Comparison of the Rheological Properties of Viscosity and Elasticity in Two Categories of Soft Tissue Fillers: Calcium Hydroxylapatite and Hyaluronic Acid

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BACKGROUND Two types of soft tissue filler that are in common use are those formulated primarily with calcium hydroxylapatite (CaHA) and those with cross-linked hyaluronic acid (cross-linked HA).

OBJECTIVE To provide physicians with a scientific rationale for determining which soft tissue fillers are most appropriate for volume replacement.

MATERIALS Six cross-linked HA soft tissue fillers (Restylane and Perlane from Medicis, Scottsdale, AZ; Restylane SubQ from Q-Med, Uppsala, Sweden; and Juvéderm Ultra, Juvéderm Ultra Plus, and Juvéderm Voluma from Allergan, Pringy, France) and a soft tissue filler consisting of CaHA microspheres in a carrier gel containing carboxymethyl cellulose (Radiesse, BioForm Medical, Inc., San Mateo, CA).

METHODS The viscosity and elasticity of each filler gel were quantified according to deformation oscillation measurements conducted using a Thermo Haake RS600 Rheometer (Newington, NH) using a plate and plate geometry with a 1.2-mm gap. All measurements were performed using a 35-mm titanium sensor at 30°C. Oscillation measurements were taken at 5 pascal tau (τ) over a frequency range of 0.1 to 10 Hz (interpolated at 0.7 Hz). Researchers chose the 0.7-Hz frequency because it elicited the most reproducible results and was considered physiologically relevant for stresses that are common to the skin.

RESULTS The rheological measurements in this study support the concept that soft tissue fillers that are currently used can be divided into three groups.

CONCLUSION Rheological evaluation enables the clinician to objectively classify soft tissue fillers, to select specific filler products based on scientific principles, and to reliably predict how these products will perform—lifting, supporting, and sculpting—after they are appropriately injected.

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Temporary soft tissue fillers in current use consist of various materials, including hyaluronic acid (HA), calcium hydroxylapatite (CaHA), collagen, and carboxymethylcellulose. All of these are defined as gels because they consist of particles (a solid phase) suspended in a fluid phase. The physicochemical structure of a soft tissue filler gel is established during the manufacturing process by the adjustment of variables such as concentration of the solid-phase molecules, the method and percentage of cross-linking of solid-phase molecules, and the proportion of the overall gel that the fluid phase constitutes (gel-to-fluid ratio). Soft tissue fillers with different physicochemical structures behave differently with respect to their rheology (their viscosity, elasticity, and plasticity). Two important rheological properties of a soft tissue filler gel that can be quantified are its complex viscosity (η^*) and its elastic modulus (G'). Complex viscosity is primarily a function of the solid phase of the gel and its

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interactions with the fluid phase; conversely, elastic modulus is primarily a function of the fluid phase of the gel and its interactions with the solid phase.

The physicochemical structure of a soft tissue filler and its resultant unique rheological properties are clinically relevant because they play a pivotal role in determining how the filler behaves during and after injection. Under physiological conditions that are typical of an injection procedure, the η^* of a filler relates to how it flows from the needle, and the G' of the filler relates to its stiffness or ability to resist deformation while it is being injected. After the filler has been injected, its η^* and G' influence how well it withstands skin tension forces due to facial movements.

It is also important to consider clinical variables, including needle gauge and size, syringe size, injection force, and injection technique (e.g., serial puncture vs serial threading), because they affect shearing forces upon the soft tissue filler as it is being injected. Shearing forces may alter how the filler flows during injection by affecting its viscosity, elasticity, or both. If shearing forces are strong enough, they may alter the physicochemical structure of the filler; this is more likely to happen with a filler of low viscosity.

In a recent report, Kablik and colleagues[1] ably elucidated the physicochemical structure of a number of commercially available cross-linked HA fillers. This study included measurements of HA concentration, gel-to-fluid ratio, gel concentration, particle size, gel swelling (a measure of hydrophilicity) and percentage of cross-linking. The conclusion was that the studied fillers differed significantly in their physicochemical structure and rheological properties and that these differences accounted, at least in part, for varying clinical outcomes. A high G' in a HA filler appears to be a predictor of better resistance to skin tension forces. Therefore, a HA filler with a high G' value may be well suited to clinical applications such as volumization and lifting of facial zones that have high levels of muscle activity (and thus high skin tension forces) such as the nasolabial folds, the midface, and the lower face. Likewise, a HA filler with a high G' value may be less appropriate for filling of fine rhytides, because of its stiffness.

In the study described here, researchers sought to compare the rheological properties of a CaHA filler with those of six cross-linked HA fillers, three of which were also studied in the Kablik article, to draw conclusions regarding the appropriateness of the CaHA filler for facial volumization and lifting. Volumization is a clinical application for which CaHA filler has previously been reported to be effective.[2–6] The η^* and G' of the seven commercially available soft tissue fillers were evaluated under identical, physiologically relevant study conditions.

Study Materials

Six cross-linked HA soft tissue fillers (Restylane and Perlane, Medicis, Scottsdale, AZ; Restylane SubQ, Q-Med, Uppsala, Sweden; and Juvéderm Ultra, Juvéderm Ultra Plus, and Juvéderm Voluma, Allergan, Pringy, France) and a soft tissue filler consisting of CaHA microspheres in a carrier gel containing carboxymethyl cellulose (Radiesse, BioForm Medical, Inc., San Mateo, CA) were obtained.

The η^* and G' of each filler gel were quantified according to deformation oscillation measurements made using a Thermo Haake RS600 Rheometer (Newington, NH), using a plate and plate geometry with a 1.2-mm gap. All measurements were performed using a 35-mm titanium sensor at 30°C. Oscillation measurements were taken at 5 pascal tau (τ) over a frequency range of 0.1 to 10 Hz (interpolated at 0.7 Hz). Researchers chose the 0.7-Hz frequency because it elicited the most reproducible results and was considered physiologically relevant for stresses that are common to the skin. These researchers considered the expected range of physiological stress to which the tested soft tissue fillers would be subjected when used for facial volume replacement to be between 0.1 and 2 Hz, which is consistent with previous analysis[7,8] but at variance with the 5-Hz frequency selected for the Kablik study.

Determination of Rheological Properties

The basic methodology of rheometry is that the gel is placed between two nondeformable plates, one of which is fixed and the other mobile. The gap between the plates is adjusted so that there is complete contact between the gel and the plates. Oscillating pressure is applied to the gel by moving the mobile plate back and forth across it at varying frequencies, which generates a variable shear force. Measurements of viscosity and elasticity can then be obtained at different oscillation frequencies, which correspond to different levels of shear force.

Complex Viscosity, Viscous Modulus, and Shear Thinning

Viscosity of a gel, quantified as η^*, refers to the ability of the fluid phase to resist shearing forces. A high-viscosity gel is more difficult to spread. All soft tissue filler gels have higher viscosities when the shear force is low. Viscosity decreases (the filler "thins out") as shear force increases—a phenomenon known as shear thinning. Soft tissue fillers that behave in this manner are defined as being pseudoplastic.

An everyday example of shear thinning can be visualized in the spreading of peanut butter, which has relatively high viscosity, on a piece of toast. The shear force is provided by the pressure of the knife as it moves across the surface of the toast. As the shear force is increased to a certain level, the viscosity of the peanut butter remains essentially the same, as manifested by the same level of friction when attempting to spread the peanut butter on the toast. If shear force is increased beyond this level, a point is reached at which the peanut butter becomes easier to spread because of decreased friction with the toast. This point represents a decrease in viscosity due to shear thinning.

It can easily be deduced from this everyday example that the relationship between applied shear force and viscosity is nonlinear. There is little change in viscosity up to a certain level of applied shear force, whereas beyond this level, there are significant changes in viscosity as shear force is increased. Further insight can be obtained by expanding this everyday example to include the spreading of room temperature butter—which has a lower viscosity than peanut butter—on toast. The level of applied shear force at which the butter becomes easier to spread on the toast is considerably lower than the level of force required for the higher-viscosity peanut butter. By extrapolation, a low-viscosity gel is more susceptible to shear thinning than is a gel of high viscosity. A level of shear force that is insufficient to cause shear thinning of a high-viscosity gel may be sufficient to cause shear thinning of a low-viscosity gel.

Elasticity of a gel, quantified as the elastic (storage) modulus (G'), is a measure of the gel's ability, because of its stiffness, to resist deformation when pressure is applied. The higher the G' of a gel, the less it deforms under pressure and the more stored energy it retains. As an everyday illustration of differences in elasticity, a gelatin mold can be considered a gel with high G', whereas chocolate pudding is a gel with low G'. Fillers with high G' are better able to resist outside forces and provide better structure than are fillers with low G'. For this reason, high-G' fillers are well suited to mid- and lower-face volumization.

Results

Figure 1 shows the complex viscosity (η^*) for each of the seven soft tissue fillers evaluated. Data are also included for CaHA filler mixed with lidocaine, according to a protocol that recently received Food and Drug Administration (FDA) approval and results in a final lidocaine concentration of 0.3%.[9]

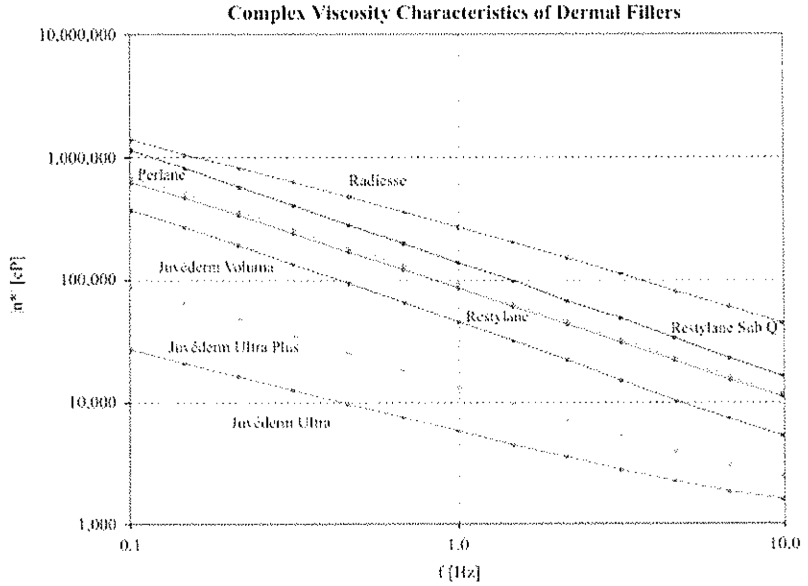

Figure 1. Complex viscosity characteristics of dermal fillers.

Elasticity modulus (G') measurements paralleled the complex viscosity measurements (Figure 2).

The table summarizes the measured values of η^* and G' (Table 1).

Clinical Implications of Rheological Comparisons of Selected Soft Tissue Fillers

The rheological measurements obtained in this study for three cross-linked HA fillers are consistent with

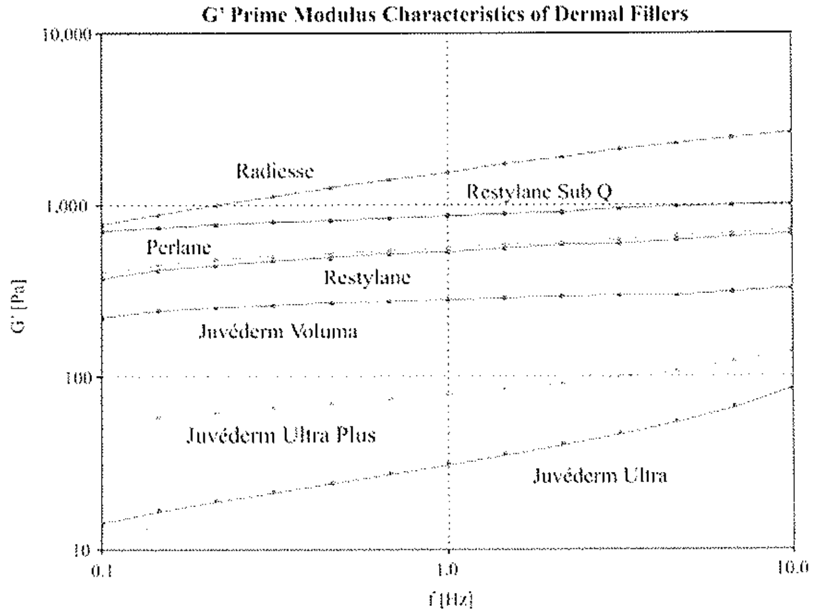

Figure 2. Elasticity characteristics of dermal fillers.

TABLE 1. Rheology (Gel at 0.7 Hz)

Product	*Viscosity (cPa)*	*Elasticity (Pa)*
Radiesse	349,830	1,407
Radiesse Mix Kit	116,113	429
Restylane SubQ	198,370	863
Perlane	124,950	541
Restylane	119,180	513
Juvéderm Voluma	62,902	274
Juvéderm Ultra Plus	17,699	75
Juvéderm Ultra	7,307	28

those of Kablik and colleagues.[1] The additional rheological measurements in this study support the concept that soft tissue fillers that are currently used commonly can be divided into three groups. CaHA (Radiesse) is in the high-viscosity and -elasticity (G') group. CaHA filler with 0.3% lidocaine and three HA fillers (Restylane and Perlane, available in the United States, and Restylane SubQ, not available) are in the medium group. Three HA fillers (Juvéderm Ultra and Juvéderm Ultra Plus, available in the United States, and Juvéderm Voluma, currently not available) are in the low-viscosity and -elasticity group. Each group has distinct benefits and disadvantages.

When reviewing or presenting rheological data, it is important to note the oscillation frequency at which measurements were obtained. This affects the absolute values of η^* and G. Oscillation frequency also affects whether the applied shear force falls within a range (the linear viscoelastic range) that produces the consistent, reproducible changes in η^* and G' necessary for study integrity and meaningful comparisons between fillers. Ideally, studies should be performed using a physiologically relevant oscillation frequency. In this study, the investigators preferred a frequency of 0.1 to 2 Hz to evaluate fillers for injection into the skin, given its low-frequency stresses. Frequencies as high as 250 Hz have been used when evaluating fillers for injection into the vocal cords, which are subject to much higher-frequency stresses.[10]

Today's clinician is faced with an array of soft tissue filler products for aesthetic use. As filler options have expanded, so too have their applications. The notion of merely filling individual rhytides has been replaced to a large extent by the philosophy of volume restoration to various zones of the face and also to non-facial areas such as the dorsum of the hands. It seems a natural transition to now consider the desired end points of this volume restoration and how these end points may be best achieved via the selection of appropriate fillers.

The rheological properties of a filler can be used as a scientific rationale for this selection process—a strategy known as rheological tailoring. Rheological tailoring allows the palette of fillers to be refined and individualized for each patient and for each facial area based on the desired end points. The clinician's use of different injectable products for specific aesthetic objectives has been compared with an artist's use of a palette of paints to create a complete picture. As part of the selection process, filler viscosity and elasticity should be considered in the context of other physicochemical characteristics such as hydrophilicity and clinical considerations such as injection techniques.

One important objective of filler injection is to lift and support zones of the face that have high levels of motor muscle activity and are susceptible to gravitational forces as skin laxity increases with age, for example, the nasolabial folds, the midface, and the lower face. It may also be desirable to precisely sculpt the lateral portion of the midface, the chin, and the nose, because better definition and shape of these zones facilitate the restoration of ideal facial contours. These clinical objectives—lifting, supporting, and sculpting—are achieved in the most volume-efficient and clinically predictable manner using fillers that have higher η^* and G'. High viscosity confers the advantage that the filler will tend to remain where it is injected rather than spreading out, allowing for precise sculpting. High elasticity confers the advantage of resistance to applied forces (e.g., from facial musculature and gravity).

A product with high η^* and high G' provides efficient facial lifting and support and remains where it is injected with minimal product migration. Where appropriate, deep injection of these fillers—into the subdermal, subcutaneous, or supraperiosteal tissue planes—will further augment their lifting effect. Split-face study data support the hypothesis that a high-viscosity and -elasticity filler provides more efficient volume replacement and tissue lifting, because optimal nasolabial fold correction with CaHA (Radiesse), the highest-viscosity and -elasticity filler tested, required a smaller volume than that required when a HA filler with lower η^* and G' was used.[11,12]

Other objectives of filler injection include rounded contouring and augmentation of areas such as the lips, and filling of fine rhytides. Crosslinked HA fillers are customarily used for the lips because they are translucent, whereas CaHA filler is opaque and thus not considered suitable for the lips. Filler selection for the lips may represent a balance between the clinician's desire to provide a lifting effect and stable contours, and the patient's preferences in regards to filler palpability. A low-viscosity and -elasticity filler will tend to spread into the tissue and have a softer feel, whereas a higher-viscosity and -elasticity filler will feel firmer and tend to spread less. Lips augmented with low-viscosity and -elasticity HA products are visually quite distinct from those augmented with high-viscosity and -elasticity HA products, as are lips augmented with hydrophilic versus nonhydrophilic HA products; each style of lip augmentation has its own aficionados.

HA fillers may also be considered most appropriate for the periocular region, including the tear trough, and for fine rhytides because their lower η^* and G'—in comparison with CaHA—could decrease the risk of contour irregularities after injection. The complete reversibility of HA fillers via extrusion or hyaluronidase injection allows for postinjection adjustment if needed in these anatomically unforgiving areas, although CaHA filler is not absolutely contraindicated for the periocular region because it is adjustable to some extent via postinjection massage or the injection of lidocaine suspension,[13] and some clinicians report good results with the injection of CaHA into this region.[14]

Once a filler product has been selected on the basis of rheological characteristics, specific injection techniques may help to insure patient satisfaction. A high-viscosity and -elasticity filler will retain its lifting effect and stable postinjection contours but will be less palpable within the tissue if it is injected with serial threading or in microaliquots through serial puncture rather than as large boluses. Conversely, the lift of a low-viscosity and -elasticity filler can be augmented by injecting larger boluses through serial puncture so that the filler is laid down in the tissue in depot fashion.

The recently FDA-approved protocol for mixing lidocaine with CaHA filler (Radiesse) offers the intriguing possibility of titrating this product's elasticity and viscosity for optimal results in different clinical situations. Although the primary intent of adding lidocaine just before injection is to decrease patient discomfort, lidocaine mixing also affects the η^* and G' of the CaHA filler. When lidocaine is added to Radiesse at a concentration of 0.3% in accordance with the FDA-approved protocol, the η^* at 0.7 Hz is reduced from 349,830 to 143,100 cPa, and the G' is reduced from 1,407 to 554 Pa.[15] These values are slightly higher than, but comparable with, those of the medium-viscosity and -elasticity HA fillers, Restylane ($\eta^* = 119{,}180$ cPa, $G' = 513$ Pa) and Perlane ($\eta^* = 124{,}950$ cPa, $G' = 541$ Pa).

The effect is to reduce extrusion force of the CaHA filler from the needle and to make it more spreadable and less palpable in the tissue while retaining its ability to provide excellent lift and stable postinjection contours. If a still more spreadable form of CaHA filler is desired, as when injecting the dorsum of the hands, the addition of more lidocaine will further reduce elasticity and viscosity.

Conclusions

Rheological evaluation enables the clinician to objectively classify soft tissue fillers, to select specific filler products based on scientific principles, and to reliably predict how these products will perform after they are appropriately injected. Based on the characteristics that are conferred upon fillers by their rheological properties, the ideal palette of fillers should include products of high, medium, and low η^* and G'. A broad palette enables the skilled clinician to achieve the best results from facial volume restoration and, in doing so, to meet or even exceed patient expectations. Because lifting is invariably a fundamental objective of filler injection, a high-viscosity and -elasticity product that provides volume-efficient lifting and stable postinjection contours can be considered a workhorse filler to optimally restore structure and support to the nasolabial folds, the midface, and the lower face. It may be desirable to add lower-viscosity and -elasticity fillers for softer contouring of other facial areas, for the filling of fine rhytides, and for patients in whom the desire for the injected areas to have a soft feeling overrides other considerations.

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