

# Principles of soft tissue augmentation for the aging face

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**Abstract:** In the quest for the “ideal” soft tissue filler, many diverse products have been developed. The expanding market of available fillers is a testament that no one product will ideally suit all patients or clinicians. In addition, the challenge of satisfying the criteria of an ideal filler has driven researchers to take a variety of development paths. This has resulted in multiple categories to characterize soft tissue fillers. These fillers are categorized according to: (1) filler material, eg, autologous, natural, synthetic; (2) mechanism of action, eg, void filler, neocollagenesis, fibroblast stimulation; (3) patient type and profile, eg, younger versus older patient, rhytids versus “sinking and sagging” skin; or (4) durability of treatment effects, eg, temporary, semi-permanent, or permanent. Although strategies for soft tissue augmentation may be quite diverse, strategies should share a universal goal to address fat redistribution (atrophy and hypertrophy), the primary underlying morphological cause of facial aging. To accomplish this, volumizers are now available that are injected more deeply, resulting in the restoration of supportive structure and foundation. These can be used in combination with other products that are used more superficially for smoothing skin surfaces. As numerous soft tissue fillers enter the market, mechanisms and injection techniques become more divergent, and therefore require that the dermatologist and cosmetic surgeon receive adequate training to use products safely and effectively. This manuscript provides an overview of soft tissue fillers and their proper use.

**Keywords:** soft tissue augmentation, fillers, fat atrophy hypertrophy, highly active anti-retroviral therapy, lipoatrophy

## Introduction

The quest for ideal fillers for soft tissue augmentation has resulted in the development of many diverse products with divergent augmentation strategies and mechanisms of action. This is partially a testament to the fact that no one product will ideally suit the desires of all patients and all clinicians. Moreover, the formidable biological and aesthetic criteria of “the ideal filler” have driven researchers to take a variety of development paths. This has led to the development of multiple categories of soft tissue fillers that are shown in Tables 1 and 2.

The primary actions of these products are to occupy physical space, to induce collagen formation, and/or increase volume. Soft tissue fillers are commonly categorized by durability. Both clinicians and patients have different preferences for durability. Convenience drives the use of more durable (semi-permanent and permanent) soft tissue fillers or implants, because these products require fewer or no follow-up treatments. However, because the face continues to age following procedures, temporary or semi-permanent effects may be preferred, so the face can be periodically augmented to accommodate ongoing morphological changes. Some clinicians have also voiced concerns about the potential for long-term complications that may arise after treating with permanent soft tissue fillers.

In general, soft tissue augmentation techniques have evolved from an early focus on the treatment of lines to, more recently, focusing on the treatment of facial areas. In

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**Table 1** Soft tissue fillers categorized by material

<b>Natural implants</b>
<b>Autologous materials</b>
<ul style="list-style-type: none"><li>• Fat transfer</li><li>• Fat autograft muscle injection</li><li>• Cultured human fibroblasts</li></ul>
<b>Cadaver-derived materials</b>
<ul style="list-style-type: none"><li>• Dermis and extracellular matrix</li><li>• Acellular allogeneic dermis</li><li>• Injectable microparticulate acellular allogeneic dermis</li><li>• Lyophilized human particulate fascia lata</li></ul>
<b>Collagen</b>
<ul style="list-style-type: none"><li>• Bovine-derived collagen</li><li>• Human-derived collagen from tissue culture</li></ul>
<b>Hyaluronic acid</b>
<ul style="list-style-type: none"><li>• Hyaluronic acid derived from rooster combs</li><li>• Nonanimal stabilized hyaluronic acid from bacterial fermentation</li><li>• Viscoelastic nonanimal hyaluronic acid derived from bacterial fermentation</li></ul>
<b>Synthetic or pseudo-synthetic implants</b>
<ul style="list-style-type: none"><li>• Silicone oil</li><li>• Expanded polytetrafluoroethylene</li><li>• Dual-porosity expanded polytetrafluoroethylene</li><li>• Polymethylmethacrylate microspheres in denatured bovine collagen</li><li>• Poly-L-lactic acid</li><li>• Synthetic calcium hydroxylapatite microspheres suspended in aqueous polysaccharide gel</li><li>• Alkyl-imide gel polymer</li></ul>

addition, earlier methods focused on injection techniques that treated the superficial levels of the skin. More recently, methods have progressed to injecting soft tissue fillers into deeper regions. Another important development in the science of soft tissue augmentation is the growing acknowledgment of the fundamental morphological changes in the aging face that cause the outward appearance of aging.

The culprit, generally implicated for the appearance of the aging face, is gravity. However, gravity is not the primary underlying cause of facial signs of aging. Rather, one of the primary causes of the aging face is the redistribution of fat (Donofrio 2000). The other causes of the aging face include environmental factors, dermal thinning, bone resorption (Vleggaar and Bauer 2004), and the loss of elasticity and collagen in the skin. Rhytids and wrinkles, caused by facial expressions, also contribute to the aging face. However, we now know that lines, caused by the underlying facial muscle contractions, respond best to botulinum toxin A, as opposed

to using soft tissue fillers to fill in the lines and creases. (Burgess 2005).

## The atrophy/hypertrophy model for aging

In the young face, superficial and deep fat is distributed evenly, creating a homogenous topographical appearance with smooth primary arcs and convexities. With intrinsic aging, the distribution of fat becomes altered. Fat atrophy and hypertrophy cause hills and valleys to develop, and produce demarcations between the cosmetic units. Fat atrophy begins to become clinically apparent in the temple and cheek and is followed by fat loss around the chin and mandibular areas. Features become concave, characterized by flat lips, sunken temple and cheek, scalloped mandible, and increased shadowing among the resulting hills and valleys. With aging, the most significant change in appearance is the sagging of excess skin caused by the conversion of primary arcs to straight lines. When evaluating the tendencies of facial skin vectors, the skin drapes inferiorly and diagonally from the temporal area towards the perioral region, thus creating a

**Table 2** Soft tissue fillers categorized by durability

<b>Temporary fillers</b>
<ul style="list-style-type: none"><li>• Fat transfer</li><li>• Fat autograft muscle injection</li><li>• Dermis and extracellular matrix</li><li>• Acellular allogeneic dermis</li><li>• Injectable microparticulate acellular allogeneic dermis</li><li>• Lyophilized human particulate fascia lata</li><li>• Bovine dermal collagen</li><li>• Bovine collagen cross-linked with glutaraldehyde</li><li>• Human-based collagen isolated from human fibroblast tissue cultures</li><li>• Human-based collagen cross-linked with glutaraldehyde</li><li>• Nonanimal stabilized hyaluronic acid derived from bacterial biofermentation process</li><li>• Viscoelastic nonanimal hyaluronic acid gel</li><li>• Viscoelastic acid gel from rooster combs</li><li>• Poly-L-lactic acid</li></ul>
<b>Semi-permanent fillers</b>
<ul style="list-style-type: none"><li>• Synthetic calcium hydroxylapatite microspheres suspended in polysaccharide gel</li><li>• Expanded polytetrafluoroethylene</li><li>• Dual-porosity expanded polytetrafluoroethylene</li><li>• Alkyl-imide gel polymer</li></ul>
<b>Permanent fillers</b>
<ul style="list-style-type: none"><li>• Silicone oil</li><li>• Polymethyl-methacrylate microspheres in denatured bovine collagen</li></ul>

central focus on the perioral and mandibular regions. Intrinsic aging is characterized by fat atrophy in the periorbital, forehead, buccal, temporal, and perioral areas. Fat atrophy results from the collective effects of decreased fat cell size, diminished fat cell function, impaired fat cell differentiation, and redistribution of fat cells. Fat hypertrophy occurs submentally, in the jowl, lateral nasolabial fold, lateral labiomental crease, and lateral malar areas. The accumulation of fat pulls the encumbered skin downward under the force of gravity. In contrast, the loss of fat leaves excessive skin in proportion to the diminished volume, causing the excess skin to sag (Alster et al 2004; Donofrio 2004).

Reversing the effects of fat atrophy/hypertrophy cannot be adequately accomplished through conservative techniques. A comprehensive approach that considers the entire face and all the underlying causes of aging is necessary. Volume must be restored in regions experiencing fat atrophy and excess fat must be removed from regions where fat has accumulated. Correcting the distribution of volume throughout the face can help restore homogenous topography, eliminate demarcations between cosmetic units, and restore the primary arcs (Donofrio 2004).

The atrophy/hypertrophy model for aging represents a shift from focusing on wrinkles and gravitational sagging to a more comprehensive approach that treats the aging face from “the inside out.” As stated earlier, acquiring the “ideal soft tissue filler” is hopeless, since preferences of patients and clinicians are not universal. However, the goal of soft tissue augmentation should involve a universal acknowledgment of the fundamental causes of the aging face. Products and treatment protocols can be tailored to the individual needs of the patient.

Chronological age is among a variety of factors that may influence the choice of soft tissue filler(s). In general, older patients are likely to require soft tissue fillers that primarily produce volume and correct the results of fat atrophy by recreating the foundation and underlying structure of the face. Younger patients are more likely to require soft tissue fillers that smooth surfaces, such as creases and folds. In younger patients, the typical goal of lip augmentation is to make lips appear bigger and fuller, whereas in older patients the goal is to restore volume to lips that has been lost through fat atrophy.

Ethnicity is another significant determinant used to match soft tissue fillers with the specific needs of the patient. Based on the particular ethnic skin-type, some soft tissue fillers will achieve better results than others will. For example, volumizers are generally more effective in ethnic skin, due

to the presence of sagging skin. Histologically, there is less thinning of collagen bundles and elastic tissue in this skin-type. The treatment of ethnic skin does not involve correcting the typical photodamage that occurs in Caucasian skin, such as creases and surface lines.

For soft tissue augmentation, a variety of products exists, and new products are continually entering the market. These soft tissue fillers provide correction by two basic mechanisms: (1) the filler material occupies a void space, or (2) the filler material stimulates processes that produce volume. An overview of historical developments in the science of soft tissue augmentation is presented here, including a discussion of current products, patient selection, and injection techniques.

## Soft tissue fillers

### Early emergence of fillers (fat, paraffin)

Groundbreaking work in the science of soft tissue fillers began in the late 1800s after Neuber reported using blocks of free fat, harvested from the arms to reconstruct depressed facial defects. Only a few years later, Gersuny became the first to use the injection technique for cosmetic correction; the injected substance was paraffin. In 1911, injection of autologous fat into the subcutaneous space was reported by Bruning. However, advances in the use of autologous fat were tempered by the limited efficacy of fat injection, since transplants lost 50% of their volume after only one year (Klein and Elson 2000). This drove researchers to continue pursuit of more ideal fillers.

Today, autologous fat transfer remains a popular procedure because there is no risk of rejection and no cost for materials. Recent advances in fat transfer include suspending the autologous fat in the patient's plasma, which increases the longevity of the procedure. Autologous fat is injected into subcutaneous fat layer and/or muscle. Overcorrection and repeated treatment sessions are often necessary. The treatment lasts from several months to several years, depending on technique and transplant preparation (Burgess 2005).

### Emergence of collagen and hyaluronic acid

Collagen is a fibrous protein found in both humans and animals. In soft tissue augmentation, collagen preparations are used to fill in voids. Development of bovine collagen for soft tissue augmentation began in the 1950s with the work of Gross and Kirk, who were the first to successfully prepare a

bovine collagen gel. However, in the 1960s, the use of bovine collagen received a significant boost from the development of a process that reduced the antigenicity by removing the nonhelical amino and carboxy terminal telopeptides. This led the way to the development of a clinically useful preparation of bovine collagen. In 1981, Zyderm® I Collagen Implant (INAMED Aesthetics, CA, USA) received approval from the Food and Drug Administration (FDA) and quickly became a popular filler for soft tissue augmentation (Klein and Elson 2000). Preparations are available with either low or high concentrations of cross-linking. These fillers are injected intradermally into the superficial papillary dermis of the nasolabial folds (Klein 1989). They usually require overcorrection due to resorption of water from the preparation, which occurs within 24 h (Cheng et al 2002).

Further developments led to a more durable bovine collagen filler that retains its integrity and inherent water content to a greater degree because of cross-linking with glutaraldehyde. Cross-linking strengthens the collagen and makes it more resistant to proteolytic degradation (Elson 1999). Bovine collagen cross-linked glutaraldehyde is injected into the mid-reticular or deep reticular dermis at the dermal subcutaneous interface (Cheng et al 2002). Unlike collagen fillers with low concentrations of cross-linking, Zyplast does not require overcorrection.

Human-based collagen is available in two forms: (1) isolated from human fibroblasts cell cultures, and (2) cross-linked with glutaraldehyde. CosmoDerm® (INAMED Aesthetics, CA, USA) is an example of highly purified human-based collagen, available in two different concentrations. CosmoPlast® (INAMED Aesthetics, CA, USA) is an example of human-based collagen cross-linked with glutaraldehyde. Both human collagens are FDA-approved for rhytids and scars. CosmoDerm is used more superficially (Bisaccia and Scarborough 1992), whereas CosmoPlast is reserved for deeper lines and is used off-label for the lips. Corrections using collagen-based fillers last from several weeks to several months (Glogau et al 2004).

Hyaluronic acid is a naturally occurring polysaccharide, a glycosaminoglycan that is a component of the "ground substance" or extracellular matrix of the dermis (Lupton and Alster 2000). Hyaluronic acid provides volume to the skin, shape to the eyes, and is chemically identical across all species and all tissue types (Larsen et al 1993). It has natural hydrating functions that form the basis of its role in soft tissue augmentation (Lupton and Alster 2000). Fillers containing hyaluronic acid are true fillers, in which the mechanism of

augmentation is simply to fill space. There are two sources of hyaluronic acid used for soft tissue augmentation: (1) nonanimal stabilized hyaluronic acid (NASHA) produced from a bacterial biofermentation process (eg, Restylane®, Medicis Aesthetics, AZ, USA; and Juvederm®, INAMED Aesthetics, CA, USA), and (2) animal-derived hyaluronic acid purified from rooster combs (eg, Hylaform®, INAMED Aesthetics, CA, USA) (Burgess 2005). Hyaluronic acid is readily broken down in the dermis and eliminated via the lymphatics and the liver (Klein and Elson 2000). However, cross-linking with ester and ether linkages stabilizes the molecule for greater durability in dermal processes (Burgess 2005).

Bacterial-derived hyaluronic acid is available in different concentrations. Depending on the concentration, it can be injected into either the (1) reticular dermis and/or subcutaneous-dermal plane, or (2) papillary dermis. Various injection techniques apply and should not be overcorrected (Lowe et al 2001).

Viscoelastic hyaluronic acid is also available. Viscoelastic nonanimal hyaluronic acid gel (eg, Juvederm) is available in three different concentrations. It is intended for injection, based on concentration, into either: (1) the superficial dermis, (2) the mid dermis, or (3) the mid to deep dermis. Hyaluronic acid derived from rooster combs (eg, Hylaform) is available in a 5.5 mg/ml concentration with a particle size of 500 µm, and 20% cross-linking as a result of glutaraldehyde and vinyl sulfone stabilization (Burgess 2005). Hylaform is indicated for injection into the mid-to-deep dermis. It can be used in younger patients for shaping and volumizing in addition to restoring lost lip structure in older patients. All hyaluronic acid fillers can be used in the body of the lips to reshape or enlarge the lips. However, collagen fillers are reserved for use in the vermilion border. Fillers containing hyaluronic acid are generally considered to last twice as long as fillers containing collagen. Both collagen and hyaluronic acid are indicated for the treatment of more superficial corrections, such as smoothing surfaces, as opposed to fillers used in deeper regions to create more supportive structure and foundation. Theoretically, hyaluronic acid can be used to volumize. However, this application is considered cost-prohibitive.

## Recent developments in soft tissue fillers

Poly-L-lactic acid (PLA) (Sculptra®, Sanofi-Aventis, NJ, USA) is a biodegradable bioabsorbable synthetic polymer that has

been used for several decades in resorbable medical devices, such as sutures, surgical sealant meshes, screws, plates, and membranes for guided tissue regeneration (Vleggaar and Bauer 2004; Burgess and Quiroga 2005). In soft tissue augmentation, PLA is used exclusively to produce volume in areas of “sinking and sagging” skin. It is not intended for the focused treatment of specific wrinkles, as is the case with most traditional soft tissue fillers. Rather, PLA is intended for the treatment of areas requiring contouring or sculpting. Although other volumizers can be used to treat facial areas, this can be quite costly. In many patients, PLA can also be used in combination with other soft tissue fillers for a variety of applications in soft tissue augmentation.

Poly-L-lactic acid was recently approved in the US for the treatment of facial lipoatrophy in patients with human immunodeficiency virus (HIV). Moreover, it has been used since 1999 in more than 30 other countries to treat a variety of facial volume and contour deficiencies (Vleggaar and Bauer 2004).

Facial lipoatrophy occurs in healthy adults from the natural course of aging. Facial lipoatrophy may also occur as a result of surgical procedures to cause extensive weight loss. It can also be manifested by specific disease states, either inherited or acquired, in which lipodystrophy results in metabolic disturbances that lead to abnormalities in adipose tissue. In addition to disease states, facial lipoatrophy also results from the treatment of certain diseases, such as the use of anti-retroviral therapy to treat HIV. In particular, facial lipoatrophy has been associated to a large degree with the use of protease inhibitors, and to a lesser degree with the use of nucleoside reverse transcriptase inhibitors, as part of highly active anti-retroviral therapy for treatment of HIV (Ascher et al 2006). Facial lipoatrophy has been treated using silicone oil, bovine collagen, particulate human fascia lata, and autologous fat. (James et al 2002). Safety and efficacy of PLA for treatment of facial lipoatrophy has been demonstrated in several studies with immunocompromised patients (Valantin et al 2003; Moyle et al 2004; Onesti et al 2004; Mest 2005).

For example, Burgess and Quiroga (2005) used PLA to treat lipoatrophy in 61 HIV-infected patients over a 5-month period. The amount of PLA varied from 1–4 vials, depending on the degree of lipoatrophy severity and areas of involvement. The number of treatment sessions also varied. Mild cases required 1–2 treatment sessions; moderate cases, approximately 4 treatment sessions; and severe lipoatrophy required 4 or more treatment sessions. The amount of PLA

was gradually decreased over subsequent sessions. All patients experienced significant clinical improvement, defined as smoothing of the skin with decreased concavities or depressions, and improved overall appearance. The effect was long lasting, remaining for up to 30 months in patients, depending on initiation of treatment and length of follow-up (Burgess and Quiroga 2005). At the time of writing, there have been no reported adverse events. In addition to treating HIV-infected patients, significant experience has also accumulated in the treatment of immunocompetent patients for cosmetic reasons (Vleggaar and Bauer 2004).

Poly-L-lactic acid is distinct from other soft tissue fillers, due to its mechanism of action, treatment plan, preparation of injection material, and injection technique (Burgess and Lowe 2006). The application of PLA in soft tissue augmentation exploits a mechanism of action not seen in any other soft tissue filler. Although the injection of PLA causes an immediate effect by physically occupying space, this initial response is temporary and only lasts one week or less (Mest 2005). Once the carrier solution is absorbed, a delayed but progressive volumizing effect begins. The process of hydration, loss of cohesion and molecular weight, and solubilization and phagocytosis of PLA by the host’s macrophages, slowly degrades PLA into lactic acid microspheres and eliminates CO<sub>2</sub> by way of respiratory excretion. Crystals are left behind to stimulate collagen and a granulomatous reaction. This inflammatory reaction elicits resorption and the formation of fibrous connective tissue about the foreign body, causing dermal fibroplasia that leads to the desired cosmetic effect (Burgess and Quiroga 2004).

Poly-L-lactic acid is injected into deeper regions for creating supportive structure and foundation. In addition, it can be used to build up the maxillary fat pads. Poly-L-lactic acid cannot be injected into the lips. Effects of volume restoration can persist for as long as 18–24 months, but are not permanent (Burgess and Quiroga 2005; Mest 2005).

Beljaards and colleagues (2005) has reported the late onset of granulomatous skin reactions in three immunocompetent patients receiving PLA treatment. The report underscores necessity for dermatologists to recognize and acknowledge the distinct differences between PLA and other soft tissue fillers. The characteristics that distinguish PLA from traditional fillers are: (1) the mechanism of action, (2) the treatment plan, (3) the preparation of the injection material, and (4) the injection technique (Burgess and Lowe 2006).

Poly-L-lactic acid causes a gradual volume restoration that may take 3–6 months to develop. In addition, the rate of



dermal thickening increases from the first to last injection. Since immediate correction is not the primary goal, as is the case in most traditional fillers, the use of PLA requires a markedly different approach and treatment plan. Physicians should treat, wait, assess, and then decide how to proceed. Unlike other cosmetic injectables, PLA requires reconstitution before use. Although manufacturers recommend diluting in 3–5 mL of sterile water, 5–7 mL of sterile water is the customary reconstitution volume in the US. What is most critical for successful outcomes is that physicians receive sufficient training before attempting to inject PLA. This training should include distinctions in injection technique. For example, as opposed to treating a specific line, the strategy of PLA treatment is to return volume to a facial area. In addition, PLA is injected into the dermal–subcutaneous plane, unlike collagen or hyaluronic acids. Finally, it is important that PLA injection be accompanied by massage of the treatment area and continued by the patient post-treatment (Werschler 2005).

At the Center for Dermatology and Dermatologic Surgery (Washington D.C., US), PLA has been successfully used to treat lipoatrophy of the hands, feet, face, and buttocks in both immunocompetent and immunocompromised patients. In addition, PLA has been used effectively in both the younger and older patient. However, in the older or aging patient, the thickness of the dermis plane is diminished, leading to a greater likelihood for bruising that results from increased fragility of blood vessels. In these patients, it is recommended that clinicians allow 8 weeks between treatment sessions, as opposed to the regular 4–6 week waiting period. For clinicians, the learning curve is longer in these patients, due to the concerns associated with treating patients with a thin dermis plane (Burgess 2006).

## Conclusion

The growing marketplace of available soft tissue fillers is a testament to the necessity for individualized treatment to suit the individual desires of the patient and clinician. The fact that fillers provide augmentation through a variety of divergent mechanisms of action is also reflective of the great challenges of developing an effective filler. The attributes and use of one particular filler are not exclusive to the use of another filler. However, not all fillers are appropriate for various indications and successful treatment depends on tailoring appropriate fillers to the desired outcome. For example, PLA cannot be injected into the lips, whereas collagen and hyaluronic acid are well suited for injection into

the lips. To accommodate the patient's individual needs, soft tissue fillers can be used either individually or combined, depending on treatment goals.

Soft tissue fillers may be more effective when used within a comprehensive strategy that addresses the underlying morphological causes that produce facial signs of aging. Although the aging face is a result of a number of processes, the primary cause of the aging face is the redistribution of fat and facial muscular activity. Fat atrophy and fat hypertrophy cause the development of hills and valleys, demarcation of cosmetic units, and disruptions of the primary arcs in the face. Therefore, strategies to restore the youthful appearance of the face should address these changes in a comprehensive manner. This represents a significant shift from merely treating lines to treating entire areas of the face. This can be accomplished by using volumizers that are interjected more deeply, alone, or in combination with products that are injected more superficially. However, as the marketplace of soft tissue fillers continues to grow, techniques become more divergent, and therefore, requirements for adequate training on specific products becomes increasingly crucial.

The potential of soft tissue augmentation continues to grow in step with increasing demand. Today, new clinical applications are gaining interest, such as the use of soft tissue fillers in the treatment of nonfacial areas. Moreover, an increasing number of clinical trials are underway to assess the effectiveness of these new clinical applications. For the dermatologist and cosmetic surgeon, this represents an exciting, but challenging era.

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