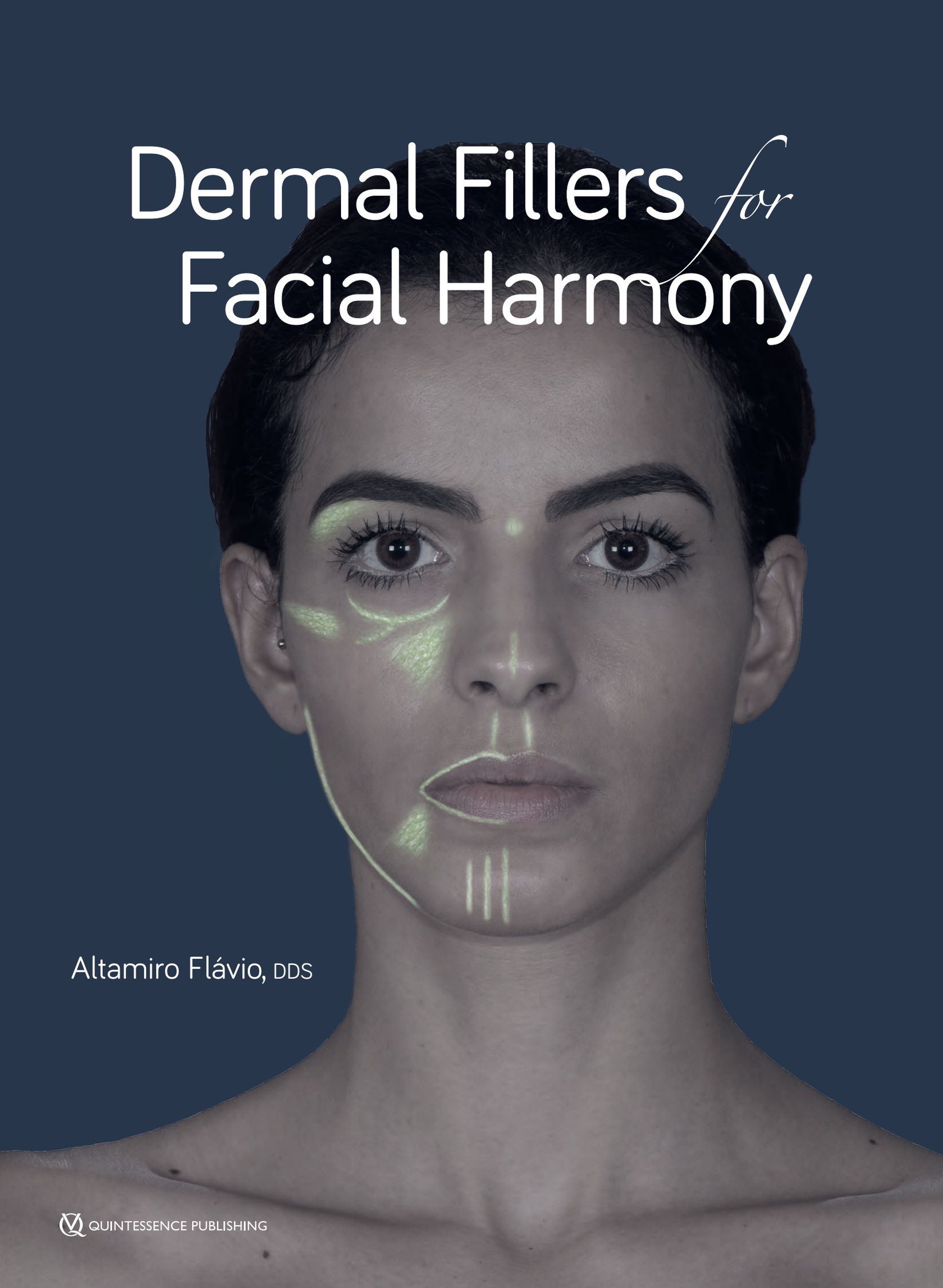
Dermal Fillers *for* Facial Harmony



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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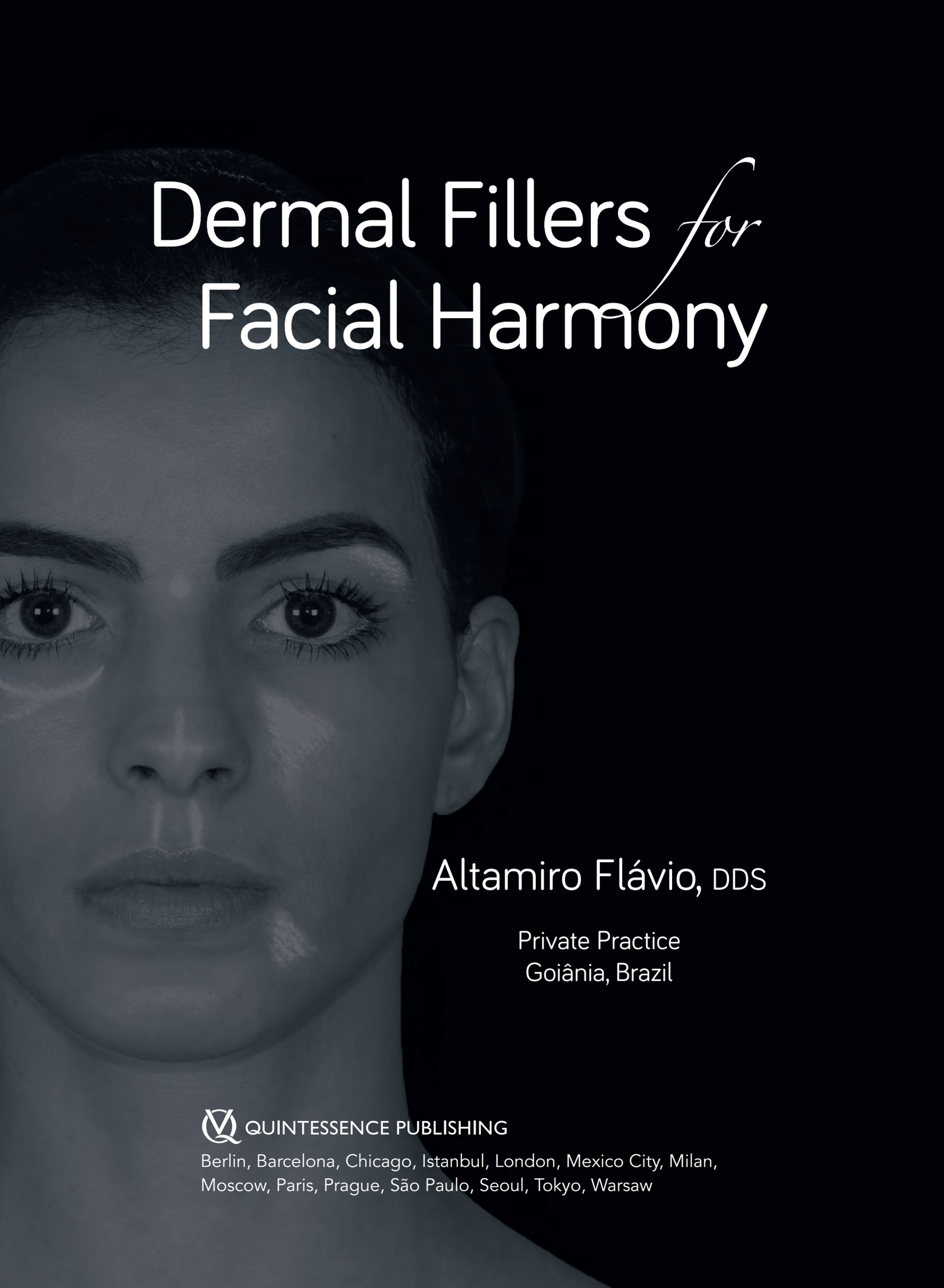

Dermal Fillers *for* Facial Harmony

Altamiro Flávio, DDS

Private Practice
Goiânia, Brazil

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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.

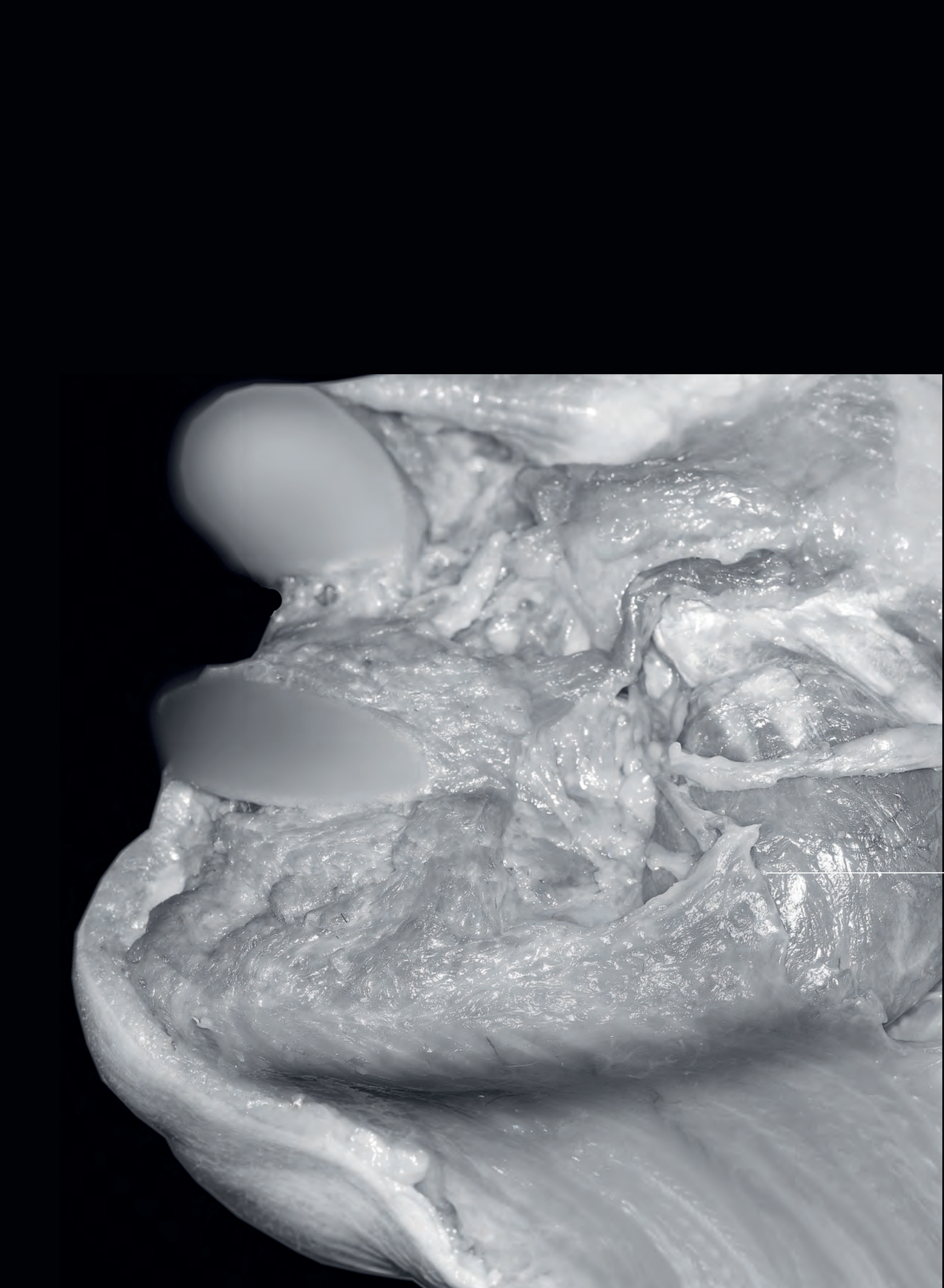
The second step is to practice everything that was learned. I believe that all injectable facial procedures should be initially practiced in a cadaver. The procedures described herein can be practiced by attending our course of anatomy applied to facial fillers at the Miami Anatomical Research Center, 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]

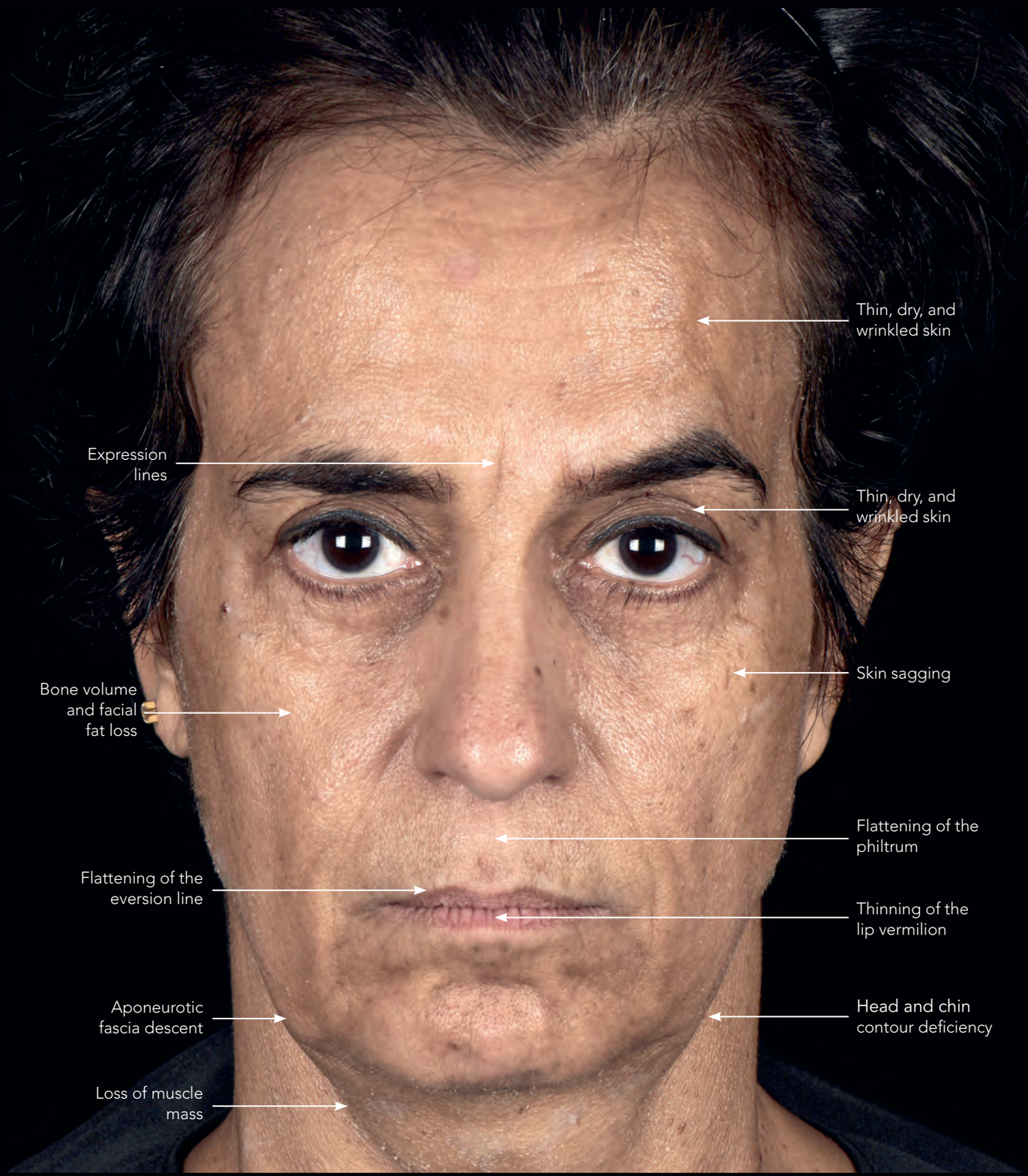


Fig 1-1 Various manifestations of facial aging.

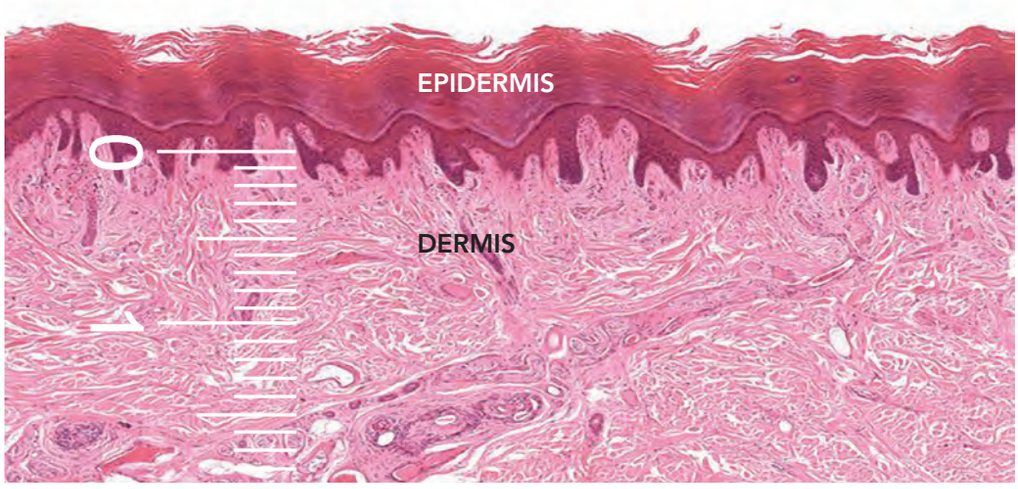


Fig 1-2 Layers of the skin. The dermal thickness varies from 1.04 to 1.86 mm.

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.

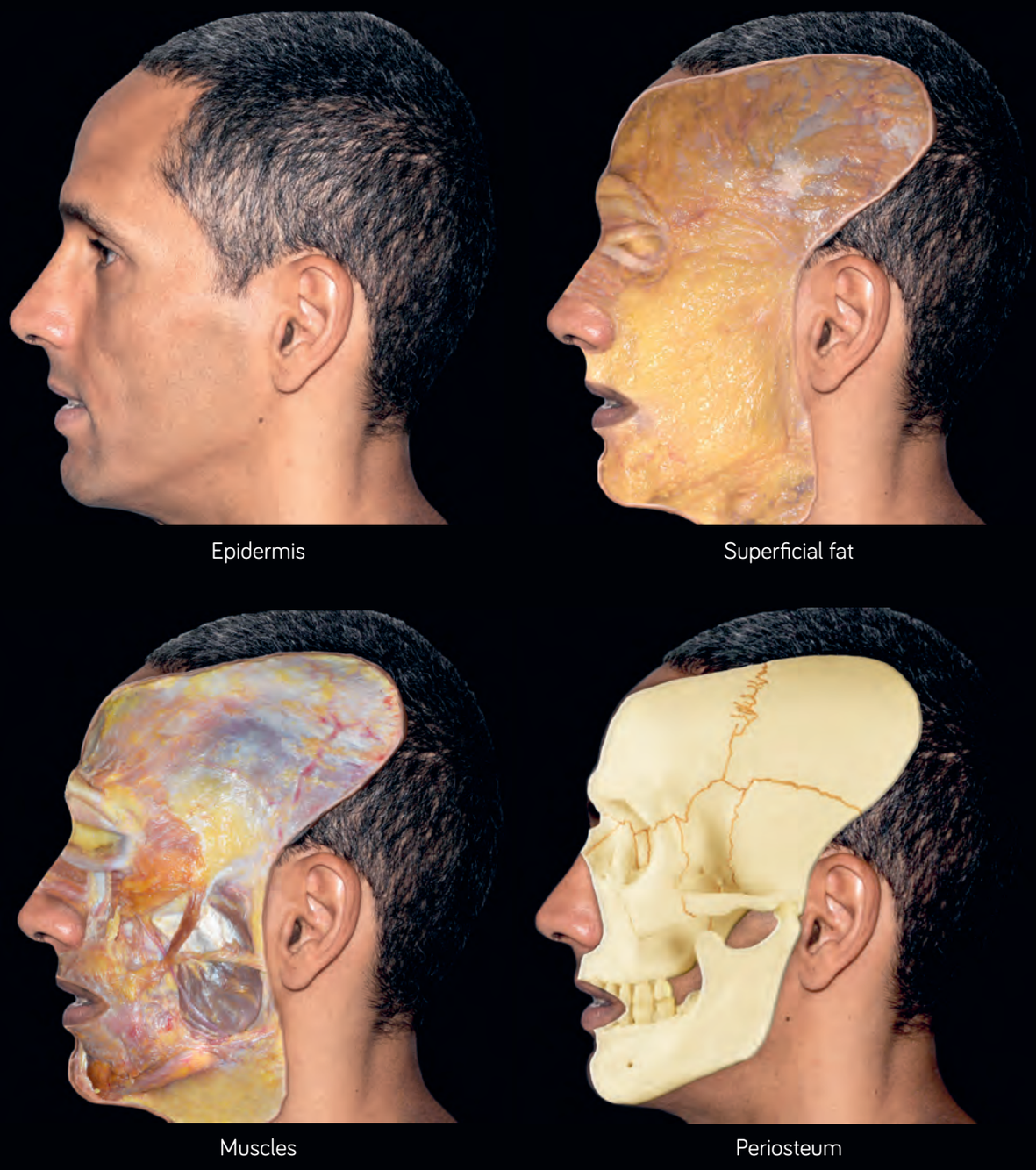


Fig 1-3 Layers of facial tissues.

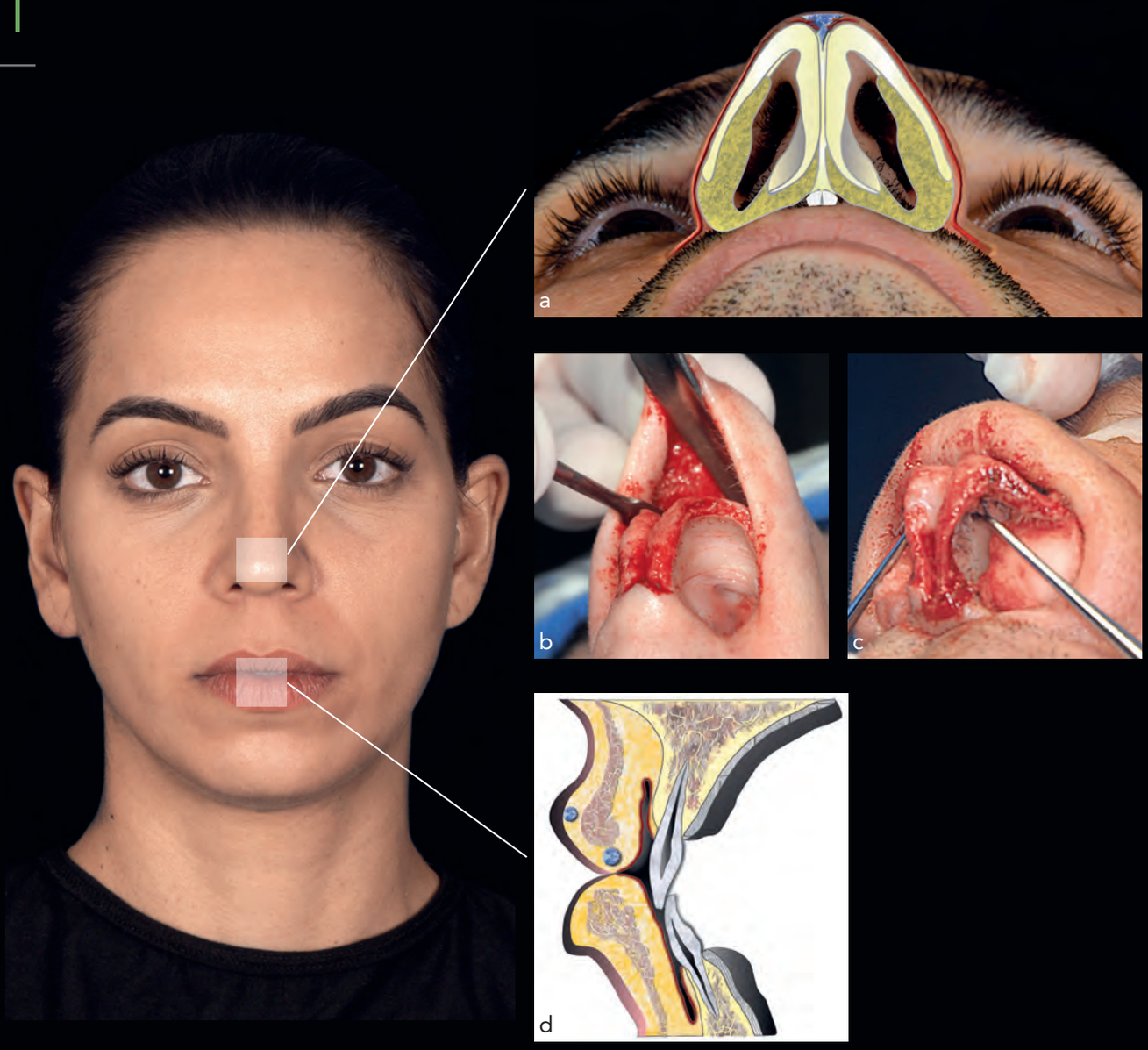


Fig 1-4 *(a to c)* The supratip is an area with a low capacity for volumization. There is little space between the deep dermis and the cartilage. Therefore, this region only supports a very small amount of fillers. *(d)* The lip vermilion is a region that shows elasticity and malleability, allowing it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