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Research Paper

Key importance of compression properties in the biophysical characteristics of hyaluronic acid soft-tissue fillers

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ABSTRACT

Hyaluronic acid (HA) soft-tissue fillers are the most popular degradable injectable products used for correcting skin depressions and restoring facial volume loss. From a rheological perspective, HA fillers are commonly characterised through their viscoelastic properties under shear-stress. However, despite the continuous mechanical pressure that the skin applies on the fillers, compression properties in static and dynamic modes are rarely considered.

In this article, three different rheological tests (shear-stress test and compression tests in static and dynamic mode) were carried out on nine CE-marked cross-linked HA fillers. Corresponding shear-stress (G', tan δ) and compression (E', tan δ_c, normal force F_N) parameters were measured. We show here that the tested products behave differently under shear-stress and under compression even though they are used for the same indications. G' showed the expected influence on the tissue volumising capacity, and the same influence was also observed for the compression parameters E'.

In conclusion, HA soft-tissue fillers exhibit widely different biophysical characteristics and many variables contribute to their overall performance. The elastic modulus G' is not the only critical parameter to consider amongst the rheological properties: the compression parameters E' and F_N also provide key information, which should be taken into account for a better prediction of clinical outcomes, especially for predicting the volumising capacity and probably the ability to stimulate collagen production by fibroblasts.

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1. Introduction

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide composed of repeating disaccharide units of N-acetyl-D-glucosamine and D-glucuronate. HA is omnipresent in the human body and occurs in almost all biological tissues and fluids (Anderegg et al., 2014; Volpi et al., 2009).

Thanks to its favourable biophysical properties, HA is used in a broad range of medical applications, e.g. as adjuvant for cataract surgery in ophthalmology (Mencucci et al., 2015), as a viscosupplement for the treatment of osteoarthritis in rheumatology (Ammar et al., 2015), and for filling wrinkles and/or restoring facial volume in aesthetic medicine (Alam et al., 2008; Kogan et al., 2007; Volpi et al., 2009).

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Table 1 – CE-marked cross-linked HA fillers.

Product reference	HA product name	Manufacturer	Manufacturing technology	HA content (mg/ml)	CE registered indications
A	BELOTERO Balance lidocaine	Anteis (Geneva, Switzerland)	CPM HA	22.5	Indicated to fill moderate facial wrinkles and folds as well as for lip enhancement
B	BELOTERO Intense lidocaine	Anteis (Geneva, Switzerland)	CPM HA	25.5	Indicated to fill deep wrinkles and folds, as well as to restore and enhance soft-tissue volume (e.g. contour of the face, lip volume, etc.)
C	BELOTERO Volume lidocaine	Anteis (Geneva, Switzerland)	CPM HA	26	Indicated to restore facial volume, e.g. to enhance cheeks or chin
D	JUVÉDERM Volbella	Allergan (Pringy, France)	Vycross	15	Indicated for the treatment of fine lines and medium-sized depressions of the skin, as well as for enhancement and pouting of the lips
E	JUVÉDERM Volift	Allergan (Pringy, France)	Vycross	17.5	Indicated for the treatment of deep skin depressions, face contouring, and volume restoration, as well as for restoration of lip volume
F	JUVÉDERM Voluma	Allergan (Pringy, France)	Vycross	20	Indicated to restore facial volume
G	RESTYLANE lidocaine	Galderma (Uppsala, Sweden)	NASHA	20	Indicated for correction of wrinkles and lip enhancement
H	Restylane PERLANE lidocaine	Galderma (Uppsala, Sweden)	NASHA	20	Indicated for shaping the contours of the face, the correction of folds, and lip enhancement
I	JUVEDERM Ultra 3	Allergan (Pringy, France)	Hylacross	24	Indicated for the treatment of mid and/or deep depressions of the skin and for lip definition and enhancement

HA soft-tissue fillers are commonly used in aesthetic medicine to treat signs of facial ageing (Bass, 2015; Humphrey et al., 2015; Monheit, 2014; Pons-Guiraud, 2015). In 2014, 2.3 million treatments with injectable filler products were performed in the United States alone and more than 70% of these procedures were done with cross-linked HA fillers (ASPS, 2014). This represents the second most common minimally invasive cosmetic procedure, after treatment with botulinum toxin type A.

The HA soft-tissue fillers currently on the market are chemically cross-linked, in order to improve the biophysical characteristics and the in vivo duration of the products (Edsman et al., 2012). Most of them are manufactured using 1,4-butanediol diglycidyl ether (BDDE) as cross-linking agent (Ågerup et al., 2005; De Boulle et al., 2013; Wende et al., 2016). The cross-linking process connects the linear HA chains together, transforming them into a three-dimensional network. Performing this process according to different manufacturing technologies leads to hydrogels with specific rheological properties, cohesivity levels, and matrix structures (Flynn et al., 2015; Stocks et al., 2011; Sundaram and Cassuto, 2013; Sundaram and Gavard Molliard, 2015; Sundaram et al., 2015; Tran et al., 2013).

Rheology is a very valuable and powerful tool to characterise such a wide variety of HA hydrogels. The rheological properties allow the researchers to understand how a HA soft-tissue filler deforms and reacts under mechanical stress, such as during injection or after gel implantation, both on the short and long term. Consequently, rheology can help clinicians to select both the best product and the best injection technique for each specific indication and facial region. This strategy, which is called 'rheological tailoring', facilitates the achievement of the clinical objectives set by the clinicians (Sundaram and Cassuto, 2013; Sundaram and Fagien, 2015; Sundaram et al., 2015).

In most current research, the rheological characterisation of the cross-linked HA fillers is based on the assessment of the viscoelastic parameters G' (elastic modulus), G'' (viscous modulus), and $\tan \delta (G''/G')$. These parameters are measured by oscillatory shear-stress experiments (Baumann et al., 2009; Bogdan Allemann and Baumann, 2008; Edsman et al., 2012; Gold, 2009; Sundaram and Cassuto, 2013; Sundaram and Fagien, 2015; Sundaram et al., 2015). However, the contribution of the static and dynamic compression forces exerted by the skin tissues on the fillers, after their implantation in different layers of the skin, has seldom been discussed in the literature. Therefore, this article aims to highlight the importance of taking into account the compression properties in the characterisation of HA filler products, in order to complete the information currently provided by the common shear-stress parameters.

This study consists of two main tasks: (1) determining the common shear-stress parameters G', G'' and $\tan \delta$,as well as the compression parameters in dynamic and static mode E' (elastic modulus), E'' (viscous modulus), $\tan \delta_c$ (E''/E'), and F_N (normal force) of nine Conformitée Européenne (CE)-marked cross-linked HA fillers; and (2) investigating the importance of these in vitro parameters on the volumising capacity of the HA soft-tissue fillers in clinical applications.

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