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Rheological properties of hyaluronic acid-based fillers for facial cosmetic aesthetics

Propriedades reológicas de preenchedores à base de ácido hialurônico para estética cosmética

Propiedades reológicas de rellenos a base de ácido hialurónico para estética cosmética facial

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Abstract
Hyaluronic acid-based dermal fillers are the most used materials in cosmiatry, and their clinical implications are linked to their viscoelastic properties. This study aimed to determine the rheological behavior of HA products used in Brazil by changing specific physicochemical characteristics under different test frequencies. Laboratory analyses of 0.9 mL of samples were performed in a TA-Instruments AR-1500ex Rheometer at 25 °C, at oscillation frequencies of 100, 10, 1, and 0.1 radians/second, considering the measurements of G′, G″, and Tan δ. The value of G' increased as the oscillation frequencies were increased. In parallel, the changes in G" were the ones that varied the most for frequencies 0.1 and 1 radian/second. The maximum G' was observed with Hialurox Ultra Lift® 26 mg/g (793.45; 554.06; 423.44 Pa, 100, 10 and 1 rad/s, respectively). While the lowest G' values were obtained with Rennova Ultra Deep® (43.01; 19.75; 10.75 and 10.42 Pa at 100, 10, 1, 0.1 rad/sec, respectively). The changes that occurred in the investigated properties indicated that hyaluronic acid-based fillers vary when subjected to different conditions of shear rate, which should be considered in their clinical indication for choosing the most appropriate material according to the region to be treated.
Keywords: Hyaluronic acid; Soft tissue fillers; Rheological properties; Viscoelastic properties.

Resumo
Os preenchedores dérmicos à base de ácido hialurônico são os materiais mais utilizados em cosmiatria, e suas implicações clínicas estão ligadas às suas propriedades viscoelásticas. Este estudo teve como objetivo determinar o

comportamento reológico de produtos de AH utilizados no Brasil, alterando características físico-químicas específicas em diferentes frequências de teste. Análises laboratoriais de 0,9 mL de amostras foram realizadas em Reômetro TA-Instruments AR-1500ex a 25 °C, nas frequências de oscilação de 100, 10, 1 e 0,1 radianos/segundo, considerando as medidas de G', G", e Tan δ. O valor de G' aumentou à medida que as frequências de oscilação foram aumentadas. Paralelamente, as alterações de G" foram as que mais variaram para as frequências 0,1 e 1 radiano/segundo. O G' máximo foi observado com Hialurox Ultra Lift® 26 mg/g (793,45; 554,06; 423,44 Pa, 100, 10 e 1 rad/s, respectivamente). Enquanto os valores G' mais baixos foram obtidos com Rennova Ultra Deep® (43,01; 19,75; 10,75 e 10,42 Pa a 100, 10, 1, 0,1 rad/seg, respectivamente). As mudanças nas propriedades investigadas indicaram que os preenchedores à base de ácido hialurônico variam quando submetidos a diferentes condições de taxa de cisalhamento, o que deve ser considerado em sua indicação clínica para a escolha do material mais adequado de acordo com a região a ser tratada.
Palavras-chave: Ácido hialurônico; Preenchedores de tecidos moles; Propriedades reológicas; Propriedades viscoelásticas.

Resumen
Los rellenos dérmicos a base de ácido hialurónico son los materiales más utilizados en cosmiatría, y sus implicaciones clínicas están ligadas a sus propiedades viscoelásticas. Este estudio tuvo como objetivo determinar el comportamiento reológico de los productos HA utilizados en Brasil, cambiando características fisicoquímicas específicas en diferentes frecuencias de prueba. Los análisis de laboratorio de 0.9 mL de muestras se realizaron en un Reómetro TA-Instruments AR-1500ex a 25 °C, a frecuencias de oscilación de 100, 10, 1 y 0.1 radianes/segundo, considerando las medidas de G', G", y Tan δ. El valor de G' aumentaba a medida que aumentaban las frecuencias de oscilación. A su vez, los cambios en G" fueron los que más variaron para las frecuencias 0,1 y 1 radian/segundo. El máximo G' se observó con Hialurox Ultra Lift® 26 mg/g (793,45; 554,06; 423,44 Pa, 100, 10 y 1 rad/s, respectivamente), mientras que los valores más bajos de G' se obtuvieron con Rennova Ultra Deep® (43,01; 19,75; 10,75 y 10,42 Pa a 100, 10, 1, 0,1 rad/seg, respectivamente). Los cambios en las propiedades investigadas indicaron que los rellenos a base de ácido hialurónico varían cuando se someten a diferentes condiciones de velocidad de cizallamiento, lo que debe ser considerado en su indicación clínica para elegir el material más adecuado según la región a tratar.
Palabras clave: Ácido hialurónico; Rellenos de tejidos blandos; Propiedades reológicas; Propiedades viscoelásticas.

1. Introduction

There is a growing trend in using hyaluronic acid (HA)-based dermal fillers to smooth the effects of facial aging and wrinkle correction (Fundarò et al., 2022). This tendency is reflected in various HAs with different characteristics based on their rheological properties (Cotofana et al., 2021). The choice of HA depends on some factors, such as clinical indication, anatomical region, and skin quality. Furthermore, the facial filler must take into account the various dynamics in each part of the face, thus, it is necessary to use hyaluronic acid fillers with various characteristics (Choi, 2020).

It is considered that HA implanted for aesthetic purposes is exposed to the interaction of intrinsic forces exerted by muscle activity, fat volume, and skin tension. In addition, extrinsic forces such as head position during sleep and physical activity also participate in this mechanism (Casabona et al., 2019). The rheological study of HA becomes essential to assess how its deformations and changes occur after its implantation in tissues under the influence of mechanical stress. The intensity and frequency of mechanical forces can vary in different anatomical regions, leading the material to suffer different degrees of deformity depending on the region and depth in which it is applied (Pierre et al., 2015; Sykes et al., 2015; Michaud, 2018; Casabona et al., 2019).

The rheological and physicochemical properties of HA are linked to the degree of crosslinking, particle size, length of the polymer chain, and concentration of the material. These industrialized products are composed of linear polysaccharide chains of HA, stabilized by chemical crosslinking with 1,4-butanediol diglycidyl ether, which is responsible for delaying enzymatic breakdown and promoting a lasting correction result (Pierre et al., 2015; Fallacara et al., 2017; Kablik et al., 2009). More concentrated HA gels result in more significant molecular interaction, promoting an in-crease in the elasticity and rigidity of the gel (Kablik et al., 2009).

The Crosslinked hyaluronic acid possess unique viscoelastic properties intended to match specific product indications

(Faivre et al., 2021). The viscoelasticity of the HA allows it to deform and flow through a needle or cannula during implantation. This property is also able to keep its shape after being injected (Pierre et al., 2015; Michaud, 2018; Fagien et al., 2019). However, other properties can compromise product injection and clinical out-comes. For example, extrusion force to inject HA, ease of spreading, and ability to project, integrate and mobilize tissue during facial dynamics can be cited (Pierre et al., 2015; Fallacara et al., 2017; Michaud, 2018).

HAs with lower cohesiveness exhibit weaker adhesive forces and become more susceptible to loss of projection when compared to materials with higher cohesiveness and equivalent G'. Likewise, fillers with high cohesion and more vital adhesive forces can re-sist vertical compressive forces while remaining virtually intact in the treated plane (Sundaram et al., 2013; Pierre et al., 2015; Michaud, 2018; Fagien et al., 2019).

The most studied rheological properties of HA are elastic modulus (G′), viscous modulus (G″), the ratio between G" and G' (tan δ), and the complex modulus (G*). G' is responsible for promoting the product's resistance to shear forces. The higher the G', the greater the strength of the product. O G″ refers to the inability of HA to recover its original state after deformation, making the product more liquid. A ratio between G″ and G′, known as tan δ, determines its viscoelastic properties. Finally, the complex modulus G* defines its final viscosity (Borell et al., 2011; Pierre et al., 2015; Lorenc et al., 2017; Fagien et al., 2019).

Evidence shows that dermal fillers' viscoelastic properties are constant, without significant physicochemical changes when implanted in soft tissues. Despite this hypothesis, it is known that the face is an anatomical area with excellent expression dynamics. Therefore, studies investigating whether the physicochemical and viscoelastic characteristics of the fillers change due to constant movements of the soft tissues of the face are still missing (Cotofana et al., 2021).

Information on the properties of HA is essential for its indication, which is individualized for the clinical case in which it is applicable. Generally, professionals are unaware of this information, which represents a severe flaw in the selection of the product, and this is particularly true for the HA available in Brazil. This way, this study aimed to determine the rheological behavior of HA products used in Brazil by changing specific physicochemical characteristics under different test frequencies.

2. Methodology

2.1 Samples

Fifteen HA-based facial fillers belonging to six commercial brands distributed in Brazil were tested by oscillatory rheometry without preference for brand and batch. All samples were randomly selected for the study and sent to an independent laboratory (BioSmart Nanotechnology LTDA - Incubadora Municipal de Araraquara, Distrito Industrial VIII, Araraquara-SP, Brazil) for product rheology testing. The list of products can be seen in Table 1.

Table 1 - AH brand and batch analyzed.

Brand	Batch
Saypha® Chroma	(10) 204446
eptq S 100®	YLA20007
eptq S 300®	YLB21002
eptq S 500®	YLC21002
Hyalurox Ultra Soft 8 mg/g®	OFH-SOFT 210619-01
Hyalurox Ultra Fine 16 mg/g®	OFH-FINE 210616-01
Hyalurox Ultra Fill 24 mg/g®	OFH-FILL 210601-01
Hyalurox Ultra Lift 26 mg/g®	OFH-LIFT 210608-01
Perfectha Derm®	200928-2
Perfectha Subskin®	201110-2
Rennova Fill Lido®	105041
Rennova Lift Lido®	904042
Rennova Ultra Deep®	0062101
Yvore Classic Plus®	ICK19004
Yvore Volume Plus®	IVP20004

Note: Chroma Saypha produced by CROMA® (G1); eptq S produced by Jetema Co., Ltd., Korea (G2); Hyalurox Ultra Soft/Fine/Fill/Lift produced by HIALUROX®, Brazil (G3); Perfectha Derm/Subskin produced by Sinclair Pharma, France (G4); Renova Fill Lido/Lift Lido/Ultra Deep produced by INNOVA PHARMA/Croma-Pharma, Austria (G5); Yvore Classic Plus/Volume Plus produced by LG Chem Life Sciences Company, South Korea (G6). Source: Authors (2022).

As can be seen in Table 1, the fillers and their respective manufacturing batches are listed. The values of the analyzes may vary according to their processing. Therefore, products from the same manufacturer and from different batches may present differences in their rheological characteristics.

2.2 Rheological measurements

The amplitude oscillation test was performed for all fillers to determine the linear viscoelasticity (yield point) for the practical steps. After determining the linear viscoelasticity, the amplitude values were applied to a rheometer (TA-Instruments® AR-1500ex, New Castle-DE, England) to obtain the oscillatory (G', G" and Tan δ).

The analysis to determine the rheometric behavior of the samples consisted of an oscillatory technique, where the samples were exposed to different frequency bands. The tests were conducted on the rheometer, equipped with a 40 mm, sandblasted, parallel plate geometry measuring system and a GAP of 500 µm. All measurements were performed at 25 °C and with a volume of 0.9 mL, exposed to oscillation frequency sweeps (0.1 to 100 radians/second (rad/s) during test processing) after a 60-second equilibration time at 25°C (Cotofana et al., 2021).

The rheological parameters examined in this study were the modulus of elasticity (G′), viscous module (G"), and tan delta (tan δ) of the operating procedures (Cotofana et al., 2021), which can be seen in Table 2.

Table 2 - Operating procedures used in rheometric analysis (Cotofana et al., 2021).

Oscillating Amplitude	**Oscillation frequency**
Temperature: 25°C	Temperature: 25°C
Immersion time: 30 seconds	Immersion time: 30 seconds
Angular frequency: 1 rad/s	Angular frequency: 100 - 0.01 rad/s
Deflection: 0.01-10%	Deflection: value obtained in the previous procedure
Points per decade: 5	Points per decade: 5

Source: Authors (2022).

The table 2 showed Operating procedures used in rheometric analysis. Note that the conditions employed were used for the present study, and that these may vary according to the equipment and applied methodology.

2.3 Statistical analysis

After completing the experiments, the data were plotted and analyzed using descriptive statistics to organize and summarize the results.

3. Results

The fifteen HA fillers were successfully analyzed using Oscillatory Rheometry. The samples were injected into the Rheometer, processed at the frequency and amplitude defined in the study, and forwarded to the software (TRIOS, TA Instruments. The rheological parameters were measured and tabulated results of the rheological characteristics of the 15 facial fillers at frequencies of 100, 10, 1, and 0.1 Hz for G′, G″, and Tan δ are shown in Table 3.

Table 3 - G ', G" and tan δ values for the 15 HA-based dermal fillers selected at 100, 10, 1 and 0.1 Hz frequencies.

Analyze	sample name	100 Hz			10 Hz			1 Hz			0.1 Hz		
		G' (Pa)	G"(Pa)	Tan δ	G' (Pa)	G"(Pa)	Tan δ	G' (Pa)	G"(Pa)	Tan δ	G' (Pa)	G"(Pa)	Tan δ
1	Saypha® Chroma	318.65	62.10	0.1949	265.09	32.39	0.1222	229.59	26.58	0.1158	199.59	31.18	0.1562
two	eptq S 100®	178.92	105.46	0.5894	85.31	46.74	0.5478	44.50	21.21	0.4766	69.02	15.22	0.2205
3	eptq S 300®	316.46	117.70	0.3719	239.62	72.94	0.3044	183.16	46.25	0.2525	172.87	37.05	0.2143
4	eptq S 500®	400.64	100.78	0.2513	335.80	66.94	0.1993	270.23	50.92	0.1884	228.71	56.15	0.2455
5	Hyalurox Ultra Soft® 8 mg/g	326.35	149.09	0.4568	204.02	82.45	0.4041	167.94	47.49	0.2826	196.98	63.72	0.3235
6	Hyalurox Ultra Fine® 16 mg/g	369.08	176.51	0.4782	248.38	89.89	0.3619	211.62	48.88	0.2310	221.35	82.57	0.3730
7	Hyalurox Ultra Fill® 24 mg/g	646.46	225.25	0.3484	431.15	132.80	0.3080	344.18	80.08	0.2327	327.32	74.13	0.2265
8	Hyalurox Ultra Lift® 26 mg/g	793.45	224.48	0.2829	554.06	141.53	0.2554	423.44	92.93	0.2195	333.51	85.89	0.2575
9	Perfectha Derm®	540.11	60.35	0.1117	469.89	49.99	0.1064	400.12	57.66	0.1441	321.28	60.38	0.1879
10	Perfectha Subskin®	421.08	50.33	0.1195	364.54	35.67	0.0978	322.88	29.88	0.0925	286.24	29.50	0.1031
11	Rennova Fill Lido®	266.54	82.99	0.3114	190.55	42.45	0.2228	148.37	24.63	0.1660	149.96	19.96	0.1331
12	Rennova Lift Lido®	426.78	79.10	0.1830	390.19	40.08	0.1027	343.41	37.11	0.1081	355.37	53.06	0.1493
13	Rennova Ultra Deep®	43.01	34.92	0.8120	19.75	11.92	0.6035	10.75	4.66	0.4339	10.42	2.31	0.2216
14	Yvore Classic Plus®	359.95	59.28	0.1647	297.25	33.44	0.1125	257.22	34.33	0.1335	209.47	42.62	0.2035
15	Yvore Volume Plus®	419.09	61.43	0.1466	365.36	35.78	0.0979	326.22	32.78	0.1005	275.30	47.15	0.1713

Source: Authors (2022).

For changes in Elastic Modulus (G′), the lowest values were found for the filler Ren-nova Ultra Deep® (INNOVAPHARMA/ Croma-Pharma, Austria), with a minimum G′ of 43.01; 19.75; 10.75, and 10.42 Pa, tests corresponding to 100, 10, 1, 0.1 radians/second, respectively.

Maximum G' were observed for Hialurox Ultra Lift® 26 mg/g (HIALUROX®), with 793.45; 554.06; 423.44 Pa, corresponding to 100, 10 and 1 radians/second, respectively. In addition to these, Rennova Lift Lido® was the second filler with maximum G', with a value of 355.37 Pa at 0.1 radians/second. Detailed information for G' values at frequencies of 100, 10, 1, and 0.1 radians/second for all analyzed fillers are shown in Table 1.

The maximum G″ were found for the fillers Hialurox Ultra Fill® 24 mg/g (225.25 Pa at 100 radians/seconds) and Hialurox Ultra Lift® 26 mg/g (141.53; 92.93; 85.89 Pa at 10, 1, and .01 radians/second, respectively). While the minimum G″ were coincidentally lower in their values for the Rennova Ultra Deep® filler at all frequencies, which were 34.92; 11.92; 4.66, and 2.31 Pa at 100, 10, 1, and 0.1 radians/second. Detailed values for all frequencies tested for G″ of fillers are provided in Table 3.

The lowest Tan δ ratio (G″/G′) tested at 100 radians/second was 0.1117 Pa for Perfectha Derm® (Sinclair Pharma) filler. In the other frequencies, the lowest values were found for the Perfectha Subskin® filler with reductions of 0.0978; 0.0925; 0.1031 at 10, 1, and 0.1 radians/second. While the highest proportions were achieved for Rennova Ultra Deep® at 100 and 10 radians/second with 0.8120 and 0.6035 Pa, respectively. Followed by eptq S 100 with a value of 0.4766 Pa at 1 radians/second and Hyalurox Ultra Fine 16 mg/g with 0.3730 Pa at 0.1 radians/second. All information regarding the Tan δ ratio is detailed in Table 3.

Eptq S® hyaluronic acid has intermediate elasticity and viscosity compared to Hyalurox®, correlating with an intermediate pattern of tissue integration (Table 3). The two presentations of Yvore® hyaluronic acid gels exhibited similar viscosity characteristics between each shear frequency, with values of G′ and tan δ higher than each other. The Chroma Saypha® filler exhibited good elastic characteristics at the four shear frequencies, with low tan δ values. However, the viscous modulus was only higher when the gel was subjected to shear force at 100 radians/second, 62.10 Pa, respectively (Table 3).

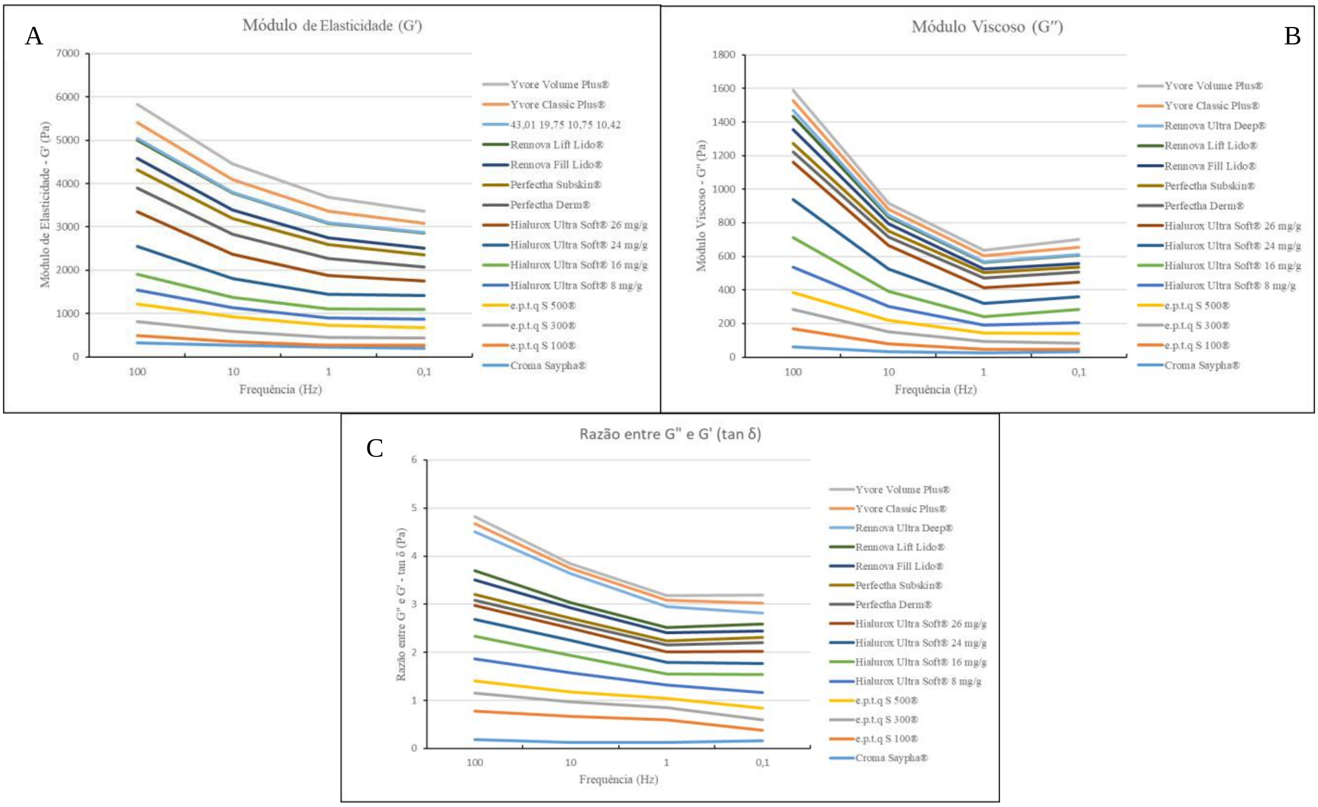
The magnitude for the modulus of elasticity (G'), viscosity (G") and tan δ of fillers sold in Brazil are shown in figures 1A-C. The images show that, depending on the indication of HA gels and the manufacturing process, there is a variation in the rheological parameters when the shear frequency is increased.

For changes in Elastic Modulus (G′), the lowest values were found for the filler Ren-nova Ultra Deep® (INNOVAPHARMA/ Croma-Pharma, Austria), with a minimum G′ of 43.01; 19.75; 10.75, and 10.42 Pa, tests corresponding to 100, 10, 1, 0.1 radians/second, respectively.

Maximum G' were observed for Hialurox Ultra Lift® 26 mg/g (HIALUROX®), with 793.45; 554.06; 423.44 Pa, corresponding to 100, 10 and 1 radians/second, respectively. In addition to these, Rennova Lift Lido® was the second filler with maximum G', with a value of 355.37 Pa at 0.1 radians/second. Detailed information for G' values at frequencies of 100, 10, 1, and 0.1 radians/second for all analyzed fillers are shown in Table 1.

The maximum G″ were found for the fillers Hialurox Ultra Fill® 24 mg/g (225.25 Pa at 100 radians/seconds) and Hialurox Ultra Lift® 26 mg/g (141.53; 92.93; 85.89 Pa at 10, 1, and .01 radians/second, respectively). While the minimum G″ were coincidentally lower in their values for the Rennova Ultra Deep® filler at all frequencies, which were 34.92; 11.92; 4.66, and 2.31 Pa at 100, 10, 1, and 0.1 radians/second. Detailed values for all frequencies tested for G″ of fillers are provided in Table 3.

Figure 1 - Values of elasticity modulus G '(A), values of viscosity modulus G' '(B) and values of tan δ (C).



Source: Authors (2022).

The lowest Tan δ ratio (G″/G′) tested at 100 radians/second was 0.1117 Pa for Perfectha Derm® (Sinclair Pharma) filler. In the other frequencies, the lowest values were found for the Perfectha Subskin® filler with reductions of 0.0978; 0.0925; 0.1031 at 10, 1, and 0.1 radians/second. While the highest proportions were achieved for Rennova Ultra Deep® at 100 and 10 radians/second with 0.8120 and 0.6035 Pa, respectively. Followed by eptq S 100 with a value of 0.4766 Pa at 1 radians/second and Hyalurox Ultra Fine 16 mg/g with 0.3730 Pa at 0.1 radians/second. All information regarding the Tan δ ratio is detailed in Table 3.

4. Discussion

This study evaluated and described physical-chemical parameters of the rheological characteristics of 15 types of hyaluronic acid fillers commercially available in Brazil. These analyzes are essential to verify the rheological behavior regarding the viscoelasticity of these materials at different frequencies between the G′, G″ and Tan δ modules, objectives of this research, and to compose the correct clinical indication of each material investigated here.

The interpretation of the frequencies applied in this study correlates with fillers' behavior at different strategic injection points. When the literature is reviewed1, it is verified that the frequency in radians/seconds represents the effect of the different movements that occur in the areas of the face, such as, for example, on the lips (high frequency and greater movement), zygomatic arch (low frequency and, therefore, less movement) (Casabona et al., 2019; Cotofana et al., 2021). And, as seen, the viscoelastic properties of all products change when the angular frequencies (100 to 0.1 radians/second) change. These properties are altered, revealing distinct behavioral patterns (Table 3) for each movement situation. Thus, this knowledge should be projected to the clinical practice of facial aesthetic treatments.

This study revealed that Rennova Ultra Deep® has the lowest values for viscoelasticity compared to the other facial fillers analyzed. According to the rheological parameters responsible for determining the indication of the product, it would be indicated for surface areas, such as for example, the lips, a region of excellent mobility. Since it reported the lowest G' value at 100 rad/sec compared to other commercial fillers. Hyalurox Ultra Fill® and Ultra Lift® fillers revealed more excellent elasticity and viscosity and low tan δ, predicting its firm and less fluid qualities (Table 3).

The modulus tan δ corresponds to the extent of elasticity, and thus, a filler with a high value of tan δ means having greater fluidity over elasticity; and, conversely, a lower value of tan δ corresponds to a product with a more significant elasticity overflow. As a result, commercial dermal fillers such as Croma Saypha®, Perfecta Derm®, Subskin®, Rennova Lift®, and Lido®, as well as the two Yvore® filler presentations analyzed in this study, can be characterized based on this rheological parameter and considered as products of higher elasticity compared to the other investigated fillers (Table 3).

Evaluating the values of tan δ, which determines the gelatinous behavior of the materials, in general, for all fifteen fillers, it was observed that the values ranged from 0.0978 to 0.8120 (Table 3). Thus, these values determine that all materials fit as elastic materials (tan $\delta < 1$) (Silva, 2019). A material based on HA with a tan δ lower than 1 corresponds to a filler with a gelatinous appearance, and this same material can be considered elastic enough for im-plantation in different regions of the face (Silva, 2019).

It is argued that facial fillers have low tan δ values with indices between $0.05 \leq \tan\delta \leq 0.80$. Therefore, our results agree with the expected parameters described in the literature (Silva, 2019), proving that the six groups of materials are within the expected standards regarding the elasticity extension requirement. Except for Rennova Ultra Deep® (0.8120) at 100 Hz. This finding leads us to believe that the behavior of Rennova Ultra Deep® is elastic under shear frequencies of 10, 1, and 0.1 radians/second. Clinically, this means that when subjected to deformation, this filler will immediately recover its original dimensions, maintaining the aesthetic result.

Issues involving the manufacturing, storage, and application of dermal fillers have been discussed in the past. This is because each category of filler must provide an adequate rheological property according to its application indication at the end of the aesthetic procedure. Therefore, it is imperative to know the deformation speeds of the product and information about its transport and conditioning to avoid deformations influenced by avoidable extrinsic factors (Leonardi & Campos, 2001; Borzacchiello et al., 2015; Micheels et al., 2016).

Studies on the rheology of dermal fillers have shown substantial evidence through rheometric tests (Borell et al., 2011; Sundaram & Cassuto, 2013; Pierre et al., 2015; Lorenc et al., 2017; Michaud, 2018; Fagien et al., 2019; Silva, 2019; Cotofana et al., 2021). From this perspective, this study was developed with test conditions identical to those presented in the literature1 (Values of G′, G″, Tan δ, at angular frequencies between 0.1 and 100 radians /second, 25°C) to analyze the 15 fillers sold in Brazil and used in orofacial aesthetic treatment. However, in Brazil, there are other fillers sold and those listed (Table 1), which may represent a limitation of this study. In addition, the results presented here (Table 3) refer only to the batches analyzed in this study, and the parameter values may change according to the product manufacturing process, transport, and storage.

The face areas with greater active mobility correspond to the areas medial to the line of ligaments, that is, to the medial face. In contrast, the area with the lowest active mobility correlates laterally to the line of ligaments, that is, on the lateral surface (Casabona et al., 2017; Cotofana & Lachman, 2019). It should be noted that almost all muscles of facial expression correlate with skin movements, whereas laterally, muscles of facial expression do not attach to the skin (Cotofana & Lachman, 2019).

Again, it is necessary to consider the values of G' and G" for the indication of HA for these areas. Those with low G" can be indicated for these areas since they do not show an inference of extrinsic deformation factors. However, it is also necessary to consider the depth of the application, where the G' should be analyzed. The deeper the application, the more tissue will rest on the HA. Consequently, the greater the pressure to which it will be subjected. This weighting between the values of G' and G" must be constantly analyzed by the professional when indicating the product. The diagnosis becomes paramount in selecting the material and its amount of tissue deposition.

According to the results, the value of G′ changed for the 15 fillers at frequencies from 0.1 to 100 radians/second. In clinical practice, it is considered that when high G′ fillers are implanted in an area of high mobility, they can become more consistent over time. The movement and the shear frequency will undoubtedly affect the material (Cotofana et al., 2021). This change is unfavorable to the cosmetic procedure because it will reduce soft tissue mobility causing an artificial appearance. An adverse event can also occur due to superficialization of the material on the skin, resulting in a surface nodule (Cotofana et al., 2021). More fluid and less viscous products tend to be distributed in more superficial layers of the fascia when compared to less fluid and more viscous products. Therefore, the HA product must be chosen based on the ability of the material to maintain a natural aesthetic result (Swift et al., 2011).

Interestingly, the viscous moduli (G″) of the materials varied the most in different directions for frequencies 0.1 and 1 radians/second when compared to the other two tests (G′ and Tan δ). It is possible to assume that, in cases where the G″ decreases with increasing frequency, there is an HA with less competence to resist shear forces in areas of high facial mobility. There are greater chances of product migration to softer and more mobile facial tissues (Cotofana et al., 2021). In this sense, these data allow us to know how much a filler can vary according to mobility in different situations and its contraindication for areas with high mobility.

The technologies used HA formulations have prioritized the production of fillers with low viscosity at a high shear rate when they are extruded with a fine needle during their implantation in the soft tissues of the face. Therefore, it is known that the lower the viscosity at a high shear rate, the lower the extrusion force exerted during the injection of the filler (Rosamilia et al., 2020).

Crosslinked HA is a filling gel with a viscous modulus, whose measurement guides the ability to dissipate energy when a shear force is applied. After passing the HA through the needle, it will redistribute itself through the soft tissues (Sundaram & Cassuto, 2013). The distribution capacity of the material will be guided by its intrinsic rheological and physicomechanical properties of the receptor tissue, as well as by the cohesiveness of the gel (Molliard et al., 2018). Thus, cohesiveness refers to the ability of a material not to dissociate, as there is a high affinity between its molecules (Micheels et al., 2017). However, cohesiveness was not a parameter evaluated in this study.

The lower the viscosity at high shear, the easier it is for the extrusion force to propel the material through the needle. In this sense, viscosity is an ideal parameter to estimate effort for the HA filler injection since this characteristic will influence the extrusion force exerted during the facial aesthetic procedure (Molliard et al., 2018).

The average strength of an HA-based filler is a rheological parameter of great im-portance during the implantation of the material in the soft tissues of the face, and this parameter is preponderant for the ability to project the material into the tissues (Molliard et al., 2016). The normal force causes the gel to pass through the surrounding tissues and opposes the de-formation and flattening of the product under pressure caused by the soft tissues. Thus, the greater the normal force (high G), the greater the force to protect the soft tissues.

Dermal fillers must have a high ability to follow the mechanical movements of the face smoothly and naturally during dynamic facial expressions. The E' modulus (modulus of elasticity in compression), which is also an important rheological parameter to rep-resent the firmness of the gel under dynamic conditions of AH (Molliard et al., 2016), must be considered in the HA studies. This work did not investigate this variable. So, it is considered that future studies should be conducted in order to correlate the data of this work with the E' module of the same materials investigated here, to improve further the possibilities of discerning the choice between the different materials when in their clinical indication.

In vivo dynamic compression stresses also influence the recovery of the HA shape during the speech, smiling, and even eating. Thus, the E' module is a rheological parameter that confers a better ability of the product to respond better to muscular forces and the natural effect of HA implanted in the tissues (Molliard et al., 2018).

Changes in viscoelastic properties indicate that HA-based fillers vary when subjected to different shear conditions, which should be considered in their clinical indication since this same behavior can occur after implantation of the product in soft tissues of the face. However, more in vitro and in vivo studies are needed to assess the elasticity and viscosity modules of these materials and blind and randomized clinical trials on their effectiveness when implanted in soft tissues and at strategic points on the face.

5. Conclusion

The changes that occurred in the investigated properties indicated that HA-based fillers vary when subjected to different conditions of shear rate, which should be considered in their clinical indication for choosing the most appropriate material according to the region to be treated.

There is still a lack of consistent information about changes in fillers when they are injected into the soft tissues of the face. So far, there are no studies that address this issue in an in vivo system. Therefore, to fill this gap, future independent blinded and randomized clinical trials should address these issues.

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