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REVIEW ARTICLE

The science of hyaluronic acid dermal fillers

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Abstract
Background: The use of injectable materials for soft-tissue augmentation has been increasing in the United States, reflecting the introduction of new hyaluronic acid (HA)-based dermal fillers. HA dermal fillers vary widely in their physical and chemical characteristics and many variables contribute to their overall performance. This article explains the basic science of HA and describes how the physical properties of HA dermal fillers may influence clinical outcomes. *Hyaluronic acid*: The chemical composition of disaccharide HA monomers, and how they form polymer chains and are crosslinked into gels for dermal fillers are described. *Hyaluronic acid dermal fillers*: Key concepts and properties relevant to the production and performance of HA dermal fillers, such as the degree of crosslinking, gel hardness, gel consistency, viscosity, extrusion force, HA concentration, and extent of hydration are explained. New formulations of HA dermal fillers that have recently been approved by the US Food and Drug Administration differ from currently available HA fillers and may provide enhanced ease of extrusion and persistence over previous fillers. *Conclusion*: Knowledge of the chemical and physical blueprint of HA dermal fillers may help physicians in choosing the appropriate HA dermal filler for facial enhancements. This, together with appropriate injector training and injection experience, should lead to results that ultimately will benefit patients.

Key words: *Dermal fillers, hyaluronic acid, soft-tissue augmentation*

Introduction

As we age, our faces begin to show the effects of gravity, sun exposure, and years of facial muscle movement, such as smiling, chewing, and squinting. The underlying tissues that keep our skin looking youthful begin to break down, often leaving laugh lines, smile lines, crow's feet, and facial creases. Soft-tissue fillers can help fill in these lines and creases, temporarily restoring a smoother, more youthful-looking appearance (1). The ideal filler would be non-permanent but long-lasting, have minimal side effects, not require allergy testing, be easy to use/inject, painless upon injection, and cost effective for both the physician and the patient (2).

For more than 20 years, bovine collagens (Zyderm, Zyplast; Allergan, Santa Barbara, CA, USA) were the only US Food and Drug Administration (FDA)-approved dermal fillers. Because these dermal fillers are bovine based, one of the main disadvantages has been the need for allergy testing. In addition to possible allergic reactions, cosmetic patients can be impulsive consumers and requiring them to wait a month for an allergy test before treatment was a significant drawback (3). In February 2003, human-derived collagens received FDA approval (CosmoDerm, CosmoPlast; Allergan); they provide the advantage of a significantly reduced risk of allergic reactions and eliminate the requirement of allergy testing.

Another significant concern with dermal fillers has been longevity. The search for fillers that do not require allergy testing and potentially last longer than collagen-based products brought about the development of hyaluronic acid (HA)-based substances. In December 2003, the first HA product was approved in the United States (Restylane; Medicis Aesthetics Holdings Inc., Scottsdale, AZ, USA), and was soon followed by other HA fillers (Hylaform, Hylaform Plus, Captique, Juvéderm Ultra, and Juvéderm Ultra Plus; Inamed Corporation, now Allergan).

HA has features that make it an attractive substance for dermal filler use, such as its ability to bind to large amounts of water, its natural presence in the skin, and its low potential for adverse reactions. Despite these general features, HA dermal fillers are not all the same. They differ in characteristics such as the type of crosslinker used, degree of

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crosslinking, gel hardness, viscosity, extrusion force, gel consistency, total HA concentration (amount of HA per milliliter of finished product), and lifetime in the skin. Key to the performance of an HA dermal filler is how all of these characteristics act in concert to deliver a product that combines ease of injection with long life and efficacy as a filler.

In order to give practitioners better tools to evaluate HA dermal fillers, this article seeks to explain the chemical and physical attributes that have been identified as most relevant to product performance. A deeper understanding of the science underlying HA dermal fillers, and the factors that influence final product characteristics, should facilitate making appropriate choices when designing therapies for the increasing number of patients seeking facial enhancement, restoration, and rejuvenation.

Hyaluronic acid

Chemical composition

Hyaluronic acid (HA, also known as hyaluronan) is a polysaccharide (specifically a glycosaminoglycan) that consists of repeating D-glucuronic acid and D-*N*-acetylglucosamine disaccharide units. Normally the carboxyl group (–COOH) of D-glucuronic acid has been converted into its sodium salt, leading to the disaccharide structure shown in Figure 1. These disaccharide units can be viewed in a broader context as 'monomers', small molecules that chemically bond to other identical or different monomers to form a macromolecule, or 'polymer'. The disaccharide monomers that constitute the HA polymer are linked together into a linear chain through beta-1,4 glycosidic bonds. Each disaccharide monomer has a molecular weight of ~ 400 Da. The number of repeating disaccharides, *n*, in an HA polymer chain can reach 25 000 or more, creating a polymer with a total molecular weight of ~ 10 MDa.

Chain length and source

HA, an essential component of the extracellular matrix of all adult animal tissues, naturally exists in tissues as a biopolymer. A common misconception about HA is that it differs according to its source: animal or bacterial. The basic unit of HA, that is, the monomeric unit that composes HA polymer chains, is identical regardless of its origin. The principal difference between animal-based and bacterial-based HA is the length (degree of polymerization *n*, or molecular weight) of the final polymer chain. Polymer chains from bacterial-based HA are usually shorter, comprising approximately 4000–6000 monomeric units per chain that correspond to an average molecular weight of approximately 1.5–2.5 MDa. Animal-based HA chains have about 10 000–15 000 monomeric units per chain that correspond to an average molecular weight of approximately 4–6 MDa (Figure 2).

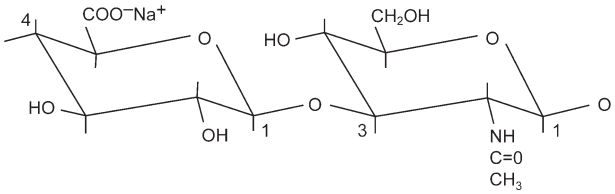

Figure 1. HA monomeric unit. One disaccharide unit consisting of the sodium salt of D-glucuronic acid (left) and D-*N*-acetylglucosamine (right) bound together by a beta-1,3 glycosidic bond. Note that two disaccharide units are linked by a beta-1,4 glycosidic bond.

Water solubility

HA derived from either bacterial or animal sources is a highly water soluble polymer that will readily dissolve into water to form a viscous clear liquid. The water solubility of HA can be traced to a number of factors, but especially to the presence of four hydroxyl (–OH) groups and one $–COO^- Na^+$ 'salt' group per disaccharide repeat unit (Figure 1). The hydroxyl groups can participate in hydrogen bonding with water, which stabilizes the solvated state. Furthermore, the salt group dissociates in water with a favorable release of free energy that derives from the solvation energy of the resulting $– COO^-$ and Na^+ ions and the gain in entropy of the released sodium ion (Na^+). The net effect is that HA polymer dissolves readily in water.

Hyaluronic acid dermal fillers

Because the chemical structure of HA is the same across all species, the potential for immunologic reactions and implant rejection is negligible, making HA a very suitable material for use as a dermal filler (4).

Crosslinking of HA polymers

A series of chemical modification and processing steps must be applied to HA to develop viable formulations for use as dermal fillers. The raw HA polymer used to produce dermal fillers is usually supplied to the manufacturer in dry powder form. Mixing this powder with water creates a viscous liquid that has the look and feel of egg white. The more HA powder added to a given amount of water, the thicker and more viscous the solution will become (Figure 3).

Such a solution is known as free HA, uncrosslinked HA, or non-modified HA. If this solution was to be used as a dermal filler, the product would be rapidly eliminated from the injection site (in less than a week). This results from the very limited

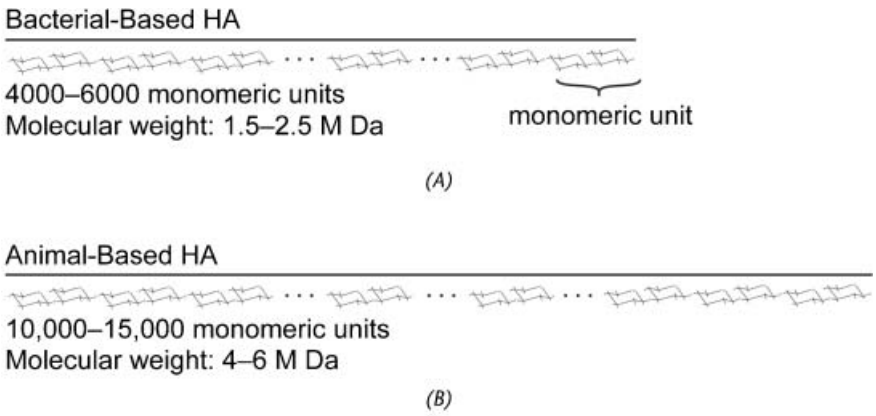

Figure 2. HA chain lengths. HA polymer chains, made up of several thousand disaccharide monomer units, differ only in their length but not in their basic molecular composition. Bacterial-based HA polymer chains (A) are generally shorter than animal-based HA polymer chains (B).

residence time of uncrosslinked HA polymers in the skin as the body quickly breaks down HA chains that are not crosslinked into a gel (see below). Enzymes such as hyaluronidase and free radicals that are naturally present in the skin can quickly degrade uncrosslinked HA polymers, cleaving off large portions of the polymer chains at a time. As a result, its half-life is 1–2 days in tissue, where it undergoes aqueous dilution and then, in the liver, enzymatic degradation to water and carbon dioxide (5). Therefore, uncrosslinked HA solutions do not provide the persistence required of a dermal filler (6).

In order to overcome the lack of persistence of uncrosslinked HA, dermal filler manufacturers use crosslinkers. The crosslinkers bind HA polymer chains to each other, creating a polymer 'network' and transforming the viscous liquid into a gel (Figure 4). The transformation from solution to gel should be familiar to readers who have prepared gelatin desserts.

The resulting HA gel acts as a single unit, imposing a physical and chemical barrier to enzymatic and free radical breakdown. Because the gel network is multiply connected, enzymes and free radicals can break down the chains only in much smaller portions at a time. Moreover, due to their large size, enzymes can have difficulty penetrating the gel network, which will in effect contribute to a slower degradation. This translates into longer persistence of the HA gel in the skin when used as a dermal filler. A useful analogy is to think of crosslinkers as mortar between bricks. Just as mortar makes a brick wall stronger, the incorporation of

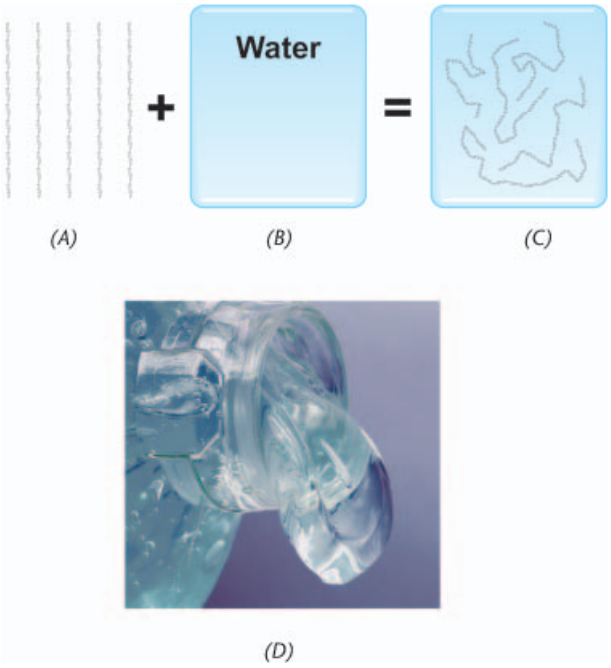

Figure 3. HA solution in water. An HA polymer, represented as chains composed of many monomeric units (A), when dissolved in water (B), produces a viscous liquid (C), that looks and feels like egg white (D).

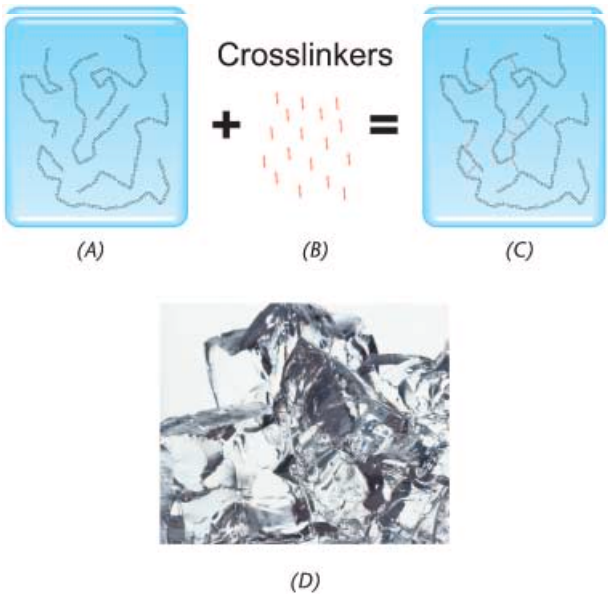

Figure 4. HA gel. Crosslinking HA polymer chains transform the HA solution (A) into a gel (C). Crosslinker molecules (B) bind individual HA polymer chains to create a network (C), which manifests macroscopically as a gel mass (D).

crosslinkers makes HA a more rigid and durable biomaterial.

Crosslinking is evidently an essential step in slowing the breakdown of HA dermal fillers. The two crosslinkers used in HA dermal fillers currently on the US market are 1,4-butanediol diglycidal ether (BDDE), and di-vinyl sulfone (DVS). Both react with hydroxyl sites on the HA chains and offer similar results in slowing down enzymatic and free radical degradation of dermal fillers once injected into the skin. Figure 5 shows BDDE used as a crosslinker, binding together two HA polymer chains.

Crosslinking HA chains can result in the presence of unreacted, or residual, crosslinker in the finished product. Residual crosslinker molecules are artifacts of the manufacturing process and can be toxic at high concentrations when unbound to other molecules. They are highly undesirable, and dermal filler manufacturers take special steps to eliminate as much of the residual crosslinking agent as possible from the finished product.

To assure the safety of dermal fillers marketed in the US, the FDA expects residual crosslinker concentrations in dermal fillers to be orders of magnitude below a level that might pose health concerns to humans.

Degree of crosslinking

When comparing HA dermal fillers, it is important to understand the concept of degree of crosslinking. The degree of crosslinking indicates the percentage of HA disaccharide monomer units that are bound to a crosslinker molecule. Thus, to say that a dermal filler has a degree of crosslinking of 4% means that, on average, there are four crosslinker molecules for every 100 disaccharide monomeric units of HA (Figure 6). Every other parameter being equal, the greater the degree of crosslinking, the harder the gel becomes. The significance of gel hardness (or softness) will be disuccsed in further sections of the manuscript.

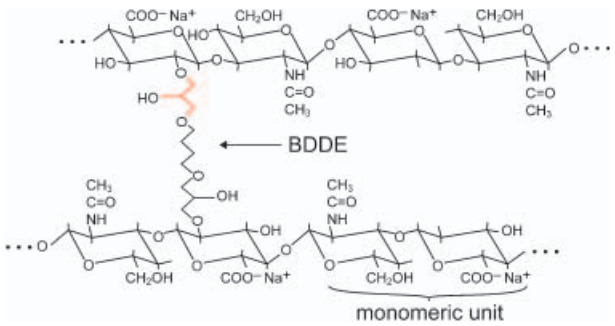

Figure 5. BDDE (1,4-butanediol diglycidal ether) crosslinking agent used to bind HA polymer chains to each other, transforming liquid HA solutions into gels. Both the primary hydroxyl site (–CH_2OH) and secondary hydroxyl sites (–CHOH) within the HA monomeric unit are possible target sites for reaction with BDDE.

When discussing the degree of crosslinking, one must recognize that many HA dermal fillers are composed of both crosslinked and uncrosslinked fractions (in the following sections of the manuscript, uncrosslinked HA is defined as the portion of the product that includes both uncrosslinked chains and lightly crosslinked chains and fragments that will aid extrusion/flow; such lightly crosslinked chains and fragments will behave similarly to uncrosslinked HA – that is, while aiding extrusion and flow, providing limited to no contribution to persistent wrinkle correction). The degree of crosslinking by definition refers only to the fraction of HA that is actually crosslinked. The crosslinked HA is relevant to maintaining the volume of the filler implanted into the skin, as the uncrosslinked HA is cleared from the body in a matter of days.

For HA dermal fillers, when all other factors are equal, a higher degree of crosslinking should translate into longer persistence of the filler in the skin. At the same time, there is an as-yet undefined threshold for the highest desirable degree of crosslinking, as very high degrees of crosslinking might reduce the hydrophilicity (water affinity) of the HA polymer chains and, hence, the lifting capacity of the gel implant (see 'Concentration and extent of hydration' below). Furthermore, exceeding this threshold might affect the biocompatibility of the product and induce an immune reaction by the body to the injected HA gel and, rather than metabolize the gel, the body might reject it, initiating undesired reactions such as encapsulation of the gel implant and formation of a granule or a sterile abscess.

Therefore, dermal filler manufacturers are prudent to stay well below that threshold, and achieve a balance between crosslinking HA polymer chains sufficient to achieve extended persistence and avoiding any undesired complications, such as rejections.

Gel hardness

Gel hardness refers to the stiffness of the HA gel formulation, namely its resistance to being deformed. Polymer scientists use a variable G′, the elastic or storage modulus, to quantify gel hardness (7). The concentration of HA, degree of crosslinking of HA, amount of uncrosslinked HA, and the manufacturing process all contribute to the resulting gel hardness, measured by G′.

Gel hardness can be illustrated as follows: if an HA gel is placed between two plates and then the upper plate is quickly displaced horizontally a small distance while keeping the lower plate stationary, a force will be required to hold the (shear) deformation in place. G′ is defined as the ratio of the shear stress (the force per unit area of plate) to the shear strain imposed (the ratio of the horizontal displacement to the vertical distance between plates). In a gel

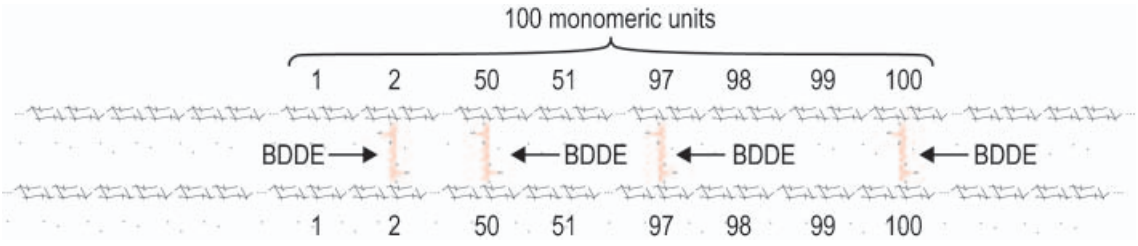

Figure 6. Degree of crosslinking. If four BDDE crosslinkers are bound to every 100 disaccharide monomeric units, the degree of crosslinking is 4%. The specific monomeric units that bind to BDDE are determined statistically by the reaction process. This figure shows one of many possibilities.

with a low degree of crosslinking, where the HA polymer chains are loosely linked to one another, the force required for displacement is low, so the gel hardness or G′ increases. As the degree of crosslinking is increased, but at the same overall HA concentration, the network formed by the HA polymers becomes more tightly connected, and a greater force is required to displace the gel, and the gel hardness or G′ increases (Figure 7).

The above discussion of gel hardness applies to a monolithic gel mass produced by crosslinking a solution of HA polymer. As will be described in more detail below, the manufacturing process used to produce HA dermal fillers involves breaking the gel mass into small HA gel particles so that they can be injected through a needle into the skin. HA products containing particles with higher G′ values are more difficult to inject, even if the gel particles of the finished product are very small in size. In order to overcome this difficulty, some manufacturers of dermal fillers add/use uncrosslinked HA as a lubricant to lower the G′ during injection and, therefore, the force required for injection. While this uncrosslinked HA aids smooth injection of a dermal filler, it has a short persistence time and, thus, does not contribute to persistent augmentation.

Hyaluronic acid gel consistency

The gel particle size of a finished product is another important property that affects the use of HA dermal fillers. As discussed above, the crosslinking step in the process used to create HA dermal fillers is similar to the preparation of gelatin – stirring a powder into hot water and letting the solution cool down. After this step, the result is a large, connected gel mass. This large gel mass must then be 'sized' to allow for injection into the skin. Sizing can be accomplished by passing the gel mass through a series of sieves or screens. HA dermal fillers produced through this method contain gel particles of a well-defined average size. Different products will have distinct average gel particle sizes according to the proprietary sieving method applied in the manufacturing process. For dermal filler products there is a maximum particle size, beyond which gel particles would not extrude easily and could clog the needle during injection.

In addition, the relationship between particle size and rate of degradation in the body has implications for 'ideal' particle size. Larger HA particles offer limited total surface areas (area per volume of gel) for enzymes to break them down, since the enzymes are sufficiently large that they cannot easily penetrate the HA gel network within a particle. Smaller HA particles offer more total surface area for enzymes to more readily degrade them. In contrast, the rate of degradation of HA gel particles by free radicals is expected to be less sensitive to particle size because many radicals are small in size and can easily penetrate to the particle interior. Nonetheless, all other relevant variables being the same, including the total volume of the implant, the smaller the average size of the gel particles, the faster the

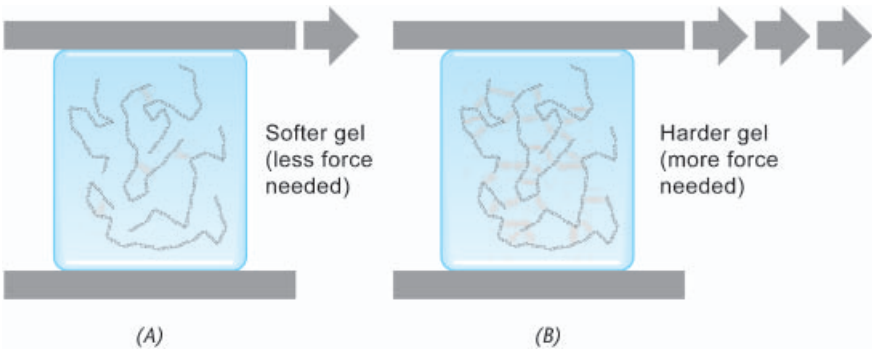

Figure 7. Gel hardness (G′-elastic modulus). G′ is measured by placing the gel between two plates and moving the upper plate horizontally relative to the lower one. With two products having the same HA concentration, the lower the degree of crosslinking, the softer the gel will be, resulting in a lower G′.

product will degrade in the body and disappear (Figure 8). However, given the limited range of gel particle sizes in the dermal fillers currently approved in the US, the differences in degradation rate may not be great enough to exhibit a clinically significant difference.

An alternative way to size a large gel mass is to break it down by a homogenization process. The result is a gel formulation that displays a smooth consistency and looks like thick egg white when compared with the more granular consistency gel particle formulations mentioned above. Presumably the smooth consistency results from a much broader distribution of gel particle sizes than in products obtained by sieving. The products manufactured with this technology are softer gel formulations with lower G′ values, and they flow easily so there is no need to use screens to limit the maximum particle size. Such products have recently been approved by the FDA and offer attractive combinations of persistence and ease of injection.

Viscosity, elasticity, and extrusion forces

We have discussed the concept of gel hardness G′, which is connected to the force required to make a small, rapid deformation of a gel. G′ thus provides information about the linear elastic properties of the gel. Of more clinical relevance is the extrusion force that the physician must apply to inject the HA filler through a needle and into soft tissue. A schematic of such an extrusion force curve is shown in Figure 9, where the force F that must be applied to the syringe plunger to inject a dermal filler is plotted as a function of displacement D of the syringe plunger. The curve is drawn assuming that the plunger is pushed at a steady rate, simulating a smooth, continuous injection. Initially, the force rises linearly with displacement D; this is the linearly elastic regime. Indeed, the slope of the curve in this regime is proportional to the gel hardness G′. A stiff gel will cause the force to rise more rapidly with displacement and the clinician will find it difficult to get the plunger moving.

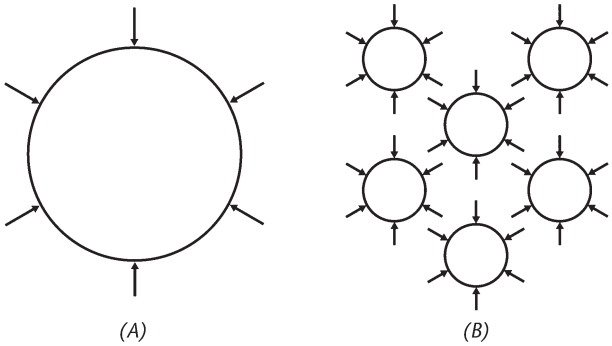

Figure 8. Particle size and rate of degradation. In theory, the larger the gel particle (A), the smaller the total surface area available for enzymatic degradation in the body. The smaller the gel particles (B), the larger the total surface area that is available for degradation. All else being equal, if a large particle (A) is sized down to a collection of smaller particles (B) that contain the same volume, in theory the larger total surface area of the smaller gel particles will facilitate more rapid enzymatic attack and, hence, more rapid degradation of the filler in the skin. However, due to the porous nature of the HA gel particles, the effects of particle size become very limited during clinical use as enzymes have access to the entire gel particle rather than having only access to the particle surface.

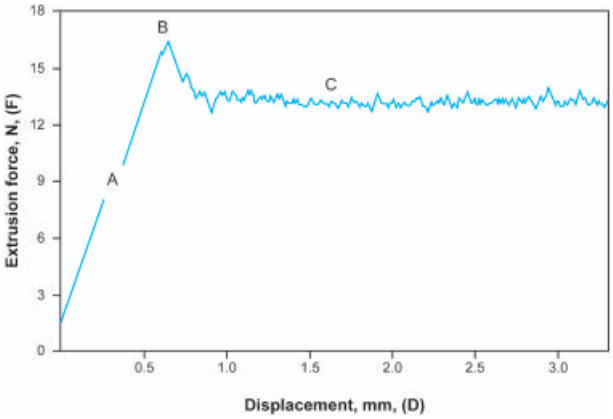

Figure 9. Force F versus displacement D required to depress a syringe plunger of an HA dermal filler injection at a constant rate. Region (A) is the linear elastic region with the slope of the curve proportional to the gel hardness G′; point (B) is the yield point at which the gel begins to flow; and region (C) is the viscous regime where F is approximately constant with D and the force level is set by the viscosity of the filler.

As the displacement is increased, the *F-D* curve becomes nonlinear and the gel begins to yield and plastically deform. After the maximum in the *F-D* curve – the so-called yield point – the gel begins to flow into the injection site and the force actually drops slightly. Finally, further continuous displacement of the plunger leads to the viscous regime in which F is nearly constant with D and the filler is injected smoothly at a steady rate. In this regime a second material parameter, the viscosity η, becomes important in dictating the level of constant force necessary for injection. It is important to note that should the clinician stop the injection process at any point, he or she will retrace the entire F versus D curve as the injection is restarted. Thus, more force and effort are required to inject the contents of a syringe in starts and stops than in one continuous injection.

The viscosity of a dermal filler and the force necessary to extrude the product through a needle are related to the degree of crosslinking, amount of crosslinked and uncrosslinked HA in the final product, sizing method, average gel particle size and size distribution, and the manufacturing process itself. When all other factors are held constant, increasing the degree of crosslinking hardens the gel, but also increases its viscosity and extrusion force. Similarly, under otherwise identical conditions, products manufactured by using sieves to create gel particles of a well-defined size tend to have a

higher viscosity and extrusion force than products of smooth consistency with a broad range of gel particle sizes.

The role of uncrosslinked HA in the flow and injection characteristics of dermal fillers is especially important. A key characteristic of HA is that it is an excellent lubricant in linear or uncrosslinked form. The lubricity of such uncrosslinked HA facilitates extrusion of the gel from the syringe through a fine needle into the skin. Products with a narrow distribution of gel particle sizes – for example, those manufactured by sieving techniques – have poor extrusion characteristics (higher extrusion force characteristics and high viscosity) unless they incorporate large amounts of uncrosslinked HA in their formulation. However, as noted earlier, the efficacy of large amounts of uncrosslinked HA does not go beyond easing the injection. The uncrosslinked HA will be quickly metabolized in the skin and, therefore, will not contribute to the final longer-term clinical outcome. The newer HA fillers that use advanced sizing techniques to achieve a broad distribution of gel particle sizes and a smooth consistency have the advantage that less uncrosslinked HA is needed to achieve injections with more even flow. Therefore, such products provide a higher percentage of crosslinked HA that can be implanted into the skin, which may improve persistence and clinical outcomes.

Concentration and extent of hydration

One of the most important features of HA relative to its performance as a dermal filler is its ability to create volume by binding large quantities of water – a function of its polyanionic and hydrogen-bonding character. One gram of a very lightly crosslinked HA gel can bind up to 3 liters (approximately three-quarters of a gallon) of water, comparable with the polyacrylic acid gels that are used as superabsorbants in modern diapers.

An HA gel achieves an equilibrium hydration when the osmotic forces associated with its hydrophilic character balance the elastic forces of the swollen HA network. Products manufactured with typical degrees of crosslinking and approximately 5.5 mg of HA for every ml of water can be considered to be close to equilibrium hydration. When these products are injected, they will not swell because they are already saturated with water. On the other hand, products with a higher concentration of HA, in the range of 20–24 mg/ml, are below their equilibrium hydration. These formulations will swell a small amount after injection by taking up water from surrounding skin tissue. It is of benefit for a dermal filler to be slightly below equilibrium hydration, as this will add to the desired volumizing effect. In order to take full advantage of this characteristic, however, injectors need to fully familiarize themselves with the particular products in order to avoid under- or overcorrection.

Summary

There are several chemical and physical characteristics that influence final HA dermal filler product performance (Table I).

Conclusions

Modern HA dermal fillers are effective hydrophilic volume restorers. Although longevity is important, purity, safety, ease of administration and patient

Table I. Chemical and physical characteristics that influence hyaluronic acid dermal filler product performance.

Crosslinking of HA polymers	Crosslinking of HA polymers is an essential step in the production of HA dermal fillers. By chemically bonding the HA polymer chains together, enzymatic degradation of the HA gel is slowed down.
Degree of crosslinking	The degree of crosslinking contributes to the overall persistence of HA dermal fillers; however, an excessive degree of crosslinking may reduce the biocompatibility of the filler, resulting in adverse reactions in the body.
Gel hardness	G′ describes the hardness of a gel. HA dermal fillers with higher G′ values are more difficult to inject through a needle into the skin unless they incorporate large amounts of uncrosslinked HA into their formulation.
HA gel consistency	Manufacturing processes determine the final consistency of HA dermal fillers. Currently available products are gel particle formulations with well-defined particle size, and 'smooth consistency' formulations with a broad range of gel particle sizes. The newly FDA-approved smooth consistency formulations may offer improved ease of injection and potentially better persistence.
Viscosity and extrusion force	The viscosity and extrusion force characterize the ease with which an HA dermal filler can be injected through a syringe into the skin. These physical parameters depend on the degree of crosslinking, amounts of crosslinked HA and uncrosslinked HA, gel consistency, and proprietary manufacturing techniques, among other variables.
HA concentration and extent of hydration	The HA concentration and extent of hydration are important features that determine both the ability of an HA dermal filler to restore volume when in clinical use and the longevity of the implant. Formulations slightly below equilibrium hydration are preferred as dermal fillers, but their use requires appropriate training in order to avoid over- or undercorrection.

comfort are all crucial factors in assessing the performance of a product. A scientific understanding of the chemical and physical characteristics of HA formulations as they relate to the above factors is also extremely important when choosing a dermal filler (8). The greatest patient concerns with most fillers relate to the safety of any particular agent; however, the impression left on the patient is based on the patient's overall experience, beginning with the consultation and informed consent and continuing through recovery to the result. Patients must be educated regarding multiregional treatments and volume (and cost) requirements, so that they have reasonable expectations about results and leave the office feeling that they received good value (9).

Currently marketed HA dermal fillers, although closer to the 'ideal' soft-tissue filler for aesthetic rejuvenation, still have their limitations related to ease of injection and persistence. Adverse events, while mostly localized and minor in nature and duration, need to be closely monitored as new products enter the market. Management of patient expectations and patient support after injections are two areas that require skill and sensitivity in order to achieve excellent outcomes (4).

With new HA dermal fillers recently approved by the FDA, the US market has gained access to formulations that, based on their chemical and physical properties, promise to take us a step closer to the ideal filler. In light of these new additions to the HA dermal filler market, and facing multiple choices, it will become more important for novice and experienced injectors alike to fully understand the key variables that play a role in HA dermal filler performance, especially those affecting handling or ease of use, efficacy in achieving optimal correction and persistence, and the safety profile in terms of lowering the incidence of adverse events such as bruising, swelling, and pain.

Finally, it cannot be stressed enough that nothing can replace the invaluable knowledge gained by observing a seasoned injector or attending live injection demonstrations (8). Therefore, a better understanding of the chemical and physical makeup of HA dermal fillers must be accompanied by appropriate training and experience to assure our ability to accomplish results that produce satisfied patients.

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References

1. American Society of Plastic Surgeons. Injectable fillers: Improving skin texture. Arlington Heights, IL: American Society of Plastic Surgeons; 2006. Accessed June 22, 2006. URL: http://www.plasticsurgery.org/public_education/procedures/InjectableFillers.cfm.
2. Dover JS. The filler revolution has just begun. Plast Reconstr Surg. 2006;117(3 suppl):38S.
3. Niamtu J III. The use of Restylane in cosmetic facial surgery. J Oral Maxillofac Surg. 2006;64:317–25.
4. Matarasso SL, Carruthers JD, Jewell ML; Restylane Consensus Group. Consensus recommendations for soft-tissue augmentation with nonanimal stabilized hyaluronic acid (Restylane). Plast Reconstr Surg. 2006;117(3 suppl): 3S–34S.
5. Monheit GD, Coleman KM. Hyaluronic acid fillers. Dermatol Ther. 2006;19:141–50.
6. Matarasso SL. Practice forum: Understanding and using hyaluronic acid. Aesthetic Surg J. 2004;24:361–4.
7. Ferry JD. Viscoelastic properties of polymers. 3rd ed. New York: John Wiley & Sons, Inc; 1980.
8. Klein AW. The art and science of injectable hyaluronic acids. Plast Reconstr Surg. 2006;117(3 suppl):35S.
9. Fagien S. The Restylane consensus statement. Plast Reconstr Surg. 2006;117(3 suppl):41S.