

LETTER TO THE EDITOR

Skin biostimulation and hyaluronic acid: Current knowledge and new evidence

To the Editor,

Skin aging encompasses changes involving all layers. A specific focus at the dermal level revealed the impact of the reduction of the extracellular matrix (ECM), including collagen fibers and hyaluronic acid (HA).¹

Skin aging can be studied with noninvasive skin imaging tools, such as optical coherence tomography (OCT). The advantage of this technique is to explore the skin noninvasively, at a depth of up to 2 mm.² Recent studies revealed that decreased OCT collagen density is considered an indirect measure of dermal/collagen characteristics when compared between older age groups to younger ones.²

Injectable fillers, such as poly-L-lactic acid, calcium hydroxyapatite, polycaprolactone, and HA have shown the ability to induce slow and sustained neo-collagenesis and ECM deposition after injection.¹ This ability to deliver cellular benefits or tissue response through specific clinical applications has been defined as "biostimulation."¹

Despite the wide use of injectable HA in daily practice, its role as a collagen-stimulatory agent has been claimed in a limited number of studies.³⁻⁶ This letter aims to preliminary address and investigate

the efficacy and safety of a HA-injectable in OCT collagen density variations and to provide a review of current knowledge on the topic.

We performed a retrospective study retrieving data concerning patients treated with an HA-based injectable in a single session, at baseline (T0). A total of 1 mL of HA-based dual injectable (made with BDDE and auto-cross-linked HA) was employed. Mini-boluses of the product were injected at the subdermal level with a 27G needle, employing 0.5 mL on each side of the mid and lower face.

All procedures performed involving human subjects were in accordance with the Helsinki Declaration and later amendments or comparable ethical standards. All patients were provided with informed written consent.

OCT imaging was available for patients treated at different time intervals: T0, 1 month (T1), 2 months (T2), and 3 months (T3) after treatment. OCT images were collected with the VivoSight OCT® (Michelson Diagnostics Ltd., Orpington, UK) at the right cheek, and collagen density was estimated, as previously described.²

Collagen density results were compared, from T0 to T3, using the Student's *t*-test. Additionally, safety was evaluated immediately

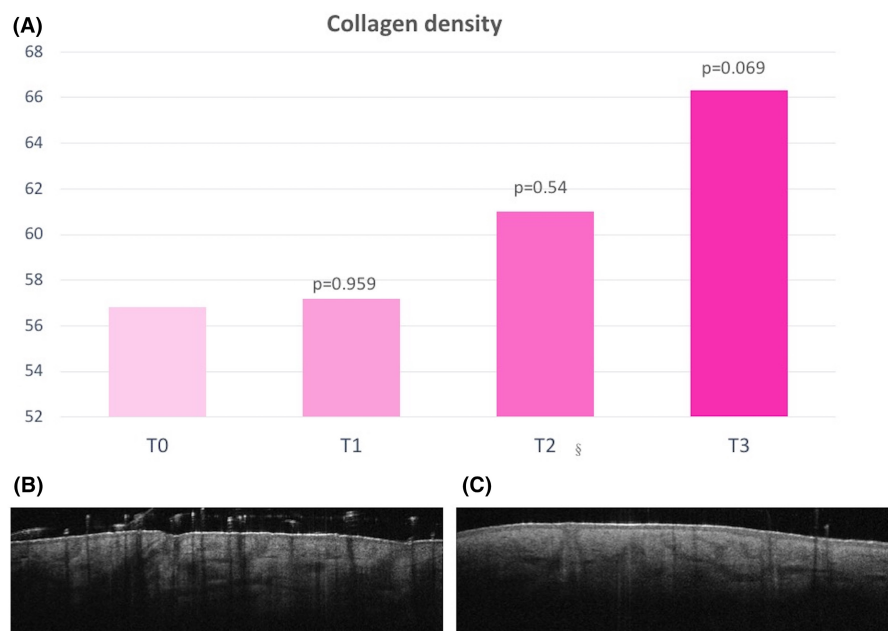


FIGURE 1 (A) OCT collagen density levels at different time intervals; histograms show an increase of collagen density up to T3 as compared to T0, after a single session of HA-based injectable, performed in a single session at T0. (B) Cross-sectional OCT images were employed for collagen density estimation at baseline and (C) at 3 months after treatment. (†Data available on five out six patients—one patient missed follow-up at T2).

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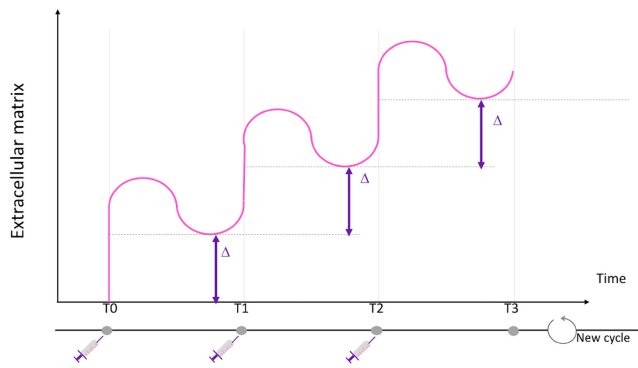


FIGURE 2 Model showing an expected progressive increase in extracellular matrix (ECM) (pink line) with subsequent sessions of cross-linked HA injections as hypothesized based on the current concept of biostimulation. Based on the model, purple arrows indicate the difference in extracellular matrix content after each session.

after treatment by the investigators and questioning subjects about adverse events (AEs) during their 1-month visit after treatment.

A total of six female patients, with a mean age of 44.6 ± 8.8 (range 34–56), were included. OCT revealed a progressive increase in collagen density from T0 to T3 (Figure 1). The safety profile was good with temporary ecchymosis being the only AE.

Based on the literature, HA-induced collagen biostimulation has been initially hypothesized to explain the longevity of results after HA-filler injection.⁴ A 10-fold increase in dermal staining for Collagen I was observed in HA-treated skin, as compared to control saline-treated skin.⁶ Additionally, prolonged activation of HA on collagen genes and protein expression remained significantly high 3 months posttreatment, compared to baseline.⁵

Our preliminary results show a progressive increase of OCT collagen density, up to 3 months, after a single session of HA-based injectable, therefore supporting the role of HA in collagen/ECM stimulation.

According to these results and evidence from the literature, highlighting that subsequent injections of biostimulatory fillers promote continuous stimulation of ECM deposition,¹ we propose herein a schematic model showing the progressive increase of ECM related to subsequent sessions of HA-biostimulatory treatment (Figure 2).

When combined, these data seem to support the biostimulatory activity of an HA-based injectable. The model of HA-biostimulation proposed herein and the contribution of cross-linked or auto-cross-linked HA should be confirmed by further investigations. This, in turn, will provide updated information related to different biostimulatory activities of diverse HA-based products available on the market.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical committee approval was waived based on Italian regulatory. The treatments were provided by a clinical dermatologist along with the standardized imaging procedure before and after treatment, as per clinical routine practice. We decided to evaluate OCT images calculating collagen density parameter in order to evaluate the trend of stroma improvement.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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