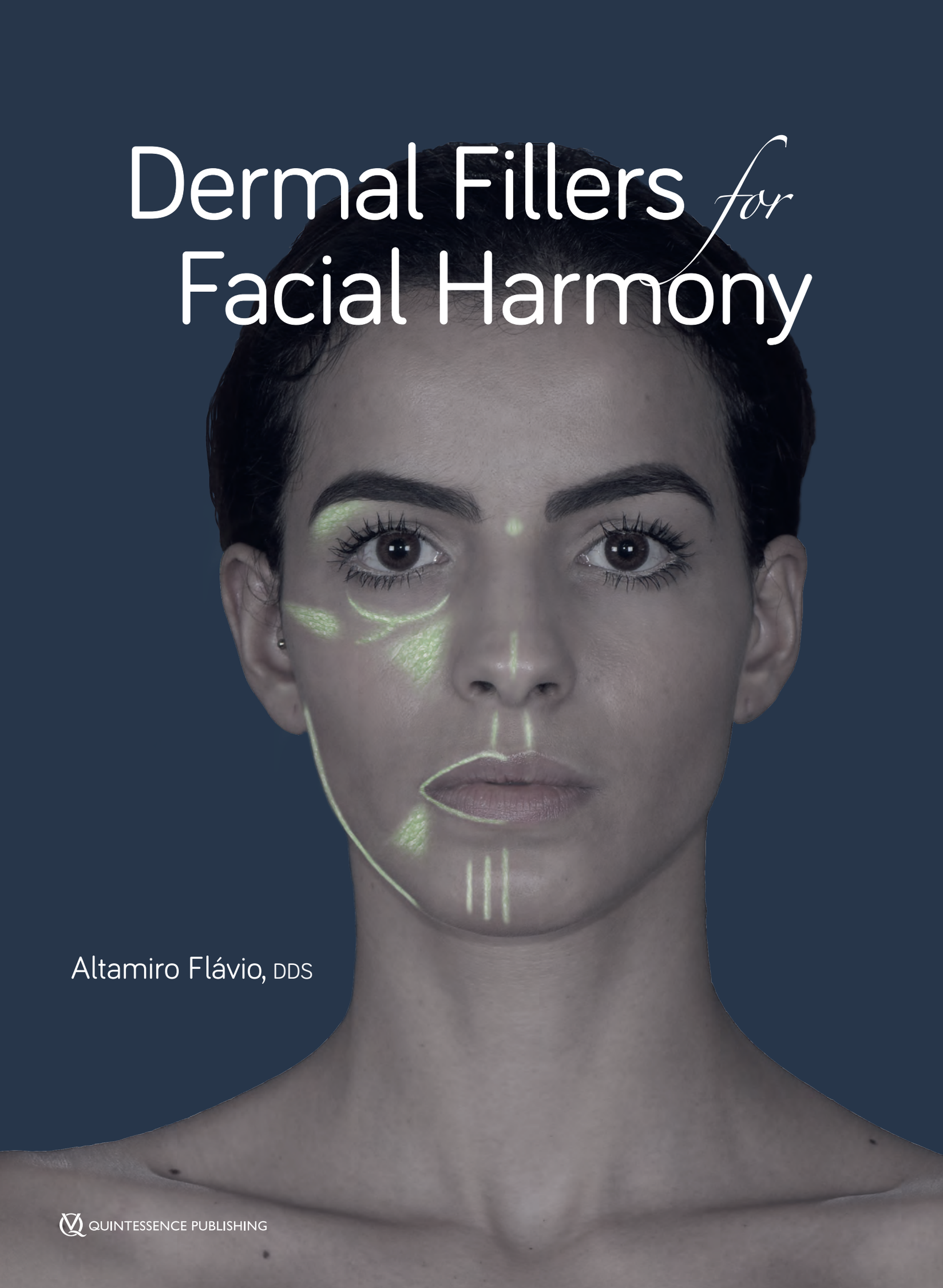
Dermal Fillers *for* Facial Harmony



Altamiro Flávio, DDS

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Dermal Fillers for Facial Harmony

Dedication

This book is dedicated to my father and mother. Along the way, I have been missing them, but all that I learned from both of them always brings light to the path. To my beloved sister, Marya, an angel of kindness and strength, always teaching me. To my brother, Antônio, with whom I learned how to write. To my beloved wife, Cláudia, the one who makes dreams come true. To Gabriel, my son, my best friend—the one who has overcome all difficulties without losing his joy. To Ana Sofia, my daughter, you make me believe that anything is possible. To Jesus Christ, my Lord, the only one who gave his life to save us. Nothing would be enough to pay for your sacrifice. Thank you, Father!

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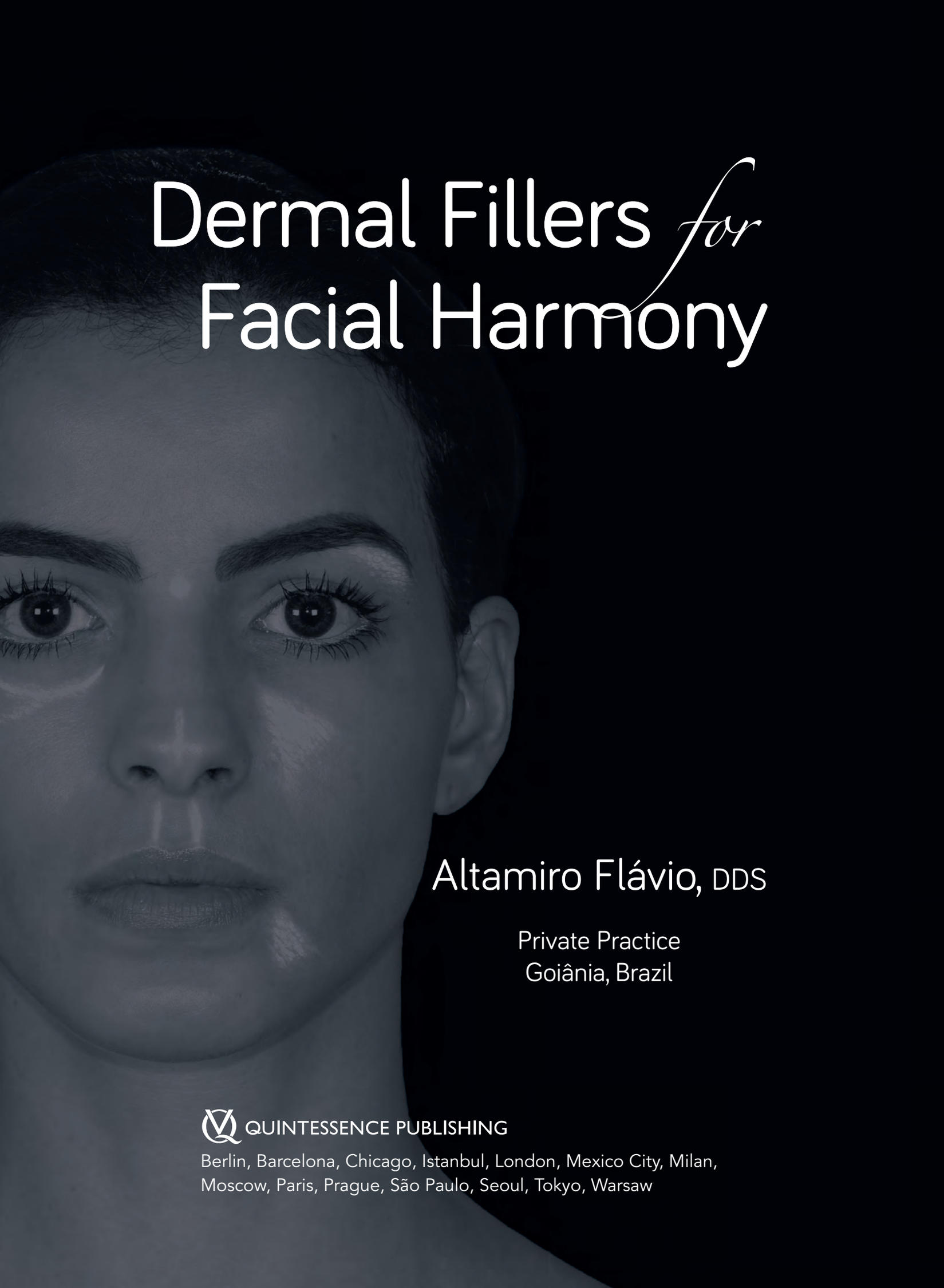

Dermal Fillers *for* Facial Harmony

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QUINTESSENCE PUBLISHING

Berlin, Barcelona, Chicago, Istanbul, London, Mexico City, Milan,
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contents

Foreword by Paulo Vinícius Soares *vi*
Preface *vii*

01 Facial Anatomy *1*

02 History, Classification, and Characteristics of Fillers *11*

03 Injection Planes and Techniques *23*

04 Complications *33*

05 Facial Analysis for Dermal Filler Injections *53*

06 Facial Anesthesia for Filling Procedures *95*

07 Facial Regions and Possible Filler Therapies *113*

Index *161*

Extra content

Extra content is available online. QR codes throughout the book link to files and videos that can be used by the professional to facilitate better treatment planning and delivery of care. Scan the QR code here to access this supplementary information. The full list of links may also be found at www.quintpub.com/fillers.

foreword

Over the years, I have been following Professor Altamiro Flávio's career, and it is an honor to write this preface as one of his former students in esthetic procedures and facial harmonization courses. Currently, I am a researcher and professor at a dental school, and without a doubt I can state that Dr Altamiro has strong and important skills as an expert clinician, opinion leader, dental photographer, and speaker. Now he shares new knowledge about dermal fillers for esthetic and functional treatments in this wonderful book. The sequence of chapters and clinical cases show how contemporary dentistry can help patients achieve a wonderful smile and nice facial esthetics, and how dentists can develop this type of procedure with safe clinical protocols. Readers will find concepts, principles, evidence-based case reports, and important clinical hints to elaborate planning and treatment protocols with several types of products. Every student and all dental professionals performing esthetic procedures need to read this book to understand injectable materials, techniques, and principles of facial esthetics and the smile. All professionals in the area of esthetic dentistry will find something to enjoy and learn in this book.

Paulo Vinícius Soares, DDS, MS, PhD
Federal University of Uberlândia, Brazil

preface

The title of professor is not 100% acquired. In part, the individual is born with this gift, while the other part comes on a daily basis after hours and hours of dedication to professional growth and sharing all our acquired knowledge with our students. When teaching, we share in a few hours what was learned from years of study and dedication. We donate the best of us to people who are sometimes unknown. Thus, our work is mainly a donation, whose reward is the satisfaction of others. This is how we share a lot of what has been given to us by God. Being a teacher is an honor to which I have tried every moment to do justice while working on this book. I tried to condense all the knowledge necessary so that students could be able to safely develop their practice.

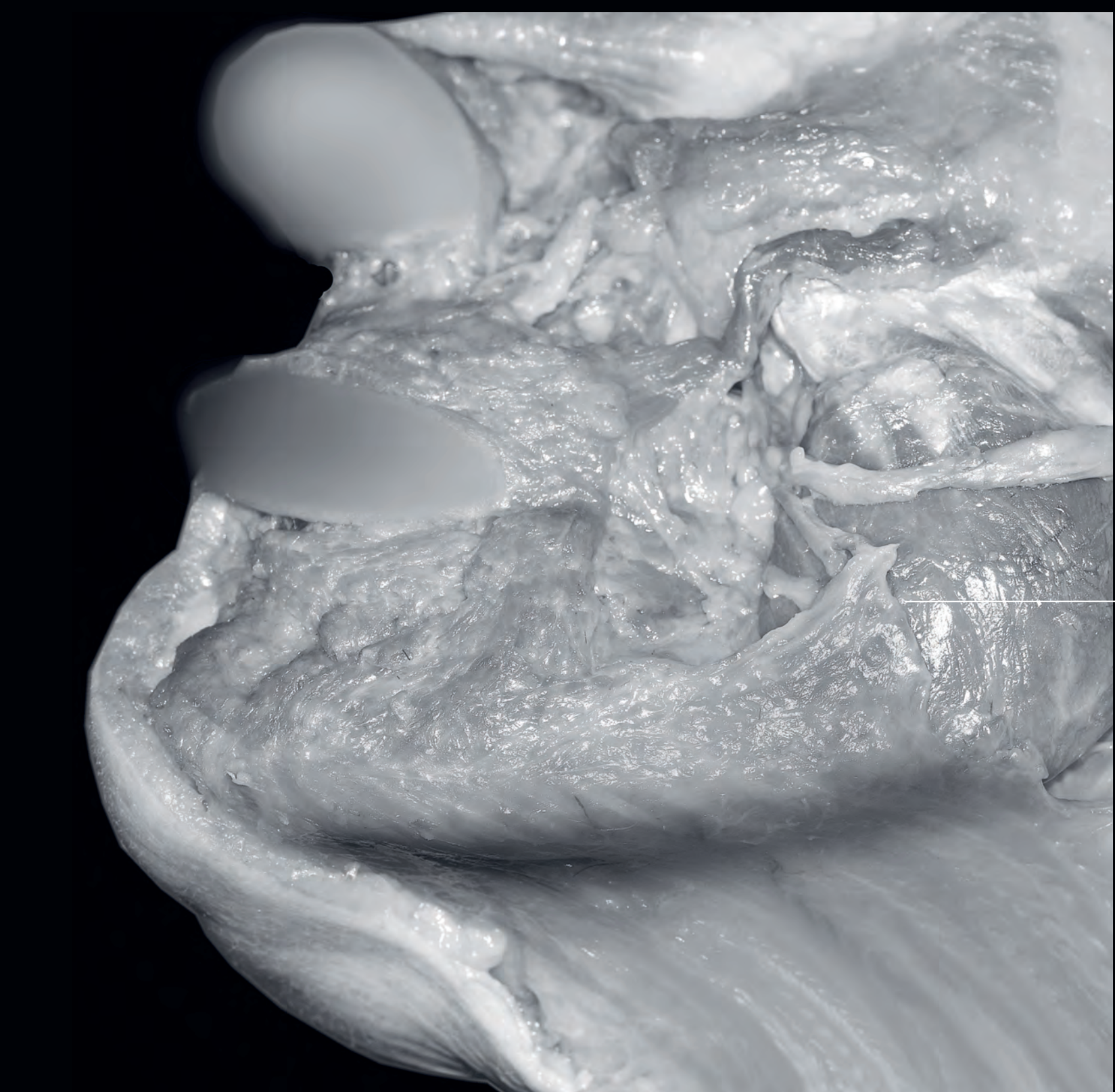
The second step is to practice everything that was learned. I believe that all injectable facial procedures should be initially practiced in a cadaver. The procedures described herein can be practiced by attending our course of anatomy applied to facial fillers at the Miami Anatomical Research Center, where we use fresh cadavers. To train as much as possible before helping a patient should be the main rule.

This book contains a lot of information that will be useful to dedicated readers who strive to fulfill their mission to treat well their patients, who are children of God and therefore our brothers.

Enjoy the reading!

Acknowledgments

I would like to express my gratitude to my friends at the Miami Anatomical Research Center—Dr Eduardo Sadao, Heloíse Peixoto, Justin Fraioli, Steve Canona, Sheila Herrera, Jorge Carrasco, and Maylin Peres Carrasco—for their effort in keeping up with our courses that help educate so many professionals. A special thanks to Mr Al Weinstein, the great entrepreneur, who once told me "if you are always by the book, you will never be on the book." Thanks for your unique view. Dear Dr Paulo Vinícius Soares, you were the first one to believe in this book, and now it is a reality. Thank you Dr Christian Coachman, who linked facial aspects to the smile, and Dr Rubelisa Cândido Gomes de Oliveira, who once again has assisted me with the scientific format of the book, contributing much to its success. My appreciation to Denise Riley, who has spent so many hours dealing with words that will spread knowledge, you are great my sister. I also wish to acknowledge my assistant professors—Márcia Viotti, Rogério Zambonato, Dr Francisco Célio Dantas, Luciana Rezende, Maria Geovânia, Danielle Dias, and Rosa Amaoedo—for the amazing support they have given me during so many courses. I wish to thank my secretary, Walquiria, for her dedication to our courses. My greatest respect and gratitude for all those who have selflessly given their precious bodies to Science. To my dear patients who allowed me to use their photographs and clinical history to improve the knowledge of so many health professionals through this book, I cannot thank you enough. I would like to acknowledge the important role of so many teachers I have had throughout my lifetime. I will always carry with me their teachings. Finally, my eternal gratitude to the greatest teacher of all, Jesus, for the daily blessings.



CHAPTER

01

Facial Anatomy

The search for beauty seems to be a natural human instinct—beauty in nature, beauty in art, beauty in manmade design, and perhaps above all else, beauty in our own physical esthetics. For many centuries, humans have sought to enhance natural beauty and slow aging. The recent discovery of safe dermal fillers has ushered in an era of minimally invasive treatment for wrinkles, depressions, grooves, and volume deficiencies, revolutionizing the way patients perceive aging and their ability to control its physical consequences.

Understanding the basic anatomy of the face and the natural aging process is central to effective treatment with dermal fillers. This chapter details the facial manifestations of the aging process and describes the tissue layers and blood supply of the face. Chapter 2 introduces dermal fillers, and chapter 3 illustrates their various injection techniques.

Facial Aging

Skin, like many other organs, undergoes deleterious changes with the passage of time and the associated hormonal and dietary variations. Unlike most other organs, however, skin is also directly affected by exposure to the environment, especially ultraviolet (UV) irradiation from the sun. Chronic exposure to UV irradiation causes an aged phenotype (photoaging) that is superimposed with aging caused by the passage of time (chronologic aging). As a result, areas of the body that are frequently exposed to the sun, such as the face, neck, forearms, or back of the hands, acquire visible signs of aging more rapidly than other areas of the body. Evidently, photoaging is a cumulative process and, as such, is more severe in older individuals. The passage of time and repeated exposure to harmful aspects of the environment alter both the epidermal and dermal compartments of the skin.[1]

Aging of the face is characterized by different phenomena happening at more or less the same time (Fig 1-1). Flattening of the dermal-epidermal junction is thought to reduce the exchange surface between the epidermis and dermis, thereby reducing the nutrient flux; as a result, this flattening might have a role in reducing keratinocyte proliferation.[2] Flattening of the dermal-epidermal junction also reduces epidermal resistance to shearing forces and thereby makes the epidermis more fragile.[2] The thickness of the stratum corneum remains unaltered with advanced age,[2,3] and stratum corneum hydration is modestly lowered or unchanged in aged versus young individuals.[4,5] Accordingly, transepidermal water loss (a measure of stratum corneum integrity) is unaltered with chronologic aging.[5] However, surface lipid production decreases significantly with age on some areas of the skin,[4,5] increasing the incidence of xerosis (dry skin), pruritus (itchy skin), and skin irritation in elderly populations.[6] These modifications lead to the following:

- Variable skin atrophic changes and wrinkle formation caused by genetic, actinic, and environmental factors
- Bone volume and facial fat loss primarily in the bony skeleton and fat compartments with predictable patterns
- Skin sagging

With aging, the bony layer undergoes a reabsorption of the skeleton, mostly in the orbital, periorbital, malar, submalar, and mandibular areas,[7,8] and the fat compartments follow a rather predictable pattern of depletion. In the deep supraperiosteal layer, most of the volume loss takes place in the lateral and medial suborbicularis oculi fat, the deep medial cheek compartment, and the chin fat compartments. In the superficial subcutaneous layer, most of the volume loss takes place in the lateral compartments, both in their temporal and preauricular districts and to a lesser extent in the middle and medial fat compartments of the superficial cheek fat pad.[9,10] It is remarkable that both the superficial nasolabial compartment and the superior and inferior jowl compartments are not greatly affected by volume loss and tend to move medially due to a lack of lateral support caused by volume depletion in the lateral fat areas and a lack of fibrous fixation points.[11] All the areas of fat reabsorption are confined in between the ligaments,[9,12] so on the surface of the skin, several grooves become identifiable with this volume deflation: the tear trough and the palpebromalar groove (tear trough ligament and orbital retaining ligaments), the midcheek groove (zygomaticocutaneous ligament), the nasolabial fold (nasolabial ligament), the buccal fat groove (parotidomasseteric ligament), and the marionette line (labiomandibular ligament).[10,12,13] All these ligaments tend to keep their strength in the central area of the face, where a strong fixation point exists, and become looser laterally.[14]

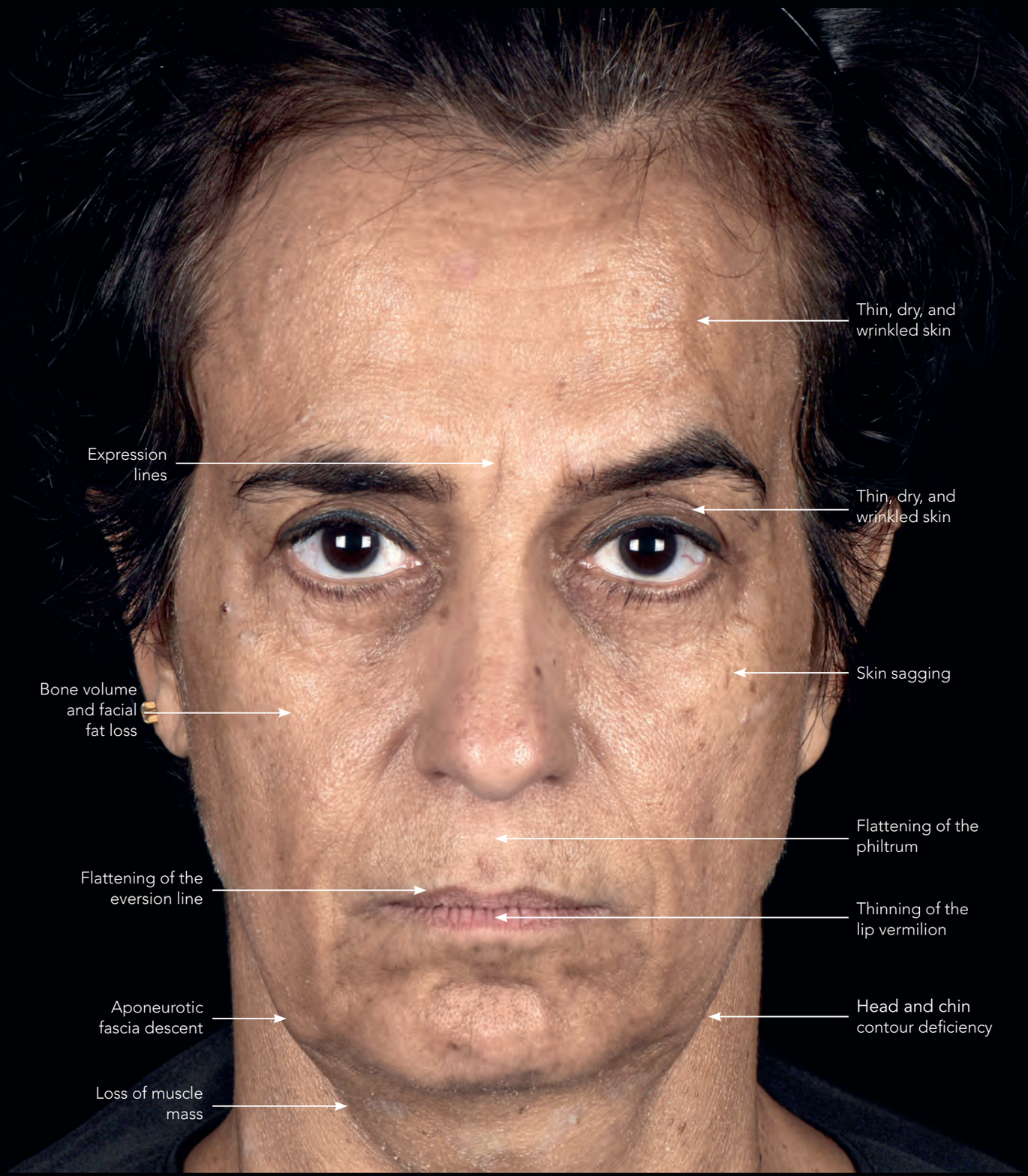


Fig 1-1 Various manifestations of facial aging.

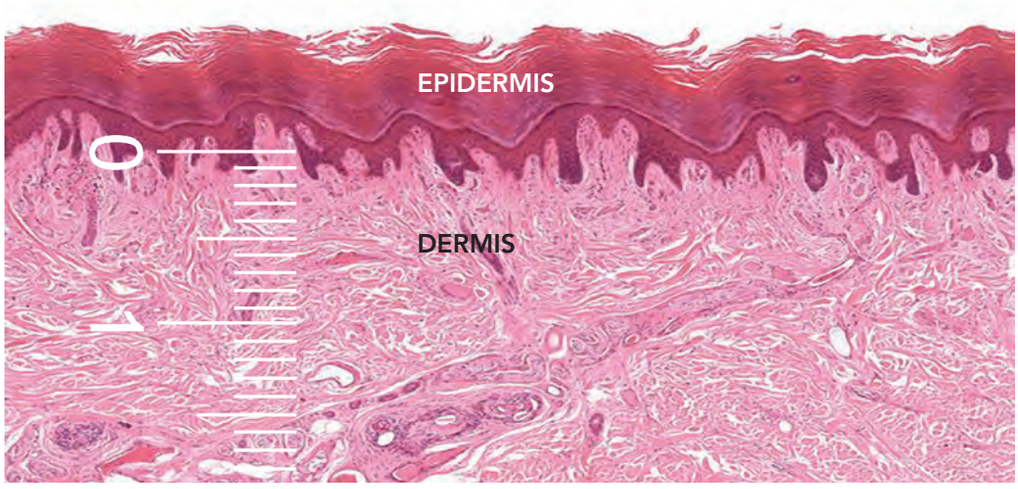


Fig 1-2 Layers of the skin. The dermal thickness varies from 1.04 to 1.86 mm.

Skin and Connective Tissue

The skin is the largest organ of the human body, and it has several functions. It acts as a physical, chemical, and bacteriological barrier; it prevents dehydration; it regulates body temperature; it mediates the sense of touch; and it plays a role in immune surveillance, hormone production, and social communication.[1]

The skin has two layers: the epidermis and the dermis (Fig 1-2). The epidermis is the outermost layer of the skin. It contains no blood vessels and relies exclusively on the underlying dermis for nutrients. The epidermis is primarily made up of keratinocytes organized in a stratified epithelium.[1] The dermis consists of connective tissue with a variable amount of elastic fibers and several nerves, blood vessels, and lymphatic vessels. Its thickness varies from 1.04 to 1.86 mm.[15] This connective tissue is composed of two different layers: a deep or reticular layer and a superficial or papillary layer. The reticular layer is made up of fibroelastic connective tissue and mainly collagen fibers. The cells in this layer are mainly fibroblasts and histiocytes. Sebaceous and sweat glands, hair follicles, and small groups of cells are also found in deeper layers of the reticular dermis.[1,15] The hypodermis or subcutaneous tissue is a layer of loose connective tissue immediately below the dermis.

Superficial Muscular Aponeurotic System

Beneath the dermis lies the superficial muscular aponeurotic system (SMAS), a layer composed of superficial aponeuroses blended with muscles and fat (top right in Fig 1-3). Contrary to the other skeletal muscles, the muscles of facial expression are not surrounded by a fascia because they originate and/or are inserted in the skin. Unlike botulinum toxin, **fillers should not be injected in the muscles**. The SMAS in the face is composed of several muscles of facial expression, and therefore the operator should carefully watch the depth of this layer to prevent fillers from being injected in this muscle layer.

Figure 1-3 illustrates the tissue layers of the human face, and Fig 1-4 illustrates how different anatomical areas can support different volumes of fillers. In most cases, the target layer for fillers is the superficial fat layer.

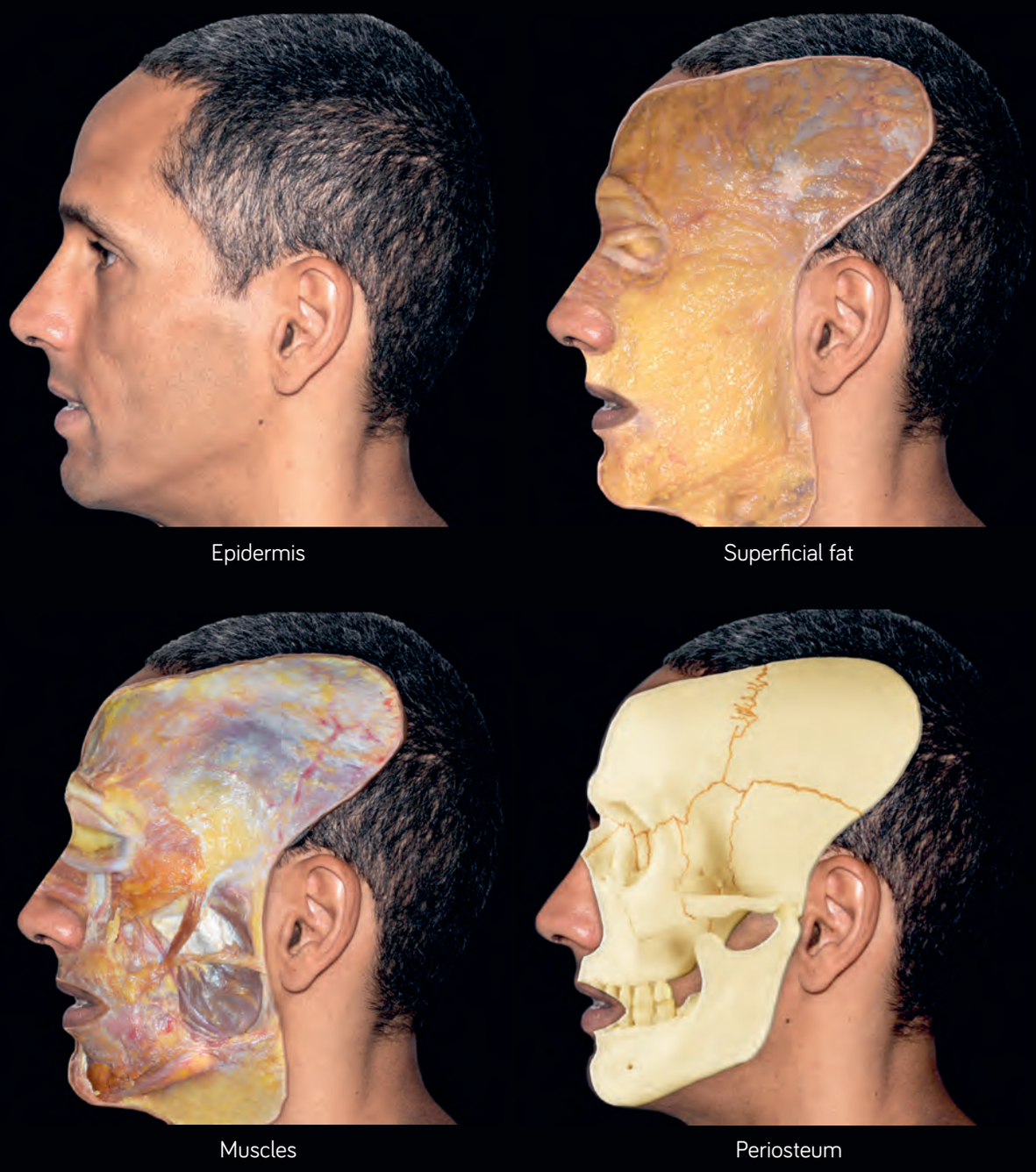


Fig 1-3 Layers of facial tissues.

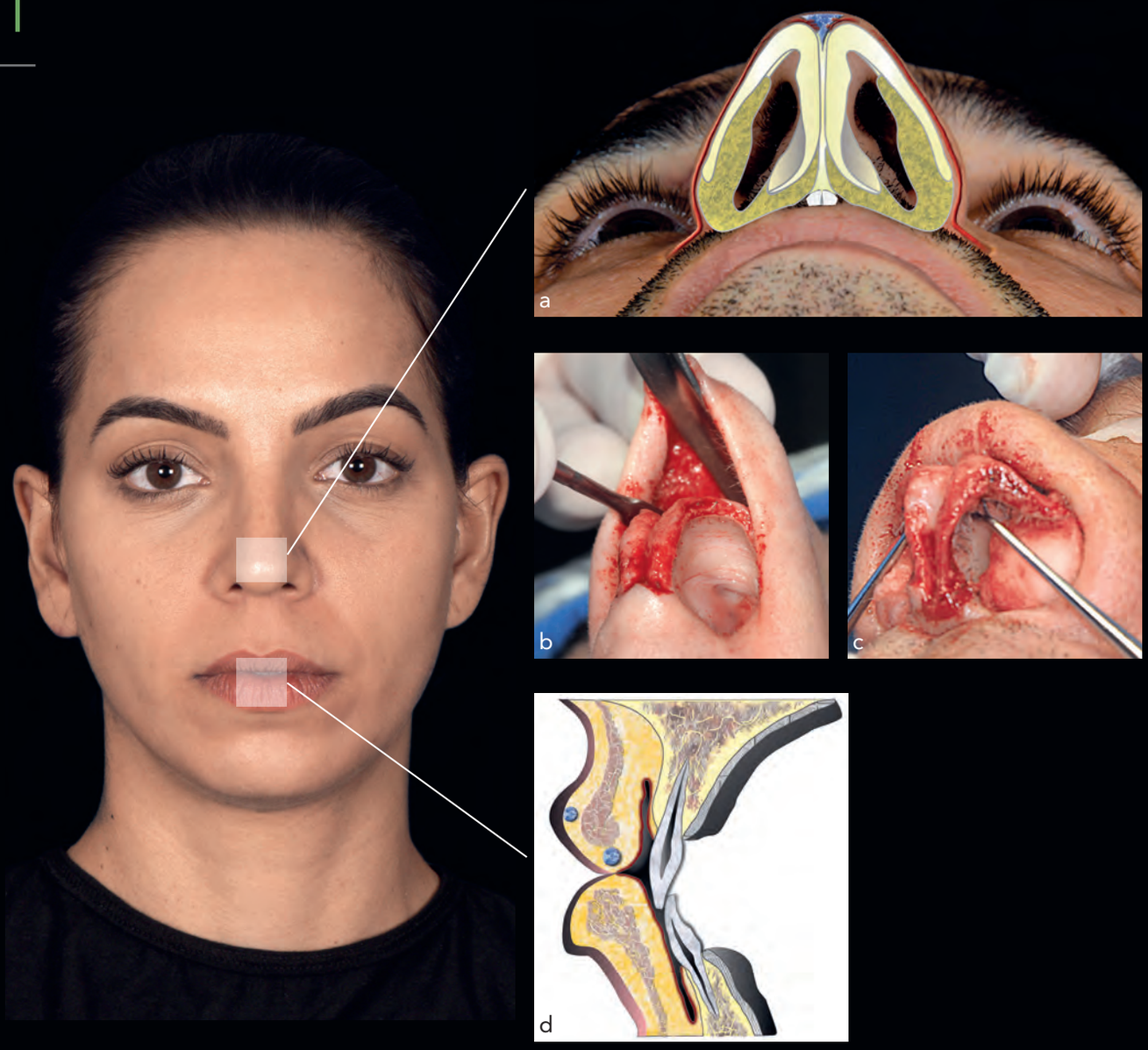


Fig 1-4 *(a to c)* The supratip is an area with a low capacity for volumization. There is little space between the deep dermis and the cartilage. Therefore, this region only supports a very small amount of fillers. *(d)* The lip vermilion is a region that shows elasticity and malleability, allowing it a good capacity for volumization. It can accommodate various volumes of fillers.

Blood Supply to the Face

Areas with minimal soft tissue coverage over the blood supply are at a risk for necrosis with dermal filler injection. The injected volume applies pressure on the vessels, decreasing blood flow and causing tissue ischemia. For this reason, it is essential that any practicing clinician know the locations of blood vessels in the face.[16]

The external carotid artery is the main artery that supplies blood to the face. Its most studied branch is the facial artery and its branches. This artery runs in the outer surface of the mandible under the platysma and up to the inner corner of the eye. It crosses the buccinator muscle and the maxilla deep to the zygomaticus major and levator labii superioris muscles. Branches of the facial artery supply the lips and lateral aspect of the nose.

Blood supply to the lips

The anatomical topography of the lips is not generally well known by clinicians.[17] However, the popularity of lip injection treatments underscores the importance of understanding the blood supply to this area of the face.

The arteries that supply the lips are the superior and inferior labial arteries (branches of the facial artery), which are connected by anastomoses with those on the opposite side of the face, forming an arterial circle around the vermilion border.[18] The superior and inferior labial arteries are located exactly where dermal fillers are injected: between the upper and lower lip's wet and dry mucous membrane line and in the internal part of the upper lip. There are also terminal infraorbital artery branches (inferior palpebral, superior, and nasal labial) that arise from the infraorbital foramen.[19]

In most cases, the superior labial artery (SLA) originates above the labial commissure and follows a route from the horizontal to medial plane, along the upper lip. In fewer than 25% of cases, its origin coincides with the labial commissure. The mean distance from the SLA's origin to the labial commissure ranges from 5 to 9 mm. The diameter is approximately 1.5 mm at its origin, and it goes deep into the orbicular oris muscle, emitting perforating branches to reach the skin, vermilion, and oral mucosa. It is located at an average depth of 4.5 mm in the skin, 2.6 mm from the oral mucosa, and 5.6 mm from the inferior border of the upper lip. Compression of the SLA at about 1 cm above the oral commissure, a point at which it passes near the oral angle, is recommended during the injection of fillers to decrease its caliber and therefore minimize the risk of perforation.

The philtrum's arterial supply is carried out by the central artery of the philtrum, the left and right lateral ascendant arteries of the philtrum, and the left and right accessory arteries of the philtrum (branches of the SLA).[16] These arteries ensure the main contribution to the ascendant columellar arteries.[20] It is important to note that the arteries that make up this arch in the philtrum are located above the orbicularis oris muscle.

The inferior labial artery (ILA) originates near the labial commissure following a route from the horizontal to medial plane, along the lower lip. Most of the time it originates below the oral commissure. The ILA's path runs close to the alveolar border, outside the lower lip's vermilion. Most labial branches cross into the vermilion perpendicularly, and the marginal arteries that connect with these terminal branches in the vermilion are of a very small caliber. The veins are tributaries of the facial, temporal, superficial, pterygoid plexus, and the superoexternal portion. The maxilla region has a deep venous compound that must be avoided when injecting fillers,[21] especially for injections close to the infraorbital foramen.

Blood supply to the nose

The angular artery is a terminal branch of the facial artery that runs along the nose to the inner angle of the eye to supply the eyelids. It supplies the lateral region of the dorsum of the nose, close to the root, and crosses the levator muscle of the upper lip and the wing of the nose. Due to its characteristics and the size of the area it supplies, the angular artery plays a very important role when we consider the consequences of its occlusion. Because of the injection, there may be spasm or compression that can lead to necrosis, ischemia, and scarring throughout the area.[21] In the inner corner of the eye, it joins the supra- and infratrochlear arteries and the infraorbital artery (maxillary branch). Thus, it also supplies part of the frontal region.[18]

The columella and lateral nasal artery branches (branches of the angular artery) irrigate the ala, dorsum, and tip of the nose. The lateral nasal and columellar arteries form an anastomosis over the dome, forming an alar arcade.[22] On the other hand, the dorsal nasal artery (a branch of the ophthalmic artery) supplies the root and dorsum of the nose. One of its branches joins the angular artery in the root of the nose while the other descends, anastomosing with the external nasal artery, which is a branch of the infraorbital artery. The lateral nasal veins are located 2 to 3 mm from the alar crease. They appear deeply in the nasal base with the columella artery and end in the tip of the subdermal plexus.[21]

Blood supply to the temporal region

The superficial temporal artery is a terminal branch of the external carotid artery. It originates at the parotid gland and ascends in a superficial plane to the posterior part of the zygomatic process of the temporal bone up to neck of the mandible. It ascends and crosses anteriorly to the external acoustic pore, giving off the terminal branches 2 to 3 cm above the zygomatic arch. In this region, it runs between the cutis and the epicranial aponeuoris.[23] It supplies the temporal, frontal, and parietal regions and the parotid gland with its duct through branches with similar names. When filling the pretragal region, injections should be delicate and slow in the subcutaneous deep plane, perpendicular to the superficial temporal artery. To prevent serious traumas, the needle must not be introduced repeatedly in the same place. Moreover, the pressure of injecting large volumes into this area can cause paresthesia and thus must be avoided.

Blood supply to the middle third of the face

The infraorbital artery originates in the pterygomaxillary fissure (close to the maxillary tuberosity) and penetrates the orbit, exiting the face through the infraorbital foramen.[23] For safety reasons, deeper filler procedures close to the foramen should be avoided because of the blood supply net in this area. The terminal branches of the infraorbital artery irrigate the soft tissues in the middle third of the face (lower eyelid), external nose, and upper lip.

Blood supply to other regions of the face

In the mentum, the most important arteries are the submental and mental. The submental arteries originate from the facial artery in the submandibular region, pass by the mandible's base up to the mentum, and irrigate the mylohyoid muscle, the digastric muscle's anterior belly, and adjacent structures. At the mandibular symphysis, it makes an ascending path that bypasses the edge of the mandible and anastomoses with the inferior labial artery. Because of this, any preparations for a chin augmentation must be made with a cannula so that the chances of embolization are smaller.

The mentum is also supplied by the mental artery, a branch of the inferior alveolar artery that emerges through the mental foramen.[23] The venous drainage corresponds to the arterial supply. The mandible is supplied by the facial and inferior alveolar arteries.[21]

In the side of the mouth, the facial artery gives off the superior and inferior labial branches and then, in its ascendant path, goes along the border of the nose to become the angular artery. At the glabella, it becomes the supratrochlear artery, supplying the medial frontal region. The frontal region above the eyes is supplied by the supraorbital artery, which is a branch of the ophthalmic artery.[18]

The orbital region concentrates some points of anastomosis of the external carotid system with the internal carotid system. One of the most important is the anastomosis of the dorsal nasal artery with the angular artery. The facial artery, a branch of the external carotid artery, leads into the angular artery after superficially crossing the medial canthal tendon, where it forms an anastomosis with the dorsal nasal branch of the ophthalmic artery, which in turn is a branch of the internal carotid artery. One of its branches joins the angular artery at the root of the nose, and the other runs downward, being joined by an anastomosis with the external nasal artery, a branch of the infraorbital artery.[19]

The supraorbital artery forms anastomosis with the superficial temporal artery and establishes limits between the central region of the forehead and the temporal region. A reference in terms of the route of the superficial temporal artery is that it passes under the preauricular crease.[17] Thus, it is important not to insert the cannula or needle in this crease when injecting fillers at the zygomat-

ic arch. Facial fillers injected with the purpose of making the face look more masculine and highlighting the border between the forehead and temple should be avoided because the superficial temporal artery and its anastomosis with the supraorbital artery are right below the fat layer and above the temporal muscle. It is also superficial to the occipitofrontalis muscle in the forehead. This is a region of high risk of vascular injury because there is little space between the surface of the skin and the bone.

Facial Lymphatic System

In practice, in cosmetic dermatology, and in physiotherapy and esthetics studies, drainage problems in the periocular region are very frequent. For instance, patient complaints about "swelling" in the eyes following the application of botulinum toxin are very common. When large volumes of fillers are injected in the tear trough or when a periocular sculpture is carried out—or even in surgeries in that area—the appearance of edema is also common. In fact, the palpebral lymphatic system is very delicate and not prepared for traumas or procedures like these.

The alteration of pressure due to a variation in volume also leads to the occlusion of the ducts, which are very delicate and sensitive. Although lymphatic drainage is usually described within a regional context, advanced studies show that massage (manual or with the aid of equipment) in the medial direction (toward the nasal region's drainage system) and lateral direction (toward the parotid gland) can help patients with lymphatic drainage problems in the eyelid area.[19]

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CHAPTER

02

History, Classification, and Characteristics of Fillers

History of Fillers

The development of biocompatible and safe fillers required many years of study and research. Table 2-1 illustrates the historical evolution of fillers. With the development of local anesthesia and surgical techniques toward the end of the 19th century, more invasive cosmetic procedures became available, including soft tissue fillers. Fat was one of the first soft tissue fillers to be used after trauma and is still widely used today. However, autologous fat transplantation is considered a relatively major procedure, as it requires the transplantation of fat from another site, and its results may be variable. Prior to the introduction of autologous fat grafting, paraffin oil had been used for the restoration of volume and symmetry. However, its use was accompanied by a high incidence of inflammatory foreign body granulomatous nodules (paraffinomas), with consequent facial distortion and occasionally life-threatening pulmonary emboli. Hence, the use of paraffin oil was discontinued.[3]

In the mid-20th century, a shift was seen toward purified synthetic polymers in the form of injectable silicone. Although seemingly promising at first, the US Food and Drug Administration (FDA) eventually banned this material because of its similar complications of granuloma formation.[8] However, microdroplet injection of limited amounts of silicone material is still used today as an off-label use for silicone that is FDA approved for ocular injections.[9–11] Teflon, a synthetic polytetrafluoroethylene polymer, was next tested as a soft tissue filler, but it was quickly abandoned because of the resultant inflammatory reaction and the difficulty of injection.[12]

The first facial filler to receive FDA approval was bovine collagen, under the trade name Zyderm (Inamed, now Allergan), in 1981. The approval of Zyderm led to widespread research and development of other fillers, including alloplastic and implantable materials, as well as a renewed interest in and use of autologous fat.[13] Despite this added research, bovine collagen remained the only FDA-approved filler until 2003, when the FDA approved the first hyaluronic acid (HA) dermal

Table 2-1 History of facial fillers

YEAR	FILLER	DESCRIPTION
1863	Paraffin	Used during and after the Civil War. Complications included migration, foreign body granuloma, and pulmonary embolism.[1,2]
1923	Autologous fat	Used to fill volumes after trauma or to treat diseases such as lipoatrophy, scars, lipodystrophy (aging), and gluteal augmentation.[1,2]
1950	Silicone	At first, the same silicone used to manufacture flexible catheters to correct urethral strictures was employed as a filler.[1,2]
1961	Liquid silicone	Liquid injectable silicone used for breast augmentation and facial surgeries. It was banned by the US Food and Drug Administration (FDA).[3]
1962	Polydimethylsiloxane (PDMS)	Pasty, noninjectable silicone for industrial use. Because it is an alloplastic material, it tends to be encapsulated.[1,2]
1981	Bovine collagen	The first agent to be approved by the FDA for cosmetic injection. Because it caused allergies, an allergy test was necessary before injection into the patient. In addition, its effect was short.[1,2]
1989	Polymethyl methacrylate (PMMA)	Nonresorbable and provides a permanent result.[4]
2003	Hyaluronic acid (HA)	First HA dermal filler to be approved by the FDA (Restylane, Galderma).[5] It is the most popular dermal filler.[4]
2003	Calcium hydroxyapatite (CaHA)	Semisolid, cohesive subdermal product; its main component is the synthetic CaHA.[6]
2004	Poly-L-lactic acid (PLLA)	Biodegradable and bioresorbable polymer used in areas of high loss of tissue volume; not suitable for filling individual wrinkles.[7]

Table 2-2 Injectable fillers listed by date of FDA approval

YEAR OF FDA APPROVAL	TRADE NAME (MANUFACTURER)	DESCRIPTION
1981	Zyderm 1 (Inamed/Allergan)	Bovine collagen (35 mg/mL)
1983	Zyderm 2 (Inamed/Allergan)	Bovine collagen (65 mg/mL)
1985	Zyplast (Inamed/Allergan)	Bovine collagen (35-mg/mL collagen crosslinked with glutaraldehyde)
2003	Cosmoderm (Inamed/Allergan)	Human collagen
	Cosmoplast (Inamed/Allergan)	Human collagen
	Restylane (Galderma)	HA
2004	Hylaform (Inamed/Allergan)	Animal-derived HA
	Captique (Genzyme)	Non–animal-derived HA
	Sculptra (Valeant)	PLLA
2005	Cosmoderm 2 (Inamed/Allergan)	Human collagen
2006	**Juvéderm Ultra** (Allergan)	Non–animal-derived HA
	Juvéderm Ultra Plus (Allergan)	Non–animal-derived HA
	Artefill (Suneva Medical)	PMMA
	Radiesse (Merz)	CaHA
2007	**Perlane** (Medicis)	Non–animal-derived HA
	Elevess (Anika)	Non–animal-derived HA
2008	Prevelle Silk (Mentor)	Non–animal-derived HA
	Evolence (ColBar LifeScience)	Porcine collagen
2009	Hydrelle (formerly Elevess) (Anika)	Non–animal-derived HA
	Sculptra Aesthetic (Valeant)	PLLA
2010	**Juvéderm XC** (Allergan)	Non–animal-derived HA with lidocaine
	Restylane-L (Galderma)	Non–animal-derived HA with lidocaine
	Perlane-L (Medicis)	Non–animal-derived HA with lidocaine
2011	**Belotero** (Merz)	Non–animal-derived HA
	LaViv (Fibrocell)	Autologous fibroblasts
2013	**Juvéderm Voluma-XC** (Allergan)	Non–animal-derived HA with lidocaine
2017	**Juvéderm Vollure-XC** (Allergan)	Non–animal-derived HA

Products in **boldface** are currently available. The FDA is aware that unapproved versions of Juvéderm, such as Juvéderm Ultra 2, 3, and 4, are being sold and distributed in the US, including by online retailers.
(Data from Kontis.[8])

Box 2-1 FDA-approved indications for dermal fillers

- Mid to deep dermis to treat facial wrinkles and folds
- Perioral rhytids
- Dorsum of the hands
- Lips for lip augmentation
- Contour deficiencies
- Acne scars

filler, under the trade name Restylane (Galderma), for temporary soft tissue augmentation.[14] Since then, numerous fillers have received FDA approval in response to the growing popularity of minimally invasive facial rejuvenation procedures[5] (Table 2-2 and Box 2-1). Further investigations and research have continued, and more long-lasting synthetic fillers have become available, including calcium hydroxyapatite (CaHA) and poly-L-lactic acid (PLLA).[15]

Classification of Fillers

Dermal fillers can be classified according to their material properties, biodegradability, and duration of effect:

Material properties

- Autologous: Derived from the same individual (eg, autologous fibroblasts)
- Heterologous: Derived from a different species (eg, bovine collagen)
- Alloplastic: Nonbiologic material such as metal, ceramic, or plastic (eg, polymethyl methacrylate [PMMA])

Biodegradability

- Biodegradable: Capable of being broken down, especially into innocuous products (eg, HA, PLLA)
- Nonbiodegradable: Substance or chemical that cannot be changed to a natural state (eg, PMMA)

Duration of effect

- Temporary: Effective for less than 6 months (eg, collagen)
- Long-lasting: Effective for 6 to 24 months (eg, HA [12–24 months], CaHA [18–24 months])
- Semipermanent: Effective for 2 to 5 years (eg, PLLA [2–3 years])
- Permanent: Nonfading results (eg, PMMA)

HA is a naturally occurring polysaccharide found in the skin dermis, umbilical cord, synovial joint fluid, hyaline cartilage, and connective tissues. Because it is biodegradable, biocompatible, and nonimmunogenic, it is an ideal filling agent.[8]

Characteristics of Fillers

Fillers are materials used to add volume to soft tissues. Characteristics of an ideal soft tissue filler include the following[16,17]:

- Adds volume
- Easy to use, giving an opportunity to shape the tissues
- Has reversible results
- Durable and good duration of effect
- Safe to use, giving satisfaction to the patient and the physician
- Has a natural effect
- Does not cause the patient discomfort
- Requires no time for recovery
- Predictable
- Does not cause allergic reactions or irritation

The two most important characteristics for any soft tissue filler are its viscoelasticity and cohesivity.[18] *Viscoelasticity* describes the hardness or softness of a gel and is defined by its elasticity (elastic modulus, G')—that is, how the filler is able to retain its shape when a force is applied—and its viscosity (viscous modulus, G")—that is, how the filler resists gradual deformation by shear stress. These accumulated values identify the viscoelastic modulus (G*). The higher the G*, the higher the resistance to deformation and the greater capacity to keep its shape and, hence, a major lifting effect. *Cohesivity* describes the property of the gel to stick together when an external force is applied. Gels with higher cohesivity tend to uniformly infiltrate the tissues and are not fractionated by movements.[17]

For reasons of cost and patient comfort, a filler should also have good durability. However, it is known that facial topography changes over time; therefore, the use of permanent fillers will result in an unnatural facial appearance because the filler will not undergo changes in contrast to the surrounding tissues.[16]

It is important to understand that soft tissue fillers work using two main mechanisms: The filler material occupies space in the tissue and stimulates fibroblasts to synthesize collagen, resulting in tissue volume.[19]

Table 2-3 lists the characteristics of currently available dermal fillers.[20–22]

Table 2-3 Characteristics of currently available dermal fillers

AGENT	CONTENTS	MECHANISM OF ACTION	INDICATIONS
Restylane Lyft with lidocaine (1,4-BDDE*)	HA chemically crosslinked with BDDE and formulated to a concentration of 20 mg/mL and suspended in a physiologic buffer at a pH of 7.0. The largest fraction of gel particles are 940–1090 µm in size.	Adds natural volume as it integrates into the deep dermal tissue or subcutis, then attracts and binds water molecules to help maintain volume.	Implantation into the deep dermis to the superficial subcutis for correction of moderate to severe facial folds and wrinkles, such as nasolabial folds, or in patients older than 21 years who have age-related volume loss.
Radiesse (CaHA)	Sterile, nonpyrogenic, semisolid, cohesive implant whose principal component is synthetic CaHA suspended in a gel carrier of sterile water for injection, glycerin, and sodium carboxymethylcellulose. Radiesse (1.5 mL, 0.8 mL) has a CaHA particle size range of 25–45 µm and should be injected with a 25G to 27G needle.	Stimulates formation of new collagen (collagenesis) in the skin, adding volume over time.	Subdermal implantation for restoration or correction of signs of facial fat loss (lipoatrophy) in people with HIV infection. Also for subdermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.
Restylane and Restylane-L (HA)	Medium-sized particles of stabilized HA generated by streptococcal bacteria and formulated to a concentration of 20 mg/mL and suspended in a physiologic buffer at a pH of 7.0.	It adds natural volume as it integrates into the dermal tissue, then attracts and binds water molecules to help maintain volume.	Mid to deep dermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds; submucosal implantation for lip augmentation in patients older than 21 years.
Sculptra (PLLA)	Synthetic, biodegradable, biocompatible, immunologically inert polymer from the alphahydroxy-acid family. Must be reconstituted with at least 3–5 mL of sterile water for injection, and must stand for at least 2 hours to ensure hydration prior to treatment.	Particles of PLLA stimulate the formation of new collagen (collagen neosynthesis) in the skin, adding volume over time.	Intended for the restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV infection; in immunocompetent people, it is used as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles for which a deep dermal grid pattern (crosshatch) injection technique is appropriate.
Bellafill (previously Artefill; PMMA)	Composed of PMMA microspheres (diameter 30–50 µm) suspended in a water-based gel carrier containing 3.5% purified bovine collagen, 92.6% buffered isotonic water for injection, 0.3% lidocaine hydrochloride, 2.7% phosphate buffer, and 0.9% sodium chloride.	Microspheres provide permanent volume for wrinkle correction.	FDA approved for correction of nasolabial folds. Lip volumizing contraindicated.
Serial microdroplet silicone (SMDS; liquid silicone)	Synthetic polymer of dimethylsiloxane	It elicits a fibrosis-granuloma tissue response with new collagen formatting around the injected silicone, such that tiny collagen pearls develop around each microdroplet.	Liquid injectable silicone (LIS) has been utilized for soft tissue augmentation for more than five decades. Currently, only two LIS products (AdatoSil and Silikon 1000) are FDA approved and only for the treatment of retinal detachment. Therefore, any cosmetic injection of these products is off-label.

*BDDE = 1,4-butanediol diglycidyl ether, the crosslinking agent used in the majority of the market-leading HA fillers.

	INJECTION	DURATION	LIMITS
	Supplied in 1-mL glass syringes for injection; injected into the mid to deep dermis.	Approximately 6–12 months.	20 mL/60 kg (130 lb) body mass per year.
	Supplied as a 1.5-mL or 0.8-mL syringe. Insert the needle with the bevel down at approximately a 30-degree angle to the skin; the needle should slide under the dermis to the point where the injection should begin. Advance the needle into the subdermis to the starting location; slowly inject the material in linear threads, while withdrawing the needle, until the desired level of correction is achieved.	Approximately 1 year, although the gel carrier is lost by 6 months, causing depreciation of initial gain.	Amount injected varies depending on the site and extent of restoration or augmentation desired. Use a 1:1 correction factor. No overcorrection needed.
	Supplied in a disposable glass syringe; each syringe contains 0.4 mL, 1 mL, or 2 mL of gel for injection into the mid dermis.	Approximately 6 months.	20 mL/60 kg (130 lb) body mass per year.
	Supplied as a sterile, freeze-dried preparation for injection in a clear glass vial; to be injected into the deep dermis or subcutaneous layer.	Approximately 1 year.	Volume should be limited to approximately 0.1–0.2 mL per each individual injection; the volume of product injected per treatment area varies depending on the surface area to be treated.
	Aseptic product that has an opaque, off-white appearance and is supplied in a sealed tray containing five syringes (three with 0.8 mL, two with 0.4 mL). Must be brought to room temperature prior to use. A 26G needle is used, and the best cosmetic result is achieved by moving the needle back and forth two to three times beneath each skin fold being treated, while maintaining constant pressure throughout the implantation procedure. Do not overcorrect because the result is considered permanent.	Permanent support structure for wrinkle correction.	The safety of injecting more than 3.5 mL per treatment site or 8.9 mL overall has not been established.
	When used in the dermis, 0.005–0.01 mL of microdroplets of silicone are injected at 1- to 2-mm intervals along the length of a rhytid.	To achieve the desired result, a series of at least four or five sessions of injections, at 4- to 6-week intervals, is needed.	Not for use in cosmetic injections.

Hyaluronic Acid

The techniques and clinical cases described in this book use HA fillers because of their practicality and biosafety. HA is a natural polymer biologically synthesized by cells in the body via an enzymatic process. It is produced and secreted by cells including fibroblasts, keratinocytes, and chondrocytes.[23] It has a linear structure, composed of fragments of polysaccharides of D-glucuronic acid and N-acetyl-D-glucosamine arranged alternately.

HA was first discovered in the vitreous humor of the eye in 1934 and subsequently synthesized in vitro in 1964. It is one of the major elements in the extracellular matrix (ECM) of vertebrate tissues, including the connective tissue (eg, dermis), synovial fluid, vitreous and aqueous humor of the eyeball, umbilical cord, and hyaline cartilage.[24–27] It shows no species or tissue specificity, in contrast to collagen.[7]

The HA biopolymer functions as a scaffold binding other matrix molecules[3] and is involved in several important biologic functions:

- *Regulation of cell adhesion and motility:* Several cell surface receptors such as CD44, RHAMM, and ICAM-1 have been shown to interact with HA, influencing cellular processes including morphogenesis, wound repair, inflammation, and metastasis.[28,29]
- *Manipulation of cell differentiation and proliferation:* See previous point.
- *Provision of mechanical properties to tissues*[17]*:* Viscoelasticity of synovial fluid and vitreous humor of the eye and control of tissue hydration and water transport.[30]
- *Stimulation of gene expression in macrophages, endothelial cells, eosinophils, and certain epithelial cells:* Wound healing and scar formation.[31]
- *Activation or suppression of inflammation (repair process after damage):* Cell infiltration and proliferation of proinflammatory cytokines.[31,32]

The degradation byproducts of HA seem to have properties that actively affect wound healing and cellular kinetics.[33] In addition, HA has been found during embryonic development in the umbilical cord, suggesting that materials composed of HA may persuade favorable conditions for tissue regeneration and growth.[34,35]

As mentioned above, HA performs several structural tasks in the ECM as it binds with cells and other biologic components through specific and nonspecific interactions. Several ECM proteins are stabilized upon binding to HA. Specific molecules and receptors that interact with HA are involved in cellular signal transduction. Molecules such as aggrecan, versican, and neurocan and receptors including CD44 (cell surface glycoprotein), RHAMM (receptor for HA-mediated motility), TSG6 (35-kDa glycoprotein with a link module in the N-terminus), GHAP (glial hyaluronate-binding protein), ICAM-1 (intracellular adhesion molecule-1) and LYVE-1 (lymphatic vessel endothelial HA receptor) are examples of cell components that bind to HA.[30] New receptors for HA have been identified recently, and the functions of some HA receptors have also been recently described. RHAMM, for example, has been found on cell surfaces as well as in the cytosol and nucleus. It regulates cellular responses to growth factors and plays a role in cell migration, particularly for fibroblasts and smooth cells.[30,36,37]

Hyaluronic acid as a filler

HAs work well as fillers because of their low potential for allergic reactions, their consistency across species, and their viscoelastic and hygroscopic (swelling by the absorption of water) properties (Box 2-2). Some early HA fillers were derived from rooster combs; however, residual avian proteins caused allergic reactions in some patients.[8] Non–animal-derived stabilized HAs were developed by the fermentation of *Streptococcus equi* bacterium and are currently the only class of HA fillers used today for cosmetic purposes.[38]

HA fillers can differ from one another by their degree of crosslinking, gel consistency properties, and concentration. Crosslinking is required to stabilize the HA and prevent degradation when injected into the skin. The degree of crosslinking determines the durability and biocompatibility of the formulation. In addition, HAs can be classified as either monophasic or biphasic gels.[39] Biphasic gels such as Restylane and Perlane (Medicis) are particles of crosslinked HA suspended in a liquid. They differ by particle size: Restylane particles are roughly 250 μm in diameter, while Perlane particles are about 550 μm in diameter, with concentrations of 100,000 particles/mL and

Box 2-2 Properties of hyaluronic acid

- Low allergenicity
- Crosslinking provides stability
- Effective
- Viscoelastic
- Consistent across species
- Hygroscopic
- Biocompatible
- Good safety profile

Box 2-3 Adverse events related to HA fillers

- Bruising
- Swelling
- Tenderness
- Redness
- Pain
- Itching

8,000–10,000 particles/mL, respectively. Monophasic gels such as Juvéderm Ultra and Juvéderm Ultra Plus (Allergan) are crosslinked in one process (Hylacross technology, Allergan), producing an entirely stabilized smooth gel without particles. Belotero (Merz) is also a monophasic gel crosslinked by cohesive polydensified matrix technology, which produces increased elastic and viscous properties.[39]

HAs have a high molecular weight (50 kDa) and connect a large amount of water (one molecule is able to join a weight 1,000 times larger than itself). The content of HA in the skin decreases with age, leading to its dehydration and wrinkle occurrence. Due to the stabilizing, hydrating, and cushioning properties and high biocompatibility of HA, it is an ideal material for soft tissue filling.[40]

The concentration of the gel is reduced during its resorption, but the volume remains high until the last molecules of HA are subject to degradation. Depending on the concentration and crosslinking, HA fillers can be applied to the superficial layers of the dermis, the middle layers of the dermis, the lower layers of the dermis, and subcutaneously.[19]

Since their introduction in 2003, HA fillers have been shown to have excellent effectiveness and acceptable safety profiles. They have been used on-label to improve the nasolabial folds and lips as well as off-label to correct lines and wrinkles and to volumize the aging face.[8] They have been found to provide a longer-lasting improvement over both collagen-based products and animal-derived HA. Safety was reviewed from worldwide data of 144,000 patients treated with HA (Restylane and Perlane) in 1999 and 262,000 patients treated in 2000.[41]

In regard to total adverse events, they decreased from 0.15% to 0.06% after the introduction of a more purified HA raw material. The most common adverse event is a hypersensitivity reaction, seen in 1 of every 5,000 patients treated. Temporary events include redness, swelling, localized granulomas, and bacterial infections[21] (Box 2-3).

As the most widely used filler substance currently on the market, HA has a number of advantages over its predecessors. Crosslinked HA fillers have been used for longer than 15 years and are considered to be generally well tolerated. They have structural properties similar to those of native tissue, excellent biocompatibility, and good tissue integration. They have a tunable duration of action spanning the entire range of the temporary filler category (6–24 months), and because of

Table 2-4 Indications for HA fillers based on consistency

FILLER	INDICATION	CONSISTENCY
Restylane Volyme	Loss of malar, mentum, or mandibular volume	High
Restylane Defyne	General volume loss and deep creases	
Restylane Kysse	Lip shape and texture	
Restylane Refyne	Moderate wrinkles like marionette lines	
Restylane Fynesse	Fine wrinkles like perioral rhytids	
Restylane Skinbooster	Deep moisturizing of the skin	Low

their relatively stable molecular composition, they can be stored without refrigeration for up to 2 years. Because of the hydrophilic nature of HA, these fillers also serve to hydrate the skin, and uniquely among other filler substances, HA can be reversed using hyaluronidase. In most commercial products, HA is crosslinked to increase its longevity, and the crosslinking agent used has an important effect on the properties of the final product; 1,4-butanediol diglycidyl ether (BDDE) is the crosslinking agent used in the majority of the market-leading HA fillers, and its stability, biodegradability, and long safety record spanning more than 15 years are what make it the industry standard, ahead of other crosslinkers such as divinyl sulfone and 2,7,8-diepoxyoctane.[21]

Table 2-4 illustrates the indications for HA fillers based on consistency.

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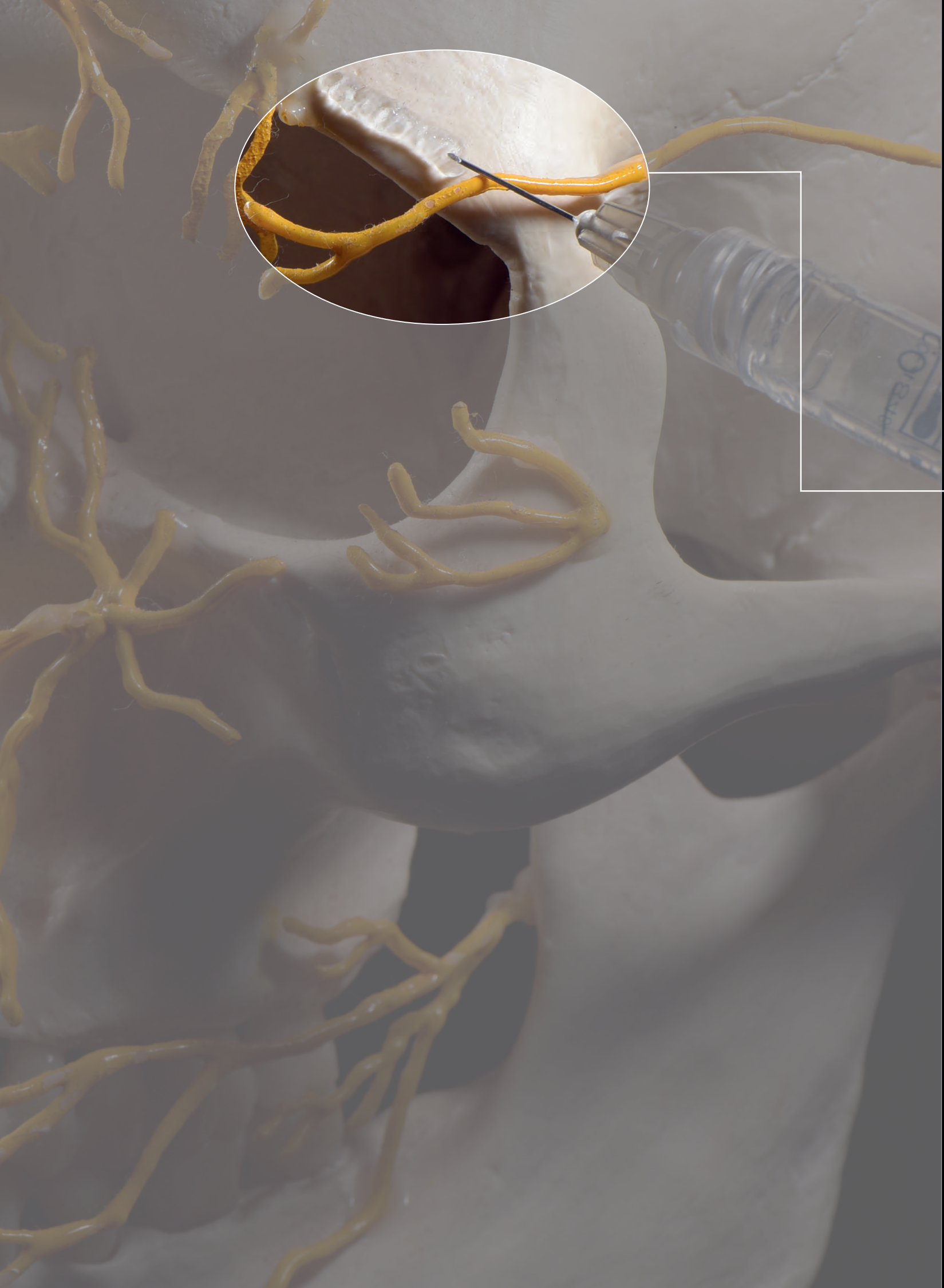


CHAPTER

03

Injection Planes and Techniques

Table 3-1 Injection planes and their characteristics

CHARACTERISTIC	SUPERFICIAL FAT	DEEP FAT
Duration	Long	Short
Injected volume	Small	Large
Depth	3 mm	Bone plate
Instrument	Needle or cannula	Needle or cannula
Regions	All	Tear trough
Result	Concentrated	Diffuse
Layers to elevate	Two	Four

Planes of Injection for Fillers

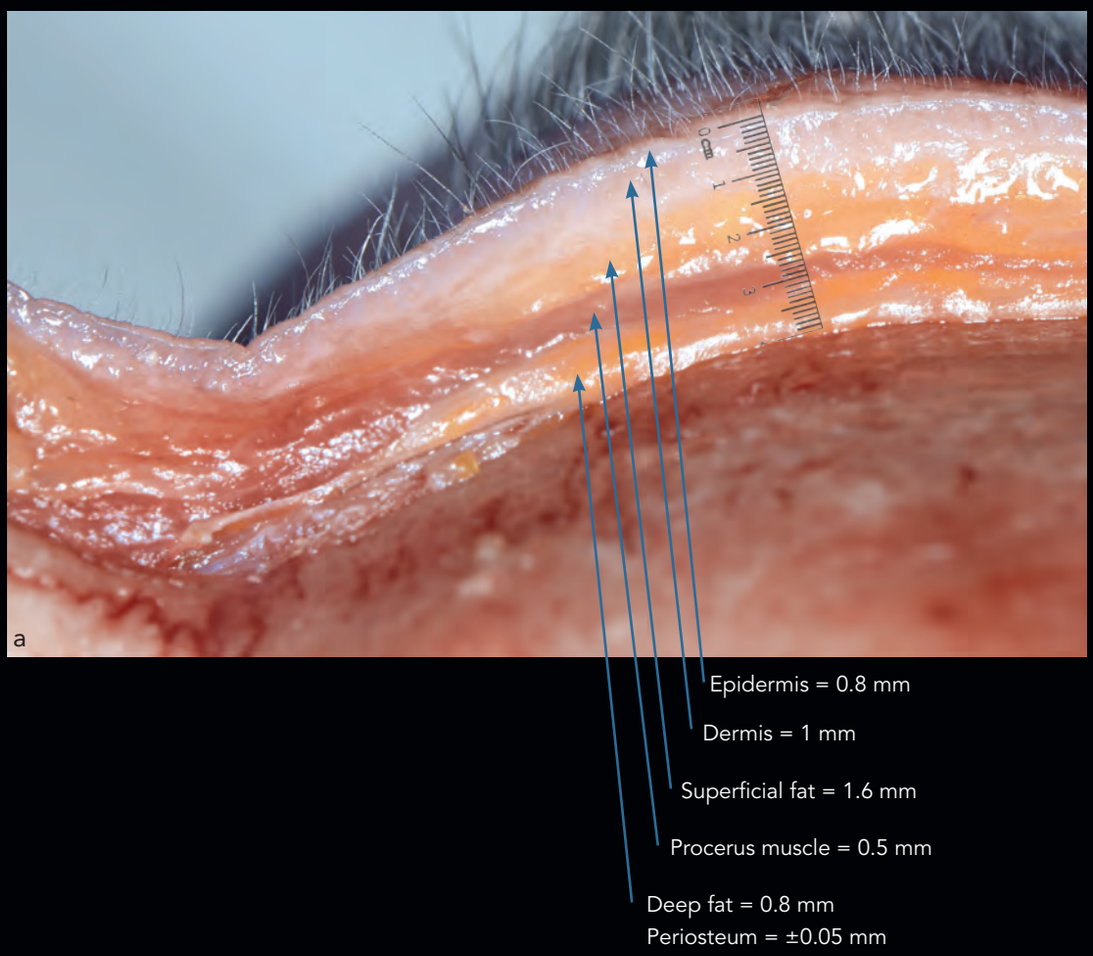
While botulinum toxin should be injected intramuscularly, *fillers should not be*. The separation of muscle fibers caused by the filler injection would result in damage and inflammation. The ideal injection plane for dermal fillers is the fat area. In terms of anatomy, fat works as a natural filler, so it stands to reason that fatty areas are good sites to inject fillers.

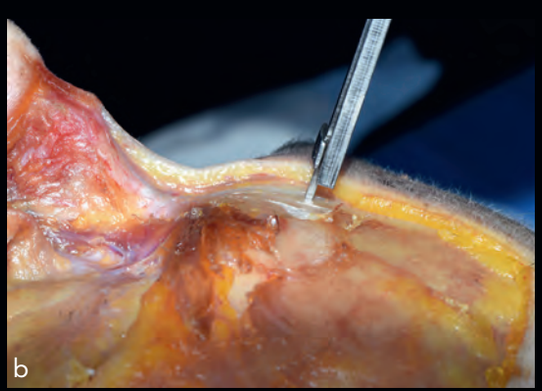
Facial mimetic muscles do not have a fascia that separates and envelops them. Instead, a layer of fat is responsible for separating the muscles from each other and from bone. The fat located in the face also has the function of filling and smoothing the facial anatomy and is distributed into two planes: shallow and deep. The shallow plane lies just underneath the skin, while the deep plane is beneath the muscle layer. Different results can be achieved when fillers are injected into these two planes.

Injections in the deep layer of fat demand a larger amount of filler for a noticeable result in the skin of the face. This can be explained by the fact that the product physically would have to elevate the muscle layer and the skin. On the other hand, applications made in the superficial fat demand a smaller amount of the filler to obtain a similar result, because the filler has fewer layers to physically elevate (ie, only the superficial layer of fat and the skin).

Because the deep fat layer is beneath the muscle plane, injections in this area might have a shorter duration in that the repeated contraction of the muscle could flatten the enhanced volume. Therefore, *the ideal technique is to inject facial fillers in the superficial fat layer*. A notable exception is the tear trough. This is the only area in the skin that is exceptionally thin, with a tendency to make the filler too evident when deposited in this region. The solution for this undesirable effect is a deep injection of the filler, that is, at the deep fat layer between the orbital bone and the orbicularis oculi muscle. When depositing the filler under the orbicularis oculi muscle, it works as a shield to disguise the filler volume under the muscle, resulting in a natural appearance.

In order to find the correct injection plane, the clinician should take into consideration the depth required. For instance, if the plane is the superficial fat, the depth should be approximately 3 mm under the epidermis. In the deep fat, the plane of reference is the contact between the needle or cannula and the bone plane (Table 3-1). Fillers should be injected at the right depth not only to achieve the desired results but also to prevent damage to the patient. Clinicians who have not been trained in fresh cadavers might find it more difficult to perceive these planes. Figures 3-1 and 3-2 illustrate these distinct planes as well as their indications.[1,2]





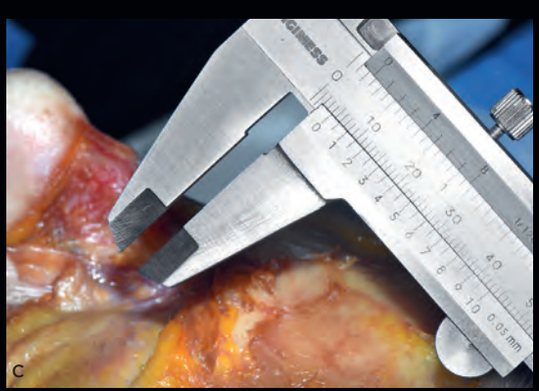
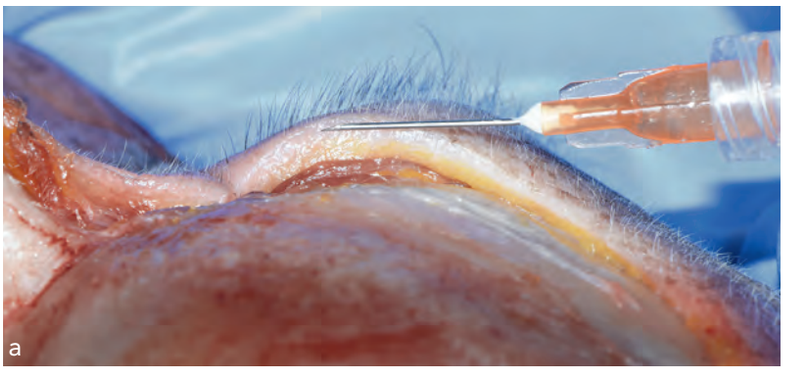


Fig 3-1 Tissue layers of the forehead. *(a)* The total thickness of the glabella is 4 mm. These measurements of thickness are different for distinct areas and individuals.[1] *(b)* A caliper being used to measure the depth. *(c)* Caliper showing the depth measurement.

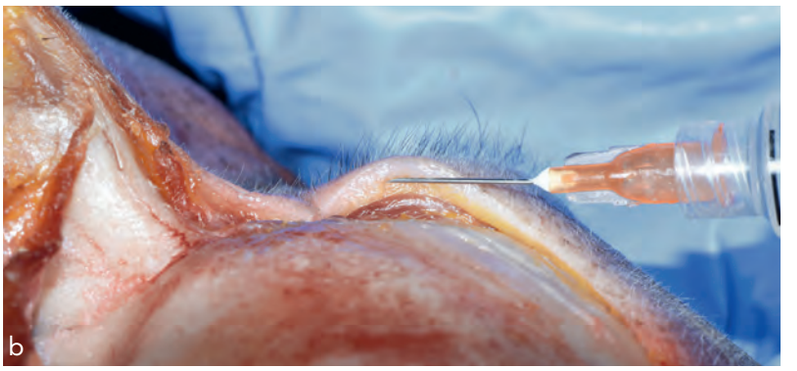


DEEP DERMAL FILLING

Purpose: It is not used for volume enhancement. Instead it is only used for subcutaneous hydration because the dermis is not expandable.

Instrument: Needle. Cannulas are not able to divulse the dermis because it is firm.

Product: Skin booster or thin fillers.

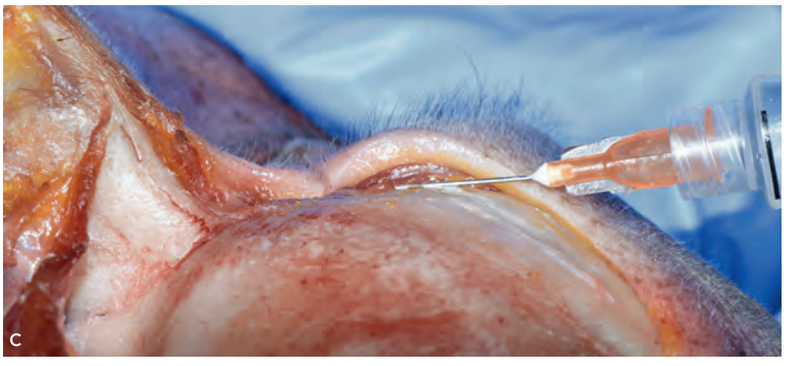


SUPERFICIAL FAT FILLING

Purpose: Volumization with or without defining the sculpt.

Instrument: Needle or cannula. Cannulas easily divulse this layer of fat.

Product: Filler of an average consistency.



SUPRAPERIOSTEAL FILLING

Purpose: Volumization without defining the sculpt.

Instrument: Needle or cannula. Because they are blunt, cannulas slide over the periosteum, decreasing the possibility of damaging the muscles.

Product: Thick fillers.

Fig 3-2 The glabellar region of a fresh cadaver with the three possible injection planes to deposit the filler. The clinician might choose one, two (dual-plane technique involves injections in the supraperiosteal layer and the superficial fat layer),[2] or three planes in the same region in a single session. *(a)* Deep dermal filling. *(b)* Superficial fat filling. *(c)* Supraperiosteal filling.

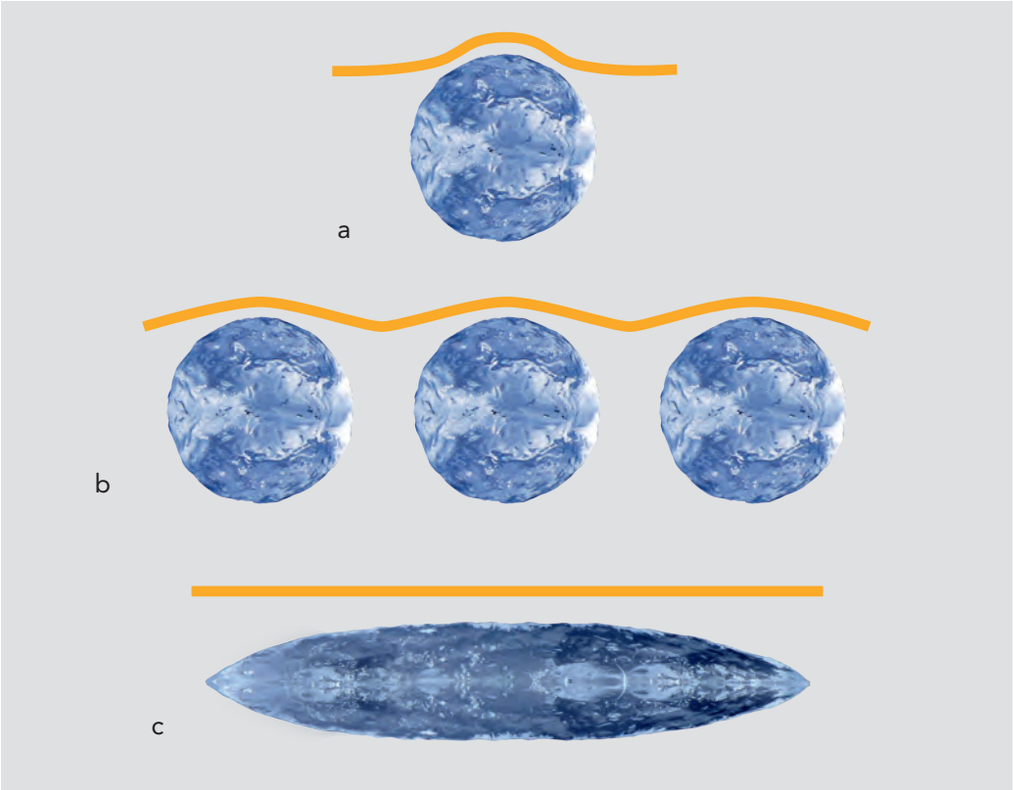


Fig 3-3 Effects of different injection techniques on the superficial anatomy of the skin: *(a)* Puncture. *(b)* Serial puncture. *(c)* Linear threading.

Injection Techniques

The different injection techniques affect the superficial anatomy of the skin in several ways (Fig 3-3):

- *Puncture:* If superficially injected, the filler causes a noticeable elevation in the skin surface. When deeply injected, it only makes the punctual flaws uniform without lifting the skin beyond surrounding areas. It is used in punctual depressions and/or to sculpt a visible volume such as the upper lip stomion, acne scars, malar region, nasolabial angle, glabella, and lateral depression of the chin region.
- *Serial puncture:* If injected superficially, the filler might cause a lump in the skin surface. Although this is an easy technique, it tends to produce irregularities, and for this reason it is not recommended. The results using this technique are poorly predictable.
- *Linear threading:* If superficially injected, the filler causes a linear elevation noticeable in the surface of the skin. When deeply injected, it only levels the depressions. Sites include the philtrum of the upper lip, eversion area of the lip vermilion, malar region, lateral depression of the chin region, marionette lines, jawline, supratip, bone structure of the orbit and zygomatic bone, infrapalpebral depression, and sulcus in general.

The techniques described in Fig 3-4 can be used with needles or cannulas. The clinician should choose the technique according to the desired final result.

Because fillers come in the form of a gel, they demand a stronger manual pressure on the plunger when using needles and cannulas. For this reason, filler syringes are like the Luer-Lok (BD Medical) type and require that the needle or cannula is strongly screwed to the tip of the syringe to avoid the extrusion of gel in the side of the hub during injection (Fig 3-5).

PUNCTURE

Technique:

1. Insert the needle to the desired depth.
2. Apply pressure to the plunger and keep the syringe steady.

SERIAL PUNCTURE

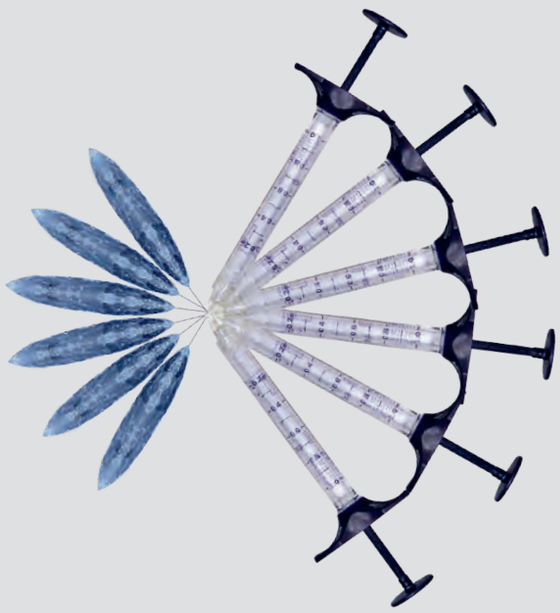
Technique:

1. Insert the needle to the desired depth.
2. Apply pressure to the plunger and keep the syringe steady.
3. Repeat the same procedure throughout the area to be sculpted.
4. Massage the site to make the surface uniform.

LINEAR THREADING

Technique:

1. Insert the needle to the desired depth.
2. Apply pressure to the plunger and simultaneously pull the syringe in order to make a regular thread.
3. Massage if necessary.



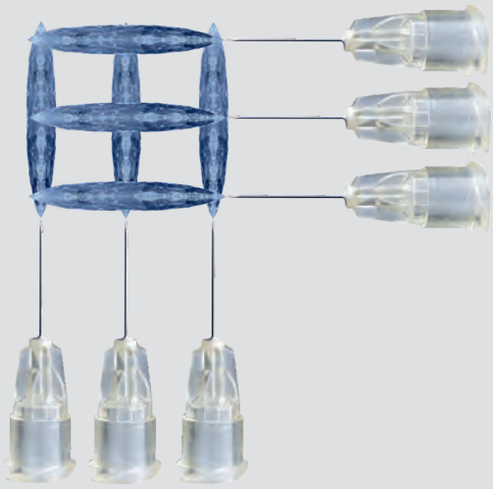
FANNING

Technique: It consists of multiple injections with a retrograde insertion using the same entrance point. The needle or cannula is not completely withdrawn between the retrograde injections.

Sites: Areas of depression (wider than the sulcus)—eg, marionette lines.

Characteristics: It produces a regular surface and natural appearance.

Fig 3-4 Different injection techniques.



CROSSHATCHING

Technique: It consists of a series of parallel linear injections in a grid pattern.

Sites: Broad areas of the depression and/or for subcutaneous hydration—eg, side of the face.

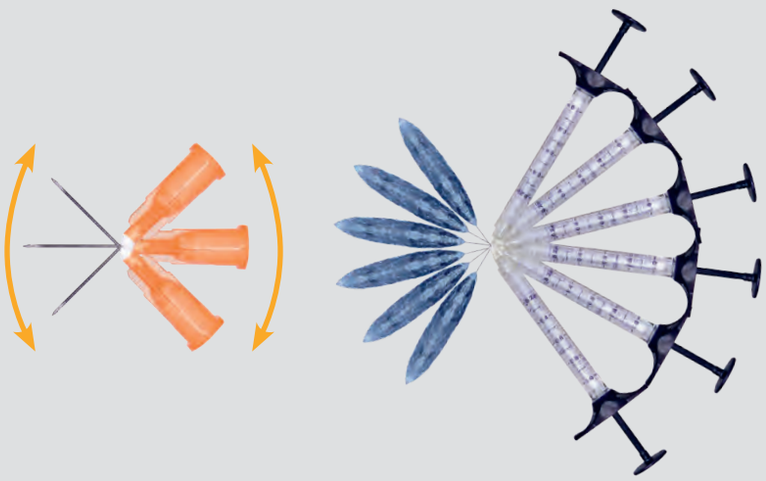
Characteristics: It produces a regular surface and a natural appearance.

SUPRAPERIOSTEAL BOLUS

Technique: It consists of a puncture application in contact with the periosteum.

Sites: Depressions caused by bone losses and deficiencies—eg, the malar and chin region.

Characteristics: It simulates the support provided by the bone tissue to the skin.



SUBCISION

Technique:

1. Using a conventional needle or Nokor needle (BD Medical), insert the needle in only one entry point following the length of the area to be filled.
2. At the same time the syringe is removed, shake it upward to remove the adherence. The undulations should not be larger than the area to be filled.
3. Deposit the filler in the same extension of the area to be filled to prevent the formation of new adhesion of the skin.

Areas: Areas of adhesion of skin—eg, scars.

Fig 3-5 The needle or cannula must be strongly screwed to the tip of the syringe to avoid gel extrusion during injection.

Needles and Cannulas

Dermal filler syringes can be used with needles or cannulas.

Needles

The manufacturers of gel fillers provide syringes along with the needle appropriate for each type of filler (Fig 3-6). Smaller needles (around 0.3 mm) are included in the packaging for thinner fillers and bigger needles (around 0.4 mm) for thicker ones. The advantages of needles are that they are provided by the manufacturer, and self-piercing, and can be used for intradermal filling. However, because of the cutting bevel, they might puncture a blood vessel and cause embolism. Because they are short, they require a larger number of perforations to reach broader areas. They can also cause bruises, tear the skin, and traumatize the tissues.

Cannulas

Cannulas are sold separately and are not provided by the manufacturer (Fig 3-7). The clinician might choose the length according to the size of the area to be filled. The gauge can be chosen based on the filler density. The primary advantages of cannulas are that they do not cause trauma and divulse the tissue instead of cutting it, which prevents bruises and possible embolization. They are also long, thereby demanding fewer piercings, and are able to make uniform threads. They can also be curved, enabling them to adjust and be pressed against the internal surface of the skin without tearing it when the goal is a superficial filling.

Cannulas smaller than 25G are sharp and do not offer the safety profile of the other sizes. Because they are so thin, they effectively function as needles. This type of cannula might cause embolism in the vessels and result in necrosis. For this reason, 25G, 22G, and 18G cannulas are recommended. Some brands of cannulas include a needle for the entry point. The needle should have the same gauge as the cannula. Different cannula gauges are indicated by different colors (Fig 3-8).

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2. Salti G, Rauso R. Facial rejuvenation with fillers: The dual plane technique. J Cutan Aesthet Surg 2015;8: 127–133.

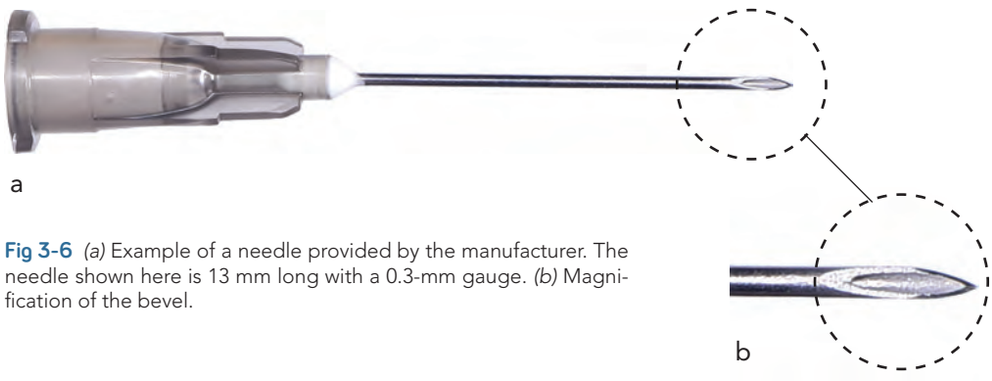


Fig 3-6 *(a)* Example of a needle provided by the manufacturer. The needle shown here is 13 mm long with a 0.3-mm gauge. *(b)* Magnification of the bevel.

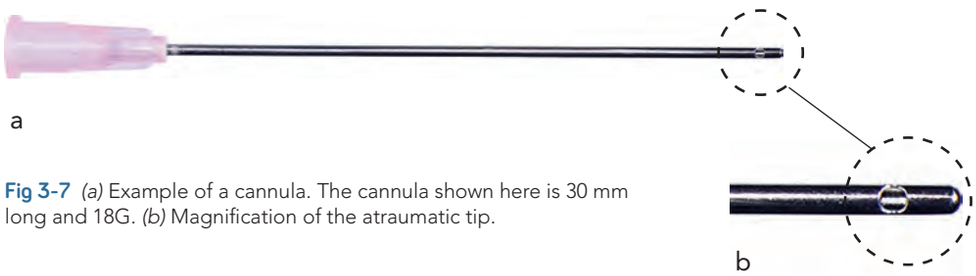


Fig 3-7 *(a)* Example of a cannula. The cannula shown here is 30 mm long and 18G. *(b)* Magnification of the atraumatic tip.

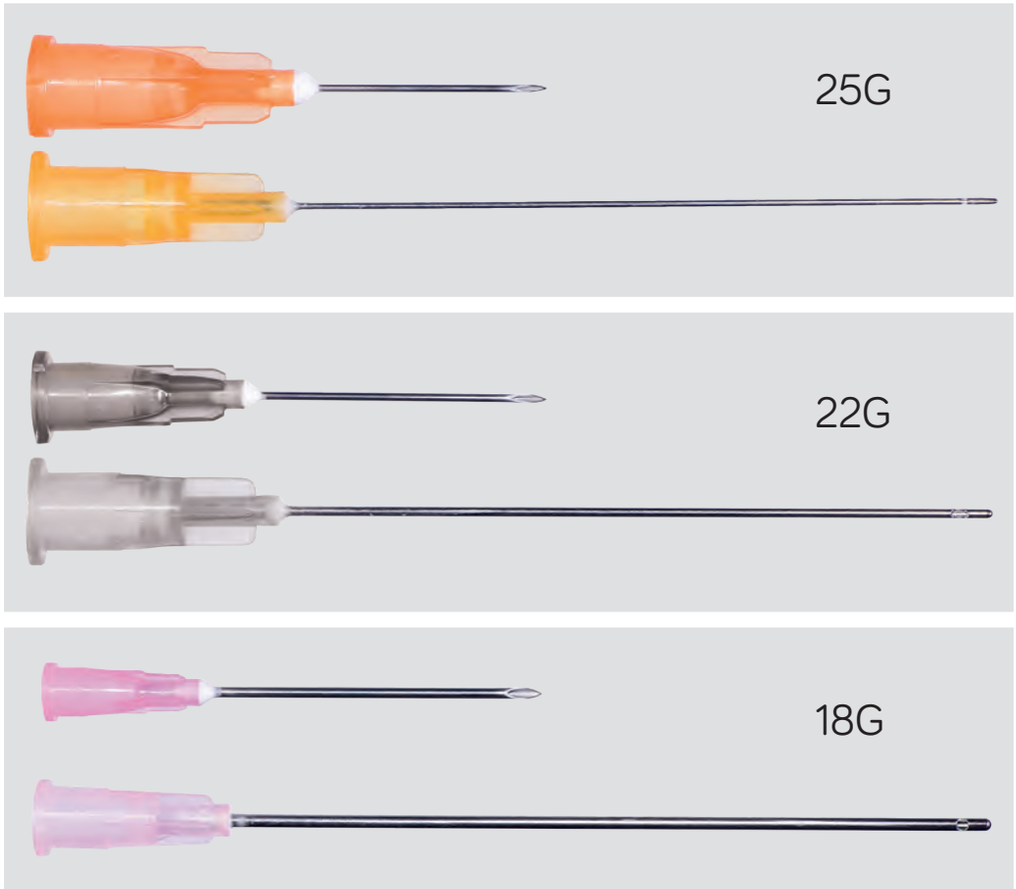
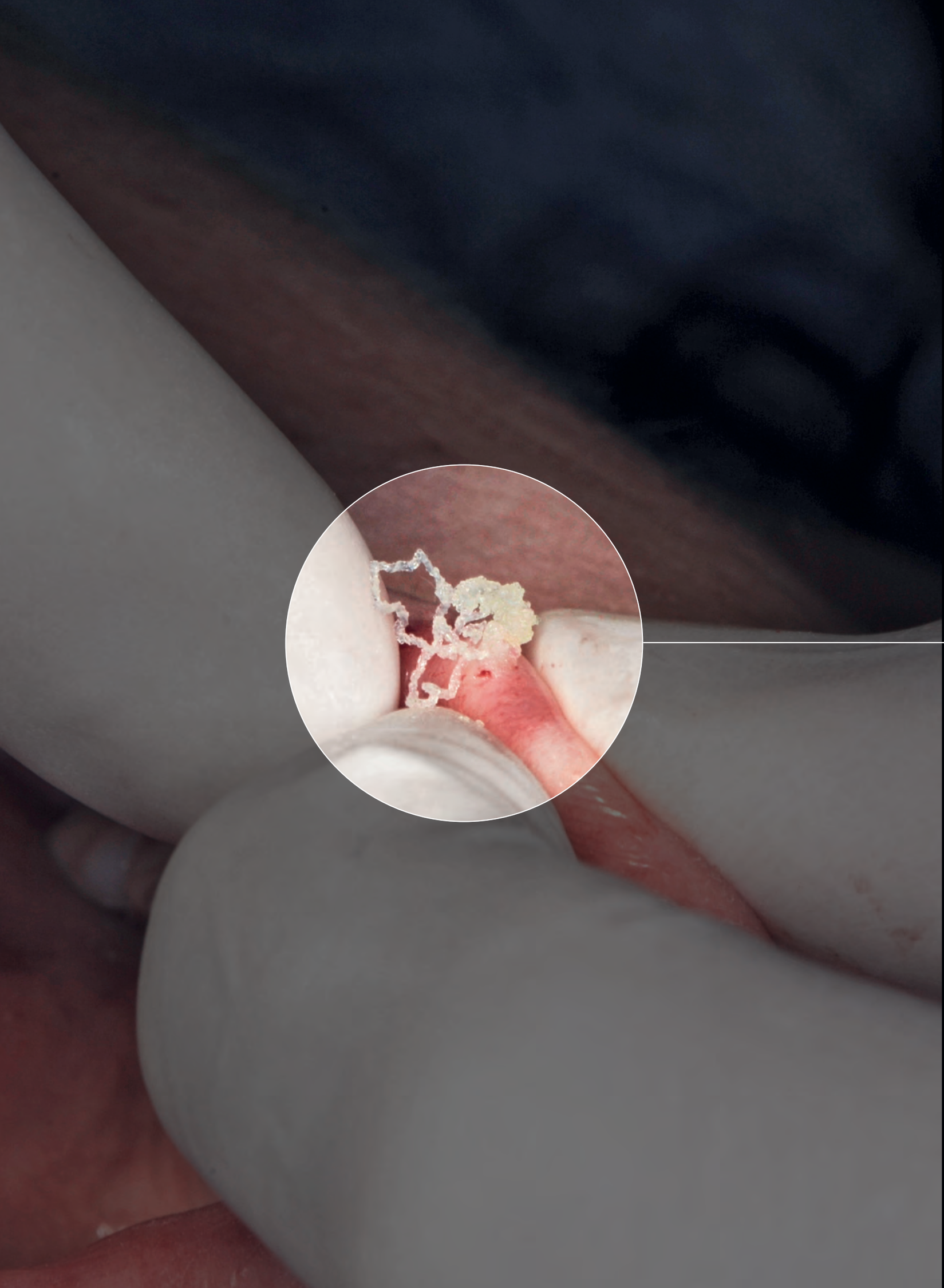


Fig 3-8 Different cannula gauges.



CHAPTER

04

Complications

Box 4-1 Classification of soft tissue filler complications by onset of adverse event[4]

EARLY REACTIONS	LATE REACTIONS
• Vascular infarction/soft tissue necrosis	• Infection
• Inflammatory reactions (acute/chronic)	• Granuloma (typically chronic)
• Allergic reactions/hypersensitivity	• Nodules
• Injection-related events	• Dyspigmentation
• Pain	• Displacement of hyaluronic acid filler material
• Ecchymosis	
• Erythema	
• Bruising	
• Bleeding	
• Inappropriate/superficial placement	
• Distant spread	

Dermal fillers vary in their composition, duration of effect, palpability, ease of administration, potential complications, and other factors, all of which affect the therapeutic results.[1,2] Hence, achieving desirable outcomes with dermal fillers depends critically on understanding their different characteristics, capabilities, methods of injection, risks, and limitations. In addition, there is a learning curve associated with the administration of dermal fillers; it requires practice to achieve consistently desirable results. Perhaps the most important guideline for preventing complications with dermal fillers, more so than selecting the appropriate patients, is not to treat inappropriate ones.[3]

Box 4-1 classifies soft tissue filler complications according to onset.[4] Some anatomical areas, such as the glabella, alar base, nose, and temple, are known to be associated with higher risks of vascular complications.[5–8] In addition, patient history may be a pertinent factor in the emergence of adverse reactions. Insufficient operator experience is also a contributory factor to the development of complications.[9] Clinicians should select products appropriately and practice proper techniques to minimize adverse reactions. Clinicians performing injections should have a thorough knowledge of injection-related anatomy as well as a full patient history of previous cosmetic procedures to determine whether relative or absolute contraindications exist. Specifically, the clinician should query the patient regarding previous complications with dermal fillers, significant allergy, or other significant medical conditions.

With hyaluronic acid (HA) in particular, the following guidelines will help clinicians minimize the risk of adverse reactions[4]:

- Understand the anatomy of the injection site.
- Beware of "danger" areas.
- Aspirate before injecting.
- Slowly inject with the least amount of pressure possible.
- Incrementally inject 0.1 to 0.2 mL of product.
- Use blunt microcannulas.
- Carefully consider the patient's medical history.
- Stop injecting if resistance is encountered or if the patient experiences pain/discomfort.
- Always monitor the patient.

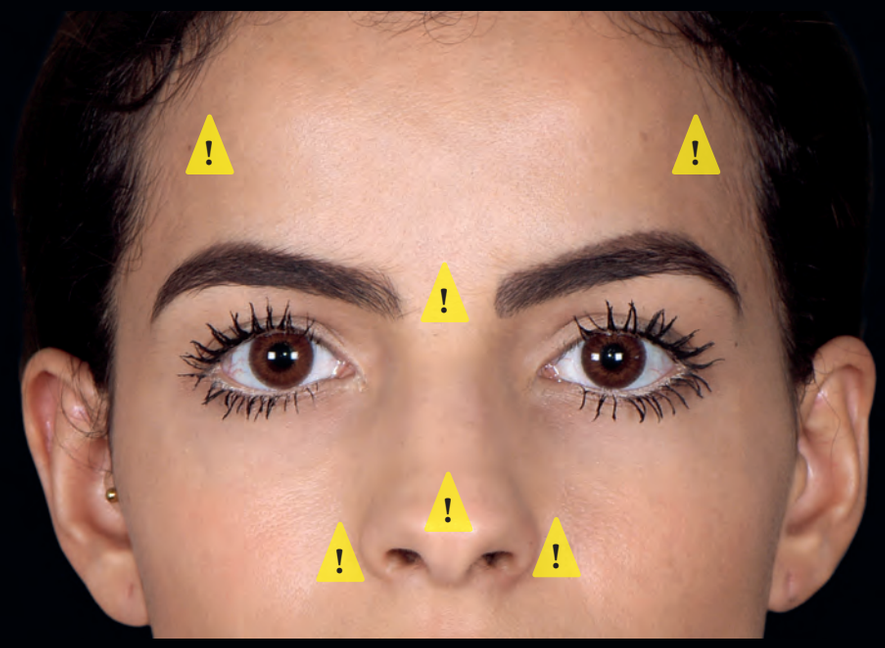


Fig 4-1 Highest areas of risk for tissue ischemia.

Vascular Obstruction and Skin Necrosis

One uncommon but potentially serious complication of HA filler injection is skin necrosis.[10] It has been proposed that ischemia may occur secondary to compression of the vasculature by extravascular filler material after the HA hydrates and expands, or through inadvertent intra-arterial HA injection or intravascular embolism[11–13] (Fig 4-1). There are also reports of skin necrosis in areas distant from the injection site, suggesting embolization after introduction of intra-arterial filler material.[11,14] One particularly ominous complication is the potential for visual impairment secondary to intra-arterial injection and obstruction of branches of the retinal or ophthalmic arteries,[15,16] which has most commonly been reported after filler injection into the glabella or nasolabial folds.[13] Similarly, the glabella and nasal ala are the injection sites most commonly associated with skin necrosis[11,15] (Fig 4-2), as these regions have limited collateral blood supply.[11] Skin necrosis generally presents with blanching and dusky discoloration, along with pain in the affected area.[10,11] Venous occlusion has also been described, presenting with the delayed onset of vague discomfort and ecchymotic-appearing lesions.[15]

Management of ischemic complications may include the promotion of vasodilation through warm compresses, 2% nitroglycerine paste, or sildenafil, as well as systemic corticosteroids, anticoagulation with aspirin or low–molecular weight heparin, and intralesional hyaluronidase injection.[13] The key to preventing the skin ischemia from progressing to necrosis is to identify and treat it as early as possible. There is no consensus on the ideal treatment in these cases, but it is important to maintain good local hygiene, use warm compresses and 2% nitroglycerine paste, and massage the area to dissolve the embolus.[17] In cases of tissue necrosis, hyaluronidase injection is recommended as soon as possible (ie, within 24 hours) to reduce damage caused by the necrosis.[11] In case of embolization, full heparin therapy might also be necessary.[18] In this context, the hyaluronidase should be given in doses ranging from 30 to 75 units in normal saline or lidocaine.[13,17]

When managing a case of intra-arterial HA injection, studies suggest that direct intravascular administration of hyaluronidase is not typically required, as hyaluronidase readily diffuses into the vascular lumen.[1,2] Therefore, hyaluronidase may be injected into the region of a suspected obstruction rather than directly into the vasculature.[19,20]

CAUTION

- At supratip, the amount to be injected at the filament located at the midline should not exceed 0.1 mL (10% of the syringe). Lateral filaments tend to block blood supply at the midline.
- A greater blood vessel compression occurs when using high-density fillers, increasing the risk of necrosis.
- The use of needles at supratip increases the chance of vascular embolization and necrosis.
- The amount to be injected at the region of the anterior nasal spine should not exceed 0.3 mL.
- The base of the alar cartilage is located at the danger triangle of the face, described as such because of its proximity to the facial vein. Its embolization may flow back to the cavernous sinus as a result of a thrombophlebitis, which, if infected, may progress to a meningitis (through the propagation inside the intracranial venous system) and even death. On the other hand, the thrombosis may affect the central retinal vein, leading to an irreversible vision loss. Another complication that may occur at the same area is a retrograde embolism of the angular artery at the end of the nasolabial fold that presents anastomosis with the ophthalmic artery; this can result in irreversible blindness. Avoid this area.
- The use of Nexcare micropore tapes or similar tapes as well as nasal decongestants are not recommended within 20 days after the surgery. Many of these products contain benzalkonium chloride (BKZ, quaternary ammonia-based disinfectants), a bactericide ineffective against spore-forming bacteria, fungi, and viruses. BKZ causes histomorphologic alterations at the cells of the nasal mucosa and decreases local immunity (reducing phagocytic activity of neutrophils). Consequently, it can increase the risk of opportunistic infections.
- Nasal decongestants cause local vasoconstriction, which can lead to necrosis.
- Previous rhinoplasties increase the risk of necrosis.

Fig 4-2 The delicacy of the nose's vascularization increases the potential for complications after filler injections.

Noninflamed Lesions

Excessive quantities or misplacement of HA may result in the development of subcutaneous nodules.[7,20,21] Given that HA is resorbable, uncomplicated nodules will eventually self-resolve over time.[21] However, if a nodule is painful or if the patient is bothered by its appearance, hyaluronidase can be injected to resolve the nodule.[13]

Lumps, asymmetries, or contour deformities occurring in the early posttreatment period may respond to massage. Needle aspiration or minimal stab wound incision with evacuation may be an option. A benefit of HA fillers is that irregularities can be reversed with hyaluronidase, a feature that other fillers do not share.[4,8,10,22] Products with a higher elastic modulus (G′) are not recommended in delicate areas such as the tear trough.

Inflammatory Nodules

The development of inflammatory nodules has also been described after HA injection and may occur due to infection and development of an active biofilm in the region of application.[20,22] If infection is suspected, initial management may include oral antibiotics, incision and drainage if the lesion is fluctuant, and intralesional corticosteroids.[18,20] Steroids should be administered after antibiotic treatment has been initiated.[20] Hyaluronidase injection has also been described in the management of painful inflammatory nodules. Hyaluronidase has been demonstrated in vitro to effectively break down bacterial biofilms[23] and has been shown to have a clinical role in the management of infections related to filler injections.[24] Concurrent management with oral antibiotics is recommended because the administration of hyaluronidase may disseminate the injection by breaking up the collection.[25]

Inflamed nodules may also occur due to granulomatous reactions associated with HA gel or contaminating proteins.[13] The following empiric antibiotic regimen is recommended: clarithromycin 500 mg plus moxifloxacin 400 mg twice daily for 10 days, or ciprofloxacin 500 to 750 mg twice daily for 2 to 4 weeks, or minocycline 100 mg once daily for 6 months.[4]

Undesired Volume

A potential complication of filler treatment is undesirable volume, and effective treatment relies on appropriate diagnosis. Table 4-1 illustrates the common diagnoses for undesirable volume and their therapies.

Table 4-1 Diagnoses for undesirable volume and their appropriate treatment

DIAGNOSIS	CHARACTERISTICS	THERAPIES
Low-quality HA	Relevant product-related factors include the concentration and rheologic properties of the filler and the manufacturing processes (eg, purification). After the procedure = regular volume. Postsurgery = palpable nodules of a stable size.	1. Massage. Proceed to step 2 if not resolved. 2. If located at the lip vermilion, apply pressure, make a puncture using an 18G needle, and squeeze the nodule. In areas under the skin, an incision in the area will not be effective. Hyaluronidase will not dissolve a low-quality HA because it is not made only of HA.
Excessive HA	Appropriate injection techniques as well as appropriate dosage help to limit the risk of adverse reactions and contour irregularities. After the procedure = excessive volume. Postsurgery = excessive and stable volume.	If located at the lip vermilion, apply pressure with the fingers, puncture the nodule with an 18G needle, and squeeze it. In areas covered by dermis, the nodules cannot be punctured or squeezed. In these situations, hyaluronidase is required.
Allergy	After the procedure = progressive volume. Postsurgery = volume rapidly increases and redness develops.	Wait 48 hours for a spontaneous resolution or prescribe an oral antihistamine for 2 days to make the patient more comfortable.
Infection	Effective skin asepsis using 2% chlorhexidine gluconate in 70% isopropyl alcohol can reduce the risk of infection. Disposable sterile gloves and sterile dressing trays and drapes should be used. After the procedure = normal volume. Postsurgery = volume slowly increases and pain and redness develop. Noticeable after 2 days.	Prescribe antibiotics according to the clinical history of the patient. Prescribe anti-inflammatory agents in case of excessive edema. Prescribe analgesics in case of pain.
Acute/chronic inflammation (occurs with alloplastic material)	After the procedure = normal volume and redness. Postsurgery = volume presents oscillations from normal and is slightly increased with palpable nodules and redness. **HA does not present this adverse effect because it is bioidentical**.	Prescribe oral anti-inflammatory and/or local infiltrations (eg, triamcinolone) and/or topical anti-inflammatory agents (eg, betamethasone).
Compression over lymphatic vessels resulting from excessive product injected superficially	After the procedure = normal volume. Postsurgery = volume ranges from normal to excessive. The most common site for this adverse reaction is the tear trough. The volume is high in the first hours of the day and decreases after noon.	Inject hyaluronidase.

Hyaluronidases

In the uncommon event that an undesirable outcome occurs with HA, correction is possible with the injection of commercially available hyaluronidase, an enzyme that breaks down the unwanted HA dermal filler.

Hyaluronidases are a family of injectable enzymes that act as dispersion agents. These help speed up the natural breakdown of HA through hydrolysis.[26] Licensed for therapeutic indications, such as increasing tissue permeability to enhance the delivery of drugs or to increase the uptake of subcutaneous fluids, in esthetics it is widely used off-label.[27] *Off-label* does not necessarily mean that it is unsafe to use but rather that it is being prescribed and administered in a way that is different from its licensed use.[28]

In addition to humans, hyaluronidases have been found in a variety of venoms from snakes, lizards, and insects. In this capacity, they contribute to the local damage and accelerate the spread of toxins at the bite site and affect the local integrity of the extracellular matrix due to degradation of HA.[29] Moreover, various species of gram-positive bacteria (eg, *Staphylococcus aureus*) are capable of producing bacterial HA lyases as a potential virulence factor to promote tissue penetration.[30,31]

Hyaluronidase treatment and application is generally well tolerated, and adverse events are rare.[32] Allergy tests must be performed before its application as a precaution, because side effects such as temporary postinjection pruritus or allergic reactions have been reported.[31,33] Wohlrab et al[31] investigated the influence of adjuvant hyaluronidase on wound healing using the suction blister method in a prospective, single-center, placebo-controlled, double-blind, intraindividual comparison study of 20 participants, and no retardation of wound healing or other relevant risks were observed. These clinical results are in line with the author's in vitro wound healing analyses using primary human structural skin cells (primary human keratinocytes and dermal fibroblasts, unpublished data).

Based on the literature, Buhren et al[34] propose the following recommendations for the use of hyaluronidase in esthetic medicine:

- When working with dermal HA filler, hyaluronidase should always be immediately available.
- For esthetic indications, hyaluronidase (Hylase, Dessau) should be dissolved in 1.0 mL saline solution (0.9% NaCl).
- Severe complications of vascular necrosis following accidental intravascular HA filler injection should be immediately treated with infiltrations of large volumes of hyaluronidase in the entire area (ideally less than 4 hours after filler injection).
- For the correction of HA overfill, the applied volume of hyaluronidase should not exceed the estimated volume of the overcorrection in order to avoid complete degradation of the effect of HA augmentation. Ideally, hyaluronidase should be injected gradually in small volumes and, when necessary, over multiple sessions in order to achieve the desired extent of correction and to prevent overtreatment.
- For the treatment of lower eyelid edema following HA augmentation of the tear trough, only a small volume of hyaluronidase should be applied at a time in order to gradually dissolve excessive HA and to avoid complete reversal of the effect of HA augmentation.
- The efficacy of hyaluronidase treatment in the management of lower eyelid edema following HA augmentation of the tear trough is more effective when applied early (within weeks of the first appearance of edema).

The use of hyaluronidase for esthetic purposes is not approved by the US Food and Drug Administration and is considered an off-label use. In many cases, 10 to 30 units of unpreserved hyaluronidase is sufficient to achieve the desired correction. Local site reactions may occur in up to 25% of patients, but they are typically transient and mild. Initial treatment with as little as 5 to 10 units of hyaluronidase is commonly recommended and is often effective, although some clinicians treat with as much as 75 units with few adverse effects. Additional corrections can be performed, although full correction may take up to 4 weeks to fully appreciate. Some preparations are bovine derived, and skin testing should be considered prior to treatment with these dermal fillers.[35,36]

Hyaluronidase preparations are clear, concentrated liquids that are stored in a refrigerated vial (Table 4-2). To reconstitute these dermal fillers, physicians typically add normal saline or lidocaine (with or without epinephrine). When using Amphadase (Amphastar), reconstitution in 3 mL of 1% lidocaine with 1:100,000 epinephrine has been commonly used with great success. After mixing, the vial is gently swirled. Prior to treatment, a skin test can be performed by injecting 3 to 5 units (0.06–0.1 mL) of the reconstituted solution into the superficial dermis at the antecubital fossa. A positive hypersensitivity reaction consists of a wheal appearing within 5 minutes and lasting 20 to 30 minutes, accompanied by local itching.[37]

Table 4-2 Commercially available hyaluronidase products

TRADE NAME	SOURCE	PRODUCT DETAILS	DOSAGE
Amphadase (Amphastar)	Bovine derived	150 USP units per mL in 2-mL vial. Contains edetate disodium, calcium chloride, monosodium basic buffer, and thimerosal.	**Vascular/tissue compromise:** 30–75 units of hyaluronidase reconstituted in normal saline[a] **Noninflamed nodule or overcorrection:** 5–15 units of hyaluronidase reconstituted in normal saline[b]; 1.5–3 units for eyelid area[c] **Inflamed or painful nodule:** 5–15 units of hyaluronidase reconstituted in normal saline[b]
Hydase (PrimaPharm)	Bovine derived	150 USP units per mL in 2-mL vial. Contains edetate disodium, calcium chloride, sodium chloride, and monosodium basic buffer.	
Hylenex (Halozyme)	Human recombinant source (significantly reduced risk of hypersensitivity)	150 USP units per mL in 2-mL vial. Contains human albumin, edetate disodium, and polysorbate 80.	
Vitrase (Bausch and Lomb)	Ovine derived	200 USP units per mL in 2-mL vial. Contains lactose, potassium phosphate dibasic buffer, and potassium phosphate monobasic buffer.	

[a] Reconstitute 0.5 mL of a 150 IU hyaluronidase vile in 1 mL of normal saline (75 units total). Inject 0.06 to 0.2 mL (equivalent to 30–75 units).
[b] Reconstitute a 150 IU hyaluronidase vile in 1 mL of normal saline. Inject 0.2 to 0.5 mL (equivalent to 5–15 units).
[c] Reconstitute 0.1 mL of a 150 IU hyaluronidase vile in 1 mL of normal saline (15 units total). Inject 0.1 to 0.2 mL volume (equivalent to 1.5–3 units).
(Data from Cohen et al.[13])

Case Report: Ischemia

A patient presented to the office after having another professional inject a dermal filler in the base and tip of her nose. Four hours after the procedure, the patient noticed a "whitish area" at the injection site and felt a "slight pain" in the filled area (Figs 4-3a and 4-3b). She also complained of a numbness in the area under her nose.

Signs and symptoms

Change in color

Redness after the filling might occur and is considered normal as a result of trauma from the injection. This redness appears up to 12 hours after filling and tends to resolve within 3 days. However, in cases of ischemia, the color observed is not exactly red but rather bluish-red (see Fig 4-3a). At first, the distribution is not homogenous but intermittent, similar to the aspect of small vessels. On palpation, these areas feel cold and painful to the touch compared to other areas of the face.

Pain at the injected site

Pain at the injected site might result from trauma caused by the cannula, needle, or even the filler itself, which causes the divulsion of tissues. This type of pain is a normal occurrence after filling procedures. However, in this case the pain increased in the first 3 days, which is not considered normal.

Prolonged numbness

If anesthesia is administered before the filling and/or if the filler has an anesthetic in its composition, the patient will immediately feel numbness in the area. The numbness will fade with time,

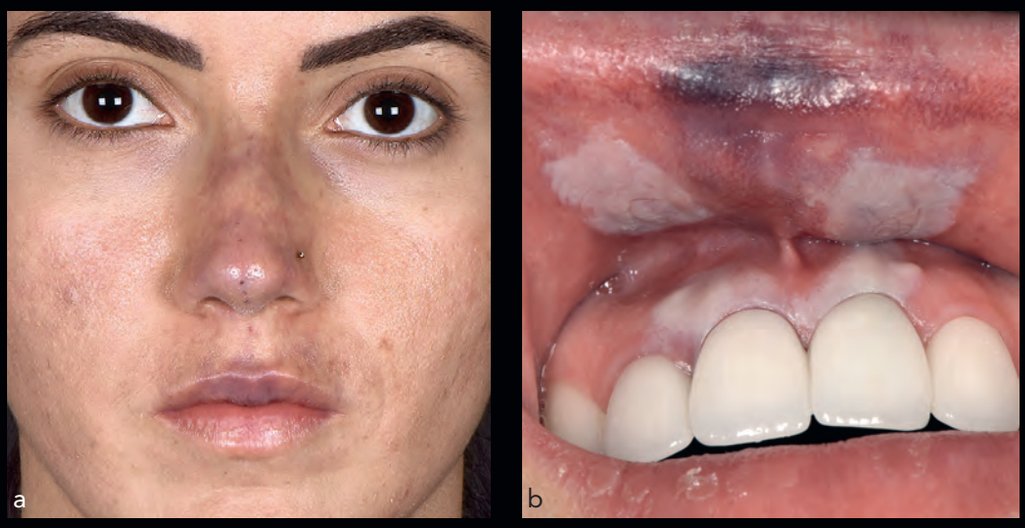


Fig 4-3 Case report of ischemia after filling. *(a)* Frontal view of the patient 12 hours after the filling. Note a bluish-red color of the skin in the nose and upper lip. *(b)* Intraoral view showing that the filler injected at the base of the nose affected the blood supply in the upper lip and anterior upper gingiva.

eventually disappearing entirely. However, when numbness is felt after the procedure and lasts longer than normal, it can be considered a sign of ischemia. Necrosis might occur when an excessive amount of filler compresses a blood vessel or nerve.

Diagnosis

The combination of bluish-red color, progressive pain, numbness, and cold tissue led to a diagnosis of necrosis.

Not all patients with necrosis show the signs and symptoms described above. Therefore, it is crucial that all information about the products used, injection planes, instruments, and data are available and correctly recorded.

Therapeutics

Most clinicians simply wait for the spontaneous resolution of ischemia. However, this is a dangerous practice. As soon as the diagnosis is made, the patient should be immediately treated while the tissue still shows some integrity. When the therapeutic procedure is delayed, tissues become fragile and might be easily traumatized during procedures such as massage.

1. Allergy test

Before injecting hyaluronidase to eliminate unwanted or problematic HA, an allergy test on the inside of the forearm is necessary (Figs 4-3c and 4-3d). The skin test is performed as follows:

1. An anesthetic cream is applied to the area.
2. Once anesthesia is confirmed, chlorhexidine is applied to disinfect the skin.
3. One unit of diluted hyaluronidase (as recommended by the manufacturer) is injected immediately under the epidermis.
4. A pen is used to mark the injection site. Do not use a red pen because it can stain the skin when in contact with sweat or humidity, resulting in a false-positive result.
5. Wait 20 minutes to read the result.

If the test is negative, the patient is ready for the corrective hyaluronidase injection.