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RESEARCH ARTICLE

FACIAL AND LIP FILLER BIOMATERIALS: A GENERAL COSMETIC APPLICATION REVIEW

Beavers, P.J., Khan, A.B. and *Merhavy, Z.I.

Ross University School of Medicine, Bridgetown, Barbados

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***Corresponding author:** *Merhavy, Z.I.*

ABSTRACT

Facial proportion changes and volume loss are commonly experienced corporeal changes, whether due to the natural process of senescence or as a side effect of systemic illness. Because these physical transformations are inevitably experienced by most people, treatments that assist in the maintenance or restoration of a youthful, yet natural appearance have long been a subject of great interest in the medical field. Thanks to the relative ease and low cost with which they ameliorate certain aspects of the aging process, facial and lip filling treatments have developed into a point of focus in the world of aesthetic medicine. As it currently stands, facial and lip volume enhancement or restoration can be achieved with a multitude of injectable products, including temporary and permanent fillers. With an ever-increasing number of materials at their disposal, providers in the cosmetic industry have many important choices to make when advocating biomaterials to their patients based on desired aesthetic outcomes. This review aims to meticulously discuss different aspects of the most commonly employed biomaterials in the cosmetic facial and lip filler industry today, as well as the particular treatments for which each material is best suited. The specific biomaterials addressed in this review include: collagen (human bioengineered and bovine), hyaluronic acid (HA), poly(L)-lactic acid (PLLA), calcium hydroxyapatite (CaHA), polymethyl methacrylate (PMMA), and autologous fat grafting (AFG). For each biomaterial discussed, the review provides information on how they became commonly used in aesthetic medicine, specific injection techniques, desirable cosmetic medicinal properties, and optimal situational applications for each biomaterial in the setting of elective patient cosmetic augmentation.

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INTRODUCTION

Since its conception in the early 19th century, the field of plastic surgery and cosmetic procedures has evolved and developed extensively into the global industry known today (1). After the conclusion of both World Wars, plastic surgery was primarily used by oral maxillofacial surgeons to aid in facial reconstruction of injured soldiers (1). Now, with the development of cosmetic plastic surgery, facial and lip enhancements can be made with ease and are highly accessible and affordable (1). The market for injectable lip fillers is fueled by individuals' desires for more shapely and fuller lips due to poor lip genetics, trauma, the natural aging process, or general dissatisfaction with their look (2). Aesthetic lip properties change over time with age, and facial fat, tendons, and bones can begin to degenerate (2). Other factors also affect this natural degeneration such as genetics, facial activities, environment, sun exposure, smoking, excessive pursing, etc. (2). This degeneration starts with the lengthening and concurrent volume loss of the upper lip; as the amount of natural collagen begins to decrease, the lips begin to lose their shape as collagen is the primary driver for continued maintenance of lip volume and shape (2). Slowly, as oral maxillo-mandibular bone resorption continues and soft tissue volume decreases, vertical creases called marionette lines, commonly referred to as frown lines, are formed bilateral to the lips (2). Simultaneously, lip margins flatten, become blunted, and the cupids' bow protrudes less (2). In order to combat these facets of the natural aging process, botulinum toxin as well as injectable and implantable biomaterials have been developed (2). Currently, lip augmentation and age correction are performed using a multitude of products, including both permanent and temporary fillers, neurotoxins, lasers, and implants, with lip fillers, specifically HA, being the choice route of correction in the vast majority of patient cases (2). Minimally invasive cosmetic procedures such as lip filler injections have piqued the interest of physicians and patients alike (2). These procedures allow for very precise placement of biomaterial in the lips, are relatively quick procedures requiring little if any recovery time, are easily repeatable, reduce wrinkles, increase the amount of soft tissue in the surrounding area over time, and produce aesthetically pleasing contours (2). The most important aspect of using injectable lip fillers is ensuring that the correct biomaterial is chosen, taking into account the patient's age, target duration of efficacy,

anatomic lip genetics, and most importantly their desired look (2). Generally, the injector will fill the patient's lips in a way that complements their natural features, and specifically accentuates the cupid's bow and vermillion borders while targeting the ideal 1:1.6 ratio of lower lip to upper lip volume, all of which are sought-after factors in optimal lip aesthetics (2). Today, the most commonly used lip filler biomaterial is HA, by a wide margin (1). Injectors often prefer HA over other biomaterials due to its superior biological properties, collagenesis induction, temporary nature, and ease of reversibility (1). HA also contains the synthetic hydrogel particle Artecoll, which remains in the soft tissue even after HA is resorbed for longer periods of effect between injections (1). Many times, fine perioral wrinkles are smoothed with collagen (3). Fine perioral wrinkle correction is performed with the patient sitting upright to make visible all defects to be corrected (3). Biomaterials are sometimes utilized as scaffolding for tissue regeneration, as seen when reversing the atrophic effects that HIV can induce in facial soft tissues for example. Non-resorptive properties allow them to remain in effect for years, and for this reason many deep tissue regenerating fillers are considered permanent (4). Natural and biological fillers are highly resorbable and are therefore considered temporary treatments, requiring repeated procedures in order to ensure desired effect is maintained (1). As new biomaterial technology surfaces and is introduced into the field of plastic surgery, safer and more effective cosmetic procedures are continually arising (1). Biomaterials intended for cosmetic and corrective plastic surgery should aim to meet certain core criteria: (1) excellent tissue compatibility, (2) non-carcinogenic, (3) non-allergenic, (4) non-inflammatory, (5) non-antigenic, (6) easy to store with long shelf-life, and (7) easy to mold and shape for different applications (1). Figure 1 displays the number of administered treatments by filler material during 2008 (10). The data shows the popularity in choice by healthcare professionals for use in treatment.

Figure 1. 2008 statistics on injectable filler use

Filler Material	Treatments Administered
Hyaluronic acid	1,260,000
Calcium hydroxyapatite (Radiesse)	123,000
Collagen	58,000
Poly-L-lactic acid (Sculptra)	32,000

*Courtesy of American Society for Aesthetic Plastic Surgery.

Lip and facial filler biomaterials: People desire a look that is youthful, beautiful, and can be maintained for an extended duration (5). A heightened emphasis in the western world on these particular facets of personal appearance has resulted in an increased demand for cosmetic procedures (5). Utilizing different injectable biomaterials, lip augmentation is one of the most popular, accessible, and effective procedures available today (5). With a thorough understanding of different injectable biomaterials, patient expectations, and anatomy, injectors can help patients achieve youthful full-lip profiles, all while retaining an organic, natural aesthetic (5). Injectable fillers are also widely used to correct age-induced facial volume loss (6). The following biomaterials were chosen for review based on common usage in the lip and dermal filler markets today, as well as the availability of extensive primary research as to the best applications for each (6). Materials focused on within this review include collagen, HA, PLLA, CaHA, PMMA, and AFG. Each filler material was evaluated individually using six parameters: permanence, invasiveness, reversibility, risk of allergic reaction, storage requirements/shelf-life, and typical duration in vivo with therapeutic efficacy.

Collagen: Bovine collagen was the first agent approved by the FDA for cosmetic injection, known commercially as Zyderm or Zyplast (7). Since this approval in 1981, it continues to see use today as both a stand-alone and adjunct temporary filler (7). Cosmoderm and Cosmoplast, human bioengineered collagen formulations, received FDA approval for cosmetic injection in 2003 (3). Both Zyderm/Zyplast and Cosmoderm/ Cosmoplast contain 3.5% collagen (35 mg/mL solution of phosphate-buffered saline and lidocaine suspension) and are available in 0.5 mL to 1.5 mL syringes (3). In the modern era, cosmetic collagen for lip and face injections typically lasts from three to four months, but some formulations can last from four to six months (3). Zyplast, a glutaraldehyde cross-linked bovine collagen, and Cosmoplast, a glutaraldehyde cross-linked human bioengineered collagen, are still in common use today (3). Bovine collagen requires an allergy test for reactivity before injection while human bioengineered collagen does not (3). Both bovine and human bioengineered collagen require refrigeration when stored (3). The use of glutaraldehyde for cross-linking strengthens the fibers and decreases the rate of degradation by collagenase, resulting in a longer lifespan of four to six months compared to the lifespan of three to four months for non-cross-linked collagen (3). Collagen is well suited for smoothing out superficial and fine skin lines around the eyes, mouth, and forehead via upper to mid-dermal injection (8). Zyderm and Cosmoderm are recommended for treating superficial defects, while Zyplast and Cosmoplast are better suited for addressing deeper imperfections due to their increased concentration of collagen cross-linking (3).

Hyaluronic acid: Since its introduction in 2003, HA has become the gold-standard of temporary, noninvasive cosmetic lip augmentation due to its superior bioactivity and biocompatibility properties compared to other fillers (9). HA is a non-stimulatory filler injected in the upper to mid-dermis (8). HA was first approved by the FDA for cosmetic injection in 2003 under the commercial name Restylane (10). HA is the first recommendation of many injectors in the modern era when discussing lip enhancement as research shows that HA injections have the added benefit of stimulating collagen and elastin regeneration (9). No pre-injection testing is needed for HA due to the nonspecific nature of the glycosaminoglycan chains that make up HA, and also has the benefit of not requiring refrigeration during storage (10). HA fillers include 1,4-butanediol diglycidyl ether for cross-linking and are suspended in phosphate-buffered pH 7 saline solution, typically at a concentration of 20mg/mL (10).

The degree of cross-linking is the chief determinant of a HA's chemical properties, where a higher percentage of cross-linking gives HA a longer effective life span (10). This also increases the molecular weight, ultimately making the HA take longer to massage and blend seamlessly into the lip tissue (10). Hyaluronidase can be injected to quickly break down HA that has already been injected into the lips, and this is used by injectors to sculpt the HA in the lips and preserve natural contours, as well as reverse misinjections or over injections (10). It is common for manufacturers to have variants of their HA lip fillers on the market, differing in

proportions of cross-linking (10). For example, Juvederm Ultra contains 6% cross-linking, while Juvederm Ultra Plus contains 8% cross-linking (10). No allergy testing is required for HA injections as the HA fillers are not ideal for every lip enhancement situation (10). When applied to perioral fine lines, bluish tint can sometimes result when injecting very superficially; this is known as the Tyndall effect (10). In summary, HAs with a low concentration of cross-linking are the ideal biomaterial for contouring and volumizing medium depth facial wrinkles, as well as lip augmentation (11). HAs with a higher degree of cross-linking are better suited for volumizing and correcting deeper facial folds (11). Thanks to their wide range of possible applications, relatively long duration, decreased immunogenicity, and convenience, HA encompasses the greatest share of the temporary dermal and lip filler sector in the cosmetic world today (11).

Poly (L) lactic acid: PLLA possesses unique attributes that are desirable in the cosmetic industry; namely, its ability to safely and effectively address changes observed in the aging face (12). In 2004, the FDA approved the use of PLLA, under the name Sculptra, for correcting nasolabial fold defects and other deep facial wrinkles, as well as facial lipoatrophy (13). PLLA is a temporary, injectable biomaterial that gradually restores volume (14). As a stimulatory filling agent, PLLA is injected submuscularly or pre-periosteally, and the mechanism behind PLLA's ability to engender neocollagenesis lies in its stimulation of a localized foreign body reaction at the site of injection, leading to local collagen production and a substantial increase in subcutaneous tissue (8,15). Typically, approximately half of the injected PLLA will be broken down in six months, with a duration of action of 12 to 24 months (14). The build-up of collagen over time creates volume at the site of injection, while the injected PLLA microparticles are metabolized to carbon dioxide and water (13). PLLA is completely biodegradable, biocompatible, and biologically inert, requiring no allergy testing (13). PLLA is initially in powder form not requiring refrigeration, and commonly packaged into individual 367.5g units; prior to injection, it is reconstituted using 4 mL of sterile water and 1 mL of lidocaine into a 4.45% PLLA suspension (14).

When correcting for volume loss in the cheeks, nasolabial folds, or lower face, PLLA should be injected in the deep subcutaneous plane under the muscle in the medial cheek, the chin, and in the superficial subcutaneous fat above the parotid gland (12). PLLA may also be placed as depot injections supraperiosteally along the zygoma, maxilla, and mandible, followed by firm massaging (12). Lastly, when PLLA is used in temple applications, it should be placed deeply under the temporalis fascia (12). PLLA acts to volumize deeper set tissues in a gradual, progressive, and predictable manner (12). This approach has proved capable of delivering the subtle and natural-looking facial composition desired by many patients (12).

Calcium hydroxyapatite: In recent years, CaHA has been increasingly used as a biostimulatory agent to improve skin quality and firmness in facial and corporal areas (16). CaHA is unique in that it provides both volume replacement and collagen biostimulation as primary mechanisms of action (16). CaHA was first released as a cosmetic filler in 2004 under the commercial name Radiesse, which is a synthetic form of the CaHA found naturally in bones and teeth, and since its introduction, CaHA has become the second most popular soft tissue filler after HA (15). Radiesse is biocompatible, biodegradable, and resorbable biostimulatory filler containing CaHA microspheres that can stimulate the endogenous production of collagen (16). When formulated as a lip or dermal filler, CaHA microspheres are suspended in a sodium carboxymethylcellulose gel which dissipates as it is digested in vivo, while the CaHA microspheres act as a platform for newly synthesized collagen (15). Studies show that neocollagenesis begins in the fourth week after injection and persists for over 12 months (17). An undiluted, highly viscoelastic Radiesse formulation provides immediate volume correction that is gradually followed by new tissue formation through neocollagenesis, elastin production, angiogenesis, and dermal cell proliferation (16). Supraperiosteal and subdermal placement is well-suited for the undiluted form of Radiesse, and the result is an aesthetic improvement that can last 18 months or more (16). When used in a hyper diluted form, Radiesse has minimal immediate volumizing effects and generates only long-term tissue remodeling, allowing for superficial injection techniques ideal in dermal rejuvenation and the treatment of larger areas (16). Often, cosmetic CaHA procedures are broken up into two sessions, allowing for more layering and enhanced fold softening, resulting in higher retention of natural facial motions (8). It has been observed that CaHA produces more type 1 collagen and elastin and results in a greater proliferation of fibroblasts when compared to hyaluronic acid (18). When utilized in large area dermal rejuvenation, hyper diluted Radiesse is typically recommended (16). Radiesse applications result in cosmetic improvement for more than 18 months with tight, elastic skin and increased skin thickness (16). CaHA has found a niche in large area dermal rejuvenation, in addition to creating defined shapes, sculpting, and filling deep nasolabial facial folds (16).

Polymethyl methacrylate: PMMA is a permanent, noninvasive filler that achieves immediate, stable, and long-term results (19). Due to its inert and biocompatible nature, PMMA requires no allergy testing prior to injection and is not biodegradable, remaining in vivo at the injection site decades after it is first injected (19). Cosmetic-grade PMMA microspheres are purified, polymerized, always larger than 20 mm, and uniform in both shape and size to avoid granuloma formation (19). PMMA solutions contain either bovine-sourced collagen or magnesium-carboxy-gluconate-hydrolactic gel as a base (19-20). Artefill, previously known as Artecoll, is a PMMA solution using bovine collagen as a base that was approved for cosmetic injection by the FDA in 2006 (21). The reviewers recommend PMMA solutions containing magnesium-carboxy-gluconate-hydrolactic gel for aesthetic injection procedures because this eliminates the need for allergenicity testing, while pre-injection reaction testing is always necessary with any collagen-containing product such as Artefill (19,21). As another benefit, PMMA chains also innately contain gentamicin, which is a common aminoglycoside antibiotic; this allows PMMA to be used on infected wounds when other filler biomaterials are contraindicated by the presence of current infections (19). Conveniently, PMMA is easily stored in vials or syringes and kept at room temperature for extended periods of time without deterioration (19). For most cosmetic applications of PMMA, deep dermal injection is recommended to avoid bead visibility (21).

Neurosurgeons and orthopedists alike use PMMA as a bone cement, while dentists use it in denture bases (19). Plastic surgeons inject PMMA in facial bone deformity amelioration, and some cardiologists even employ PMMA pacemaker cases (19). In the world of elective cosmetic enhancement procedures, PMMA is a filler biomaterial ideal for correcting deep nasolabial folds, facial lipodystrophy, marionette lines, and providing permanent facial contouring and lip enhancement (19-20). Additionally, PMMA is also routinely utilized as an adjunct filler in rhinoplasty procedures (19).

Autologous fat grafting (AFG): Aesthetic manifestations of the aging process result in part from midface volume loss, with cheek flattening and inferior orbital hollowing often seen as the earliest indicators (22). Most facial volume loss is attributable to gradual degradation of subcutaneous fat that occurs naturally with aging, as well as similarly gradual loss of interstitial colloidal fluid (22). Thickness of the mandibular and maxillary bones can also diminish over time, creating even more pronounced volume loss and wrinkling effects (22). Along with decreased bone thickness, lost dentition can also severely impact the perioral region from a cosmetic standpoint (22). AFG is very unique in its ability to effectively address these problematic regions and permanently to semi-permanently restore facial volume, particularly in the cheeks, inferior orbits, and perioral regions (22). With the publishing of "Structural Fat Grafting" in 2005 by Dr. Sydney Coleman, small volume fat grafting, defined as fat grafts smaller than 150mL, became commonly accepted in the aesthetic plastic surgery industry as a viable method for facial rejuvenation and volume loss correction (22)(23). Dr. Coleman's small volume fat grafting technique, widely known as the Coleman technique, is a well-established and proven approach that emphasizes fat harvesting, processing and purification, and proper fat graft injection practices (23). Firstly, syringe aspiration is used to harvest the desired amount of fat (23). The fat aspirate is then centrifuged to isolate the viable adipocytes (23). Finally, the fat is concentrated into a graft solution and injected into the desired tissue site in an even distribution with multiple small passes in different planes and directions (23). In AFG procedures, majority of the transplanted fat becomes a permanent graft in the tissue, accounting for the desired increase in volume, while a small portion of the transplanted fat is resorbed (22).
In many cases, facelifts are followed by adjunct AFG procedures (22). This is because even after undergoing an adequate facelift, some patients continue to experience persistent jowling (22). This post facelift jowling is generally attributable to facial volume deficiency at the mandibular angle, which can be alleviated by AFG in the lateral jawline (22). From a cosmetic perspective, AFG is most useful in correcting global facial volume loss (22). It is especially effective in providing cosmetic rejuvenation through volumization of the cheek, inferior orbital, and perioral regions (22).

CONCLUSION

The discovery of new biomaterials for facial and lip cosmetic procedures, as well as finding varied uses for existing biomaterials, has developed into a field of continuously increasing activity and interest. This review focused on providing a recapitulation of contemporary biomaterials commonly used in lip and facial rejuvenation and enhancement procedures in the field of cosmetic medicine. These modern biomaterials allow for precise and easily repeatable injection placement, relatively quick injection times, wrinkle reduction and enhanced soft tissue bulk, fast patient recovery, and produce patient gratifying results with low adverse outcome risk in comparison to other cosmetic medical procedures. The biomaterials evaluated by the reviewers encompass the following: collagen, HA, PLLA, CaHA, PMMA, and AFG. This review also assessed several facets of each biomaterial for the sake of comparison, including: permanence, invasiveness, reversibility, allergenic testing requirements, and typical duration in vivo. The individual materials have distinct aesthetic procedures for which they are optimally suited and specific facial or lip cosmetic defects they excel in correcting. The procedures and defects best suited to each biomaterial are laid out in this review, as well as the discrete benefits they all bring to the table in the locus of human tissue injection.

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