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Comparative Rheology of Hyaluronic Acid Fillers, Poly-l-lactic Acid, and Varying Dilutions of Calcium Hydroxylapatite

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Background: This study examines the rheological properties of various dermal fillers, including hyaluronic acid (HA) fillers, poly-L-lactic acid (PLLA), and calcium hydroxylapatite-carboxymethylcellulose (CaHA-CMC) gels, with a particular focus on the impact of aqueous dilution on CaHA-CMC's rheology and potential clinical implications.

Methods: Using standardized rheological analysis, we measured and compared the elastic modulus (G′), viscous modulus (G″), and the tan δ values of different dilutions of CaHA-CMC against published values of HA and PLLA fillers. The study aimed to determine the potential clinical use of application-specific CaHA-CMC hydrogel dilutions along a range of gel strength and cohesion for hydrogel fillers in current use.

Results: The findings demonstrate that CaHA-CMC's rheological properties can be tailored across a broad spectrum of viscoelastic parameters through titrated dilution, ranging from high elasticity to low cohesion. Varying the aqueous volume allows for the rheomodulation of CaHA-CMC, potentially matching the entire rheological spectrum of HA fillers and suggesting an expanded range of clinical applications.

Conclusions: The versatility of CaHA-CMC through dilution may offer a customizable approach for clinical applications, providing practitioners with the ability to fine-tune the properties of fillers to meet specific patient needs and treatment goals. This study lays the groundwork for the potential future use of filler dilutional rheomodulation in clinical practice, tailored to patient- and application-specific needs.
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INTRODUCTION

The early 21st century evolution of dermal fillers has paved the way for a broad spectrum of applications in aesthetic medicine, from mitigation of fine lines to augmentation of soft tissue volume and bony contour. Alongside, the incorporation of innovative bioregenerative applications and the increasing awareness of use-specific parameters have fueled the diversity of fillers available today (Fig. 1).[1,2] However, the exuberant cost and redundancy of stocking the current multiplicity of product options invites the question of whether product optimization through titrated aqueous mixing could serve a role in improving the versatility and cost-effectiveness of dermal filler use. Already, the practice of "filler blending" has gained popularity among practitioners, as recently evidenced by a survey of nearly 500 dermatologists, with the main purpose of altering of product rheology.[3]

The concept of dilutional rheomodulation of dermal fillers has been recently explored in the study of hyperdilute calcium hydroxylapatite-carboxymethylcellulose (CaHA-CMC) implant gels (Radiesse, Merz Aesthetics, Raleigh, N.C.).[4] CaHA-CMC is composed of 25–40 μm diameter calcium hydroxylapatite microspheres (30% w/v) suspended in a CMC gel carrier (70%). In clinical practice, the use hyperdilute CaHA-CMC has

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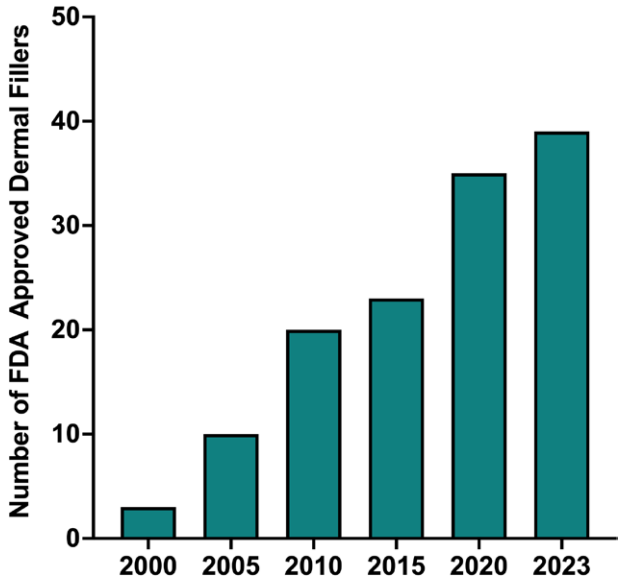

Fig. 1. Cumulative number of US Food and Drug Administration–approved dermal filler products since 2000.

demonstrated safety and effectiveness in bioregenerative applications, with positive effects on skin quality, elasticity, and superficial rhytids of aged skin.[5–8] Despite the established practice of product hyperdilution, the effects of titrated hypodilution (less than 1:1) on gel rheology, have not yet been fully characterized. Rheomodulation is suggested as a newly developed practice where clinicians can manipulate the rheological characteristics of dermal fillers to achieve desired physioclinical measures, typically with decreased gel strength and cohesion compared with the nondiluted product. Rheometric evidence points to the possibility that CaHA-CMC gels may be tailored to achieve a customized rheological profile along a resiliency-regeneration continuum, with high elasticity/resiliency, direct filling at one end and low-cohesion, biostimulatory action at the other end.[9–11]

In this study, we perform a comparative rheological analysis of different dilutions of CaHA-CMC product relative to existing dermal fillers and biostimulators gathered under the same testing conditions. In addition, we draw dilutional correlates necessary to closely mimic the rheological properties of different HA fillers by dilution of CaHA-CMC with precise volumes. We conclude with an overview of the potential applications of fillers of differing rheological strength, elasticity, and cohesion in clinical practice, proposing a framework for their utilization based on anatomical regions/planes and intended outcome.

METHODS

This study used CaHA-CMC (Merz Aesthetics), a dermal filler composed of synthetic 25–45-μm CaHA microspheres (30% by volume) suspended in a gel carrier of sterile water, glycerin, and sodium CMC, manufactured according to the valid Bill of Materials by Merz North America, Wis.

Takeaways

Question: This study evaluated the rheological properties of calcium hydroxylapatite-carboxymethylcellulose (CaHA-CMC) at different dilutions and compared them with various hyaluronic acid fillers and poly-L-lactic acid biosimulators.

Findings: This study showed that CaHA-CMC diluted past 1:1 exhibited predominantly fluid behavior, whereas dilutions under 1:1 exhibited predominantly gel-like behavior. This analysis provides a framework for tailoring CaHA-CMC dilution to match the general rheological properties of different hyaluronic acid dermal fillers.

Meaning: Minimal dilutions of CaHA-CMC maintain direct volumization, providing effective results, whereas hyperdilutions lose this capability, making them suitable for biostimulatory applications.

Preparation of CaHA-CMC Dilutions

Before testing, diluted samples of CaHA-CMC were created. In short, all dilutions beyond the original undiluted product were prepared by transferring 1.5 mL of each gel into a fitting mixing syringe (either 5 or 10-mL Luer Lock syringe, Becton Dickinson and Company, Franklin Lakes, N.J.) through a Luer-to-Luer connector (Baxter Rapidfill Connector, Baxter Healthcare, Deerfield, Ill.). The smallest appropriate graded syringes were used to draw the specified volume of 0.9% saline into the secondary mixing syringes. The dilutional saline volumes added to each sample of undiluted, 1:0.25, 1:0.5, 1:1, 1:2, and 1:3 included 0, 0.38, 0.75, 1.5, 3, and 4.5 mL, respectively (Table 1). After all observable air bubbles were eliminated by allowing the solid contents to settle and air bubbles to rise toward the syringe tip, the materials in the two mixing syringes (containing 1.5 mL of CaHA-CMC and 0.9% saline) were uniformly blended by applying the plungers for a minimum of 20 mixing strokes, where one stroke was defined as two pump movements. After the mixing process, each solution was closely examined for uniformity and then immediately subjected to testing.

Rheological Measurements of Diluted CaHA-CMC Gels

Measurements of G′, G″, and tan δ were taken in triplicates for each dilution using an Anton Paar oscillatory rheometer (Anton Paar GmbH, Graz, Austria), employing a 35-mm parallel plate geometry (PP35). The undiluted CaHA-CMC was directly assessed from the syringe, whereas the diluted CaHA-CMC samples were evaluated directly after mixing. These tests were performed with a steady shear deformation of 0.1%, across a frequency spectrum that ranged from 10 to 0.1 Hz. G′ and tan δ were specifically evaluated at 0.1 Hz under ambient conditions (25°C). Thirteen data points were gathered from the machine during each sample run and measured in triplicate. The average and SD were subsequently

Table 1. Amounts of CaHA-CMC and Saline Used at Each Dilution Ratio

Dilution Ratio	CaHA-CMC (mL)	Saline (mL)
1:0	1.50	0.00
1:0.25	1.50	0.38
1:0.5	1.50	0.75
1:1	1.50	1.50
1:2	1.50	3.00
1:3	1.50	4.50

calculated. These values were compared against the values of hyaluronic acid (HA) fillers reported at the same frequency by Fagien et al[12] and the value derived by PLLA by Kwon et al.[13]

Correlation Analysis

The correlation analysis approximating dilution volumes for CaHA-CMC to match comparative HA filler G′ values was constructed by deriving G′ values from our experimentally gathered data fit with a nonlinear curve (two-phase decay; R2 = 0.9993). Dilution values intended to approximately match different G′ values from HA fillers, were extrapolated from the equation generated from the two-phase decay curve from this work's experimentally derived G′ values. Mean values from our collected data and the reported values from Fagien et al were graphed via GraphPad Prism 10.1.1 (GraphPad Software; La Jolla, Calif.), and figures were collaged using BioRender (BioRender.com; Toronto, ON, Canada).

RESULTS

Rheological parameters (G′, G″, G*, and tan δ) for different aqueous dilutions of CaHA-CMC gel are presented (Table 2) and compared against the entire range of HA filler parameters, reported by Fagien et al in Figure 2 (product coding listed in Table 3).

The G′, G″, and G* values for all HA fillers spans a large range of G′ values, with the dilutional rheology of CaHA-CMC spanning the entire range of the HA G′ spectrum. The G′ values of the HA fillers range from ~10 Pa (XPRESS RF) to ~545 (NASH LYF), representing a difference of 535 Pa across multiple classes of HA fillers. The G′ values of CaHA-CMC range from ~0.1 Pa (1:3) to 989 Pa (undiluted), representing a difference of 989 Pa, nearly twice that of the entire range of HA fillers tested by Fagien et al.[12]

Notably, Table 4 lists the previously reported G′ values of the Food and Drug Administration–approved HA fillers investigated by Fagien et al and, by extrapolating from the dilution-dependent CaHA-CMC data, expresses the necessary volume of saline required to attenuate CaHA-CMC's G′ to match each HA filler's G′ values.

Similar trends were observed for G″, with XPRESS RF having the lowest G″ at ~5 P and NASH R having the highest G″ at ~99 Pa, representing a difference of 94 Pa. Dilutions of CaHA-CMC encompassed the entire range of G″ for HA fillers, with the lowest G″ (1:3) being ~1 Pa and the highest G″ (undiluted) being 427 Pa, representing a difference of 426 Pa. Tan δ measurements (Fig. 2D) reveal that all the HA fillers, undiluted CaHA-CMC, and 1:0.25 CaHA-CMC have predominantly elastic behaviors (tan δ < 1), but that dilutions of CaHA-CMC to 1:0.5 and greater have predominantly viscous behaviors (tan δ > 1). Notably, hyperdilutions (>1:1) of CaHA-CMC have exceptionally high tan δ values, suggesting they retain little elastic properties and largely behave as fluids.

DISCUSSION

In the clinical application of dermal fillers, a nuanced understanding of rheological properties is pivotal to guiding optimal product selection (Table 5). Among the multitude of rheological parameters, the complex modulus (G*), elastic modulus (G′), viscous modulus (G″), and dissipation factor tan δ are perhaps the most informative, as they describe material behaviors that relate to specific physical properties (cohesion, stretch, and malleability).

The response of a viscoelastic material to a shear stress is contingent upon the partitioning of its elastic and viscous parameters (Fig. 3), the sum of which represents the total energy that a material can absorb and is quantified by the complex modulus (G*). G* describes the pressure that must be applied to a material to induce a specific degree of shear deformation.[11] All else being equal, a higher G* translates into a gel that is stiffer or harder to deform, that is, stronger, or more cohesive.

The elastic and viscous properties of a gel are evident upon the removal of an applied stress. A gel that is highly elastic will recover its initial shape, akin to a spring, converting stored energy from the applied stress back into kinetic energy as it returns to its original shape. This elastic behavior is measured by the shear elastic modulus G′, which specifies the amount of energy stored elastically. All else being equal, a higher G′ renders a gel more "bouncy" or "springy" to the touch (eg, gummy bears). In contrast, a gel that is highly viscous will remain deformed upon removal of the applied stress, having dissipated the energy in the form of heat via friction. This viscous, or plastic behavior, described by the shear viscous modulus G″, represents the ability of a material to dissipate energy, akin to a shock-absorber. All else being equal, a higher G″ renders a gel more pliable, feeling more "doughy"

Table 2. Summary Data for CaHA-CMC at Different Dilutions with 0.9% Aqueous NaCl Solution

Measure	Undiluted	1:0.25	1:0.5	1:1	1:2	1:3
G′ [Pa (0.1 Hz)]	962.0	113.2	40.78	8.369	1.021	0.1190
G″ [Pa (0.1 Hz)]	422.9	92.49	42.61	12.42	2.512	0.6164
G* [Pa (0.1 Hz)]	1050.851	146.180	58.980	14.977	2.712	0.628
tan(δ) (0.1 Hz)	0.440	0.817	1.045	1.484	2.460	5.180

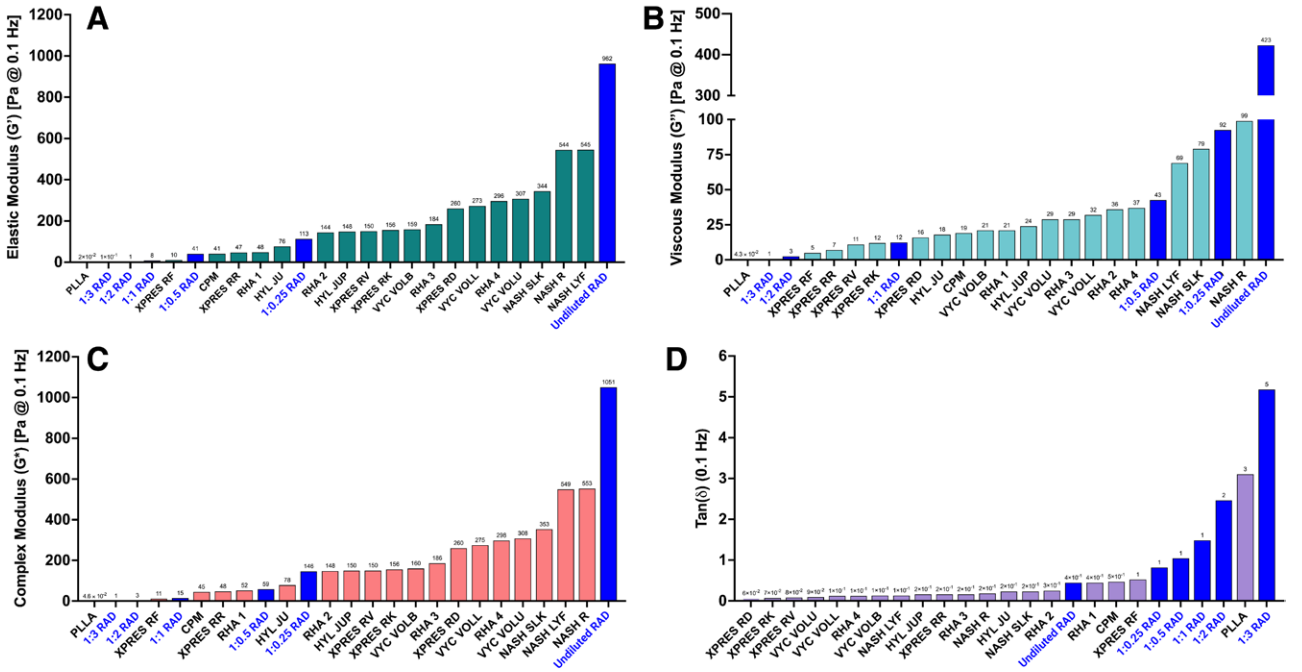

Fig. 2. Comparison of (A) elastic modulus (G′), (B) viscous modulus (G″), and (C) complex modulus (G*), and (D) tan δ values for multiple HA filler brands published by Fagien et al and different dilutions of CaHa-CMC gel experimentally derived in this work.

Table 3. Product Coding

Technology	Abbreviation	Name
CPM (HA)	CPM BB	Belotero Balance
Hylacross (HA)	HYL JU	Juvéderm Ultra XC
	HYL JUP	Juvéderm Ultra Plus XC
	VYC VOLB	Juvéderm Volbella
Vycross (HA)	VYC VOLL	Juvéderm Vollure
	VYC VOLU	Juvéderm Voluma XC
XpresHAn (HA)	XPRES RF	Restylane Fynesse
	XPRES RK	Restylane Kysse
	XPRES RV	Restylane Volyme
	XPRES RR	Restylane Refyne
	XPRES RD	Restylane Defyne
NASHA (HA)	NASH SLK	Restylane Silk
	NASH R	Restylane
	NAS LYF	Restylane Lyft
RHA (HA)	RHA 1	Teosyal RHA 1‡
	RHA 2	Teosyal RHA 2
	RHA 3	Teosyal RHA 3
	RHA 4	Teosyal RHA 4
CaHA-CMC	RAD	Radiesse (undiluted)
	1:0.25 RAD	Radiesse (1:0.25)
	1:0.5 RAD	Radiesse (1:0.50)
	1:1 RAD	Radiesse (1:1)
	1:2 RAD	Radiesse (1:2)
	1:3 RAD	Radiesse (1:3)
PLLA	PLLA	Sculptra Aesthetic

or deformable to the touch (eg, saltwater taffy). The Pythagorean relationship that exists between G*, G′, and G″ (Fig. 4) reminds us that these moduli should always be considered together when discussing the behavior of viscoelastic materials.

The relationship between G′ and G″ is conveniently represented by the ratio of G″/G′, known as the dissipation factor or tan δ, and assists us in predicting the properties of a product. Viscoelastic solids, including most dermal filler gels, have tan δ values between 0 and 1. A low

Table 4. Dilution Volumes Required to Match the G′ of CaHA-CMC to Different HA Fillers

Filler	Reported G′ (Pa)	Dilution Volume (mL) for CaHA-CMC
CPM	41	1.34
HYL JU	76	0.981
HYL JUP	148	0.625
VYC VOLB	159	0.591
VYC VOLL	273	0.377
VYC VOLU	307	0.34
XPRES RF	10	2.245
XPRES RK	156	0.6
XPRES RV	150	0.618
XPRES RR	47	1.26
XPRES RD	260	0.393
NASH SLK	344	0.307
NASH R	544	0.195
NASH LYF	545	0.195
RHA 1	48	1.247
RHA 2	144	0.638
RHA 3	184	0.525
RHA 4	296	0.351
PLLA	0.015	3.23

Table 5. Rheological Measurements, Their Symbols, and Brief Descriptions

Measure	Symbol	Rheological Description	Physical Correlate
Elastic (storage) modulus	G′	Ability to store energy elastically and resist shear deformation	Because G′ and G″ should be considered together, they are best described by the ratio G″/G′, or tan δ. Low tan δ (G′ > G″)—A higher G′ relative to G″ equates with a more elastic gel that is bouncier. High tan δ (G″ > G′). A higher G″ relative to G′ equates with a more viscous gel that is doughier
Viscous (loss) modulus	G″	Ability to dissipate energy through shear plastic deformation or flow	
Complex modulus	G*	A measure of the overall resistance to deformation	Gel strength. G* describes the total resistance to deformation, both elastic and plastic (viscous). A high G* equates with a gel that is stronger

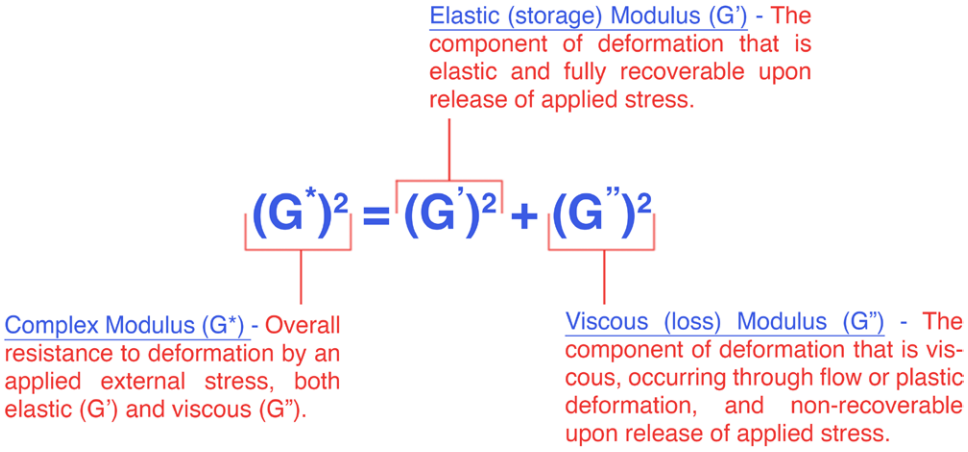

Fig. 3. Mathematical relationship between the complex modulus (G*), elastic modulus (G′), and viscous modulus (G″).

tan δ value (eg, tan δ = 0.1) indicates that the gel is 10× more elastic than viscous, having a predominantly springy nature that resists permanent deformation. Nonetheless, the magnitude of G* must also be considered; for example, a gel with a tan δ = 0.1 and a very low G* may still feel soft to the touch, like a soft ointment, due to an overall weak resistance to deformation. In contrast, a gel with a tan δ = 0.1 but a high G* can feel thick and bouncy, like a block of gelatin or silicone elastomer.

Conversely, an increase in tan δ, in which G″ is closer to G′ in magnitude (eg, tan δ = 0.9), translates into a gel that is more pliable and spreadable. Given specific testing

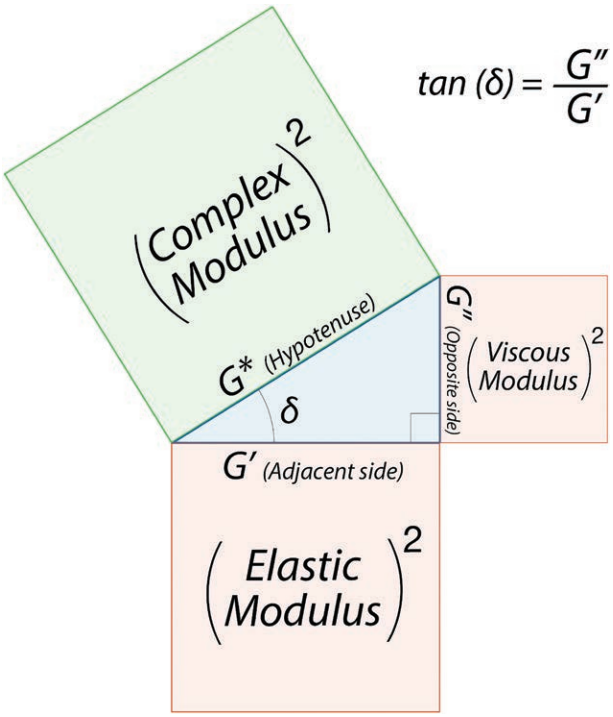

Fig. 4. Illustrative representation of the Pythagorean relationship between complex modulus (G*), elastic modulus (G′), and viscous modulus (G″).

conditions, once the tan δ reaches a value of greater than 1, the viscoelastic material no longer acts as a solid, transitioning into fluid-like behavior. Rheologically, a viscoelastic fluid can be defined as a material that will continuously deform under an applied stress, straining indefinitely or flowing. In contrast, a viscoelastic solid deforms finitely under a constant force, demonstrating plastic deformation rather than flow. Of note, these definitions assume short time scales, where the experimental observation time is smaller than the material's relaxation time. Over sufficiently long timescales, even highly resilient viscoelastic materials, such as bitumen (ie, asphalt), will flow.[14] In addition, the complex, elastic, and viscous moduli of a material are ever-changing, varying in response to the magnitude and frequency of the stress applied, as well as with ambient temperature. For this reason, a holistic interpretation of rheometric parameters that accounts for varying conditions is necessary to prevent misunderstanding.

In their clinical application, dermal fillers should demonstrate a rheologically based, tissue-matched aptitude for their intended therapeutic effect (Fig. 5A–E). For instance, dermal fillers used in the correction of superficial dermal rhytids should demonstrate a sufficiently elastic, G′-weighted profile (ie, lower tan δ), temporarily adapting to the high shear stresses that occur during facial animation without permanent deformation.[15,16] In addition, their G* should be sufficiently high to prevent fracture or failure but low enough to confer a smooth consistence that is less prone to nodularity when injected superficially. On the other hand, a gel intended for deep contouring and projection of bony eminences should possess a low tan δ and a high G*, with an enhanced ability to resist deformation from overlying tissues or external compression. Furthermore, fillers that are purely intended to fill a contour deformity should be sufficiently pliable to adapt to the contour irregularities of the defect and facilitate shaping during treatment, having a higher tan δ and a tissue-matched (ie, equitissular) G*. Finally, dermal filler products designed for bioregenerative applications should feature a fluid-like rheology, having a tan δ greater than 1 and a low G* that renders them noncohesive and easily dispersible for maximal tissue integration and biostimulatory activity.

The dilutional effect of saline mixing in this study demonstrates a substantial impact of filler blending on the overall product rheology. Beyond 1:1 dilutions (ie, hyperdilutions), CaHA-CMC gel mixtures displayed predominantly viscous behavior, with tan δ values greater than 1 and a 98% reduction in elastic modulus. In addition, hyperdilutions of CaHA-CMC gels resulted in a 95% loss in G″ and 97% decrease in G*. These parametric alterations describe hyperdilute mixtures as being noncohesive and fluid in nature, featuring properties that are ideal for bioregenerative applications but eliminate direct filling capabilities.[4] In contrast, hypodilution (ie, less than 1:1 volume mixing) of CaHA-CMC results in reduced elasticity and lower G*, with modest increases in tan δ (0.6503 and 0.784 for 1:0.25 and 1:0.5, respectively). Mild dilutions therefore alter the product away from tissue projection and toward passive filling, serving a traditional mid-range role.

There are several methodological limitations in the present study. First, only rheological values for CaHA-CMC were experimentally derived in the dataset, and therefore, our comparisons, though not statistical, rely on the reproducibility of the dataset reported by Fagien et al. This is particularly noteworthy, as reported rheological values are known to vary based on the parameters of the experimental setup. Second, although the CaHA-CMC samples were conducted in triplicates, the values reported by Fagien et al do not report SDs, making statistical analysis impossible. Finally, the rheological data reported by Kwon et al were reported at 1 Hz rather than 0.1 Hz and thus were normalized by comparison with 1:2 dilute CaHA-CMC based on their similar rheological values at 1 Hz.

CONCLUSIONS

CaHA-CMC is an injectable hydrogel notable for its direct filling and biostimulatory capabilities, which exist along a resiliency-regeneration continuum. This study investigated the effects of titrated aqueous dilution on the specific rheological parameters of CaHA-CMC gels, revealing a general decrease in gel strength (G* and G″), an increase in viscosity (as indicated by an increased tan delta), and diminished cohesiveness. By varying the dilution volume, it is possible to match the full range of elastic strengths exhibited by currently available HA fillers, at the

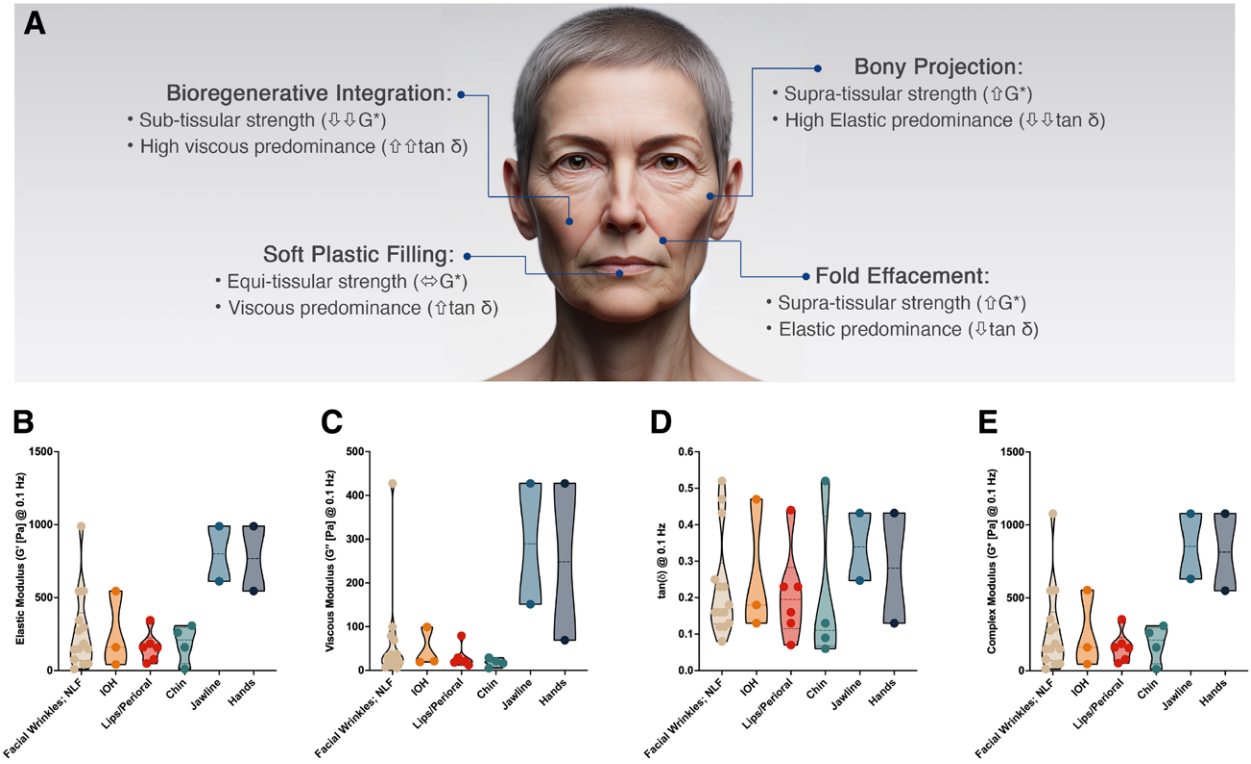

Fig. 5. Ranges of rheological values by Food and Drug Administration approval and preferred values by anatomy. A, Rheological considerations for the face for optimal outcomes. B, The elastic modulus, (C) viscous modulus, (D) tan δ, and (E) complex modulus for dermal fillers by anatomical Food and Drug Administration approval.[1]

expense of increased viscous behavior and greater potential for fragmentation. Such titrated dilutional rheomodulation could theoretically be used to optimize product rheological parameters to suit specific applications, where applicable, ranging from high-strength tissue projection and contouring to low-cohesion biostimulatory effects. This study lays the groundwork for further research on the potential use of rheomodulation in clinical practice, tailored to patient- and application-specific needs.

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DISCLOSURES

Drs. McCarthy, Radia El-Banna, and Nadine Hagedorn are employed by Merz Aesthetics. Dr. Soares is a paid speaker and trainer for Revance Therapeutics, Inc. and has received research grant funding from Merz Aesthetics. Dr. Chandawarkar is a paid clinical consultant and shareholder for Cypris Medical and Allergan Aesthetics, an Abbvie Company and has received travel support from Merz Aesthetics. Dr. Faria has received research grant funding and is a paid speaker and trainer for Merz Aesthetics.

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