quite simple: the molecule consists of remnants of D-glucuronic acid and D-N-acetylglucosamin connected alternately with b-1-4- and b-1-3-glycosidic bonds. All

HA used in fillers is obtained by bacterial synthesis. Through biotechnological synthesis, it is possible to create HA molecules identical to natural ones.

Native HA is broken down by hyaluronidase within 1-3 days upon being injected into the tissues. It was supposed that an increase in the molecular weight of the HA can extend the time when the filler stays in the tissues. However, Brown et al. have shown that the speed of biodegradation (better to say, the half-life) of HA in the synovial fluid lies within 10 hours (for endogenic HA with a molecular weight of 100,000 Da) and 16 hours (for exogenic HA with a molecular weight of 13,000,000 Da). Therefore, a molecule's molecular weight has little effect on the half-life of HA (8).

To ensure a longer stay of the filler in the tissues, HA structure is modified (6). Any alteration in the structure of HA makes it "unrecognizable" to hyaluronidase. Such alterations may consist in making biologically active agents or another HA molecule (stabilization) join the initial HA molecule. Once in the skin, this complex first loses the supplementary elements (this occurs through hydrolysis), and then, hyaluronidase breaks down the HA that remains outside the complex. HA stabilization consists in the formation of cross-links between two HA molecules or between different parts of the same molecule, using a sealing agent. The best properties of the fillers are due to the links between two different HA molecules. Such links are called "effective". They are important in contour correction (prolonged filler effect); biorevitalizers and biorepairs have no need for extended filler effect.

The traditional method of HA stabilization comprises the effect of a chemical that forms cross-links between HA chains. Sealing agents can include 1,4-butanediol diglycidyl ether (BDDE), which is the most popular one today, as well as divinylsulphone or biscarbodimyde. The presence of a non-linked sealing agent negatively affects a preparation's biocompatibility with tissues, therefore it may only be present in minimum quantities. Russian and European quality standards put restrictions on the maximum contents of free sealing agents. To reduce the amount of unlinked sealing agent and increase the efficiency of the stabilization process, different manufacturers perform the processes under preset values of temperature, pH, and HA concentrations; such values constitute a part of patented technologies.

For instance, Suisselle (Switzerland) uses the A.P.R.I. technology for the manufacture of their contouring products. This is a patented, environmentally safe method of one-phase sealing of HA molecules. This ensures modification of HA through 100% efficient sealing. The A.P.R.I. intelligent modification comprises a change of HA structure in a highly concentrated aqueous solution, using efficient bonds only, when BDDE is linked to two different chains in HA macromolecules. The HA sealing process is performed in a one-stage technological mode, under a neutral pH and without addition of any supplemental chemicals or catalysts. Thereby, the APRILINE® production technology ensures efficient stabilization, outstanding safety and fineness of the products (no free BDDE, no additional chemical stabilizers).

The percentage of the number of cross-linked HA chains against the overall amount of chains in the molecule is called the degree of stabilization. This degree varies from 1 to 20% in different products available at the market (7). Increased

degree of stabilization means that the product is more stable (half-life), dense, and resistant within the tissues. On the other side, there is a certain critical level after which the gel is recognized by the body as a foreign substance, which results in the activation of immunologic protective systems. Excessive increase in gel density and resistance also has an adverse effect on the process: the denser the gel, the harder it is to inject it and to have it distribute in the tissues.

In some cases, filler manufacturers use additional technologies intended to improve the quality of contour correction products. For instance, ObvieLine (France) employs the E-BRID® Technology, which consists in using two kinds of bonds for the stabilization of HA. First, native HA undergoes etherification (reaction of compound ethers formation). In the process, intrinsic etheric bonds are formed between hyaluronan chains. Partly stabilized HA is unrecognizable to hyaluronidase. The next stage consists in traditional stabilization using BDDE, but since some bonds are already occupied by intrinsic etheric ones, the overall amount of BDDE in the product is way less, resulting in better product safety and less toxical effect of the stabilizing chemical without loss of biodegradation time. Also, the links with intrinsic etherification ensure better product plasticity than do the links formed using special sealing agents. Thus, Perfectha products stand out due to their good plasticity amid their low contents of chemical stabilizer.

## DEFINING PRODUCT PHASICITY

At IMCAS 2013, an agreement was accepted for the concept of phasicity to describe product behavior.

Stabilized HA is a fairly dense substance that is not suitable for injections. To have a gel that is suitable for use in injection contour correction, this dense substance has to be softened. The way how the dense gel is softened defines the product's phasicity.

As stabilized HA is forced through cells of a certain size, same-size HA particles are obtained in the result. To improve fluidity required for injection contour correction, native (non-stabilized) HA is added to the "bolted" mass of same-size particles. This results in the formation of a biphasic gel consisting of same-size particles of stabilized HA and a small amount of native HA. In different product ranges, particle sizes are given in micrometers (mkm) or in particles per 1 ml (accordingly, the more particles per milliliter, the smaller the particles themselves). Biphasic products have a more homogeneous structure and get better distributed in the tissues. Biphasic products with larger particles are better in maintaining the newly formed shape of the area in treatment and have a somewhat better lifting ability. The volumizing effect is better pronounced in them than in monophasic products, ensuring harsher outlines of the area in treatment.

To get a monophasic gel, stabilized HA is ground, resulting in a mass of different-size gel particles. In this case, the size of the particles shall be limited by their ability to pass freely through the needle. This monophasic gel looks more homogeneous, is more easily injected, better distributed in the tissues, and easier to mold. Monophasic products create a softer volumizing effect. Accordingly, the area in treatment looks more natural.

## CONCENTRATION OF HYALURONIC ACID AND ITS EFFECT ON PRODUCT FEATURES

HA concentration in a product affects the physical and chemical properties of the gel: higher concentration means higher viscosity. Also, concentration is proportional to the duration of the product's half life in the tissues, however its increase means an increase in residual hygroscopicity (HA's ability to attract and retain additional water molecules). Growth of HA concentration in the product also results in the number of HA chains that are not cross-linked. The free chains contain N-acetyl and carboxyl groups. These functional groups attract water molecules, causing the injected gel to "swell".

The lowest hygroscopicity detected was shown by a product with HA concentration of 5.4 mg/ml. HA concentration of 20 mg/ml is deemed to be the optimum one, since it ensures sufficient viscoelasticity of the gel and moderate residual hygroscopicity.

Apart from concentration, the residual hygroscopicity also depends on the degree of reticulation. The higher the degree of HA stabilization, the more functional groups are "closed" from attracting water molecules, which means lower residual hygroscopicity of the gel.

A high level of residual hygroscopicity resulting from the volume of additional attracted water may become a reason for overcorrection of the area in treatment, appearing several days after the correction procedure (allowing to reach the optimum volume). Also, pronounced post-treatment oedema may result in vessel ischemia in the treatment area because of excessive pressure from the mass of gel plus the attracted water molecules. High residual hygroscopicity is unacceptable for treatment of periorbital areas.

On the other hand, residual hygroscopicity allows performing volumization with a smaller amount of the product, creating additional volume through attracting water molecules. This volume is maintained through isovolemic biodegradation of HA. Isovolemic biodegradation of HA is its ability to attract water during biodegradation, maintaining the overall filling volume (Fig. 1).

**Figure 1.** Isovolemic biodegradation of hyaluronic acid.
Right after injection
7 months after treatment
10 months after treatment
hyaluronic acid gel
water
fibrosis

## PRINCIPAL PROPERTIES OF GEL IN STABILIZED HA-BASED FILLERS

A gel's main properties are: elasticity/resistance, plasticity, and cohesiveness. These are also the features of any filler. Elasticity (resistance) is a property allowing a solid body to maintain its shape. Plasticity is a material's capacity to change its

shape (e.g., it allows a gel to pass through a needle). Cohesiveness is a substance's capacity to retain its initial shape after a significant short-term load is discontinued (e.g., a filler does not spread around when molded). Also, viscous liquids have a property called pseudoplasticity or shear thinning. This is provisional reduction of viscosity under dynamic load (a gel temporarily decreases its viscosity when pressed upon by a plunger, which allows it to be pushed out of the syringe).

Biphasic products have higher elasticity/resistance, while monophasic ones are more cohesive. Any fillers, regardless of their phasicity, HA concentration and stabilization degree, are much more plastic than the derm.

Quantitative properties of the gel are described through the elasticity and complex viscosity modulus. The elasticity modulus shows the resistance needed to deform the gel. The complex viscosity describes a liquid's ability to resist flowing (for injection products, within the needle). These figures are increased upon increase of HA particle size, concentration, and stabilization degree. Thus, products with larger particle sizes, higher concentration and higher stabilization degree are more resistant to deformations and are better at maintaining the initial shape; however, a much bigger effort is required to inject them into a tissue.

## REQUIREMENTS FOR THE "PERFECT" VOLUMIZING PRODUCT

HA-based preparations have been recognized as the "golden standard" for contour correction and filling in particular. They are biocompatible with body tissues, have a much lower plasticity than skin does, ensure a predictable and instant treatment result. They also have a specific antagonist which means that any complications can be easily corrected.

Volumizing in different areas requires various combinations of product properties. In any case, the residual hygroscopicity of the gel should be minimal, to prevent complications and get a predictable result. It is to be recalled that optimum residual hygroscopicity was detected under a HA concentration of 20 mg/ml for biphasic products, and under high levels of stabilization for monophasic products. Minimum complex gel viscosity makes it the easiest to handle the gel, since it requires minimum effort pushing on the plunger.

For treatments in the area of cheekbones, chin (at periosteal level) and mandibular angle (in subcutaneous fat), the key product property is its ability to maintain a preset shape. For that, it should be highly elastic and resistant and have a high elasticity modulus. Biphasic products with larger particles can distribute densely in the area under treatment, holding the shale well. They have a high elasticity modulus. On the other hand, the second important thing for handling these areas is high cohesiveness of the gel, allowing it to regain its initial shape after discontinuation of a short-term load. Monophasic products have high cohesiveness.

In the periorbital area (with its deep infraorbital fat pad), the preparation should have high plasticity and medium elasticity module in order to avoid contouring of the injected product. It should also hve sufficiently low residual hygroscopicity (2, 3). These are the properties of either biphasic preparations with an average HA concentration of 20 mg/ml and medium particle size, or monophasic products with medium HA concentration and medium HA stabilization degree.

When working in the areas of temples and cheeks (at the level of subcutaneous fat and under the superficial pad of the temporal fascia), the most important product features are high plasticity (much lower than the plasticity of subcutaneous fat), low elasticity module and the ability to distribute evenly among the fibers of subcutaneous fat. All monophasic products distribute better in the tissues thanks to their more homogeneous structure. Monophasic products with medium HA concentration and stabilization degree appear to have the optimum properties for handling these areas.

Monophasic products have a softer volumizing effect that looks more natural than that of biphasic products; on the other hand, biphasic ones have a better-pronounced volumizing effect.

Volumizing of cheek-bone area, mandibular angle and chin often ensures lifting of the areas lying below the specific area undergoing volumization. The vectors of aging and relocation of lowering tissues are shown on S.T. Hamra's model (Fig. 2). Involutional changes cause the soft tissues to move downward and medially, thereby we move the tissues along these vectors as we volumize the areas lying upward and laterally.

A filler's lifting capacity is defined by a set of physical properties (resistance, elasticity, and cohesiveness). Thus, we cannot definitely say which products (in terms of phasicity) have better pronounced lifting properties. In general, biphasic ones have better resistance and elasticity, while monophasic ones are more cohesive, making the results of the treatment look more natural.

**Figure 2.** Vectors of aging and relocation of dropping tissues (S.T. Hamra).

## CONCLUSION

Today, there is still no perfect and "one size fits all" filler among the countless contour correction products. Yet, HA-based preparation remain the "golden standard". They are the safest ones of all (due to their biological inertness) and ensure the most predictable results. Their different properties depending on their phasicity, concentration and stabilization degree give specialists a chance to choose a product that suits a specific procedure. Thus, biphasic products are optimum for handling deep layers of soft tissues (over the periosteum) to create sharper shapes and better pronounced lifting effects. PERFECTHA SUB-SKIN combines the benefits of biphasic products (maintaining the shape and volume of the area under treatment) with outstanding plasticity (thanks to the production technology). When handling subcutaneous fat, the product's ability to evenly distribute among the connective tissue fibers and maintain the "soft" volume is of utmost importance. APRILINE® FORTE has a lining effect so it distributes evenly among the fibers of the connective tissues, smoothes down the epidermis and compensates for the volume deficit.