

REVIEW OF DERMAL FILLERS

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ABSTRACT

Age-related volume loss; increased skin laxity, fat loss, redistribution, diminished support from underlying muscle and bone result in the observable and sometimes profound changes seen in the aging face. Aging also is associated with functional changes in the skin, such as dermal atrophy with diminished fibroblastic activity, decreased collagen production and altered elastin. With the development of synthetic fillers, such as hyaluronans, calcium hydroxylapatite, poly-L-lactic acid, and silicone, it became possible to inject fillers specifically into different tissue layers. The emergence of fillers with superior lift capabilities, while still maintaining the desired position, opened the door to the concept of volumizing for achieving optimal aesthetic results in addition to more superficial filler placement. The past century has seen an explosion of development of new fillers and their global acceptance by a patient population that would rather look restored and younger without the trauma and downtime of surgery. Indeed, the introduction of non- or minimally invasive injectable procedures represents a significant shift in the approach to facial rejuvenation.

INTRODUCTION

The chronology of the development of soft tissue augmentation in the field of dermatology has followed a distinctly non-linear path. The remarkable arrival of literally dozens of injectable filler materials on the modern European, global and domestic scenes is, however, a direct reflection of the increasingly sophisticated understanding of the aesthetic challenges of the human face. What began with the introduction of collagen as a treatment for a line or wrinkle led to use of fillers for treatment of dynamic lines of facial expression, e.g. nasolabial folds, and most recently to the concept of volumizing the face. This progression of the conceptual understanding of treating the aging face has moved from the flat world – two-dimensional problems such as a static wrinkle – to incomplete solutions for the dynamic lines of movement – e.g. glabellar lines with filler. It is fascinating that the initial movement into three dimensional correction began with the dramatic improvement seen in lip volume with the

initial collagen fillers championed by Arnold W. Klein MD in the 1980s.¹

Dermal fillers, such as collagen (bovine, human, and purified porcine), hyaluronic acids (HAs), calcium hydroxylapatite (CaHA), and injectable medical devices such as poly-L-lactic acid (PLLA) microspheres, are commonly used for facial rejuvenation. Most dermal fillers are passive spacefilling agents; however, other more deeply implanted agents, such as CaHA and PLLA, are active products that are capable of increasing fibroblast activity, which is thought to stimulate neocollagenesis. All of these products have a place in facial rejuvenation, whether used solely or combined. Technique, knowledge, and expertise with fillers, proper patient assessment, and a well-formulated treatment plan with access to agents for superficial, moderate, and deep rhytides and volume restoration provide the necessary ingredients for optimal cosmesis.²

REQUISITES OF IDEAL FILLING AGENT

The ideal filling agent should be safe, effective, easily administered, stored at room temperature, and long-lasting. In terms of efficacy, a dermal filler or injectable medical device should reliably restore facial volume with reproducible results. A safe injectable is not allergenic, carcinogenic, or teratogenic, and will not migrate once injected. Ideally, the filler should be associated with few adverse effects and complications should be minimal.

Commonly used dermal fillers are:

FAT AS FILLING AGENT (1893)

The first attempts at soft tissue augmentation revolved around the surgical use of fat. Dr Neuber is recognized as the first to perform human fat auto-grafting. It was the first pre modern era filler.

COLLAGEN BASED DERMAL FILLERS

Bovine and human collagens are relatively light, nonviscous fillers and include Zyderm 1, Zyderm 2, Zyplast, CosmoDerm 1, CosmoDerm 2, and CosmoPlast. Zyderm 1 implant (35 mg/ mL of solubilized collagen) was approved by the US Food and Drug administration in 1981 and Zyderm 2 (65 mg/mL of solubilized collagen) was

approved in 1983. Zyderm 1, Zyderm 2, and Zyplast are purified, fibrillar suspensions of bovine collagen in a saline solution containing lidocaine. Skin testing is required. Zyderm 1 and Zyderm 2 are injected into the superficial papillary dermis using a 30- or 32-gauge needle for treatment of fine lines and wrinkles. These formulations of collagen are light, nonviscous, and flow easily. Zyplast, lightly cross-linked with glutaraldehyde, is a larger collagen implant that is less susceptible to degradation. Zyplast is injected using a 30-gauge needle into the middle and deep reticular dermis to correct deeper lines and wrinkles or for lip augmentation.

The human collagen dermal fillers CosmoDerm and CosmoPlast (2003) are non-immunogenic, which eliminates the need for skin testing. These products, also relatively light and nonviscous, flow easily. CosmoDerm is injected into the superficial papillary dermis using a 30- or 32-gauge needle for fine lines. CosmoPlast, cross-linked with glutaraldehyde, is injected into the middle or deep reticular dermis using a 30-gauge needle for deeper lines and wrinkles. Overcorrection is necessary with CosmoDerm, due to reabsorption of saline and lidocaine.^{1,2,3}

SILICONE

The term 'silicone' was initially coined by a British chemist to describe a family of polymers containing the element silicon. The liquid silicones used for medical purposes are long polymers of dimethylsiloxanes. Injectable silicones are colorless, odorless, tasteless clear fluids whose viscosity varies according to the degree of polymerization. Silikon 1000 (1997) is a silicone oil with a viscosity of 1000 centistokes. Many dermatologists use Silikon 1000 off label for the treatment of acne scars, HIV lipodystrophy, traumatic fat atrophy, rhinoplasty defects, and some facial aging where volume repair gives an effective result.¹

HA FILLERS

HA is the main polysaccharide in human extracellular matrix tissue. It acts as a scaffold for collagen and elastin to bind to. Because it binds to water, it augments and hydrates the skin. The skin loses HA as it

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ages, which leads to decreased movement and elasticity. HA, when used in commercial filler agents, consists of repeating polymer chains of the polysaccharide with interval cross-links of agents that bind the polymers together. At present the source of the HA used in commercial products is bacterial, leading to the designation of this class of fillers as NASHA™ (nonanimal-sourced hyaluronic acid gel) gel, which distinguishes them from the earlier bovine and human-sourced collagen products. The current FDA-approved HA-based dermal fillers include Hylaform, Juvéderm Ultra, and Juvéderm Ultra Plus (Allergan, Inc), and Restylane and Perlane (Two other HA fillers, Hylaform Plus and Captique are no longer available.

Restylane became the first HA to enter the US market with FDA approval on 12 December 2003. Restylane has an HA concentration of 20 mg/mL with extended longevity and no skin testing. Hylaform Plus approved on 13 October 2004, had 5.5 mg/mL, larger gel particle size, and 20% cross-linking. Hylaform (2006) had 5.5 mg/mL of HA and 20% cross-linking with divinyl sulfone. Juvéderm (2006) had 24 mg/mL of HA which is manufactured by Corneal laboratories. It is a homogeneous rather than particular form of HA gel and has become the leading product in the US market. It is soft, viscous and non beaded gel.^{1,2,7}

HA fillers as a class have become the most popular type of filler in the US market and, in one form or another, worldwide. They are reversible with hyaluronidase, which is an important safety consideration. They provide more immediate 'lift' than the collagens, last much longer, and require no allergy skin testing prior to treatment. They can be easily injected through a small-gauge needle, and they eliminate the problems of products that contain animal-derived protein. As a result they have virtually eliminated collagens from the market.^{1,2,3}

CALCIUM HYDROXYLAPATITE FILLER

CaHA is the primary mineral component of bone. CaHA is highly viscous and is injected using a 27-gauge needle into the deep dermis or, for volume restoration, at or below the dermal subcutaneous junction. Injections may be painful because of the larger particle size, high viscosity, absence of anesthesia in prefilled syringes, and needle size. CaHA is stored at room temperature and does not require skin testing. An injectable formulation of CaHA (Radiesse

) is approved by the FDA on 22 December 2006 for the augmentation of moderate to severe facial lines and folds and for facial soft tissue loss from HIV-related lipoatrophy. It consists of 30% concentration of 25–45 nm calcium hydroxylapatite spherical particles suspended in sodium carboxymethylcellulose gel. It lasts approximately 1 year or more in most patients. It is inherently biocompatible because it is identical in composition to bone material. Lack of immediate reversibility and contraindication for use in the lips limit applicability to some extent.^{1,2,3}

POLYMETHYLMETHACRYLATE FILLER

PMMA is composed of non-resorbable PMMA 20% and 80% bovine collagen and was FDA approved as Artefillin October 2006. Artefill is a chemically inert and biocompatible synthetic implant used in bone and dental implants. Skin allergy pre-screening tests are needed owing to bovine collagen content. The PMMA microspheres are non-biodegradable and their persistence is extremely long lasting to permanent. The use of PMMA is appropriate for patients with well-defined deep facial wrinkle lines. Granulomas appear to be less common with the current product but sensitivity to the bovine collagen component and the animal derivation of the collagen remain issues.^{1,2}

INJECTABLE COLLAGEN FILLER

Injectable purified porcine collagen (Evolence) was approved by the United States Food and Drug Administration (FDA) in June 2008 for treatment of moderate to deep facial lines and wrinkles. Intradermal skin testing is not required because of the very low potential for hypersensitivity. Evolence (3.5% purified porcine type I collagen suspended in phosphate-buffered saline for injection) is uniquely cross-linked with D-ribose using Glymatrix technology to prevent degradation and prolong its cosmetic effects. The flow characteristics allow for easy injection into the middle to deep dermis using a linear retrograde tunnelling technique; immediate postinjection massage maintains uniform distribution. Bruising tends to be minimal because of the platelet-aggregating effects characteristic of most collagen fillers. Evolence should not be injected in patients with a history of porcine allergy or serious anaphylactic or recurrent allergic reactions. Evolence is stored at room temperature.

INJECTABLE PLLA

Injectable PLLA (Sculptra) is often described as a deep-dermal filler. PLLA is more accurately viewed as an FDA-approved injectable medical device implanted at or below the level of the dermal subcutaneous junction for global volumetric enhancement of the lower two-thirds of the face in patients with lipoatrophy associated with HIV infection. The FDA then granted a second approval for treatment of nasolabial folds and facial wrinkles to US, in August 2009 and it is marketed as Sculptra. The longevity of PLLA (18 to 24 months) is because of the slow degradation kinetics of the large, irregularly shaped PLLA microparticles. The PLLA material is thought to stimulate fibroblasts in the host to produce collagen. PLLA is nonimmunogenic, with negative skin testing. Lack of reversibility and need for dilution prior to use are its contraindications.^{1,2,8}

HYDRELLE FILLER

The next HA filler to be described is known as Hydrelle (2010) originally called Elevesse. Hydrelle contains the highest concentration of HA on the market, 28mg/mL and it also contains 0.3% lidocaine, the first of the US products receiving FDA clearance for an HA with lidocaine. It is cross-linked with phenylene bisethyl carbodiimide or biscarbodiimide, or BCDI, which is a novel HA cross-linker. Its source of HA is from equine streptococci. It has received significant results in the correction of nasolabial folds than other fillers.¹

HA DERMAL FILLER (2011)

Innovation in technology has resulted in the emergence of better, longer-lasting hyaluronic acid implants with fewer side effects. The new dermal implant Uma Jeunesse is crosslinked with butanediol diglycidyl ether (BDDE) using a new crosslinking technology. Uma Jeunesse® lasted in tissues for longer as compared to Juvéderm even in patients injected for the first time. Patient acceptability rate of Uma Jeunesse was also much higher. The new dermal implant Uma Jeunesse is a safe and patient-friendly product which resides in the tissues for longer with maintenance of aesthetic effect over and beyond 6 months, reaching 9 months in over 80% of patients.¹⁰

Belotero Balance- November 21, 2011

The US Food and Drug Administration (FDA) has approved a gel dermal filler (Belotero Balance, Merz Aesthetics) for the

correction of moderate-to-severe facial wrinkles and folds. The product combines a cohesive polydensified matrix technology with a hyaluronic acid base that attracts water to the injected area to fill and plump the wrinkle in natural way. Potential treatment areas include nasolabial folds, worry lines, crow's feet, lips/chin/cheek augmentation, marionette lines, smile lines, perioral lines, and wrinkles. The most commonly reported adverse event was a short-term, mild to moderate injection-site reaction, including swelling, bruising, and localized nodules.¹⁰

THE NEW DERMAL FILLER APPROVED IN AUSTRALIA

Ellanse is being launched at the Australian College of Cosmetic Surgery Conference in May 2012.. Ellanse is the first filler available in Australia with "tunable longevity. Ellanse's microspheres do not "degrade" as Calcium HO apatite ones, who become gradually porous, hence stimulating a strong foreign body inflammatory reaction. Here we have a "resorption" process: the molecules progressively dissolve, the spheres retaining their original volume until almost all molecules are dissolved. So the longevity depends only of the number of molecules composing the spheres. . It is used in the treatment of malars, teartrough, nasolabial folds, marionette lines, cheeks, chin, but also for filling defects, noses, hands, etc. It allows for deep (pre periosteal) injections in the malar areas, to lift up the entire facial structure. Ellanse is versatile enough to be used in dermal injections with excellent results, as it is very soft, and after disappearance, cannot be felt in the skin, as there is only the patient's own collagen left.

NEW DERMAL FILLER FOR LIPS

Allergan in LONDON, July 9, 2013 announced the launch of JUVÉDERM® VOLBELLA® with Lidocaine, a new dermal filler treatment specifically tailored for the lips and the latest addition to the JUVÉDERM range of dermal fillers. JUVÉDERM® VOLBELLA® with Lidocaine is designed to gently restore natural-looking lip volume, but also for defining the lip shape, treating 'downturned' or drooping lip corners, smoothing fine 'barcode' lines around the mouth and supporting the 'marionette' lines down to the chin. Developed using Allergan's proprietary VYCROSS[™] technology, JUVÉDERM® VOLBELLA® with Lidocaine is formulated with an innovative combination of low and high molecular weight technology, which delivers an ultra-smooth gel resulting in a natural look and

Area	Technique
Nasolabial folds	Serial puncture, threading, fanning or cross-hatching; sharp needle or blunt-tipped cannula can be used
Melolabial folds	Fanning or cross-hatching; sharp needle or blunt-tipped cannula can be used
Jowls	Serial puncture (depot) or linear threading
Cheeks	Fanning or cross-hatching; blunt-tipped cannula can be used
Lips – vermilion border	Linear threading
Lips – tubercles	Serial puncture

feel, as well as improved duration.

INJECTION TECHNIQUES

The most common injection techniques used for facial augmentation are serial puncture and retrograde linear threading or tunnelling.

ANAESTHESIA

Injection depth, anatomic area, dermal filler viscosity, and patient tolerance to pain may all contribute to the decision for anesthesia. Topical anesthetics and ice packs may minimize the pain of needle sticks and may be all that is required for implantation of superficial dermal fillers or in patients with a high pain tolerance. Human and bovine collagen are premixed with lidocaine. The addition of lidocaine 1% or 2% to PLLA, CaHA, or HA, just before injection, may supplement pain control. Bilateral infraorbital and mental regional nerve blocks may be necessary, especially for lip augmentation.

PATIENT PREPARATION

Correct positioning of the patient for the injection is critical. Patients should be upright or reclined at a 45° angle for the injection. Lying supine may alter gravitational effects on the skin and distort or obscure the defect, increasing the chances of inaccurate correction. Patient assessment and pretreatment mapping with a marking pen or eyebrow pencil while the patient is upright may help ensure a more accurate injection.

ALLERGY TESTING

Skin testing may be required before injection of dermal fillers derived from nonhuman sources such as bovine collagen, but is generally not required for fillers derived from synthetic sources, such as PLLA, CaHA, or highly purified HAs. Although the HAs used in dermal fillers may be derived from avian or bacterial sources, these products are highly purified formulations, and immunologic reactions are rare; therefore, skin testing is not recommended before use. Purified porcine collagen (Evolve) uses enzymatic treatment with pepsin to create nonimmunogenic collagen fibers, thus eliminating the need for skin testing.

PATIENT COUNSELING

Patient satisfaction is the most important end point of successful facial rejuvenation. Proper patient education, informed consent, and realistic expectations are prerequisites for treatment with dermal fillers. Patients who are not willing to tolerate possible complications may not be good candidates for soft-tissue augmentation with dermal fillers or injectable medical devices. Patients are instructed to temporarily discontinue over-the-counter blood thinners, such as vitamin E, aspirin, and nonsteroidal anti-inflammatory drugs, and only with medical clearance, prescribed anticoagulants such as warfarin (Coumadin) or clopidogrel bisulphate.

COMPLICATIONS

Although skin infections with dermal filler injections are unusual, a skin assessment before treatment for any active bacterial or

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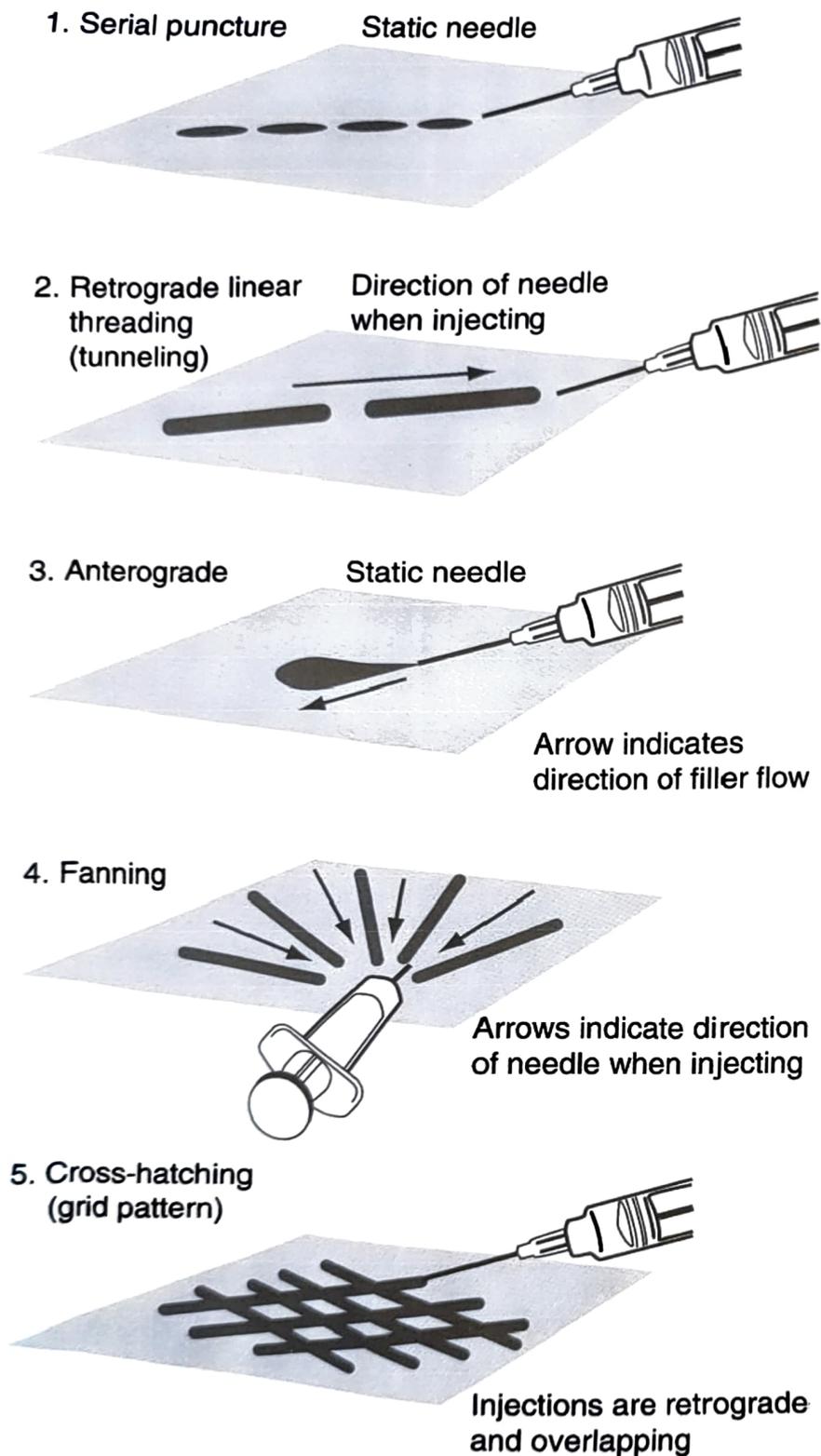


Fig. 1: Injection techniques. (Adapted with permission from The McGraw-Hill Companies, Inc © 2007.)

viral infection, makeup removal, skin preparation with antibacterial soap (eg, chlorhexidine) or alcohol, or both, and proper attention to clean/sterile technique

will further help minimize secondary infections.

The injection of almost any dermal filler may be associated with minor adverse effects, such as injection-site burning, itching, or pain (secondary to stretching of cutaneous nerves), erythema, edema, bruising or hematoma formation.

Tear-trough deformities and eye rings (ie, upper cheek hollows, infraorbital hollows) are tricky areas to treat with any filler and should be approached cautiously. Improper injection of thin periorbital skin with HAs may lead to the appearance of the Tyndall effect. The Tyndall effect manifests as a bluish or blue-gray color change that is seen when light refraction through the skin changes, as with superficial or excess implantation of clear, viscous HAs.

Overcorrection with HA products in the periorbital area also may cause a puffy, edematous appearance of the lower eyelids because of the hydrophilic nature of the filler.

Intravascular injection should be avoided. Accidental injection of a dermal filler into the ophthalmic artery through one of its proximal branches (the retinal or posterior ciliary arteries) or distal branches (many of the superficial arteries of the face) may lead to an arterial occlusion with subsequent skin necrosis or, rarely, blindness, regardless of the injection location on the face.

Papule or nodule formation, surface irregularities, overcorrection, and asymmetry may result from improper injection technique. Massage should be the immediate response to an injection that is too superficial or to an overcorrection. Fillers such as PLLA, CaHA, and Evolence should not be injected in the vermillion border or body of the lips secondary to a high rate of nodule formation.

Delayed-onset granulomas, a type of foreign body reaction occurring several months after injection, may be seen with fillers that stimulate neocollagenesis, such as PLLA and CaHA. These granulomas usually appear as asymptomatic nodules and may result from superficial implantation or deeper bolus injection.

For nodules that are sometimes rock hard, very large, or unresponsive to intralesional steroid injections alone, use a combination of intralesional steroids, subcision, and rehydration. Early treatment with oral doxycycline, 100 mg twice daily, improves the acute inflammatory reaction. As the inflammatory response improves, usually over 1 to 3 months, the doxycycline dose may be tapered and eventually discontinued.

NEEDLE AND SYRINGE SIZE^{2,3}

Table 1 Injection parameters for collagen-based dermal fillers

Product	Indication	Recommended needle size (gauge)	Depth of injection	Skin testing required
Zyderm	Wrinkles, fine lines	30 or 32	Superficial/papillary dermis	Yes
Zyplast	Deep folds, wrinkles, lip augmentation	30	Mid to deep dermis	Yes
CosmoDerm	Wrinkles, fine lines	30	Superficial/papillary dermis	No
CosmoPlast	Deep folds, wrinkles, lip augmentation	30	Mid to deep dermis	No
Evulence	Moderate to deep facial wrinkles and folds	27	Mid to deep dermis	No

Table 2 United States Food and Drug Administration–approved hyaluronic acid dermal fillers

Product	Recommended needle size (gauge)	Depth of injection
Hylaform	30	Mid to deep dermis
Restylane	30	Mid to deep dermis
Juvéderm Ultra	30	Mid to deep dermis
Juvéderm Ultra Plus	27	Mid to deep dermis
Perlane	27	Deep dermis to superficial subcutaneous space

ued. Additional therapy may include concomitant treatment with nonsteroidal anti-inflammatory drugs, systemic antihistamines, intralesional low-dose steroids, or topical agents, such as pimecrolimus cream 1% (Elidel) twice daily. Delayed hypersensitivity reactions are rare with dermal fillers that do not contain animal products.^{1,2,3}

CONCLUSION

Cosmetic facial surgery is an integral part of the specialty of oral and maxillofacial surgery, and injectable facial fillers fit well into the armamentarium of the contemporary oral and maxillofacial surgeon. Soft-tissue augmentation with dermal fillers and injectable medical devices has gained widespread acceptance as an alternative to more aggressive, invasive treatment of the aging face. These procedures are generally simple

to learn, provide high patient and doctor satisfaction, and produce few complications. Inappropriate use of a dermal filler or injectable medical device for a cosmetic procedure may lead to inadequate correction or increase the risk for adverse effects or events.

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