

Soft-tissue augmentation devices: longevity of effects

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Abstract

The search for an ideal device or technique intended for soft-tissue augmentation has led to the development of a myriad of procedures and products. Currently, minimally invasive options can be sub-divided into those which offer temporary or permanent effects. The durability of results offered by these techniques and devices are presented here, focusing on products approved in the United States. Collagens and hyaluronic acid-based products offer effective results that are short term, generally providing a few months of augmentation. Fat replacement offers variable results and devices, such as polymethylmethacrylate, can give permanent correction. Long-lasting devices that are not permanent, such as calcium hydroxylapatite and poly-L-lactic acid, fill the gap between temporary and permanent devices, and can offer effective, durable correction.

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INTRODUCTION

Injectable fillers are frequently classified by their innate product characteristics and their immunogenic properties. These can be autogenic, allogenic, xenogenic or alloplastic.¹²³⁴⁵ However, these categories do not imply the length of time that the desired result is maintained for, or indicate the degree of intrusion (financial, physical and time) into patients' lives. It is, therefore, more useful to classify these devices according to their duration of effect or mode of operation. For example, 'fillers' passively correct lines and wrinkles in the skin with inert material, while 'volumizers' can be used to globally rejuvenate the face and restore contours, and often elicit endogenous production of dermal material, such as fibroblasts or collagen. Alternatively, devices can be categorized as temporary, permanent or long-lasting, according to their durability.

Product duration directly impacts on many of the advantages and disadvantages of any intervention. Temporary products,

such as collagen, are effective for several months and require regular repeated treatments to maintain results. The effects of collagen are relatively superficial and can provide incomplete correction to the treated regions in the face. However, the transient effects mean that adverse effects are also likely to be temporary and procedures can be repeated to accommodate the changes in facial shape that occur with time. Conversely, permanent products, such as polymethylmethacrylate (PMMA) suspension, can provide results that last for years. However, as PMMA is non-resorbable this permanence may not accommodate the changes associated with continued facial aging. In this article, injectable fillers, volumizers and devices for facial augmentation that are approved for use in the United States (US) are reviewed according to the longevity of effects.

TEMPORARY PRODUCTS AND SHORT-TERM EFFECTS

INJECTABLE COLLAGENS

Injectable collagens include those derived from bovine and human sources. Injectable bovine collagen was developed in the 1970s and Zyderm® products (Allergan, Inc Irvine, CA, USA) received marketing clearance from the US Food and Drug Administration (FDA) in 1981. Zyderm I® and II® are purified suspensions of collagen fibrils derived from chemically processed bovine skin.⁶⁷ Zyderm I is used to correct fine lines and results last for approximately 3 months, depending on the condition of the treated skin and type of correction. Zyderm II is recommended for slightly

more pronounced lines and offers an average duration of 6–12 months.⁷ Zyplast® (Allergan, Inc. Irvine, CA, USA) is derived from the same material as Zyderm, which is then treated with glutaraldehyde to provide chemical crosslinks, resulting in a longer-lasting product.⁸ Zyplast is designed to correct deep wrinkles in thick skin and to fill lips. Generally, patients will require touch up injections after 6–18 months.⁸⁹

Due to the source of bovine collagen, patients are required to undergo two pre-treatment tests to determine sensitivity.⁶⁸ Indeed, bovine collagen generates an immune reaction in approximately 1–3% of skin-tested patients.^{68,10} Nevertheless, it has a good safety record and is one of the most widely used soft-tissue fillers.

Alternatives to bovine-derived collagen are products that use human collagen derived from the patient (autologous collagen), or from a donor or cadaver (isogenic collagen). Several different methods or procedures have been developed to produce/obtain human collagen for cosmetic injection. With the Isologen Process™ (Isologen, Inc., Santa Barbara, CA, USA), fibroblasts are taken from a 3 mm skin biopsy behind the ear.⁹¹¹ The tissue is triturated and placed in cell culture medium, where fibroblasts (and Type I collagen production) are allowed to develop for 4–6 weeks. Two weeks after successful allergy testing, the product can be injected and is used to correct wrinkles, scars and other skin defects. Boss et al (2000) reported that 92% of patients (n=94) receiving this treatment were satisfied with their results 1 year after treatment.¹¹ Some authors, however, report poor quality improvements compared with more conventional bovine collagen implants.⁹ CosmoDerm™ and CosmoPlast™ (Allergan, Inc., Irvine, CA, USA) consist of collagen (provided in ready-to-use sterile syringes) purified from a human fibroblast cell line and do not usually require a skin test.¹² Although they are more convenient for the patient, there is no evidence to suggest greater durability than other forms of collagen. Other products, such as Cymetra™ (LifeCell, Branchburg, NJ, USA), are cadaver-derived.¹³ Cymetra has been shown to persist longer than bovine collagen,⁵ though further studies are required to confirm these findings.

In general, there is little evidence to suggest that human-derived collagen products deliver consistent results beyond 12 months; longevity depends on skin quality, the nature of the lesions being treated and the age of the patient. However, because autologous fat can be transferred immediately or washed in a sterile buffer solution prior to reinjection into

the face, using autologous human collagen eliminates the potential for harmful virus or prion transmission, does not require pre-treatment skin testing, and has demonstrated a good safety profile for cosmetic use.^{59,14}

HYALURONIC ACID

Hyaluronic acid (HA) is a natural, viscoelastic polysaccharide that stabilizes the extracellular matrix of the dermis and maintains hydration.¹⁵ Hyaluronic acid-based products are derived from animal and non-animal sources, and can vary in longevity, depending on the extent of their crosslinking. Low-density products (e.g. Hylaform Fineline®; Genzyme Biosurgery, Cambridge, MA, USA) are designed to correct fine wrinkles, while medium-density products (e.g. Restylane®; Medicis Aesthetics Holdings, Inc., Scottsdale, Arizona, USA; and Hylaform®; Genzyme Biosurgery, Cambridge, MA, USA) are recommended for more pronounced lines and lip augmentation.⁹¹⁵ Higher density products, such as Perlane® (Medicis Aesthetics Holdings, Inc. Scottsdale, USA) and Juvederm 30® (Allergan, Inc., Irvine, CA, USA), are generally applied to deep folds and wrinkles.⁹¹⁵ Figure 1 shows an example of the correction of marionette lines achieved with Juvederm 30, 3 months post injection. This product is reported by the manufacturer to be effective (for the correction of nasolabial folds and oral commissures) for approximately 6 months.¹⁶

Figure 1

Figure 1. (a) Before and (b) after (3 months) photographs of marionette line correction with Juvederm 30



Figure 2



The patient underwent one treatment session with one vial of Juvederm 30 injected into each side of the face.

Low density HA products generally have a duration of 2–3 months.⁹¹⁵ Medium density HA products offer a longer duration of approximately 6 months, although, in a minority of patients they may be durable for up to 1 year, while high density products are generally durable for up to and beyond 1 year.⁹¹⁷¹⁸ A multicenter trial of Restylane (medium density HA product), involving 348 patients seeking correction of a variety of soft-tissue defects, showed that the level of correction fell by 20% between 3–6 months, and by another 20% from 6–10 months.¹⁹ This translated to good correction (60–70%) at 3 months, slight correction (40–50%) at 6 months and poor correction at 10 months.

During a study of Hylaform (HA derived from rooster combs; medium density product), 78% of 177 participants maintained a >33% level of initial correction at 3 months post injection. Moreover, 44% maintained this level of correction at 6 months, and 8% maintained correction at 12 months.²⁰ In comparison, a retrospective study of clinical data from a study of Juvederm 30, found that 39% of the 49 participants were satisfied with their cosmetic results 8–11 months after the first injection.²¹

Although, HA-derived products are generally well tolerated both during and following injection,¹⁷ the more viscous forms of HA can be associated with transient injection site reactions and nodule formation in certain cases.⁹²² Products derived from bacteria or avian sources may also be associated with hypersensitivity and a pre-treatment skin test may be advisable.²³

DURABILITY OF HYALURONIC ACID VERSUS COLLAGEN

A randomized, double-blind, multicenter study comparing HA (Restylane) with bovine collagen (Zyplast) for the correction of nasolabial folds, used a wrinkle severity rating

score to rate treatment efficacy.¹⁷ This was a five-point scale where 1=no fold/wrinkle and 5=extremely deep and long folds. At 6 months, the mean positive improvement from baseline was 0.93 for Restylane, compared with 0.63 for Zyplast ($p<0.0001$). However, in 29.9% and 67.2% of HA-treated and collagen-treated patients, respectively, nasolabial folds had returned to their pre-treatment condition by 6 months.¹⁷

PERMANENT FILLERS

LIQUID SILICONE

Liquid silicone was the first widely used permanent injectable product for facial augmentation, but has been associated with serious long-term complications. Specifically, granuloma formation and the migration of the injected material into remote organs, such as the spleen, brain and liver, have been reported post silicone treatment.²⁴²⁵²⁶ As a result, in 1992 the FDA issued guidelines to stop injecting liquid silicone into patients.

POLYMETHYLMETHACRYLATE

Artefill™ (Artes Medical, Inc., San Diego, CA, USA) was granted US FDA approval for aesthetic use in 2006. Artefill consists of PMMA microparticles (30–40 μm), suspended in bovine collagen, incorporating 0.3% lidocaine.²⁷²⁸ The collagen component of Artefill degrades over time, while the PMMA particles remain as a permanent implant that is eventually encapsulated by new collagen.²⁹ Artefill has a similar immunogenic profile to other non-human, collagen-based products and requires pre-treatment testing. Generally, injectable PMMA is well tolerated, although long-lasting itchiness and redness can occur with incorrect placement of the material (i.e. if injected into the shallow dermis).³⁰³¹ Post-injection palpable lumpiness at the injection site (lasting >1 month) has also been observed in some cases.³⁰³²

Despite the reported permanence of PMMA, patients should not expect a single procedure to last a lifetime, as wrinkles and folds are dynamic and change with age. A study by Lemperle et al (1998) reported new folds or deepening of pre-existing folds in one-fifth of implanted areas, suggesting that patients would require ‘touch-up’ injections.³³ Furthermore, since the junction between the dermis and subcutaneous fat allows a limited volume of material to be implanted (and most of the substance injected comprises collagen), 2–3 implantations (depending on the amount of correction required) separated by 4–6 weeks are generally necessary to achieve optimum results.²⁹³¹³⁴ Nevertheless, Lemperle et al (1998) reported that 290 patients had a high

degree of satisfaction with PMMA injections and 91% of patients experienced positive results that were maintained for at least 1–2 years.³³

LONG-LASTING (NON-PERMANENT) DEVICES

Permanent duration of effect may be undesirable, as initially pleasing results eventually deteriorate due to the dynamic changes that occur with age. Alternative long-lasting fillers are those that are durable for 12–24 months.⁷ Two injectable devices that can be considered non-invasive and non-permanent, but which offer medium- to long-term results are poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) (Table 1).

Figure 3

Table 1. Examples of product type and typical duration of correction

Product	Duration of correction	Mode of operation
Temporary products		
Low-density hyaluronic acid products (e.g. Hylaform Fineline®)	2–3 months	Direct tissue augmentation with material injected
Medium density hyaluronic acid products (e.g. Restylane®)	3–9 months	Direct tissue augmentation with material injected
High-density hyaluronic acid products (e.g. Perlane® and Juvederm®)	12 months	Direct tissue augmentation with material injected
Collagen products – 1 (e.g. CosmoPlast® and Zyplast®)	6–12 months	Direct tissue augmentation with material injected
Collagen products – 2 (e.g. CosmoDerm® and Zydem I® and II®)	3–12 months	Direct tissue augmentation with material injected
Semi-permanent products		
Calcium hydroxylapatite (Radiesse®)	~12 months	Stimulation of innate collagen
Poly-L-lactic acid (Sculptra®)	~2 years	Increase in dermal thickness
Permanent products		
Silicone	Permanent	Replacement with volume injected as well as encapsulation of material by growth of native connective tissue
Polymethylmethacrylate (Artefill®)	Permanent	Encapsulation of polymethylmethacrylate spheres by collagen

CALCIUM HYDROXYLAPATITE

Radiesse® (BioForm Inc., Franksville, WI, USA) is a biocompatible product that consists of CaHA microspheres suspended in a carboxymethylcellulose gel.⁷ In the US, Radiesse is FDA approved for the correction of HIV-related facial lipoatrophy, and the cosmetic restoration of moderate-to-severe folds or wrinkles. Initial volume with Radiesse is provided by the implant itself. However, as the vehicle gel is degraded, new collagen has been noted to form around the CaHA microspheres, thereby generating increased volume.³⁸

One trial of Radiesse in 64 patients seeking augmentation of wide-ranging facial defects concluded that aesthetic

correction was immediate and the procedure involved little downtime.³⁹ No skin test was required and patient satisfaction with results was high (with minimal side effects noted); correction in all patients persisted during a 6-month follow-up period. The most common complication was palpable, non-visible nodules reported in patients who underwent lip augmentation.^{39,40} A more recent open-label study of Radiesse in 100 subjects with HIV-related facial lipoatrophy, found global aesthetic improvements for up to 18 months in 91% of patients (as measured using the Global Aesthetic Improvement Scale¹⁷), with a 2.33 mm (48%) increase over baseline in skin thickness sustained at 12 months (18-month skin thickness data were not reported).³⁵

Injectable CaHA generally demonstrates a good safety profile, with only mild and short-term post-injection adverse events reported (edema, erythema, ecchymosis).^{35,40} Hematoma has been observed as a temporary adverse event post CaHA injection, although, it was thought to have resulted from blood vessel puncture rather than the product itself.⁴¹ The use of CaHA in lip augmentation/areas previously treated with injectable agents or under/around scar tissue may increase nodule formation and, as such, is generally not recommended. In some cases, spontaneously resolving transient lumpiness or firmness can also occur following CaHA injection.^{40,41,42}

POLY-L-LACTIC ACID

Injectable PLLA (Sculptra®; Dermik Laboratories, Bridgewater, NJ, USA) is US FDA-approved for the treatment of HIV-related facial lipoatrophy, and a cosmetic indication is currently under review by the US FDA. Sculptra consists of PLLA microparticles, sodium carboxymethylcellulose and non-pyrogenic mannitol. It is reconstituted at least 2 hours prior to injection with 3–5 mL sterilized water for injection (SWFI).^{43,44} Following injection, Sculptra is hypothesized to induce the production of fibroblasts leading to collagen production.^{45,46} Over time (6–24 months), Sculptra is degraded in the skin to carbon dioxide and water.^{45,46} Correct reconstitution and administration of Sculptra are paramount to ensure optimal outcomes with regard to safety and efficacy.^{43,44}

In clinical trials, Sculptra has been shown to be effective and well tolerated when used in patients with severe lipoatrophy.^{36,47} Studies in patients with HIV-related facial lipoatrophy have demonstrated significant increases in dermal thickness lasting up to 24 months.^{36,37} Indeed, during one study, the median total cutaneous thickness (TCT) increase from

baseline at Week 96 was 6.8 mm ($p < 0.001$), with 43% of patients also reporting a TCT > 10 mm at this timepoint.³⁶

The author has carried out more than 4000 injections with Sculptra (approximately 70% cosmetic cases and 30% HIV-related lipoatrophy cases). The patients undergoing cosmetic procedures sought to correct cheek and chin deficiencies, nasolabial folds and marionette lines, and required 1–5 treatment sessions. The patients with HIV-related lipoatrophy required 2–6 treatment sessions to correct cheek, orbitotemporal and chin concavities.⁴⁷ Quality of life questionnaires revealed that both patient populations were satisfied with their treatment outcome at 24 months; 96% of the HIV patients who reported lipoatrophy-related psychosocial effects, stated an improvement in their emotional outlook post-treatment.⁴⁸ An example of the correction achieved with Sculptra, in a patient with HIV-related lipoatrophy 18 months post injection is shown in Figure 2.

Figure 4

Figure 2. (a) Before and (b) after (18 months) photographs of showing the correction of human immunodeficiency virus-lipoatrophy treatment with Sculptra



Figure 5



The patient underwent five treatment sessions (separated by 4-week intervals), during which one vial of Sculptra was injected into each side of the face. Sculptra was reconstituted with 3 mL SWFI for the first three sessions, and 5 mL SWFI for the last two sessions.

The volume augmentation provided by Sculptra injection develops gradually and progressively in all patients. As such, patients generally require 2–3 treatment sessions in order to achieve optimal results. Volume restoration following treatment with Sculptra injection lasts approximately 2 years, although volume enhancement has been known to persist beyond 2 years in several patients.⁴⁸ Where appropriate, ‘touch-up’ corrections can be administered, as needed, to maintain volume restoration after this time interval.

With regard to safety, Sculptra may be associated with non-visible, non-symptomatic, palpable, subcutaneous papules or nodules at the injection site that generally resolve spontaneously.³⁶⁴⁹⁵⁰ However, these events have been attributed by practicing clinicians to incorrect injection technique or inappropriate placement of product.⁴³⁴⁶⁵¹⁵² With correct preparation and administration, post-injection massage and avoidance of over-correction, Sculptra generally demonstrates a good safety profile.⁴³⁴⁶⁵¹⁵²

AUTOLOGOUS FAT GRAFTS

Although fat transfer is an intuitively appealing means of augmenting soft tissue, since there is no risk of immunological reaction against fat taken from areas where the patient desires to appear slimmer, controversy surrounds the longevity of correction. The survival rates of autologous fat grafts have been reported to last several weeks to years.⁵³

A systematic review of the literature and histological studies suggests that longevity of correction after fat transfer principally depends on the transplanted tissue, along with the mobility and vascularity of the anatomic recipient site.⁵³ Interestingly, similar survival rates for aspirated fat were obtained, irrespective of whether or not local anesthesia was applied, and fat harvesting by liposuction did not result in greater adipose cell damage compared with fat harvesting by excision. Fat cells can survive long-term freezing at -20°C ; however, reinjected cell debris, such as microdroplets, are reabsorbed by the host tissue quicker than living cells.⁵³ Similarly, if fat cells are destroyed because too much tissue is injected, resulting in a response in which cells are phagocytosed, correction is relatively short lived.⁹ Excess re-implantation also tends to promote devascularisation at the injection site, which may lead to the development of small clusters of cystic fat necrosis.⁹ Otherwise, autologous fat transfers are generally well tolerated, although the additional procedure required to obtain the implant material can cause additional discomfort, including severe edema and bruising in certain cases.

Regenerative cell-based methods, such as those using pre-adipose stem cells, hold great potential in soft-tissue augmentation. Preclinical and preliminary clinical studies suggest that adipose-derived stem cells offer the possibility of use as an aesthetic filler, without some of the drawbacks of current technology.⁵⁴⁵⁵

DISCUSSION

Considerable numbers of injectable compounds and surgical procedures are available to the physician for cosmetic augmentation. With so many products available it is a challenge to match the appropriate product to the needs of the patient. Ideally, a product should have been proven to be well tolerated, effective, non-carcinogenic, non-teratogenic and non-migratory. Additional desirable product qualities include reproducibility of results and cost-effectiveness. At present HA and collagen products, botulinum toxin (Botox® ; Allergan, Inc., Irvine, CA, USA). Artefill and Radiesse are approved by the US FDA for treating wrinkles of varying severities (Botox is indicated for temporary improvements in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in patients). Additionally, Sculptra and Radiesse are approved for facial lipoatrophy in association with HIV, and a broader cosmetic approval for Sculptra is currently under review.

Short-term, temporary products can be used to accommodate

changes in facial dermal structures that occur with continued senescence, but their transient effects mean that patients may have to undergo the inconvenience and expense of many treatments. However, as effects are short-term, adverse events are likely to be temporary and procedures can be tailored relatively rapidly to accommodate changes in facial appearance. Conversely, surgical procedures and permanent implants provide long-lasting results, but at the risk of long-term complications and without the flexibility to tailor subsequent treatments to the changing face. Safe and effective procedures that offer longer-lasting, medium-term, rejuvenating results may, therefore, be optimal in certain cases and enable the physician to alter the appearance of the face as it ages, while minimizing the number of subsequent maintenance visits.

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