

Soft Tissue Augmentation: A Review

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The demand for soft tissue augmentation is rising along with the growing popularity of noninvasive facial rejuvenation. There is a wide range of facial fillers available in the United States from which to choose, including nonpermanent, semipermanent, and permanent dermal fillers. This review provides a general overview of soft tissue augmentation, evaluates various fillers, and discusses the evidence behind their efficacy to provide the cosmetic practitioner a better understanding of how to use fillers.

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Chronologic aging is marked by a gradual decline in the subcutaneous volume of the face. Clinically, skin aging in the face is characterized by an increase in both resting and dynamic rhytides as well as alterations in facial vasculature and pigmentation. Histologically, aging can result in thinning of the epidermis, dermal atrophy, loss of dermal elastic tissue and collagen, and an increase in solar elastosis.¹ From a cosmetic standpoint, multiple treatment options exist, including topical skin care products (ie, retinoids, chemical peels), energy-based devices (ie, lasers, light sources, radiofrequency devices), toxins, and fillers.

Over the last several years, there has been a dramatic increase in the demand for soft tissue augmentation using fillers for skin rejuvenation. The number of products available to dermatologists and plastic surgeons for soft tissue augmentation and cosmetic enhancement also has dramatically grown. According to the American Society for Aesthetic Plastic Surgery, approximately 1.7 million facial

filler procedures were performed in the United States in 2009, and in 2010, there was an additional 3% increase.² It is projected that this number will increase over the next several years as patients continue to seek cosmetic improvement without undergoing invasive procedures. The popularity of soft tissue augmentation with fillers has made it one of the most common cosmetic procedures performed in the United States, second only to botulinum toxin type A injections to treat facial lines and wrinkles.² Despite their higher safety profile compared to invasive procedures, all fillers are associated with general risks for pain, bruising, swelling, necrosis, and potential secondary infection. This review highlights the various fillers currently approved by the US Food and Drug Administration (FDA) for use in the rejuvenation process and will discuss their biochemical properties and safety profiles.

There are several different classifications for fillers. In this review, we have separated fillers into the following categories: nonpermanent, semipermanent, and permanent.³ In Europe, there are more than 30 different dermal fillers available for use. In the United States, however, the FDA has only approved a handful of products, including hyaluronic acid (HA) fillers such as Restylane and Perlane (Medicis Aesthetics, Inc) for mid to deep dermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds; Juvéderm Ultra and Juvéderm Ultra Plus (Allergan, Inc) as well as Hydrelle (Anika Therapeutics, Inc) for injection into the mid to deep dermis for correction of moderate to severe

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facial wrinkles and folds, such as nasolabial folds; Prevelle Silk (Mentor Corporation) for moderate to severe facial lines, folds, and wrinkles; and Belotero Balance (Merz Aesthetics, Inc) for moderate to severe facial wrinkles and folds. Semipermanent fillers include poly-L-lactic acid (PLLA)(Sculptra Aesthetic, sanofi-aventis US LLC) for shallow to deep nasolabial fold contour deficiencies and other facial wrinkles and calcium hydroxylapatite (CaHA)(Radiesse, Merz Aesthetics, Inc) for moderate to severe facial wrinkles and folds, such as nasolabial folds. The FDA has approved only 1 permanent filler (Artefill, Suneva Medical, Inc) for the correction of nasolabial folds. This article reviews these FDA-approved fillers with a particular focus on their biochemical and physical properties.

NONPERMANENT FILLERS

The most popular and frequently used fillers in the United States are HA fillers. Hyaluronic acid is a glycosaminoglycan composed of regular, repeating, non-sulfated disaccharide units of glucuronic acid and *N*-acetylglucosamine.⁴ It is a naturally occurring biopolymer, an essential component of the extracellular matrix and connective tissue of all animal tissues, which exhibits no species or tissue specificity. In effect, this property negates any potential immunologic reaction or transplantation rejection and allows for HA treatment without the requirement of any prior skin testing, which had been a standard requirement for collagen injections; however, there have been reports of hypersensitivity reactions with incidence rates ranging from 0.0005% to 0.42%.^{5,6} Friedman et al⁷ reported local hypersensitivity reactions in approximately 1 in every 1400 patients treated, with an incidence rate of 0.07%. Lowe et al⁸ reported granulomatous reactions occurring at a rate of 0.4%, and Brody⁹ reported hypersensitivity reactions in 1 in every 690 injections over a period of 9 months, with an incidence rate of 0.14%. Although most reactions are self-limiting and resolve within 2 to 4 months, some studies have reported prolonged hypersensitivity reactions lasting as long as 11 months.¹⁰ In 2004, Klein¹¹ hypothesized that hypersensitivity cannot be due to HA given its ubiquitous nature among species but rather a response to other protein contaminants. Indeed, a lower incidence of hypersensitivity reactions has been noted with the introduction of more purified, low protein load HA products in the United States over the last several years.

Hyaluronic acid is highly hydrophilic, which enables it to attract water and occupy a large volume relative to its mass. When combined with water, the HA complex develops a swelling pressure, or turgor, that enables it to withstand compressive forces. Hyaluronic acid fillers are not permanent, and although patients may find the temporary

nature of HA fillers to be less than ideal, it must be noted that undesired treatment outcomes also are temporary. Furthermore, if an unexpected reaction or undesired outcome occurs, correction is possible with injections of hyaluronidase, a commercially available enzyme that degrades the unwanted hyaluronic acid dermal filler. It should be noted, however, that the use of hyaluronidase for this purpose is not FDA approved and is considered an off-label use. Nonetheless, the advantages of HA over competing dermal fillers have, in essence, contributed to the rising popularity of HA fillers.

The first injectable HA filler was described in 1989.¹² Since then, several newer HA fillers have been developed, each with variations in characteristics including the source of HA, its concentration, particulate size, gel hardness (or G'), cohesivity, degree of cross-linking, and recently the addition of lidocaine (Table). Hyaluronic acid fillers can be grouped based on their sources of derivation. Newer HA fillers such as Restylane and Perlane, Juvéderm Ultra and Juvéderm Ultra Plus, Hydrelle, Prevelle Silk, and Belotero Balance are derived from *Streptococcus equi*. Another source of HA is avian (rooster combs), which currently is on the market as Hylaform (Genzyme Corporation) for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Most of the newer HA fillers either contain higher concentrations of HA and various degrees of cross-linking or are formulated as monophasic gels in an attempt to stabilize the molecule even further. In general, concentrations greater than 20 mg/mL are considered ideal for HA fillers. Cross-linking using agents such as 1,4-butanediol diglycidyl ether (BDDE) and 1,2,7,8-diepoxyoctane is an important property of HA fillers, allowing for greater resistance to degradation, increased stability, and in turn longer duration. The degree of cross-linking directly affects the gel hardness, or G' (pronounced "G prime"), of a product. G' is obtained when a gel is placed between 2 plates and a lateral force is applied. The measurement of resistance to deformation is G' . G' values are directly proportional to the cohesivity of a product and may be used to determine the appropriate placement of an HA dermal filler. Products with higher G' values and higher cohesivities should be used for deeper corrections, such as nasolabial folds and marionette lines, while products with low G' values should be used in more shallow areas that require a softer agent, such as the body of the lip and/or the tear trough.¹³

Hyaluronic acid fillers also can be classified as monophasic or biphasic. Monophasic HA fillers are manufactured as cohesive gels, while biphasic HA fillers are manufactured in particle form. Some argue that the benefit of monophasic HA fillers is the ability of the products to

Biochemical Properties of HA Dermal Fillers

| Nonpermanent HA Fillers | Source | Total HA Concentration | Cross-linking, % (Cross-linker) | Average Particle Size | G' Modulus, Pa | Average Duration of Effects |
|---|--------|------------------------|--------------------------------------|---|---------------------------------|-----------------------------|
| Restylane/Perlane | NASHA | 20 mg/mL | 1% (BDDE) | Restylane: 400 μ m; Perlane: 650 μ m | Restylane: 660; Perlane: 588 | 6–9 mo |
| Juvéderm Ultra/ Juvéderm Ultra Plus | NASHA | 24 mg/mL | Ultra: 9%; Ultra Plus: 11% (BDDE) | Ultra: N/A; Ultra Plus: N/A | Ultra: 170; Ultra Plus: 200 | 6–12 mo |
| Hydrelle | NASHA | 28 mg/mL | N/A (BCDI) | 200 μ m | 329 | 3–6 mo |
| Prevelle Silk | NASHA | 4.5–6.0 mg/mL | 20% (DVS) | 500 μ m | 230–260 | 3–4 mo |

Abbreviations: HA, hyaluronic acid; NASHA, nonanimal stabilized hyaluronic acid; BDDE, 1,4-butanediol diglycidyl ether; N/A, data not available; BCDI, *p*-phenylene bisethyl carbodiimide; DVS, divinyl sulfone.

last longer and not migrate, while the benefit of biphasic HA fillers is the manufacturers' ability to customize particle size per indication and anatomic area being treated.¹⁰ With these properties, most HA fillers last approximately 6 to 9 months.

Restylane/Perlane

In 2003, Restylane became the first FDA-approved filler in the United States. It is classified as a nonanimal stabilized HA that is derived from *S equi*. Restylane has a concentration of 20 mg/mL and a particulate size of 100,000 gel particles/mL. These particles are approximately 400 μ m, with 1% cross-linking using BDDE.

In a 2003 clinical trial, Narins et al¹⁴ compared Restylane injection in one nasolabial fold to Zyplast (Allergan, Inc), the standard collagen injectable material at the time, in the other nasolabial fold. The study showed that the volume of Restylane needed for optimal correction was significantly less than the required volume of Zyplast ($P < .0001$). According to both the wrinkle severity rating scale and the global aesthetic improvement scale, Restylane was rated superior by patients and treating physicians to Zyplast at all time points. The most common adverse events (AEs) in this study were mild to moderate injection site reactions, including pain, bruising,

and swelling, but no hypersensitivity reactions were reported.¹⁴ In addition, if Restylane is injected too superficially, the HA is visible through the translucent epidermis, creating a bluish Tyndall effect.¹⁵ Fortunately, these bluish cysts are easily corrected by nicking the skin with a small-gauge needle (ie, 30 gauge) or #11 blade to express the unwanted superficial dermal filler. Other rare complications such as skin necrosis have been reported following treatment with fillers including Restylane, which can be attributed to injection technique, anatomic location, and/or volume used.¹⁰

Restylane injections typically provide correction for 6 to 9 months; however, with repeat injection at 4.5 months, studies have shown that patients can maintain correction for up to 18 months.¹⁶ Restylane also can be safely used in patients with darker skin types (ie, Fitzpatrick skin types IV–VI) without any additional AEs.¹⁷ In addition to injection in the nasolabial folds, Restylane also has been used to treat marionette lines, tear troughs, and glabellar frown lines, as well as to enhance/augment lips and cheeks and correct the jowls and nasal deformities; however, with the exception of the nasolabial folds and lips, these injection sites currently are considered off label. In 2010, Restylane-L became available, which contains 0.3% lidocaine to reduce pain on injection.

In 2007, the FDA approved another HA dermal filler known as Perlane. Perlane is identical to Restylane, with an HA concentration of 20 mg/mL, but it contains larger gel particles (650 μm) and has a particulate size of 8000 gel particles/mL. Perlane is indicated for deeper injections and clinical defects, such as the correction of deeper nasolabial folds and enhancement of the cheeks and lips.¹⁰ In 2010, the FDA approved Perlane-L, which contains 0.3% lidocaine.

Juvéderm Ultra/Juvéderm Ultra Plus

In 2006, Juvéderm became the second type of non-animal stabilized HA filler approved by the FDA. Currently, there are 4 Juvéderm formulations available in the United States: Juvéderm Ultra and Juvéderm Ultra Plus as well as Juvéderm Ultra XC and Juvéderm Ultra Plus XC; the latter two are identical to the former two but contain 0.3% lidocaine to reduce pain on injection. Similar to Restylane, the Juvéderm family also is produced from the bacterial fermentation of *S equi*. Both Juvéderm Ultra and Juvéderm Ultra Plus are homologous gels that contain 24 mg/mL of HA, but Juvéderm Ultra Plus has a higher proportion of cross-linking than Juvéderm Ultra. The HA is cross-linked with a patented, single-phase, BDDE phosphate buffered to a pH of 6.5 to 7.3. Juvéderm Ultra has 9% cross-linking and Juvéderm Ultra Plus has 11% cross-linking. According to the manufacturer, the higher concentration of HA in Juvéderm and the greater percentage of cross-linking compared to other HA fillers is thought to contribute to a smoother injection flow as well as longer duration of correction.¹⁸

In a 2007 clinical trial by Baumann et al,¹⁹ Juvéderm was compared to Zyplast in the treatment of nasolabial folds in more than 400 patients. Results demonstrated that injection with Juvéderm showed greater efficacy than Zyplast using a blinded 4-point scale. An improvement of at least 1 point was noted in more than 80% of Juvéderm-treated patients compared to a 0.5-point improvement on average in the Zyplast-treated side. Approximately 1 of 5 patients treated with Juvéderm demonstrated long-term correction at 12 months posttreatment. Adverse effects of Juvéderm and Zyplast were similar, consisting mainly of mild to moderate injection site reactions, including pain, bruising, and swelling, with no reports of hypersensitivity reactions.¹⁹ Similarities in AEs when comparing Juvéderm products and Restylane/Perlane have been reported.²⁰ Juvéderm products are indicated for treatment of moderate to severe facial wrinkles and folds, such as nasolabial folds. Treatment of other areas such as lips is considered off label.

Hydrelle

Originally called Eleveess (Anika Therapeutics), Hydrelle is one of the newest HA fillers and was approved by the FDA in 2008. Although it has been approved by the FDA, Hydrelle currently is not available in the United States; however, it is available in Europe as Eleveess. Among HA fillers, Hydrelle contains the highest HA concentration (28 mg/mL), along with 0.3% lidocaine. It is cross-linked with *p*-phenylene bisethyl carbodiimide, a novel HA cross-linker. Similar to Restylane and Juvéderm, Hydrelle also is derived from the fermentation of equine streptococci. Studies for Hydrelle currently are limited, but the manufacturer claims the duration of correction with Hydrelle is approximately 6 months.¹³

Prevelle Silk

In 2008, the FDA approved Prevelle Silk, the second generation of the earlier HA filler known as Captique (Genzyme Corporation), which was FDA approved in 2004 but is no longer available. Prevelle Silk combines the original Captique formulation with 0.3% lidocaine. The product contains an HA concentration of 4.5 to 6.0 mg/mL, is 20% cross-linked with divinyl sulfone, and has a gel particle size of 500 μm . It has similar indications as other HA fillers and its duration of correction is approximately 3 to 4 months.²¹

Belotero Balance

Recently approved in November 2011, Belotero Balance is a type of monophasic polydensified HA filler. Belotero Balance contains an HA concentration of 20 to 22.5 mg/mL. It is derived by biofermentation via equine streptococci and composed of double-phase, cross-linked HA using a patented cohesive polydensified matrix technology. The particle size and cross-linking percentage have not been reported. With Belotero Balance, zones of varying densities are created by the manufacturing process, theoretically promoting optimal tissue spread into areas where conventional HA fillers would not be able to fill.²²

Preliminary studies in the literature indicate comparable aesthetic results and safety profile of Belotero Balance compared to Restylane.^{23,24} Long-term efficacy and safety remain to be seen with ongoing clinical use.

SEMIPERMANENT FILLERS

Radiesse

In 2006, the FDA approved Radiesse, a dermal filler composed of synthetic CaHA microsphere particles (30%) suspended in a carboxymethylcellulose-resorbable aqueous gel carrier (70%). The CaHA particle size is approximately 25 to 45 μm . Calcium hydroxylapatite

traditionally has been used to reconstruct bone. Because of the density of calcium, Radiesse occasionally is detectable on routine radiographic studies, but this property has not been shown to interfere with accurate interpretation of radiographic studies.²⁵

Radiesse has been approved for the treatment of moderate to severe facial wrinkles and folds as well as for the correction of facial wasting due to human immunodeficiency virus (HIV)-associated lipoatrophy.²⁶ In addition, the product recently has become the filler of choice for hand rejuvenation,²⁷ though this indication has not been FDA approved. Once injected into the dermal-subcutaneous junction, the CaHA particles act as a scaffold for autologous collagen synthesis. Clinical trials have demonstrated that the fibrotic reaction induced by Radiesse and the ensuing duration of correction can last up to 1 to 2 years.²⁶ Radiesse is safe in patients with skin of color and its effects are longer-lasting than HA fillers; however, injection of Radiesse into lips has been reported to cause granulomatous reactions²⁸ and therefore should not be administered in this area. Similar fibrotic reactions in other areas of the face have not been reported in the literature.

Sculptra Aesthetic

Sculptra Aesthetic received FDA approval in 2004, initially for treatment of HIV-associated lipoatrophy. In 2009, the FDA approved the product for use in the aesthetic treatment of lines and contour deficiencies. The PLLA particles in Sculptra Aesthetic are biodegradable, biocompatible, and immunologically inert, and do not require skin testing. They also compose the absorbable suture material in Vicryl (polyglactin 910)(Ethicon Inc, a Johnson & Johnson Company).

Sculptra Aesthetic comes packaged as a freeze-dried powder and must be reconstituted several hours prior to injection to ensure adequate hydration of the particles. Often, lidocaine is added to reduce pain on injection. Once in the skin, Sculptra Aesthetic is slowly absorbed and promotes a fibroblastic response with *de novo* collagen synthesis. In some cases, several treatment sessions at 4- to 6-week intervals are required to achieve the final result. In preliminary studies, reported side effects of Sculptra Aesthetic included the delayed appearance of small, palpable but not visible, subcutaneous nodules in the treated area.¹⁰ To reduce this unwanted effect, newer techniques suggest a greater dilution of Sculptra Aesthetic, typically 150 mg into 4 to 6 mL of bacteriostatic saline or sterile water and 1 mL of 1% to 2% lidocaine with epinephrine. Some investigators even recommend larger dilutions for areas such as the neck or hands. Regardless of the dilution, most users recommend reconstitution 12 to 24 hours prior to injection.

The areas most frequently and successfully treated with Sculptra Aesthetic include the cheeks; nasolabial and prejowl folds; and the malar, infraorbital, and temporal areas. Similar to Radiesse, injection into the lips should be avoided. Two injection techniques have been widely used with PLLA, which are known as threading/tunneling and depot. The threading or tunneling technique typically is used for the midface and lower face (preauricular and malar regions) using a cross-hatching-type pattern. Injection of PLLA is most commonly administered subdermally in a retrograde fashion, just past the deep dermis and into the junction of the upper subcutaneous layer. Another technique typically employed in the midface is the additional placement of PLLA in the supraperiosteal plane.²⁹ The depot technique is recommended for areas such as the temples and upper zygoma, with the product placed just above the periosteum. When injecting, it is important to use a reflux maneuver before depositing PLLA to ensure that a blood vessel has not been entered. A safe addition is the use of the blunt cannula technique.

The efficacy of Sculptra Aesthetic as a dermal filler initially was studied in clinical trials and showed the product to substantially improve HIV-associated lipoatrophy.^{30,31} In a more recent trial, investigators compared the efficacy of Sculptra Aesthetic to human collagen for the correction of nasolabial folds based on investigator global evaluations.³² Results demonstrated that the investigator global evaluation scores were higher for PLLA treatment than for human collagen treatment at all time points. Furthermore, PLLA treatment continued to show a beneficial effect for up to 25 months after treatment.³²

PERMANENT FILLER

Artefill

Artefill was FDA approved in 2006 and is comprised of polymethylmethacrylate (PMMA) microspheres suspended in a rapidly dissolving bovine collagen carrier along with lidocaine and buffers. The PMMA microspheres in Artefill are 30 to 50 μm in size, too large to be removed by phagocytosis within the body; therefore, Artefill is not absorbed by the body and may provide permanent support for wrinkle correction and soft tissue augmentation.

Medical-grade PMMA has been used for decades in devices such as intraocular lenses and artificial joints. In dermatology, Artecoll, manufactured in Europe and Canada, was an early product that used this PMMA technology. With Artefill, several changes have occurred: (1) inspection and approval by the FDA, (2) refinement of the PMMA microspheres, and (3) manufacture of the bovine collagen at an approved facility in the United States.

The pivotal study that led to the FDA approval of Artefill compared Artefill to Zyderm and Zylast in the treatment of nasolabial folds.³³ A total of 251 participants were enrolled. Results demonstrated improvement in the nasolabial folds of patients treated with Artefill at 6 months posttreatment, while those treated with collagen had returned to baseline.³³ Furthermore, additional follow-up studies demonstrated continued and improved wrinkle correction at 1 year and up to 5 years posttreatment with minimal AEs.³⁴

The most common AEs associated with Artefill treatments are similar to those observed with other dermal fillers and include mild transient swelling and erythema at the treatment site. Occasionally, mild bruising is noted that typically disappears in 3 to 7 days.³⁵ Less common side effects include rash, itching, persistent swelling or redness, and increased sensitivity at injection sites. Formation of nodules and granulomas requiring surgical excision also have been reported with the PMMA fillers.³⁵ With Artefill, a skin test is required before initial treatment to ensure the patient is not sensitive to bovine collagen. Given the permanent nature of Artefill, its use should be limited to cosmetic practitioners with ample expertise in the injection of facial dermal fillers.

CONCLUSION

The popularity of noninvasive cosmetic procedures continues to grow steadily in the United States and is associated with a correlated increase in the demand for soft tissue augmentation with dermal fillers. Dermatologists and plastic surgeons need to better understand the differences between facial fillers to properly select the most appropriate fillers for their patients. Although the current selection of dermal fillers may appear to be vast, the horizon for continued development of new and more efficacious fillers is immense.

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Quick Poll Question

Do you prefer to use a combination of dermal fillers and botulinum toxin for lower facial rejuvenation?

- Yes
- No

Go to www.cosderm.com to answer our Quick Poll Question