Practical Guidelines for Hyaluronic Acid Soft-Tissue Filler Use in Facial Rejuvenation

Won Lee, MD, PhD,* Seung-Gook Hwang, MD,† Wook Oh, MD,‡ Chang-Yeol Kim, MD,§ Jin-Liang Lee, MD,‖ and Eun-Jung Yang, MD, PhD¶

BACKGROUND Hyaluronic acid (HA) fillers are the most commonly used fillers for soft-tissue augmentation. The face is a dynamic structure. Facial rejuvenation by filler products depends on mechanical forces on the region of the face. The successful use of injectable HA fillers requires an understanding of the options available.

OBJECTIVE The purpose of this study is to measure the rheological properties of HA fillers and to clarify how to select these fillers considering their rheological properties.

MATERIALS AND METHODS Rheological characterization was performed on 41 fillers. Physical parameters directly linked to product performance were measured.

RESULTS The properties of the HA fillers varied. These findings provide a basis for selection guideline regarding rheological properties in facial rejuvenation.

CONCLUSION The authors' report is the largest study to determine the rheological properties of HA fillers to date. Understanding the fillers' properties can help physicians select the appropriate fillers for more predictable and sustainable results.

The authors have indicated no significant interest with commercial supporters.

Hyaluronic acid (HA) is a naturally occurring polysaccharide frequently used as a functional ingredient in subcutaneous antiaging treatments, such as dermal fillers, which use the polymer's unique viscoelastic properties.

The major challenge lies in the reasoned choice of the product to be used depending on the anatomical area to be corrected. Indeed, each region of the face is subjected to specific mechanical constraints, which the authors take into account when selecting HA. Depending on the region of the face in which it is implanted, the HA will be subjected to 2 types of forces, each causing a deformation of the product in a different plane. The first, in a horizontal plane parallel to the surface of the skin, is the force of lateral shear or torsion. The second, which is the compressive/stretching force, is applied in a vertical plane perpendicular to the surface. Facial mechanical stresses involve a combination of these 2 types of forces, and depending on the region concerned, one type of deformation may be predominant.

Hyaluronic acid can be defined by viscoelasticity and cohesiveness, which will determine the resistance to deformation during mechanical stresses. Viscoelasticity is related to the resistance to deformation in the horizontal plane (lateral shear or torsion), whereas cohesiveness is related to the resistance in the vertical plane (compression/stretching).

Yonsei E1 Plastic Surgery, Anyang, South Korea; †Sevendays Plastic Surgery, Seoul, South Korea; ‡Samsung Feel Clinic, Seoul, South Korea; §Myer's Clinic, Seoul, South Korea; ‖Justmake Plastic Surgery, Taipei, Taiwan; ¶Department of Plastic and Reconstructive Surgery, College of Medicine, Women's Healthcare Center, Cheil General Hospital, Dankook University, South Korea

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Resistance to lateral shear forces or torsion in the horizontal plane is determined by the viscous and elastic properties of HA. Multiple parameters measured using a rheometer are used to define these 2 rheological properties. The complex modulus G* represents the total energy needed to deform the product in the horizontal plane. G* reflects the overall deformability and "hardness" of the multiple units of reticulated HA. The elastic modulus G′ (storage modulus) represents the fraction of energy of G* stored by the gel and used to recover its initial shape after deformation. G′ measures the elasticity of the gel, that is, its capacity to recover its initial shape and thus to resist deformation. It depends on the degree of cross-linking of HA: the more an HA is cross-linked, the more it resists deformation and thus the more the modulus G′ increases. The viscous modulus G″ (loss modulus) represents the fraction of energy of G* lost after deformation through internal friction. G″ reflects the inability of the gel to return to its original shape after deformation and defines the product's ability to be deformed and the resistance to flow. Complex viscosity is the parameter that allows a gel to be injected through a needle. Complex viscosity is dictated by the ability of HA molecules to move relative to each other within the gel, which depends on the size and molecular weight of the particles. Tan $\delta = G''/G'$ is the viscosity/elasticity ratio. Tan δ makes it possible to measure whether a gel is more elastic ($\tan \delta < 1$) or more viscous ($\tan \delta > 1$). For injectable HAs usually used, the tan δ is generally low; the elastic component predominates over the viscous component.[1]

An injectable HA gel comprises multiple units of cross-linked HAs. The cohesiveness of the gel is defined by the internal adhesion forces or attractiveness of all its units to each other. The degree of its internal adhesion forces depends on the concentration of HA and the cross-linking technique. Cohesiveness can be defined as resistance to compression/stretching forces in a vertical plane once the product is implanted. It reflects the ability to lift the tissues (volumizing effect) and defines the initial vertical projection of the filling product.[2,3] Once implanted in the facial tissues, the HA gel is constantly subjected to extrinsic compression forces (e.g., when lying on a pillow) or intrinsic ones (skin tension when the product is injected subcutaneously). At G′ equivalent, a product with low cohesiveness will tend to lose its projection more easily than a product with high cohesiveness that will resist compression forces and maintain its volumizing effect. Cohesiveness also affects the molding ability of the product immediately after the injection. It is inversely proportional to its malleability. The less cohesive a product is, the more malleable it will be.

Naturally occurring HAs have a half-life of less than 3 days; thus, increasing the durability of the polymer is essential to developing products with greater clinical persistence.[4,5] The clinical persistence and characteristics of HA-based dermal fillers may be influenced by their physical properties. Increasing both the molecular weight and degree of cross-linking of the polymer is a proven strategy for improving mechanical strength and extending degradation times.[6] Depending on its concentration and cross-linking, the shelf life of the product varies from 6 to 18 months. In fact, the duration of action of a product is difficult to evaluate because it depends on many other factors, such as skin type, age, and lifestyle of the patient, treated area, and injection technique.

However, the methods of analysis used to determine these rheological properties vary from one manufacturer to another. The elastic and viscous modulus is measured using a rheometer for applied forces of different intensities according to the manufacturer. When attempting to account for any relationship between rheological properties and clinical benefits, the available data are not always easy to compare between products of different brands. Several physicians select fillers in clinical practice as recommended by manufacturing companies. However, the values provided by the manufacturer can be measured at high frequency and may be selected to overstate the lifting ability of the product. Therefore, it is necessary to compare the rheological properties of various fillers distributed in the filler market under the same conditions to determine whether the indications claimed by the manufacturer are appropriate. In this study, the authors aimed to measure the rheological properties of the commercially available fillers under constant conditions and provide practitioners with guidelines for filler selection.

Materials and Methods

Materials

A total of 41 fillers were analyzed. At least 2 mL of fillers was required to measure all variables. No financial support was received, and unless stated otherwise, the soft-tissue fillers discussed in this article were directly purchased from commercial sources.

Methods

Injection Properties

The HA concentration was compared with the concentration claimed by each manufacturer. The EQU-MDQC LA960 particle analyzer (Horiba, Japan) was used to measure the particle size. The injection force was measured using an IM 010 machine (Kana Technology, Daejeon, Korea). This is a measure of the force needed to inject a filler at a fixed rate through a needle. In this study, the injection was performed under the same conditions using a 27-G needle, instead of the conditions presented by each company. Coefficients of variation, calculated on the basis of 3 replicate measurements from one filler sample (to account for variations arising from the instrumentation used), lower than 10% were considered satisfactory. Coefficients of variation of 9.62% with respect to particle size and 4.25% with respect to injection force were observed.

Rheological Properties

The rheological properties were measured using an MCR 301 rheometer (Anton Paar Company, Graz, Austria) equipped with a parallel plate measuring system using a gap of 1 mm. The elastic modulus, G′, was measured in a frequency sweep within the linear viscoelastic range determined by a strain sweep. The properties were measured from 1 Hz to 0.02 Hz finally. The diameter of the plate of the rheometer was 2.45 cm, and the temperature was measured at 25°C. Three replicate measurements were performed for a single filler to account for variations arising from the instrumentation used. Coefficients of variation were 5.49% for the elastic modulus, 3.95% for the viscous modulus, 6.07% for complex viscosity, and 1.69% for cohesiveness.

Results

Hyaluronic Acid Concentration

The filler concentrations claimed by the manufacturing companies are specified in Table 1. Most of the fillers used in the authors' tests had a concentration of 20 mg/mL; the e.p.t.q. series and the Chaeum No. 4 had relatively high concentrations of up to 24 mg/mL. The Juvederm Volbella contained 15 mg/mL of HA, and the Cleviel Prime and Cleviel Contour contained high concentrations of HA at 33 and 50 mg/mL, respectively.

Injection Force

Table 1 shows the injection force for each of the 41 fillers evaluated. The injection force of the products varied from 8 N to 54.8 N. The Chaeum No. 4 showed the highest injection force value of 54.8 N. Because this filler is difficult to inject, a needle with a larger diameter is used in practice.

Particle Size

The particle size of the different fillers is shown in Table 1. Some of the subcutaneous fillers showed a relatively high particle size, over 1,100 μL/mL, such as the Restylane SubQ, Neobelle Contour, Yvoire Contour, and Cutegel Max, and most of them would be suitable for the subcutaneous layer. The particle size of the Cleviel Prime, Cleviel Contour, and Cutegel Max did not show a normal distribution.

Rheological Characterization of the Fillers

The rheological properties are summarized in Table 1. The magnitude of the elastic modulus G′ for all products is listed. The G′ values of the commercial HA fillers ranges from 4 Pa to 857 Pa depending on the manufacturing process and designed use. Figure 1 shows the variation of the elastic modulus (G′) with the applied force for each of the evaluated fillers for the superficial dermis (mean 189.67 Pa, SD 120.80, range 37–372 Pa). The authors also measured the G′ values of the filler products recommended for injection to the deep dermis (mean 227.360 Pa, SD 107.75, range 119–411 Pa) (Figure 2) and subcutaneous tissue (mean 346.75 Pa, SD 176.49, range 87–768 Pa) (Figure 3).

TABLE 1. Rheological Properties of the Fillers

Product	G′ (Pa)	G″ (Pa)	Complex Modulus	Tan Delta	Complex Viscosity (η)	HA Conc. (mg/mL)*	Cohesiveness (N)	Particle sizes (μm/mL), Median/mean ± SD	Injection Forces (N)
Restylane	349	145	378	0.4180	3,011,188	20	0.3509	547 ± 280	8
Perlane	411	199	457	0.4849	3,637,022	20	0.2869	1,024 ± 547	16
Restylane SubQ	768	245	806	0.3190	6,420,375	20	0.3387	1,393 ± 757	25
Neobelle Skin	372	136	396	0.3667	3,157,278	20	1.0296	241 ± 117	12
Neobelle Basic	365	116	383	0.3182	3,048,961	20	0.9481	447 ± 215	15
Neobelle Edge	374	110	390	0.2936	3,106,528	20	0.9183	941 ± 499	16
Neobelle Contour	387	111	403	0.2884	3,207,126	20	0.9019	1,472 ± 796	18
Hyafilia Petit	247	85	261	0.343	2,080,246	20	0.5536	227 ± 124	10
Hyafilia Classic	345	101	359	0.294	2,858,186	20	0.6038	488 ± 267	12
Hyafilia Grand	407	166	440	0.407	3,499,743	20	0.5185	991 ± 525	15
Cleviel Prime	372	180	413	0.485	3,291,663	33	0.8778	284†	16.6
Cleviel Contour	857	694	1,103	0.81	8,774,267	50	1.536	243†	20
Yvoire Classic	286	103	304	0.3624	2,424,107	22	0.2894	693 ± 344	9.8
Yvoire Volume	253	73	263	0.2910	2,097,766	22	0.3567	1,036 ± 581	12.7
Yvoire Contour	484	157	509	0.3245	4,049,358	22	0.2867	1,258 ± 742	19
Cutegel Max	701	286	757	0.41	6,024,716	20	0.57	1,106 ± 689†	20
Juvederm Volbella	99	21	101	0.2189	814,593	15	0.3046	634 ± 255	8
Juvederm Volift	179	42	184	0.2343	1,468,502	17.5	0.3417	644 ± 303	10
Juvederm Voluma	284	58	290	0.2066	2,309,805	20	0.4043	703 ± 389	25
E.p.t.q. S100	37	15	40	0.4269	323,859	24	0.4184	UD	19.6
E.p.t.q. S300	128	27	131	0.2137	1,048,864	24	0.6102	UD	29.4
E.p.t.q. S500	224	57	231	0.2551	1,847,607	24	0.8776	296 ± 168	31
Danae Original	154	81	174	0.5279	1,389,716	20	0.5531	646 ± 352	9.8
Danae Line	260	100	279	0.3869	2,222,574	20	0.3785	1,162 ± 668	19
Danae Contour	469	134	488	0.2873	3,887,740	20	0.46	1,291 ± 762	37.2
Bellast Vital	128	72	147	0.5636	1,170,954	20	0.2362	685 ± 386	15
Bellast Soft L	94	22	97	0.2400	775,485	20	0.2285	683 ± 321	12
Bellast L	119	25	122	0.2135	969,817	20	0.2880	684 ± 242	16
Bellast Plus	87	18	89	0.2062	714,771	20	0.5093	652 ± 319	32.3
Bellast Volume	106	23	108	0.215	866,658	20	0.4458	685 ± 313	33
Elravie Premium Light	140	34	144	0.2431	1,151,729	23	0.5260	UD	23

TABLE 1. (Continued)

Product	G′ (Pa)	G″ (Pa)	Complex Modulus	Tan Delta	Complex Viscosity (η)	HA Conc. (mg/mL)*	Cohesiveness (N)	Particle sizes (μm/mL), Median/mean ± SD	Injection Forces (N)
Elravie Premium Deep line	159	39	164	0.2486	1,309,982	23	0.5874	UD	25
Elravie Premium Ultravolume	198	59	207	0.2985	1,646,177	23	0.8478	UD	24.5
Neuramis Light	4	4	6	1.0530	51,271	20	0.2049	322 ± 133	8
Neuramis	57	24	133	0.4284	499,532	20	0.4532	433 ± 178	12.7
Neuramis Deep	127	38	133	0.3000	1,061,307	20	0.5998	411 ± 171	16.6
Neuramis Volume	281	71	290	0.2551	2,309,230	20	0.8003	402 ± 175	22.5
Chaeum No. 1	76	28	81	0.3733	651,115	24	0.4888	480 ± 204	14.7
Chaeum No. 2	146	29	149	0.2036	1,193,756	20	0.6716	473 ± 242	34.3
Chaeum No. 3	232	52	238	0.2200	1,896,742	20	0.7474	596 ± 291	37.2
Chaeum No. 4	340	68	347	0.2013	2,766,277	20	0.9180	664 ± 348	54.8

*From the package insert; product information provided by the manufacturer.

†Median.

HA, hyaluronic acid; UD, undetectable.

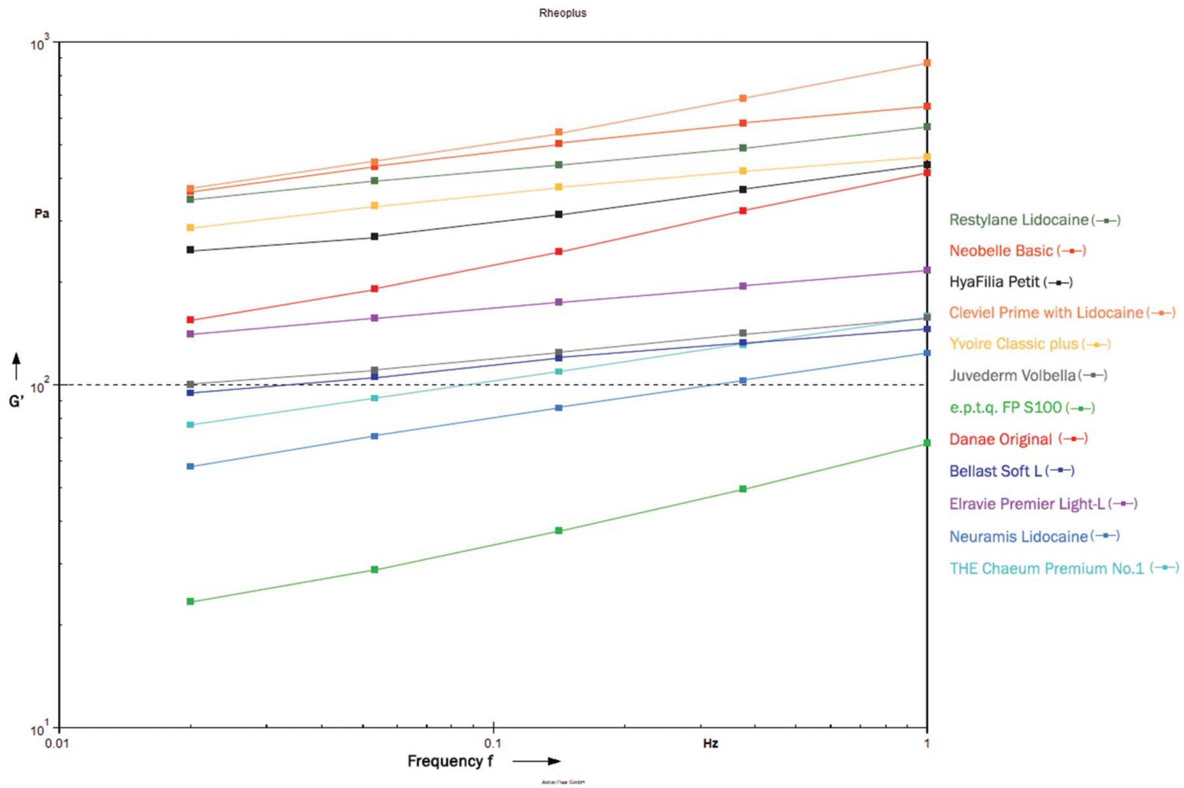

Fig. 1. Elastic modulus G′ values of the superficial dermal fillers. These are mainly used to fill fine wrinkles such as glabella and periorbital wrinkles. The fillers have a high G′ value; however, fine wrinkles do not require a filler with a high lifting capacity. Thus, the difference in the G′ value is not clinically important.

The obtained G′ values for the Juvederm, e.p.t.q. Danae, Bellast, Elarvie, Neuramis, and Chaeum series were less than 260 Pa, except for Chaeum No. 4. The G′ for the Restylane, Neobelle, Hyafilia, Cleviel, and Yvoire series was above 250 Pa. Cleviel Contour had the highest stiffness (857 Pa), followed by Restylane SubQ with a G′ of 701 Pa. On the other hand, Neuramis Light had the lowest stiffness (4 Pa). The most rigid filler, Cleviel Contour, showed the highest viscosity. The fillers showed an elastic behavior (tan $\delta < 1$), except for Neuramis Light with a tan δ of 1.0530. The elastic modulus measurements paralleled the complex viscosity measurements (Table 1).

Discussion

The HA fillers varied considerably in terms of HA concentration, injection force, particle size, and rheological properties. These variations may result from the technology used to create each filler, which in turn impacts its molecular structure and clinical performance. Manufacturers never disclose information about the rheological properties of the filler product. Therefore, physicians have to depend on the manufacturer's recommended indications when choosing the fillers. However, the rheological properties are measured under different conditions by different manufacturers. The measurements the authors performed showed that the products had a large difference in rheological properties despite being used in the same manner as recommended (Figures 1–3).

There are parameters that affect the viscoelastic properties of HA dermal fillers, including HA concentration, molecular weight, and cross-linking degree.[6] By changing these characteristics, the viscoelastic properties, especially the elastic modulus G′ and complex viscosity, can be engineered for a specific application. The elastic modulus and complex viscosity are the main rheological parameters affecting final HA performance regarding ease of injection, lifting capacity, and spreading pattern, and therefore, the recommended injection site for facial rejuvenation. Rheologic measurement is challenging due to artifacts

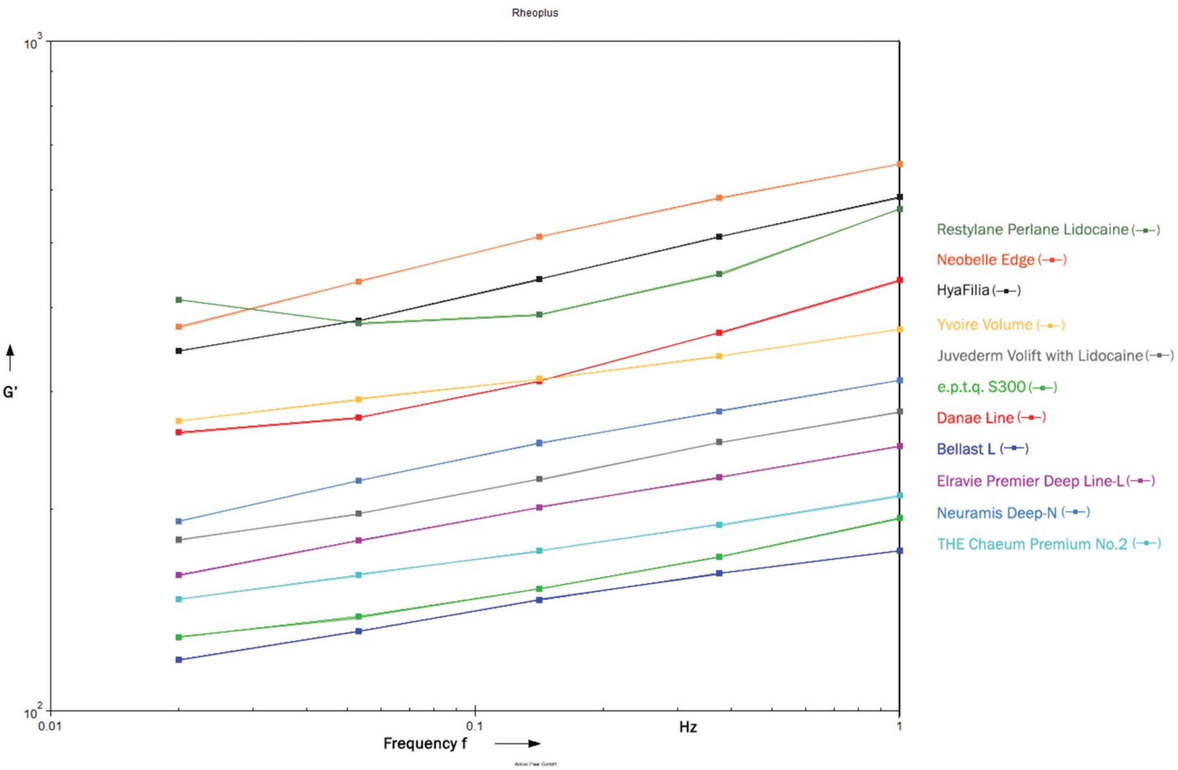

Fig. 2. Elastic modulus G′ values of the deep dermal fillers. Deep dermal fillers are most commonly used in the calibration of the nasolabial folds and marionette lines. Their G′ values are widely variable. Dermal fillers do not need to have the highest G′ value; however, deep dermal fillers with a relatively low G′ value may be insufficient for soft-tissue correction.

deriving from the rheometer systems. Coefficients of variation of this experiment were less than 5%, except those of particle size and complex viscosity.

Elastic Modulus G′

The elastic modulus G′ is a measure of the capacity of a gel to resist an applied stress. The higher the G′ value, the higher the resistance to deformation. The deformation values at the same applied stress confirmed the rank of the fillers according to rigidity (Table 1). It can be seen that the elastic modulus of the "subcutaneous fillers" is widely distributed, which allows us to infer that clinical performance of fillers may differ as well. The subcutaneous fillers Restylane SubQ, Neobelle Contour, Hyafilia Grand, Yvoire Contour, and Cutegel Max showed high G′ values, which meant that they are firmer and had less spreading tendency, allowing them to remain defined in the tissue. Therefore, they may be indicated for contouring or sculpting of deeper areas, such as the chin. The subcutaneous fillers, Juvederm Voluma, e.p.t.q. S500, Bellast Plus, Elravie Ultravolume, and Neuramis Volume, showed G′ values that were 2 to 3 times lower (<260 Pa) than what is conventionally expected. Therefore, these can also be appropriate for deeper areas but may readily diffuse into the tissue. The elastic modulus of some of the products referred to as "subcutaneous fillers" was lower than that of a "superficial or deep dermal filler" from other companies. If the G′ value is less than 100 Pa and the cohesiveness is less than 0.5 N, the filler may not be appropriate for lifting. Fillers with low G′ values are better indicated for the treatment of superficial zones such as the glabella and periorbital area.

Complex Viscosity

Viscosity is a measure of the resistance of a fluid to deformation under shear stress during extrusion and within the tissue after application. The higher the viscosity of a gel, the higher its resistance to flow. Gel viscosity is closely related to the injection force. In practice, if a volume effect is desired with a hard, high-viscosity filler, a larger-diameter needle (in place of a 27-G needle) may be used to reduce the injection force. When a filler has a high complex viscosity

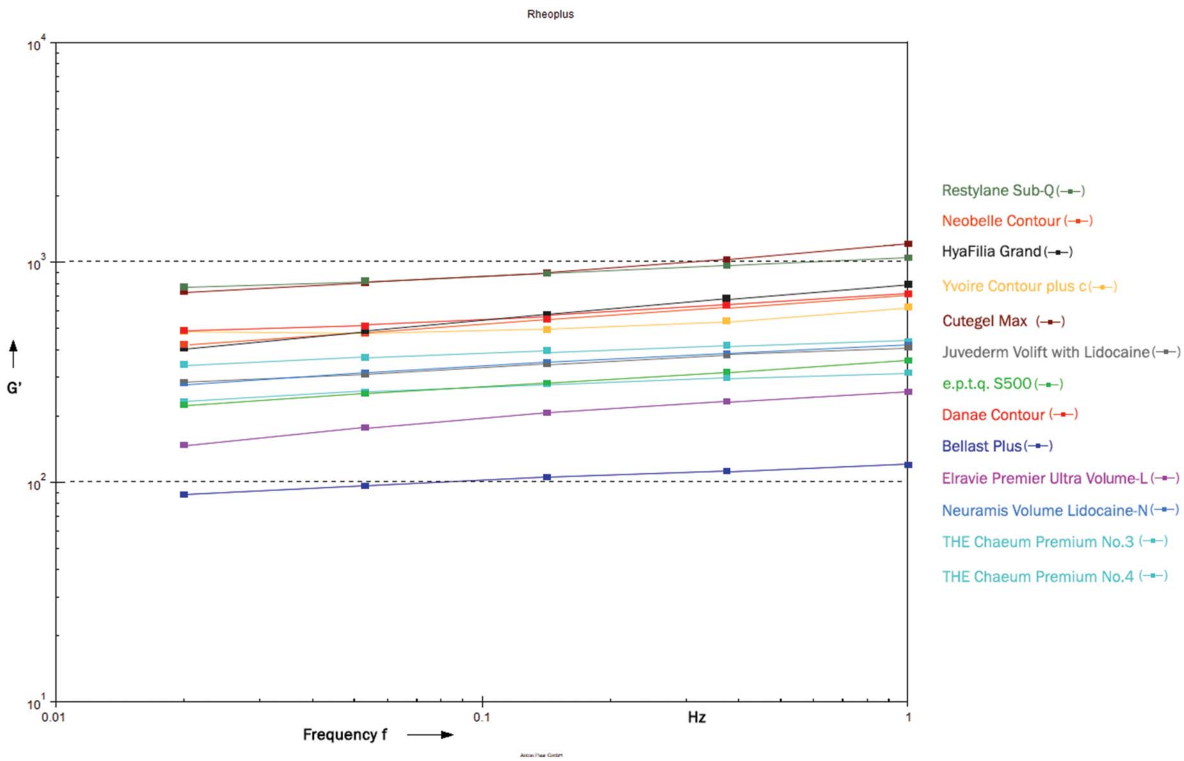

Fig. 3. Elastic modulus G′ values of the subcutaneous fillers. As the lifting capacity is important for injection to the subcutaneous level to replace volume, such as in the chin, it is considered that a certain G′ value (at least 100 Pa) is necessary. A high G′ value is clinically meaningful for lifting capacity if the other rheological properties, such as cohesiveness, are consistently high with a therapeutic objective.

and/or a high G′, it should be mixed to some extent with free HA, which can lead to some extent of swelling, to lower the injection force. In fillers with high G′ values, such as the Restylane, Neobelle, Hyafilla, Cleviel, Yviore, and Cutegel series, the injection force remained at about the midpoint of the injection force range measured in this study, although these fillers had a high complex viscosity (Table 1). This might imply that free HA was included to some extent to lower the injection force. However, the amount of free HA content is unknown, and it can be inferred that fillers showing a low injection force at a high complex viscosity might cause a certain degree of swelling. In addition, gel viscosity is a predictor of the gel spreading pattern. The results of rheological characterization indicate better spreading of the Yvoire series than other fillers with high G′ values. All fillers with low G′ and low cohesiveness, such as the Juvederm Volbella, e.p.t.q. S100, Bellast Vital, and Neuramis Light dermal filler series, are less viscous and are expected to spread more in the surrounding tissue after injection, allowing for achievement of a hydrolift effect compared with the other evaluated fillers.

Elastic Modulus G′ and Filler Viscosity Depend on Hyaluronic Acid Concentration and Cross-linking Degree

To better understand the performance of HA fillers in the clinical setting, it may be useful to simultaneously consider the HA concentration and the degree of cross-linking. Among fillers with equivalent HA concentration, the extent of cross-linking is associated with rigidity and viscosity.[7,8] The important variables determining the cross-linking extent of fillers include the amount of cross-linked HA and the degree of cross-linking within the gel network.[9] As only cross-linked, HA can resist enzymatic and radical degradation in vivo, long-lasting and highly cohesive HA fillers should contain a cross-linking agent. The most widely used cross-linking agent is 1, 4-butanediol diglycidyl ether (BDDE). Other cross-linking agents include divinyl sulfone and polyethylene glycol. As BDDE has an epoxide group, which causes the cross-linking reaction under alkaline conditions, NaOH is added to the reaction.[10] At the end of the cross-linking reaction, a washing process is performed again to optimize the pH, in which not only the NaOH but also the by-products from the manufacturing process are washed out. The cross-linking reactions, washing, sieving, and other processes, are different for each manufacturer; thus, a variety of products available in practice can be produced. This also means that physicians have to rely on the limited information provided by the manufacturer about the product properties. As BDDE is a factor that determines the longevity and cohesiveness of the filler, it needs to be quantified. The toxicity level, LD_{50}, of the BDDE cross-linking agent is only 1,130 mg/kg, and the dose used for skin sensitization is not known. In a high–cross-linking filler, the BDDE content increases and may cause allergic reactions such as immediate or delayed swelling. When the cross-linking technique is not sufficient, the amount of BDDE added to the reaction is increased, and this can also cause skin sensitization. A weakly cross-linked product will have a deformable, relatively short half-life, and more hydrophilic texture. However, excessively reduced BDDE may decrease cohesiveness, risking migration of the filler without agglomeration after the injection. When designing the filler, it is desirable that the extent of the cross-linking reaction is sufficient to achieve extended persistence while avoiding unnecessary complications.

Given the same degree of cross-linking, low concentrations will result in softer hydrogels, whereas higher concentrations will result in rigid hydrogels. The total HA concentration consists of the insoluble cross-linked HA gel and soluble free HA contents. The reason for mixing free HAs to filler products is related to viscosity. If the viscosity is too high, injection of the fillers becomes difficult. Adding some free HA decreases the viscosity, allowing for the filler to be easily injected. However, physicians cannot know how much free HA is included in the product (i.e., soluble and insoluble fractions). The total concentration of commercially available HA fillers can only be a reference value rather than an absolute parameter for assessing the filler performance.

The list is not exhaustive but could be a tool for practitioners when choosing fillers according to clinical performance. Understanding the rheological properties is essential to determining the performance and application of these products and the region to be treated.

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Address correspondence and reprint requests to: Eun-Jung Yang, MD, PhD, Department of Plastic and Reconstructive Surgery, College of Medicine, Woman's Healthcare Center, Cheil General Hospital, Dankook University, 04619, South Korea, or e-mail: enyang7@gmail.com