Injectable Safety: New Concepts and Best Practices in Hyaluronic Acid Filler Safety

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Background: As the hyaluronic acid industry evolves and new products are introduced, it is crucial for injectors to be educated on local anatomy, accurate injection techniques, the physicochemical properties of products, and evolving trends in the aesthetic injectable industry that influence patient safety and satisfaction.

Methods: A comprehensive literature search was conducted using Ovid and MEDLINE/PubMed databases. Keywords used were "filler," "hyaluronic acid," "complications," "injection," "technique," "migration," "safety," "needle," "cannula," "rheology," "face," and "facial."

Results: A total of 3980 were retrieved and filtered for publications from 2020 to 2025, yielding 1220 results. Limiting the search to original research articles, 882 were returned. Applying the keywords "face" and "facial" reduced the number to 660, and limiting the search to reviews, original research, and reports narrowed it to 562. After manually screening titles and abstracts, 100 publications were selected, and 20 were included in the final review. An additional 14 articles were included using snowball methodology.

Conclusions: As more hyaluronic acid products enter the market, the importance of a comprehensive understanding of the crosslinking technology, a thorough knowledge of the complex facial anatomy, and proper injector experience and technique are key factors in reducing the incidence of complications. *(Plast. Reconstr. Surg.* 156: 30S, 2025.)

Beginning with injections of liquid paraffins in the early 20th century to today's hyaluronic acid (HA) injections for volume restoration, softening rhytids, or enhancing facial contours, the knowledge of facial anatomy and the technologies used to manufacture HA fillers have evolved significantly.[1,2] Early fillers included permanent silicone, polymethyl methacrylate, and resorbable collagen-based options.[3] Due to biocompatibility, low toxicity and immunogenicity, and versatility of applications, HA fillers have emerged as the standard for minimally invasive methods of soft tissue augmentation.[3] The American Society of Plastic Surgeons reported an 8% increase in the use of HA filler from 2022 to 2023.[4] With growing popularity, cosmetic retailers, including Galderma (Uppsala, Sweden), Allergan, Inc. (Irvine, CA), Evolus, Inc. (Newport Beach, CA), and Revance (formerly Crown Laboratories, Inc.; Johnson City, TN), among others, have manufactured various forms of HA filler that are easy to use and relatively inexpensive.[2]

HA is a glycosaminoglycan composed of repeating D-glucuronic acid and D-*N*-acetylglucosamine disaccharide units linked through beta-1,4 glycosidic bonds, creating the HA polymer chain.[5] Early HA fillers were derived from animal sources, and as a result of the potential for significant impurities, an extensive purification process was necessary for their production.[6] The desire to reduce impurities and eliminate the need for such a thorough purification process led to the development of the first HA derived from a nonanimal stabilized HA process using microbial fermentation, Restylane (Galderma).[6] Over time, this technology gained widespread acceptance, and the use of nonanimal-derived raw materials has become the industry standard.[6]

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Received for publication April 3, 2025; accepted June 18, 2025.

DOI: 10.1097/PRS.0000000000012314

Disclosure statements are at the end of this article, following the correspondence information.

After the HA has been derived, manufacturers use various proprietary crosslinking methods to modify the rheological properties of the polymer to achieve their desired product characteristics (Table 1).[16,17] When injected into or beneath the dermis, these manufactured HAs integrate with the skin's natural HA and attract water, resulting in a volumizing effect.[18] The crosslinking technology forms larger, more stable molecules that are less water soluble, allowing them to remain in tissues longer while retaining the biocompatibility and viscoelastic properties similar to those of the naturally occurring molecule found in native tissues.[19,20]

Despite their enhanced safety profiles, HA fillers are not without risk. Treatment requires judicious facial evaluation, knowledge of anatomy, and physician expertise regarding filler choice, injection depth, and injection technique (Figs. 1 and 2).[21]

Minor complications such as overcorrection or undercorrection, bruising/bleeding, edema, pruritus, migration, and visible bumps tend to appear earlier in the postinjection course.[2] Though rare, more serious complications such as vascular compromise/necrosis, blindness, infection, papules/nodules, and granulomas remain potential risks with HA filler injection.[2] The etiology of these complications is multifactorial, but factors such as HA rheology, aseptic technique, dermal characteristics, injection technique, and experience of the injector have all been identified as potential contributors.[2]

Hyaluronidase permits potential dissolving of HA fillers in the case of unfavorable postinjection contours and for the treatment of complications, including granulomatous reactions and vascular occlusion.[22] However, the effectiveness of hyaluronidase on HA depends on factors such as the HA concentration, degree of crosslinking, particle size, and cohesivity.[16,18,23] Therefore, a thorough understanding of each product's rheology is crucial. This review provided a comprehensive literature-based overview of new concepts and evolving trends for HA fillers found in the literature published over the last 5 years.

METHODS

A comprehensive retrieval was conducted using 2 primary databases and snowball methodology. An initial search was performed using the Ovid database using the following keywords: "filler," "hyaluronic acid," "complications," "injection," "technique," "migration," "safety," "needle," "cannula," "rheology," "face," and "facial." This strategy was tailored to identify relevant publications regarding dermal HA fillers and new concepts related to safety and complications. Returned articles were filtered by publication type—original articles, review articles, and reports—and were manually screened by the authors, and those unrelated to the topic were excluded. Once the articles were compiled, they were independently screened by the authors based on titles and abstracts. The remaining publications were reviewed in their entirety, and those

Table 1. Common Crosslinking Technologies and the Corresponding Manufacturing Technique

Crosslinking Technology	Manufacturing Process
Cohesive Polydensified Matrix	The HA molecule is crosslinked and then polydensified, where the molecules are arranged in a denser, more stable structure. The molecular weight of the HA molecule is increased during the process to form a more cohesive matrix[7]
Hylacross	The HA molecule is formulated with a 3-dimensional matrix and contains a high ratio of high-molecular-weight HA to low-molecular-weight HA. The molecules are mixed in a single-step crosslinking process. A greater number of BDDE molecules are attached by bond ends, resulting in more efficient crosslinking[3,8]
Vycross	The HA molecule is a proprietary combination of primarily low-molecular-weight HA with a smaller proportion of high-molecular-weight HA, creating efficient crosslinking with an optimized, homogenous matrix.[9,10] It also contains a small amount of noncrosslinked HA to enhance delivery into tissues[10]
Resilient Hyaluronic Acid Preserved Network Technology	The HA molecule is crosslinked with BDDE at a lower temperature to optimize chemical reactions, minimizing HA degradation. This process preserves HA chain length and minimizes rigid crosslinkers[11]
XpresHAn/Optimal Balance Technology	A high-molecular-weight HA molecule is crosslinked with BDDE with a specialized proprietary method, creating fewer crosslinks in the matrix[12]
Cold-X	The HA is produced by the *Streptococcus* species and is crosslinked with BDDE. Near-freezing temperatures are used to preserve the natural structure of the HA molecule[13]
Nonanimal stabilized hyaluronic acid	This biosynthetic HA product is produced by the fermentation of streptococcal bacteria, and extracted and purified via alcohol precipitation. The molecule is stabilized through minute crosslinks between constituent polysaccharide chains, forming a gel matrix.[14] The blocks of gel are passed through sizing screens until they reach the manufacturer's desired size[15]

BDDE, 1,4-butanediol diglycidyl ether.

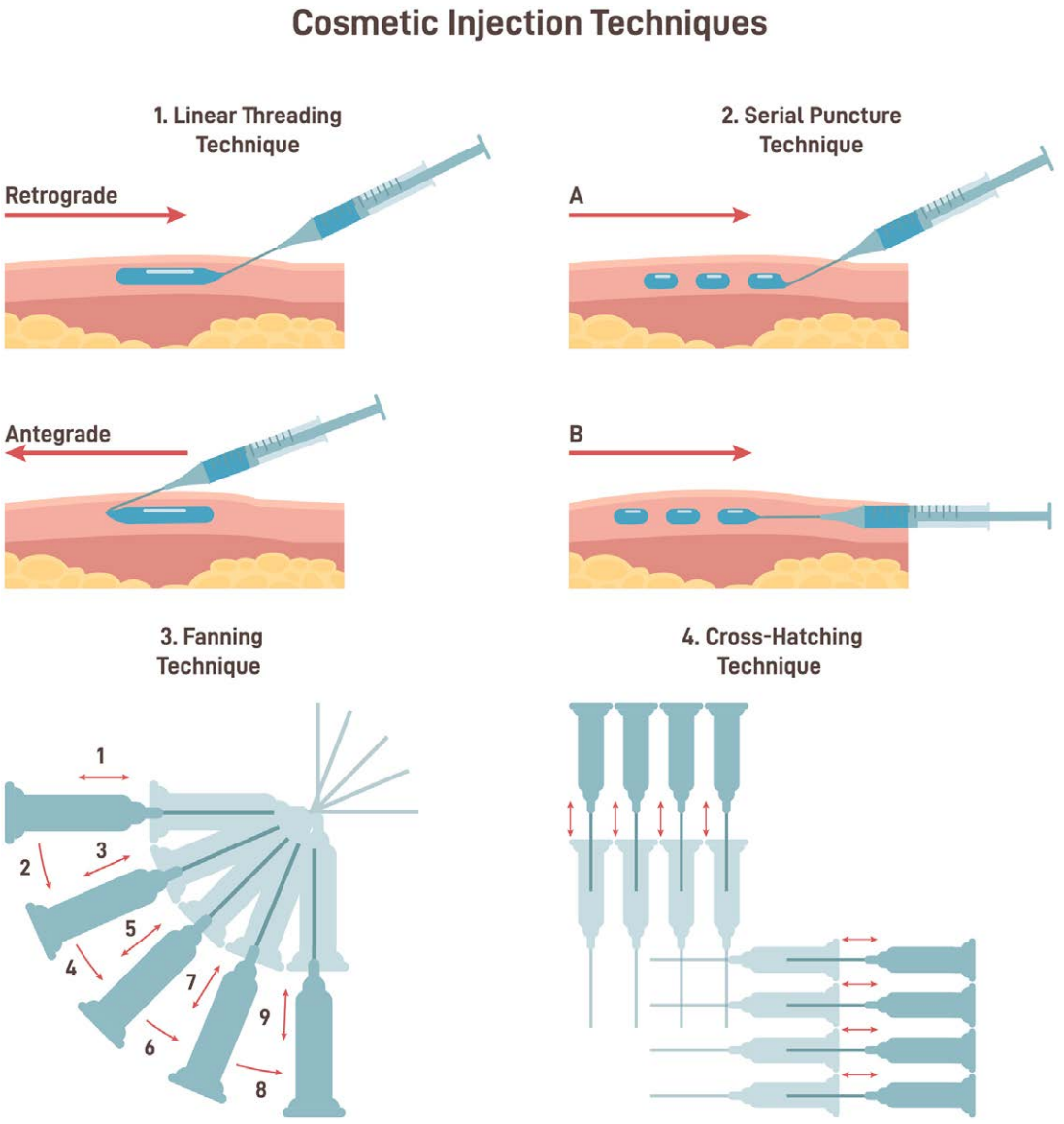

Fig. 1. A diagram of common cosmetic injection techniques. The image was licensed from Adobe Stock (image ID: 619606698). Copyright © inspiring.team/Adobe Stock. The illustration is used for visual representation only and does not depict actual clinical data.

deemed relevant by the authors were included in the review. Exclusion criteria included studies focused on a single race, studies that did not involve HA fillers, and articles related to orthopedics, neurotoxins, biostimulatory agents excluding HA, facial reconstruction or transplantation, dermal nevi, fat grafting, and oncology.

RESULTS

The initial literature search using the Ovid database yielded 3980 publications. Applying a publication date filter (2020–2025) narrowed the results to 1220 articles. These results were further filtered by publication type, including original articles, review articles, and reports, returning 562 articles. The authors reviewed the titles and abstracts of these publications and selected articles according to predefined exclusion criteria, reducing the count to 100 articles. These articles were reviewed in their entirety, and ultimately, 34 articles were selected to be included in the review. The selection was based on relevance to emerging concepts and techniques regarding HA injection safety. Articles related to the technique focused on the known anatomical danger zones and high-risk regions. Those addressing new concepts were chosen for their contribution to evolving safety

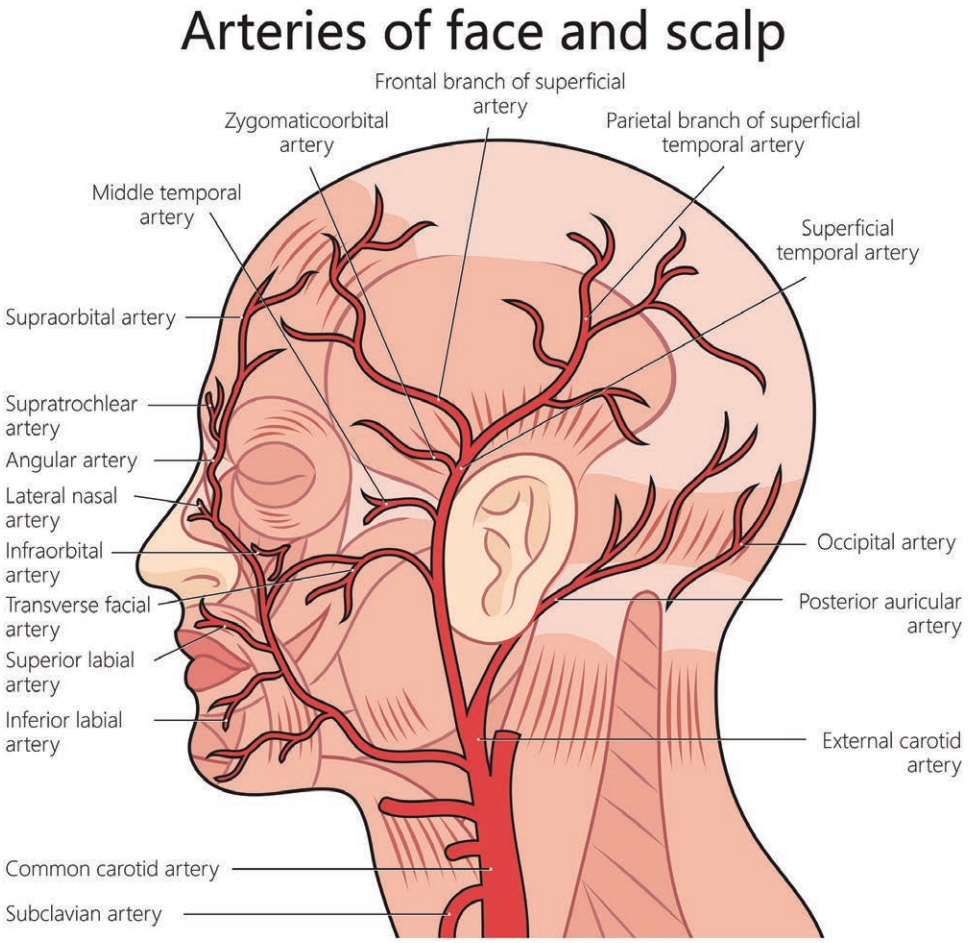

Fig. 2. A diagram of facial vasculature. The image was licensed from Adobe Stock (image ID: 71158305). Copyright © Oleksandr Pokusai/Adobe Stock. The illustration is used for visual representation only and does not depict actual clinical data.

practices and trends. An additional 7 articles were identified and included based on snowball methodology (Fig. 3).

Technique

There is currently no standardized methodology for the safest injection techniques. These methods must be tailored to each patient's unique anatomy and desired results. Thus, for patient safety, it is paramount that the injector is experienced and has a thorough understanding of local anatomy, the product's rheological properties, and precise injection techniques and depths.[7]

Upper Face

Based on the literature, no standardized technique exists for injection into the upper third of the face. Multiple techniques have been described, but the optimal approach depends on multiple factors, including the specific treatment area, clinical indication, product and supply selection, associated risks, and desired outcome.[8]

When treating regions such as the temples, it is important to consider the adjacent neurovascular structures and the presence of thin fascial planes. These anatomical features increase the risk of complications such as hematoma, vascular occlusion, and transient paresthesia.[8]

In the frontal region, the decision to use a needle versus a cannula influences the risk of complications. Each modality offers distinct advantages: needles tend to yield superior results for superficial rhytids, whereas cannulas are preferred for deeper injections.[8] The choice between the 2 should be guided by the treatment objective and intended injection depth.

Nose

The nonsurgical rhinoplasty, which uses minimally invasive techniques to enhance nasal contour, has gained significant popularity.

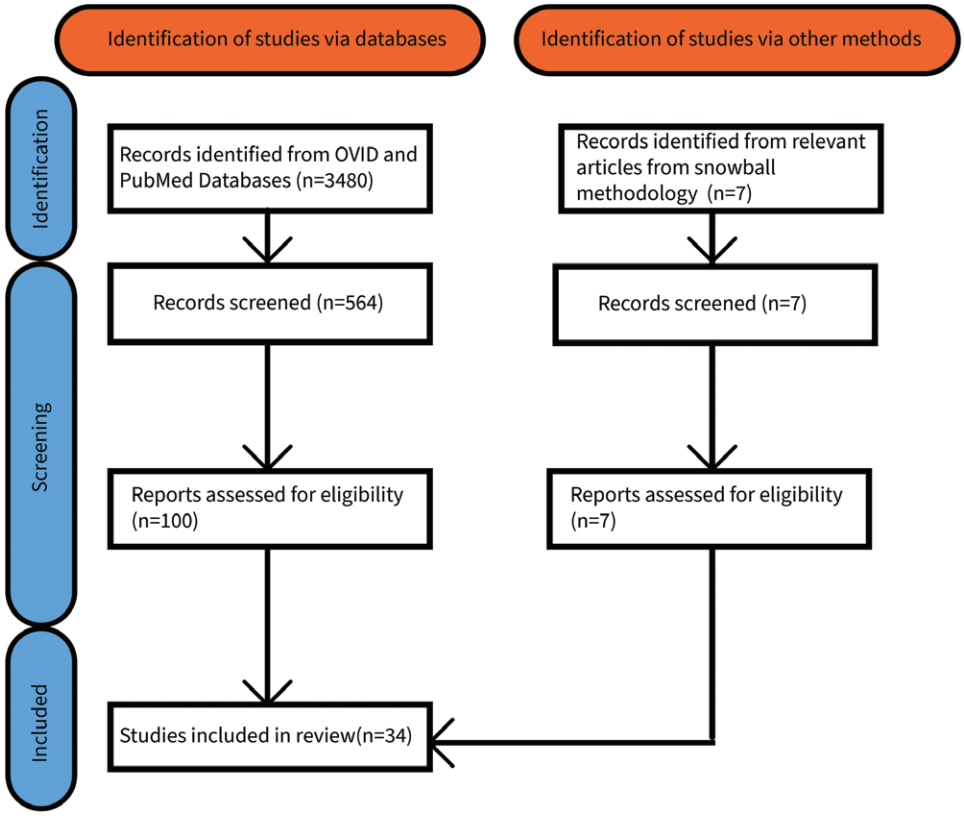

Fig. 3. Flow diagram of search strategy.

Consequently, a variety of HA-based approaches have been documented in the literature. A systematic review by Williams et al.[9] identified consistent techniques across studies, with common methods including the use of small serial droplets or retrograde linear threading.

Filler is typically placed in the supraperiosteal or supraperichondrial planes, using either a blunt or needle-tip cannula, with the objective of minimizing intravascular injection.[9] Although reported complication rates for nonsurgical nasal augmentation are low, most frequently hematoma and ecchymosis, these figures may be underestimated due to potential underreporting.[9]

Given the intricate and variable vascular anatomy of the nose, injectors must exercise extreme caution. Awareness of the surrounding complex vascular network is essential to prevent serious complications, including vascular occlusion and the rare but devastating risk of blindness.[10]

Tear Trough

Although extensive research has explored safe and effective techniques for tear trough augmentation, variability in reported methods has made it challenging to establish a standardized protocol.[11] While needle-based injection remains the traditional approach, Diwan et al.[12] demonstrated favorable outcomes using a cannula, with a lower incidence of adverse effects. Although based on a limited patient cohort, the study reported reduced injection-site pain, postprocedural edema, bruising, and blue discoloration.[12] Moreover, when complications did occur, recovery was noted to be faster compared with needle-based techniques.[12]

Midface

Midface injections are inherently complex but, when executed skillfully, can restore volume in the malar region while simultaneously improving the appearance of nasolabial folds and infraorbital hollows. The midface consists of 5 anatomical layers, each of which exhibits characteristic signs of aging over time (Figs. 4 and 5). Effective treatment begins with a comprehensive facial analysis, a solid understanding of age-related anatomical changes, appropriate product selection, and precise injection techniques and depths.

Trévidic et al.[13] advocated for a multilayered approach, initiating with supraperiosteal injections targeting the deep fat pads, followed by more superficial injections in the subcutaneous fat pads. For deep volume restoration, the authors recommend multiple bolus injections delivered with

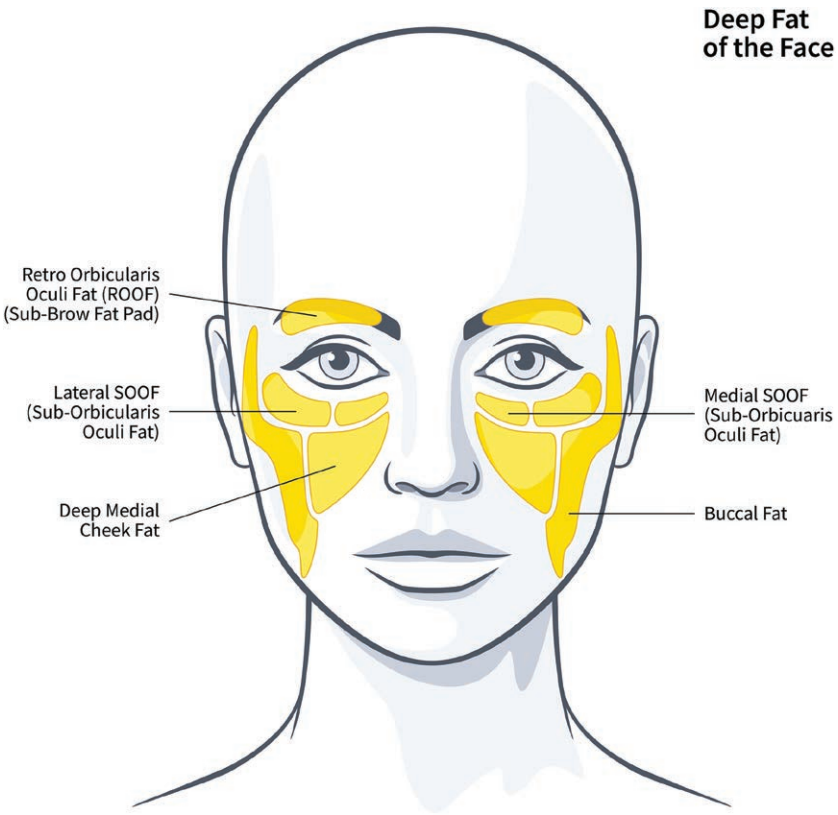

Fig. 4. A diagram of the deep fat compartments of the face. The image was licensed from Adobe Stock (image ID: 1329723461). Copyright © OrlyDesign/Adobe Stock. The illustration is used for visual representation only and does not depict actual clinical data.

either a needle or a cannula. An alternative technique involves the use of a cannula with continuous fanning motion, consisting of anterograde and retrograde injections administered without withdrawing the cannula between passes.[13]

Superficial fat pads may be addressed using either a needle or a cannula, though the latter is often preferred for safety. The recommended technique includes both retrograde and anterograde injections, focusing on the medial and midface fat pads.[13]

To minimize complications, injectors must possess a detailed understanding of the 3-dimensional facial anatomy and remain vigilant of key anatomical danger zones. Proposed safety landmarks include 2 critical lines: 1 extending from the medial canthus to the mandibular angle, and another descending vertically from the midpoint of the zygomatic arch.[13]

Lips

Experts have reported that the use of cannulas when injecting into the lips reduces the risk of bruising and may mitigate swelling during immediate submucosal injection; however, needles tend to be preferred for more precise, controlled injection.[14] Intricate injection into the lips is pivotal, as small nodules can result if too much volume is injected into a small space. Overinjection into the lips or isolated lip treatment can lead to the "duck lip" appearance, which is outdated and frankly feared by some patients.[14] More serious complications such as hematoma formation or tissue necrosis can result from an underdeveloped understanding of the local anatomy, leading to improper injection into the labial artery.[14] Though vascular occlusion is rare due to the depth of arteries and collateral circulation, the potential still remains.

Chin

Multiple techniques are available for chin augmentation, with HA fillers being a widely used nonsurgical option due to the immediate results and minimal downtime. A systematic review by Oranges et al.[15] recommends considering HA fillers for patients presenting with sagittal

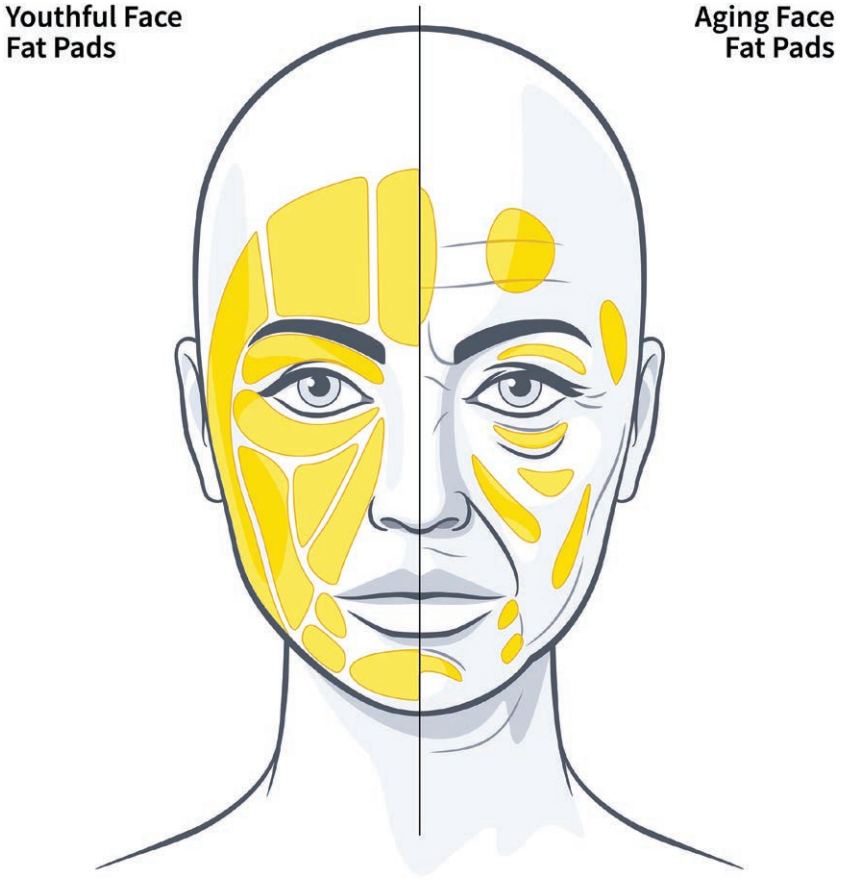

Fig. 5. A diagram of aging facial fat pads. The image was licensed from Adobe Stock (image ID: 1329723563). Copyright © OrlyDesign/Adobe Stock. The illustration is used for visual representation only and does not depict actual clinical data.

deficiencies of less than 4 mm and emphasizes the importance of careful patient selection to ensure optimal aesthetic outcomes.

High patient satisfaction was reported with techniques involving supraperiosteal or deep dermal injections.[15] Additional effective approaches included tunneling with a cannula with either centrally located or bilateral labiomental fold entry points, as well as a standardized grid-based approach.[15]

The majority of reported complications were mild, including erythema and nodules, which were able to be dissolved with hyaluronidase.[15]

New Concepts

Hybrid Filler

Advancements in technology have also led to the development of new hybrid fillers, offering promising alternatives with improved outcomes and safety profiles. Hybrid fillers combine the volumizing effects of HA with the biostimulatory properties of compounds such as calcium hydroxyapatite.[24,25] Products such as HArmonyCa with lidocaine (Allergan Aesthetics, an AbbVie company, Irvine, CA) offer immediate volume and lift while also promoting neocollagenesis, which leads to dermal thickening and improved skin structure, enhancing overall skin quality.[24] Studies have indicated that hybrid fillers have a favorable safety profile, with most reported adverse effects being mild and typical of those seen with all dermal fillers.[24] HA fillers help restore lost tissue volume, while biostimulatory agents encourage the production of collagen and elastin, improving the appearance of fine lines and overall skin texture.[26]

Ultrasound-Guided Injections

With increased caution to prevent vascular compromise, a safety measure that has the potential to reduce complication rates is ultrasound-guided injections. Due to variability in patient anatomy, it is often difficult for injectors to identify all regional vasculature during the procedure, increasing the risk of intravascular injection or

vascular compression.[27] Ultrasound guidance allows injectors to map each patient's unique vasculature, minimizing the risk of vascular complications.[28] In addition to identifying major blood vessels before injection, ultrasound-guided techniques can improve the administration of hyaluronidase in the event of vascular occlusion. Using ultrasound for hyaluronidase injections helps minimize the volume of the product injected, ensuring the least invasive approach possible.[29] This method allows for more precise, localized injections of hyaluronidase, lowering the risk of systemic allergic reactions, adverse changes in skin quality, or posthyaluronidase syndrome that can arise as a result of treatment.[29,30] Research has shown that targeting HA deposits directly, rather than direct intra-arterial injections, results in a higher rate of resolution.[29,31] A limitation of ultrasound-guided injection is the detectable sensitivity of the ultrasound machine, and therefore, most devices are unable to detect arteries smaller than 0.3 mm; however, the primary benefit of obtaining the arterial depth of the vessel correlated with the layer of facial soft tissue is preserved and some may say outweighs the limitation.[28] Although ultrasound guidance shows promise in reducing vascular compromise and promoting quicker dissolution, few protocols or guidelines for ultrasound-guided injections have been published, and the efficacy of this technique remains a topic of debate among injectors.[29]

Effect of Fillers on Surgery

Although fillers provide volumizing effects and perceived improvements in skin quality, migration is a known complication. This can result in granulomatous inflammation, though it more commonly presents as subcutaneous swelling or bluish skin discoloration, which may emerge months or even years after injection.[32] The cause of filler migration is thought to be related to various factors, including injection techniques, massage, muscle activity, gravity, pressure-induced displacement, lymphatic spread, and intravascular injection.[33,34] Certain injection practices, such as injecting filler into adjacent areas unintentionally, using high volumes, or applying pressure during injection, are believed to increase the risk of migration.[33] This underscores the importance of understanding the rheological properties of injectables and conducting thorough anatomical mapping to achieve optimal results with minimal risk.[35]

Given the potential for filler migration over time, concerns also extend to complications that may arise when performing surgery in previously injected areas, where residual filler can obscure tissue planes and alter anatomy. Filler injections can create an unfavorable soft tissue environment, sometimes requiring extensive surgery to remove the filler and restore the necessary anatomy for facial and neck surgery, which may deter surgeons from offering surgical rejuvenation options.[36] Research on surgical complications related to prior dermal filler injections discovered various forms of extracted filler, including "rice-like distribution," "large amounts of unsolidified filler," or a "cohesive mass." Studies have also shown that patients who have experienced inflammatory reactions from fillers may present with greater surgical challenges, as these reactions can lead to fibrosis and the formation of nodules in the operative tissues, disrupting the innate tissue planes.[37,38] In cases of deep filler injections, some studies have found cyst-like filler infiltrating the superficial musculoaponeurotic system layer, extending to the periosteum and involving terminal branches of the facial nerve.[36] Removing the filler can thin the tissue, making it more fragile and difficult to manipulate, while also altering the skin's characteristics. This increases the risk of postoperative complications, such as hematoma formation and skin necrosis.[36] As a result, some surgeons choose to dissolve fillers before surgery, whereas others prefer to work around affected tissues; however, no universal consensus exists on the optimal approach.

DISCUSSION

Although adverse effects from dermal fillers are uncommon, it is important to educate the public about the potential risks to reduce the likelihood of complications.[39] Research has shown that only 19% of the general public could accurately identify the risks associated with cosmetic injectables, despite 22% of respondents having a history of receiving filler injections.[40] Moreover, studies have indicated that the quality of online patient education materials about the risks of cosmetic injectables is often inadequate, with 15% of them failing to mention any risks or adverse effects.[40,41] Therefore, it is essential for plastic surgeons to educate patients by providing accurate, evidence-based information through media and clinical guidance to promote patient safety.

Advancements in HA filler techniques have improved both aesthetic outcomes and patient safety in facial rejuvenation. Emerging strategies emphasize a more nuanced understanding of

facial anatomy, particularly the layered structure of soft tissue and the complex vascular architecture of the face. The adoption of cannula-based delivery systems has gained popularity due to their lower risk of vascular injury and bruising compared with traditional needle injections, especially in high-risk zones such as the tear trough, nasolabial fold, and temporal region. Additionally, the use of ultrasound guidance during filler placement is an evolving practice that may further reduce complication rates by enabling real-time visualization of anatomical structures.

Recent literature also highlights the importance of a multilayered injection approach, targeting both the deep and superficial fat compartments to achieve natural and durable results. Safety protocols now commonly include aspiration techniques, low-pressure injection, minimal filler volumes per bolus, and thorough familiarity with "danger zones" to mitigate the risk of vascular occlusion. Moreover, patient-specific planning based on aging patterns, facial morphology, and skin quality is essential for minimizing adverse outcomes. As the field continues to evolve, ongoing research and standardized training in advanced techniques are critical to ensure both efficacy and safety in HA filler applications.

This review has several limitations to consider, including publication bias, variability in the quality of included studies, inconsistent methodologies, lack of standardization, and potential personal bias. First, the review is based on available published studies, which may lead to bias toward positive results or significant findings, potentially skewing the overall understanding of the topic. Although efforts were made to exclude low-quality and poorly designed studies, some may still have been included. Because HA injection techniques often depend on individual patient anatomy and the preferences of the injector, reported clinical outcomes may be inconsistently described across the literature. The absence of standardization in published injection techniques also contributes to inconsistencies in the results, making it challenging to offer standardized recommendations based on comparisons across studies. Finally, personal bias may have influenced the review, as the authors' preferred techniques and product usage in clinical practice could have shaped interpretations of the findings.

CONCLUSIONS

HA fillers are among the most prevalent minimally invasive cosmetic procedures and are only gaining popularity with time. With the evolution of HA filler crosslinking technology comes an increased responsibility for the injector to thoroughly understand the physicochemical properties of the agents they are using. Complications associated with the injection of HA fillers are closely linked to injector technique and knowledge of local anatomy. Therefore, it is essential for providers to stay informed about advancements in products and evidence-based best practices to avoid complications while still delivering patients the comprehensive aesthetic facial rejuvenation benefits that HA fillers offer.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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