# Hyaluronic Acid Basics and Rheology

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**KEYWORDS**

• Hyaluronic acid • Rheology • Dermal filler

**KEY POINTS**

- Hyaluronic acid (HA) is the most common dermal filler material used today.
- HA improves wrinkles and volume loss not only by filling and volumizing but also by hydrating the injected area with its water affinity.
- HA is a naturally occurring component of skin, and there is a negligible risk of immunologic or allergic reaction with injection. It is rapidly degraded by the injection of hyaluronidase, thus creating an ideal injectable material that is low risk and reversible.
- Duration of effect may be longer than expected based on bioavailability of the HA product due to collagen synthesis or fibroblast stimulation.

## INTRODUCTION

The aging face comprises many commonly observed characteristics including rhytid formation in the glabella and periorbital regions, deepening of the nasolabial grooves, formation of marionette lines, brow ptosis, periorbital and temporal hollowing, atrophy and descent of the midfacial fat pads, and jowling. These changes typically progress in a predictable fashion and are predominantly driven by 3 distinct processes: 1) loss of soft tissue elasticity, 2) gravity-mediated descent of normal structures, and 3) loss of volume.

Loss of volume may be the primary process driving some age-related changes.[1,2] Cadaver studies by Rohrich and colleagues[3] delineate the facial fat compartments, which become more discrete as age-related volume loss occurs. These compartments are both superficial and deep to the facial musculature, and the location predicts how the compartment ages. In general, the superficial fat pads tend to become ptotic or sag, whereas the deep fat pads tend to atrophy or lose volume. Volume loss may occur early in the aging process,[4] and volume restoration with soft tissue fillers can adequately address volume loss without the need for invasive surgical procedures during the early stages of aging.[1,2,5,6]

Injectable soft tissue fillers are widely used to address areas of facial volume loss and wrinkles. Many materials are available on the market, including hyaluronic acid (HA), calcium hydroxylapatite, poly-L-lactic acid, and polymethyl methacrylate. Autologous fat is also commonly used, often in conjunction with surgical procedures. In 2020, the United States (US) HA-based dermal fillers market was estimated at $1 billion and is projected to grow.[7] With numerous products available on the market, and increasing interest in facial rejuvenation, in-depth knowledge of fillers will be critical to providing optimal treatment. This article will discuss HA dermal fillers, the most popular type of dermal filler, and their rheologic characteristics.

## BACKGROUND

HA is found in all human tissues, but most abundantly in the skin, synovial fluid, vitreous of the eye, and umbilical cord. The monomeric unit that

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composes HA chains is identical regardless of origin–animal or bacterial–and therefore, there is a negligible risk of immunologic or allergic reaction with HA injection.[8] About half of the total body's HA resides in the skin.[9]

Before the development of HA fillers, collagen was the preferred dermal filler for decades, having obtained Food and Drug Administration (FDA) approval in 1981. However, the collagen was usually derived from a bovine source, and before receiving this treatment, patients required 2 rounds of skin allergy testing.[10] This delay and the potential adverse side effects contributed to why HA dermal fillers rapidly became more popular. Restylane® (Galderma Laboratories) was the first HA filler to be approved by the FDA in 2003 and was initially marketed to address deep wrinkles and folds and later for lip enhancement.[11,12] Of note, HA dermal fillers had been used in Europe for several years before US FDA approval. Shortly after Restylane's FDA approval, many other products came onto the US market, with various characteristics and indications. These products are associated with a low risk of allergic reaction and do not require skin testing before injection.[13]

The filling effect of HA is not only due to direct addition of gel volume to the dermis or subdermis. Studies were conducted based on observations that HA fillers create results lasting beyond what was expected. Its water affinity and the ability to bind large amounts of water contributes to its volumizing effect. In addition, HA dermal fillers have been shown to result in increased collagen stimulation and deposition and increased fibroblast activity around the injected filler.[14,15] Therefore, the duration of effect may be longer than expected based on how long it takes to degrade in vivo.

## CHEMICAL COMPOSITION AND MANUFACTURING

HA is a naturally occurring compound in the skin that is an essential component of the extracellular matrix of all adult animal tissues. The HA compound is a glycosaminoglycan disaccharide composed of alternately repeating units of D-glucuronic acid and N-acetyl-D-glucosamine.[15]

In the past, HA was extracted from rooster combs but currently manufacturing of the compound is performed mostly via bacterial fermentation.[16] This process produces uncross-linked HA of varying lengths. The HA chains must next undergo a stabilization process to prevent rapid in vivo enzymatic and oxidative degradation. In order to produce viable dermal HA, nonmodified HA is cross-linked to create a polymer network.[17] 1,4-butanediol diglycidyl ether (BDDE) is the cross-linker in all of the current FDA-approved HA filler products, including the Restylane® and Juvéderm® (Allergan Aesthetics) families of products, as well as Belotero® Balance (Merz Aesthetics).[18] After the cross-linking step, each manufacturer uses a proprietary technology to modify their products, unique to each line of filler. **Table 1** lists the approximate cross-linking percentage for the FDA-approved HA fillers available at this time.

## PHYSICO-CHEMICAL CHARACTERISTICS AND RHEOLOGY

### *Physico-Chemical Characteristics*

The manufacturing process for various commercially available HA fillers has direct implications for the unique gel properties and clinical applications of these products. These gel properties can be described using the science of rheology, which describes the consistency and flow properties of matter, including liquids and soft solids such as gels. Rheologic properties are determined with a rheometer, which consists of 2 nondeformable plates, one fixed and one mobile. A gel is placed between these 2 plates, such that there is complete contact between the gel and the plates. Through manipulation of the mobile plate, properties of the gel can be determined.[5]

There are many physico-chemical characteristics of HA that determine how it behaves. Notably, an injectable product needs to be able to flow through an appropriately sized needle with reasonable extrusion forces. HA is an excellent lubricant in its uncross-linked form, and the presence of uncross-linked HA in a gel facilitates extrusion of the gel through a thin needle into the soft tissues.[17]

The key clinically relevant characteristics to be aware of when selecting a filler are degree of cross-linking, HA concentration, swelling factor, elastic modulus (G′), G″, G*, and tan δ.

#### *Cross-linking*

As noted above, cross-linking of HA molecules is an essential step in producing dermal fillers that resist normal enzymatic and oxidative degradation. The degree of cross-linking refers to how many links are between 2 HA molecules on an average. For example, a 4% degree of cross-linking would indicate that there are 4 cross-linker molecules for every 100 disaccharide monomeric units of HA.[17] In the US, BDDE is the only cross-linking agent used. BDDE can react at both ends to link 2 separate strands of HA, resulting in a cross-link. However, the BDDE may bond only at one end, leaving its other end free. This is termed a pendant cross-link.

**Table 1**
**Cross-linking percentage of FDA-approved hyaluronic acid fillers**

| Product | Percentage Cross-linked |
|---|---|
| Restylane®<br>Restylane Lyft<br>Restylane Silk | ~1.2% |
| RHA® 2<br>RHA 3<br>RHA 4 | ~3%<br>~3.5%<br>~4% |
| Juvéderm® Ultra<br>Restylane Refyne | ~6% |
| Revanesse® Versa<br>Restylane Kysse<br>Restylane Contour | ~7% |
| Juvéderm Ultra Plus<br>Restylane Defyne | ~8% |
| Juvéderm Voluma<br>Juvéderm Volbella<br>Juvéderm Vollure | Highly cross-linked (proprietary) |

Belotero® Balance uses cohesive polydensified matrix technology and percentage cross-linking cannot be measured.

The degree of modification of a gel is determined by the percent of cross-links summed with the percent of pendant modifications. Although cross-linking generally results in firmer and longer-lasting gels, pendant modifications result in softer gels with an increased degree of swelling.[6] Too high a degree of cross-linking or pendant modifications can lead to problems with biocompatibility because the more a given HA product is cross-linked, the more it is altered or modified from HA in its natural form. In products with a significantly higher degree of cross-linking, the body perceives those fillers as more "foreign" and is more likely to cause an immunologic reaction, creating delayed onset swelling and inflammatory nodules. Furthermore, HA fillers with a high degree of cross-linking are longer lasting and may be more difficult to reverse with hyaluronidase because the network is more tightly woven and difficult to access, when exposed to hyaluronidase. When hyaluronidase enzymatically breaks down individual HA molecules in a highly cross-linked gel, the separated pieces may still be attached to the HA polymer network via cross-links, making the overall filler more difficult to break down or dissolve. Pendant modifications do not contribute to longevity.

### *Hyaluronic acid concentration*

HA concentration is defined as the total weight of HA per milliliter (mL) of finished product, typically expressed in milligrams (mg) per mL. See **Table 2** for the reported HA concentrations of FDA-approved fillers. The concentration matters because, in general, the higher it is, the more water a gel needs to incorporate in order to reach equilibrium hydration. The total weight includes both cross-linked and uncross-linked, or free, molecules. Only cross-linked HA resists in vivo degradation and contributes to the longevity of the gel, so it is important to note what percentage of a filler's HA concentration is cross-linked. Free HA is degraded by the body in a matter of days.

### *Swelling factor*

Swelling factor is closely related to HA concentration. HA is hydrophilic and can hold many times its weight in water, leading to increased volume and turgor. One gram of HA can bind up to 6 L of water.[19] It may seem like a higher concentration of HA is desirable; however, if the product is not at or close to equilibrium hydration, it will have a significant amount of tissue water affinity and water uptake once injected. Water may be added to an HA gel, or the HA gel may sit in a dialysis bath, during the manufacturing process to allow it to reach equilibrium hydration. However, it is beneficial for a dermal filler to be slightly below equilibrium hydration because it will then draw in some tissue water and add to the volumizing effect. The swelling factor seems to be linearly related to HA concentration, with the higher concentration HA gels pulling in more tissue water and causing more swelling. Conversely, the swelling factor is inversely related to the degree of cross-linking, as higher degrees of cross-linking reduce the hydrophilicity of a gel. This may limit the volumizing and lifting capacity of the gel.[17]

## *Rheologic Measurements*

### *Elastic modulus*

The elastic or storage modulus is designated G prime (G′). This measurement corresponds to gel firmness and is a measure of a product's ability to resist deformation. It can also be conceptualized as the amount of energy that a gel can store.

A gel with a higher G′ is considered a "firmer gel" and is ideal when there is a need for deep, targeted product deposition with less distribution of product into the surrounding tissues. However, because high G′ products resist deformation, they may feel firmer within the tissues. Higher G′ products are useful when structural definition, precision, or tissue lifting is needed. The G′ is dependent on several factors, including the cross-linking density, the HA concentration, and the presence of unbound HA. Increasing cross-linking density and increasing HA concentration both increase G'.[6]

**Table 2**
**Hyaluronic acid concentration of FDA-approved hyaluronic acid fillers**

| Product | HA Concentration (mg/mL) |
|---|---|
| Volbella<br>Vollure<br>Voluma | 15<br>17.5<br>20 |
| All Restylane products | 20 |
| Belotero Balance | 22.5 |
| RHA 2<br>RHA 3<br>RHA 4 | 23 |
| Juvéderm Ultra<br>Juvéderm Ultra Plus | 24 |
| Revanesse Versa | 25 |

Some HA formulations contain lidocaine to alleviate the pain associated with injection. Adding lidocaine to HA gels seems to modify G′ and other gel properties.[20]

### *Gel viscosity*

Gel viscosity is quantified by the viscous modulus, or G double prime (G″). G″ can be considered as a gel's resistance to dynamic forces and is also known as the loss modulus. A higher G″ gel is thicker and requires a greater extrusion force to be expressed through a needle (eg, peanut butter, rather than syrup).

G″ is a measure of a gel's ability to dissipate energy when force is applied, and this measure is reciprocally related to G′, the ability to store energy.

Together, G″ and G′ define the complex modulus, or G*, which represents a gel's total resistance to deformation, and is determined by the following formula:[21]

$$G^* = \sqrt{(G')^2 + (G'')^2}$$

Although fillers are viscoelastic, the elastic component is much more significant and the G′ value is much larger than that of G". As such, G* and G′ are almost identical. G′ is more widely reported and considered a proxy for G*.

### *Elasticity and viscosity*

Tan delta (δ) is a measure of a gel's balance of elasticity versus viscosity, and is defined by the ratio of G″ to G′.

$$\text{Tan } \delta = G''/G'$$

Gels characterized by a high tan δ, with values close to one, are predominantly viscous (eg, honey), whereas those characterized by a low tan delta, with values near zero, are predominantly elastic (eg, gelatin).

**Table 3**
**Filler selection**

| Location | Filler |
|---|---|
| Tear trough | Restylane-L<br>Belotero Balance |
| Midface | Restylane Lyft<br>Juvéderm Voluma<br>Restylane Contour<br>RHA-4 |
| Lips | Juvéderm Ultra<br>Restylane Kysse<br>Versa Lips<br>Restylane Refyne |
| Nasolabial folds/marionette lines | RHA-3<br>Restylane Refyne<br>Restylane Defyne<br>Juvéderm Ultra<br>Juvéderm Ultra Plus<br>Juvéderm Vollure |
| Fine facial rhytids | Belotero Balance<br>RHA-2 |
| Liquid rhinoplasty | Restylane-L<br>Restylane Lyft |

There is no order of preference for the listed fillers.

## FILLER SELECTION

No one product is optimal to achieve every single esthetic goal, and the rheologic properties described above must be considered when choosing the specific product and the injection tool. Consideration of all of these gel characteristics and rheologic measurements give the injector a sense of how this HA gel will behave in vivo. It is up to each injector to use this knowledge to choose the best gel to fit each area that they are choosing to inject. For example, when injecting an area such as the lips, one should choose a product that is not too firm and, depending on the patient's esthetic goals, either swells more or less. **Table 3** lists the authors' usual preferences for filler based on treatment location. There are other fillers that could be appropriate for specific indications that are not listed. In **Fig. 1**, the patient was treated with Restylane-L in the tear troughs and Restylane Lyft and Contour in the midface. Although both products support and volumize the midface, Restylane Contour is a softer gel and provides a more natural appearance in areas of movement. The patient in **Fig. 2** was treated

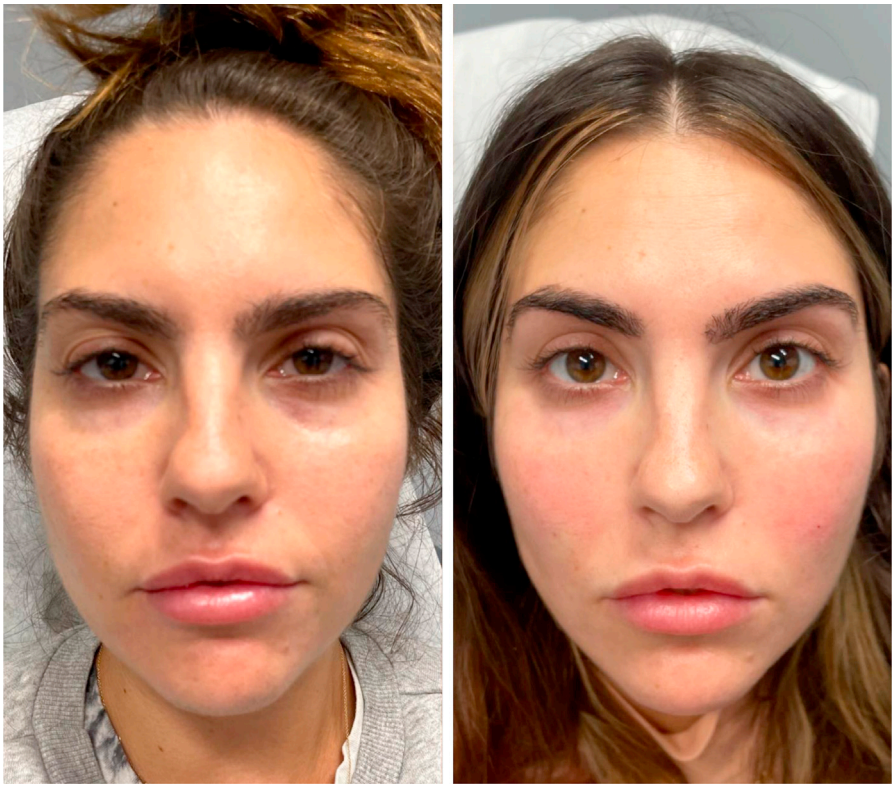

**Fig. 1.** Tear trough and midface filler. Restylane Contour and Lyft were used in the midface. Restylane-L was used in the tear troughs. (*Courtesy of* Sarah Taylor, RN/Bloom Facial Plastic Surgery.)

with Restylane-L in the nasal dorsum, which was chosen over Restylane Lyft for its smoothness and softness.

## INJECTION CONSIDERATIONS AND ADVERSE EFFECTS

To safely obtain natural-looking results with dermal fillers, a thorough understanding of facial anatomy and appreciation for the patterns of change in the aging face are essential. Before injection, the prudent clinician considers the esthetic goal of the procedure, anesthesia, the product, depth and anatomic location of injection with special attention to possible complications, volume of product to be injected, the instrument to be used for injection (cannula vs needle), as well as the gauge of the instrument. Depth of injection in each anatomic area must be carefully considered given the risk of complications that include skin necrosis, vascular injury, filler embolization, and blindness.

With regard to anesthesia, some dermal filler products contain lidocaine, assisting with patient comfort while filling. Additional anesthetic, if used, is typically applied topically in a cream or gel form. Commonly used topical anesthetics before dermal filler injection include compounded benzocaine–lidocaine–tetracaine, lidocaine–prilocaine, or one of these components alone.

Hyaluronidase is a naturally occurring enzyme that degrades HA and is a useful tool to reverse injected HA filler. Specifically, hyaluronidase can be used to eliminate inflammatory nodules, bumps, or superficially placed product. Most critically, it can treat vascular occlusion from intra-arterial injection.[22] When undesirable nodules or asymmetries occur postinjection, small doses of hyaluronidase can be used to dissolve the filler.[23] In the case of vascular occlusion, the recommended strategy is to immediately flood the area with hyaluronidase, on the order of hundreds of units in order to quickly dissolve the filler and mitigate risks of skin necrosis and other tissue compromise.[24] Some providers will administer greater than 1000 units if large areas of skin are involved.[25] There is some controversy over how to treat vascular occlusion with visual compromise but due to the favorable risk–benefit ratio, retrobulbar injection of hyaluronidase is recommended if there is true vision loss.[25–28]

Related to the injection itself, side effects include pain, erythema, hematoma, and edema. These side effects are almost always minor and

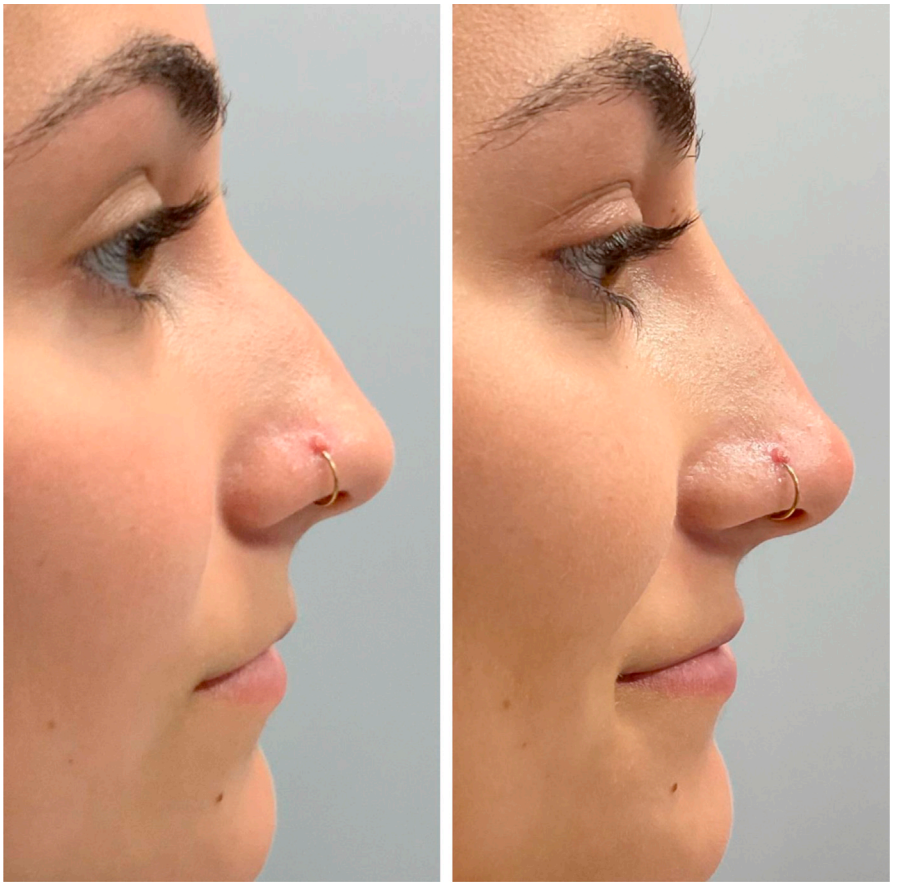

**Fig. 2.** Liquid rhinoplasty. Restylane-L was used cephalad to the dorsal hump to camouflage it. (*Courtesy of* Sarah Taylor, RN/Bloom Facial Plastic Surgery.)

self-resolving, necessitating only ice and compression for treatment.

Allergic reactions to HA filler additives—such as the cross-linker, BDDE, or lidocaine—are possible. Because chemical cross-linkers can be irritating and can incite a foreign body reaction in the skin, any residual active stabilizer must be removed from the product after the cross-linking process. Too much cross-linking may lead to biocompatibility issues, resulting in rejection, encapsulation, or delayed onset inflammatory events.

Delayed reactions include formation of foreign body granulomas, delayed onset swelling, or biofilms. After attempting to dissolve the product, these should be treated initially with antibiotics with further therapies, including oral or intralesional steroids or 5-fluorouracil, depending on response.[24]

## FUTURE DIRECTIONS

A newer application of HA dermal filler products is skin boosting. Skin boosting refers to techniques used to enhance the appearance of aging skin. HA is administered via microdroplet injections into skin in an effort to provide the long-term hydration that topical products cannot achieve. There are currently no HA dermal filler products approved for the purpose of skin boosting in the US; however, there are products available in Europe, Canada, and Asia for this purpose. There is some limited evidence that these products can improve skin moisture, firmness, and glow.[29] There is also some evidence that the addition of skin boosting injections can enhance the results produced with botulinum toxin and conventional application of HA dermal filler.[30] Repeated treatments are usually necessary.

## SUMMARY

HA is the most popular material to address volume loss and wrinkles associated with skin aging. Because HA is a naturally occurring component of the human skin, HA-derived fillers are well-suited for use in facial rejuvenation, are associated with a low risk of allergic reaction, and are long lasting.

The HA product can be reversed with injection of hyaluronidase to help mitigate any adverse events.

There are numerous HA dermal filler products available on the market, and these are differentiated by their physico-chemical characteristics and rheological properties. As the number of FDA-approved dermal filler products and approved indications for these products continues to increase, a basic understanding of these concepts is crucial to selecting the optimal filler for a particular situation.

## CLINICS CARE POINTS

- Knowledge of physico-chemical characteristics and rheologic properties of hyaluronic acid (HA) dermal fillers is critical to choosing the right product for each patient.
- Degree of cross-linking, HA concentration, swelling factor, and G′ are highly relevant clinically. All injectors should understand these concepts.
- In-depth knowledge of vascular anatomy and proper injection technique are necessary to reduce the risk of adverse events.
- In the event of vascular occlusion, hyaluronidase needs to be injected immediately, in the range of a hundred units or more. Repeat injections may be necessary.

## DISCLOSURE

Dr J.D. Bloom is a consultant, advisory board member, speaker's bureau member, trainer, and clinical investigator for Galderma and Allergan. He is also a consultant, advisory board member, speaker's bureau member and trainer for Revance Therapeutics and Endo Aesthetics.

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