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Volume Restoration in Mid-Facial Aging: A Quantitative Evaluation of the Efficacy of Hyaluronic Acid Gel Injections—The Imperative to Optimize the Injection Volume Based on Anatomical Considerations

Alberto Diaspro [1,*] and Giuseppe Sito [2]

[1] Medynet Centre, Via A. Lamarmora 80, 10128 Turin, Italy
[2] Scientific Director of the Master in Aesthetic Medicine, Pegaso University, 80143 Naples, Italy; mail@giuseppesito.it
* Correspondence: info@albertodiaspro.com

Abstract: Background: The attractiveness of the central area (the so-called mid-face area or middle third) has a strong impact on the observer, and the treatment of aging in this area is therefore considered a key component in facial rejuvenation. A standardized photographic and three-dimensional analysis was conducted in this observational study to determine the outcome of volumetric restoration procedures of the mid-face area with HA injection, providing an objective, repetitive, and reliable evaluation of this facial rejuvenation technique. Methods: In total, 47 patients were treated with two types of HA-based dermal fillers, and calibrated, stereoscopic images of the face were taken with volume reconstruction and analysis software performed before (t0), 45 days after HA implantation (t1), and at the check-up after the end of follow-up (t2). Results: In total, 39 out of 47 patients completed the study, which showed an overall volume restoration of 4.46 ± 1.34 mL at 45 days (t0–t1) after HA implantation, maintaining a value of 1.23 ± 0.68 mL at the end of the 318-day follow-up (t0–t2). Conclusions: The results of this study indicate that rejuvenation of the mid-facial region through volumetric restoration with an HA filler leads to an indirect volumetric effect that is clinically more significant than the actual injected volume and equally long-lasting.

Keywords: mid-face; hyaluronic acid; volumetric; rejuvenation

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1. Introduction

The esthetic appeal of the face is primarily influenced by the attractiveness of the central region, often referred to as the mid-face or the middle third, which exerts a significant impact on the observer's perception. Consequently, the treatment of aging within this area is considered a fundamental aspect of facial rejuvenation, as it exhibits early signs of senescence due to the atrophy of adipose tissue, resulting in the loss of malar prominence, the hollowing of the lacrimal groove and the deepening of the nasolabial folds [1].

This cumulative effect leads to the skeletonization of the zygomatic region, accompanied by sub-malar volumetric depletion, which is the primary target for restoration [2]. While advanced cases necessitate invasive interventions, such as a mid-face lift—currently considered the gold standard for rejuvenation in this area—the ongoing pursuit of less invasive alternatives remains paramount. These alternatives aim to minimize potential complications and reduce recovery time. Substances such as autologous fat, hyaluronic

acid (HA), and other resorbable agents can be employed to restore lost volume when administered promptly and at the correct anatomical depth, offering a viable option, though with a limited duration of effect [3,4].

Nevertheless, there is a scarcity of established parameters to accurately determine the optimal degree of volumization necessary to achieve esthetically balanced outcomes in this region [5]. In this context, a standardized photographic and three-dimensional analysis was performed in the present observational study to evaluate the outcomes of volumetric restoration procedures for the mid-face area using HA injections, thus providing an objective, reproducible, and reliable assessment of this facial rejuvenation technique.

2. Materials and Methods

2.1. Study Population

Between June 2022 and June 2023, a total of 47 patients underwent treatment, comprising 13 males and 34 females. The male participants were aged between 31 and 56 years (mean age 41.3 years), while the female participants ranged from 29 to 62 years of age (mean age 43.7 years).

All participants were instructed to adhere to a standardized skincare protocol, beginning four weeks prior to the initiation of the study and continuing throughout its duration.

Exclusion criteria included the following:

- The prior administration of dermal fillers;
- Previous botulinum toxin treatments;
- Rejuvenation therapies involving energy-based devices (EBDs).

These exclusionary factors were applied to both the six-month period preceding and following the entirety of the study.

2.2. Products

Patients were treated with two types of HA-based dermal fillers (Stylema®, Laboratori Collagenil, Rome, Italy) according to the authors' clinical evaluation. The fillers used were as follows:

- Stylema® Medium, a 2.5% HA-based monophasic gel (25 mg/mL), with a molecular weight of 2 M Daltons (Da) + 1 M Da. This gel exhibits an elastic modulus (G′) of 100 Pa, a viscous modulus (G″) of 20 Pa, and an extrusion force of 23N +/− 3. It is crosslinked with 1.4-Butanediol-diclycidyl ether (BDDE < 0.1 ppm) via a Conservative Crosslinking process. The gel is further purified using a Water For Injection (WFI) dialysis process. This product is indicated for volumetric restoration and the correction of medium-sized skin depressions through hypodermic injection.
- Stylema® Intense, also a monophasic HA 2.5% gel (25 mg/mL), has a molecular weight of 2 M Da + 1 M Da, an elastic modulus (G′) of 200 Pa, viscous modulus (G″) of 40 Pa, and an extrusion force of 30N +/− 3). Like Stylema® Medium, it is crosslinked with 1.4-Butanediol-diglycidyl ether (BDDE < 0.1 ppm) using the Conservative Crosslinking process and purified by WFI dialysis. This gel is specifically indicated for volumetric restoration or enhancement, as well as the correction of deeper skin depressions, typically administered via supra-periosteal or deep hypodermic injection.

2.3. Injection Technique

The treatment was administered with the patient positioned semi-reclined, following meticulous disinfection of the injection sites. No topical or infiltrative anesthesia was employed.

Injections were performed using 27 G needles, 13 mm or 19 mm in length, and 25 G cannulas, 40 mm in length, as determined by the authors' clinical evaluation. For patients presenting with moderate volumetric deflation, the deep hypodermic implantation of 1 mL of Stylema® Medium was performed, followed by a second 1 mL vial in the hypodermic region. In contrast, patients with more pronounced volumetric deficits underwent supra-periosteal or deep hypodermic implantation with 1 mL of Stylema® Intense, followed by the placement of 1 mL of Stylema® Medium in the superficial regions.

Regarding the anatomical landmarks of Hinderer's lines (extending from the external canthus to the labial commissure and from the nasal wing to the tragus), the point of entry for both the needle and cannula was consistently located approximately 1.5 cm inferior to the external canthus and 1 cm posterior to the intersection of the two lines.

Following the injections, the treated areas were gently massaged to ensure even distribution of the product.

2.4. Image Acquisition and Evaluation

Standardized life-size photographs (1:1 ratio) were taken of each patient, with the Frankfort horizontal plane parallel to the floor.

Additionally, calibrated stereoscopic images of the face were captured and stored using the LifeViz® Mini passive stereoscopic digital camera (Quantificare S.A., 06410 Biot, France) and its Quantificare 3D Viewer +® volume reconstruction and analysis software (version 3.15.29). These images were acquired at three time points: prior to the treatment (t0), 45 days post-HA implantation (t1), and at the follow-up check-up at the end of the study period (t2).

All patients provided consent for the use of identifiable photographs. The reference points for the measurement were established as follows (Figure 1):

- Tragus (point Ar—Articularis);
- Lateral canthus (point Ex—Exocanthon);
- Nostril (point Al—Alar);
- Oral commisure (point Ch—Cheilon).

These points were used to delineate the mid-facial area and assess the restoration of its volume.

The LifeViz® Mini 3D stereophotographic system (Canon 500D body, Dermapix® software, Quantificare S.A., 06410 Biot, France) simultaneously captures two images from different angles. The Dermapix® software then integrates these images to generate a 3D reconstruction, which is processed by the 3D Viewer® app to produce a 3D display. The system aligns pre- and post-treatment images along the Frankfort horizontal plane.

The "volume assessment" tool calculates volumetric changes in the outlined area by comparing the surface areas before and after the filler injection. These changes are quantified in milliliters (mL) and represented using a colorimetric scale (Figures 2–7).

Volumetric changes were calculated by comparing patient images at t0 and t1 (45 days) and t0 and t2, with a mean follow-up period of 318 $\pm$ 14 days.

Figure 1. Reference points: pre-tragal (point Ar—Articularis), lateral canthus (point Ex—Exocanthon), alar cartilage (point Al—Alare), and oral commissure (point Ch—Cheilon).

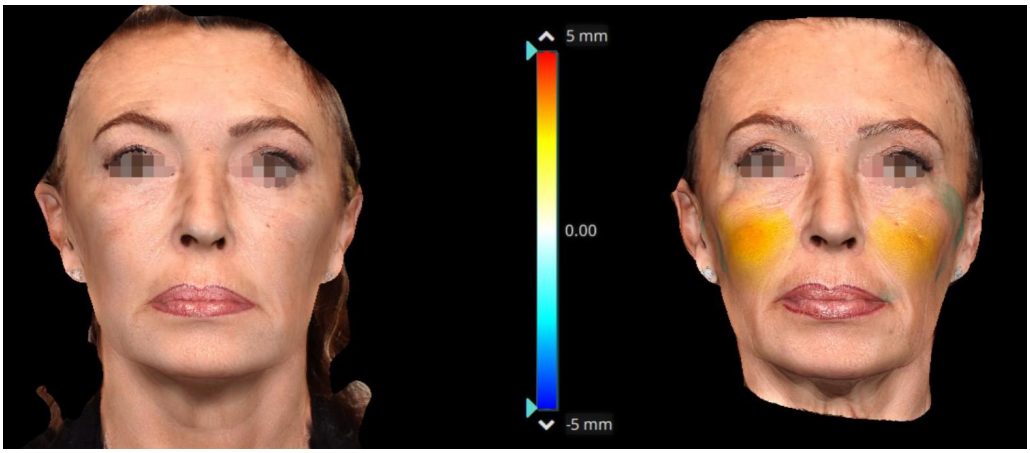

Figure 2. Frontal view with color scale, after and before injection therapy—patient 1.

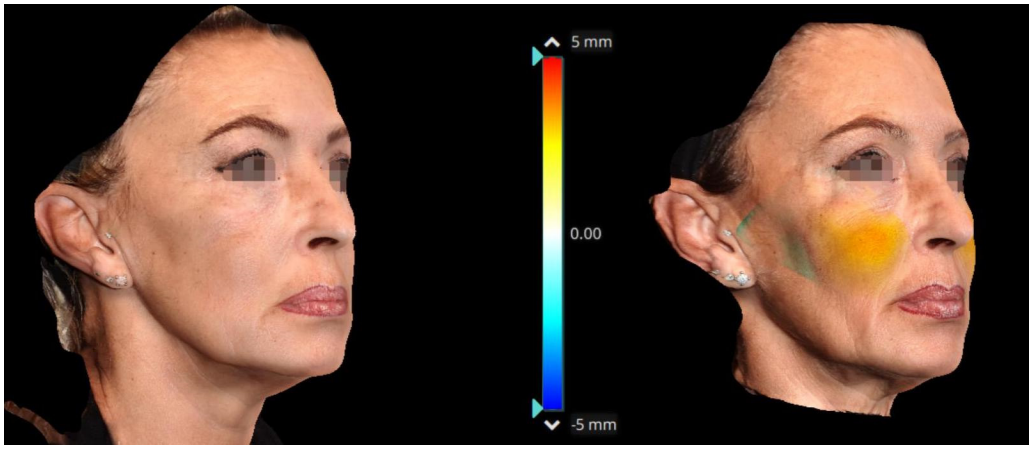

Figure 3. Oblique view with color scale, after and before injection therapy—patient 1.

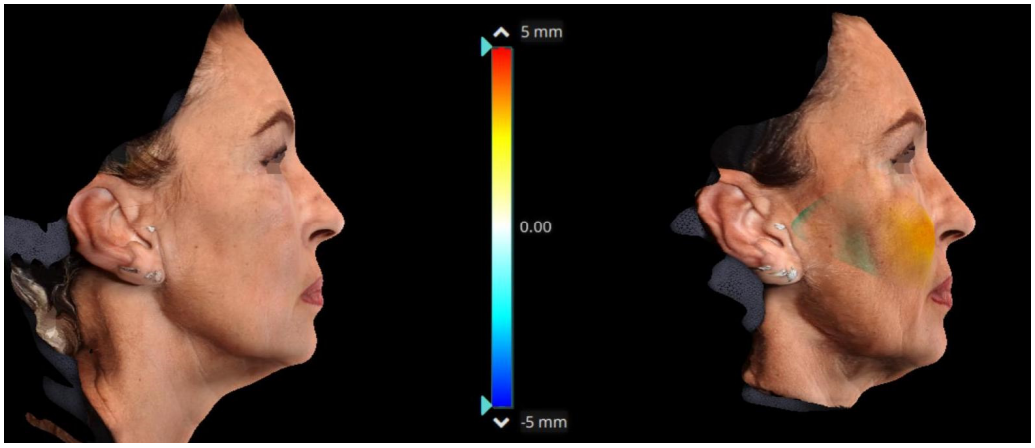

Figure 4. Profile with color scale, after and before injection therapy—patient 1.

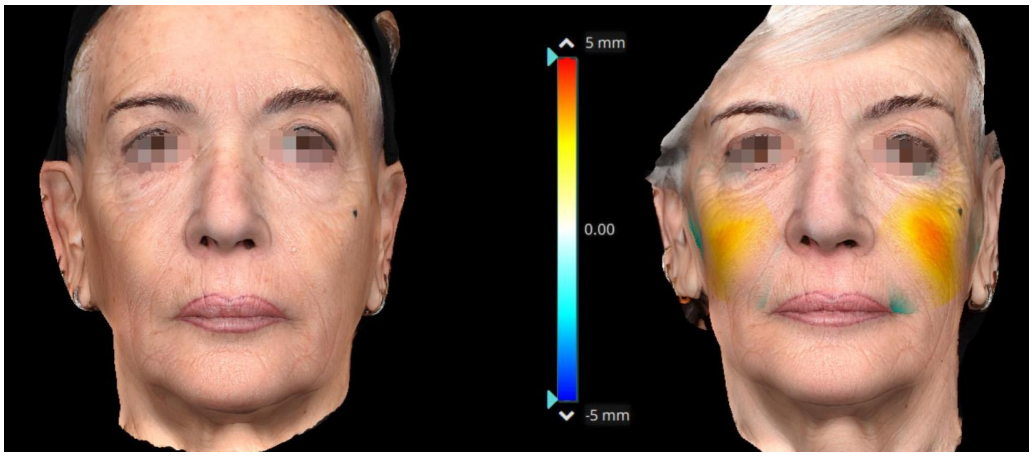

Figure 5. Frontal view with color scale, after and before injection therapy—patient 2.

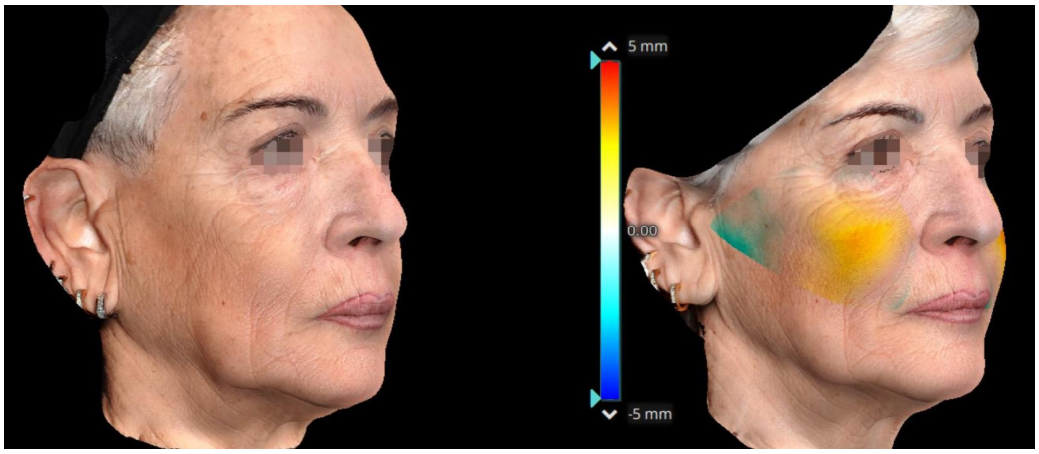

Figure 6. Oblique view with color scale, after and before injection therapy—patient 2.

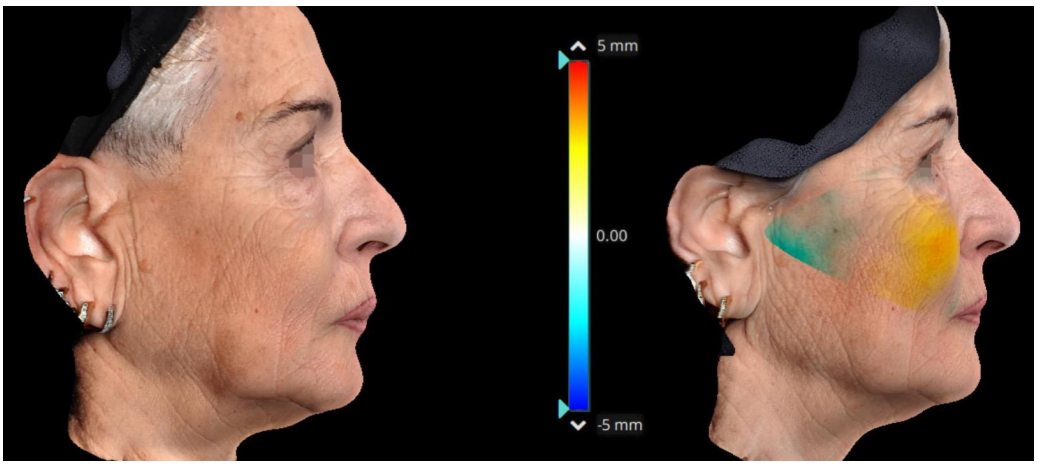

Figure 7. Profile with color scale, after and before injection therapy—patient 2.

3. Results

A total of thirty-nine out of forty-seven patients completed the study, with eight dropouts (17%) observed during the follow-up period, consisting of three men and five women. The mean age of the study population was 42.1 years.

The results demonstrated an overall volumetric restoration of 4.46 ± 1.34 mL at 45 days (t0–t1) following HA implantation, which was maintained at 1.23 ± 0.68 mL at the conclusion of the 318-day follow-up (t0–t2) (Figures 5–7). The recorded data are summarized in Table 1.

Table 1. Duration of the relative volume increase and calculated percentage increments.

∂ Volume	t_1 (45 Days; n = 45)		T_2 (318 Days; n = 39)	
	Total	**DS**	**Total**	**DS**
mL	+4.46	±1.34	+1.23	±0.68
%	223%	±67%	61.5%	±34%

No adverse events were reported during the implantation procedure, except for a mild sensation of discomfort at the supra-periosteal injection sites, which were resolved immediately prior to the completion of therapy in all patients.

During the first week following implantation, four patients—who were undergoing HA filler therapy for the first time—reported a mild sensation of deep implantation, which persisted for approximately three days. This sensation resolved spontaneously in all cases.

4. Discussion

The aging of the mid-face area is primarily attributable to the involution of the bone structure [6], changes in the volume of the superficial and deep fat compartments [7], and the connective structures between them, which are further influenced by gravitational factors [8].

Rejuvenation of the middle third of the face is undoubtedly a complex procedure that cannot be achieved without restoring volume, the so-called "third dimension." This restoration is facilitated through augmentation with dermal fillers or fat grafting, aimed at achieving a balanced result [9] and appropriate remodeling, with a gradual transition between the different facial regions and harmony between the concave and convex areas of the facial frame [10].

Improper placement and excessive injection volumes often lead to results that are not only unappealing but also distorted, lacking in harmony. As a purely additive technique, one cannot expect filler injections to entirely rejuvenate the face; however, they can restore the proportions of a youthful face, especially when considering the volume lost relative to the volume injected [11].

Furthermore, the evaluation of esthetic results remains highly subjective due to the absence of standardized measurements [5]. The introduction of three-dimensional stereophotogrammetry enables the objective comparison of results and their longevity, utilizing compact, portable equipment to acquire reliable measurements and 3D images for pre- and post-therapy comparisons [12]. This method provides not only a visual impact-based assessment but also analytically evaluable data, as corroborated by the extensive literature [13–19].

For this reason, the authors employed a three-dimensional stereophotogrammetry system to examine the results obtained. The aim of this study was to quantitatively evaluate the efficacy and long-term stability of volume restoration using HA-based fillers in a cohort of 65 patients acquiring 3D images before and after implantation.

The restoration of the mid-face volume, considering the extended follow-up period, demonstrated acceptable stability, supported by the properties of the product used. It is particularly noteworthy that, within the study population, the volumetric restoration achieved through hyaluronic acid injection—quantified using digital photography and analysis software at 45 days (4.46 ± 1.34 mL)—significantly exceeded the administered volume of hyaluronic acid (2 mL). This effect persisted at the conclusion of the study's follow-up period, with a residual volumetric effect of 1.23 ± 0.68 mL despite the anticipated resorption of hyaluronic acid over the 12-month observation period.

These findings, in addition to confirming the efficacy of the selected product, underscore a critical clinical consideration: the importance of avoiding excessive injection volumes of hyaluronic acid. In the weeks following implantation, the surrounding tissues appeared to adapt to the injected material, resulting in a volumetric effect—referred to by the authors as an "indirect" effect—which was clinically more pronounced than the actual injected volume (Figures 8–13): the clinical data regarding the volumetric restoration achieved, recorded at t1, indicate that it was 223% of the injected volume. This percentage was maintained at 61.5% at t2, when the injected hyaluronic acid was expected to be close to complete resorption, according to the manufacturer's guidelines.

Figure 8. Frontal view before and after injection therapy—patient 1.

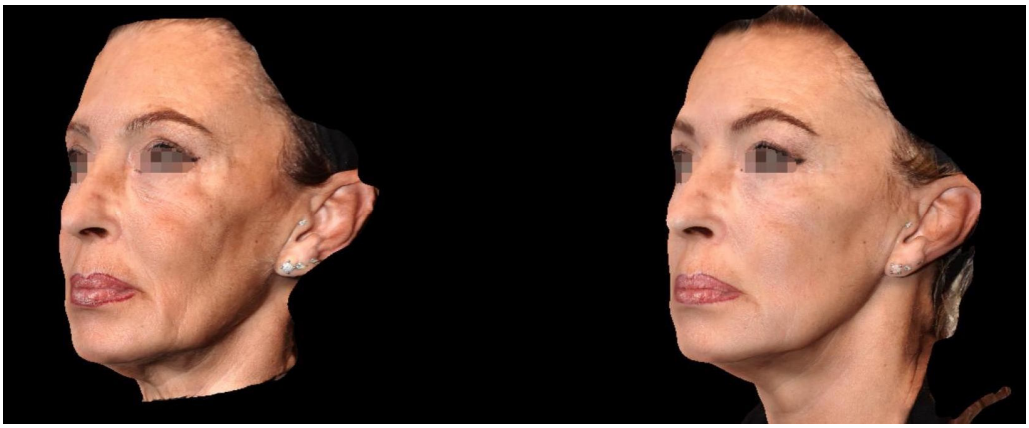

Figure 9. Oblique view before and after injection therapy—patient 1.

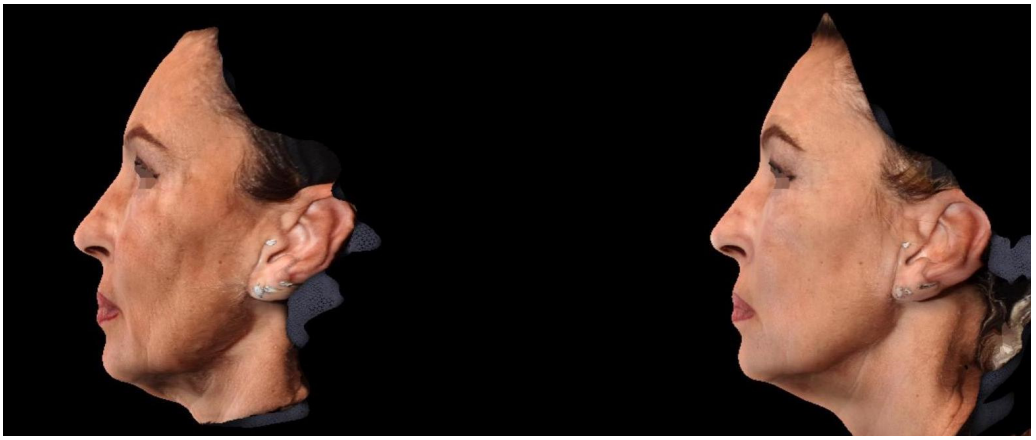

Figure 10. Profile before and after injection therapy—patient 1.

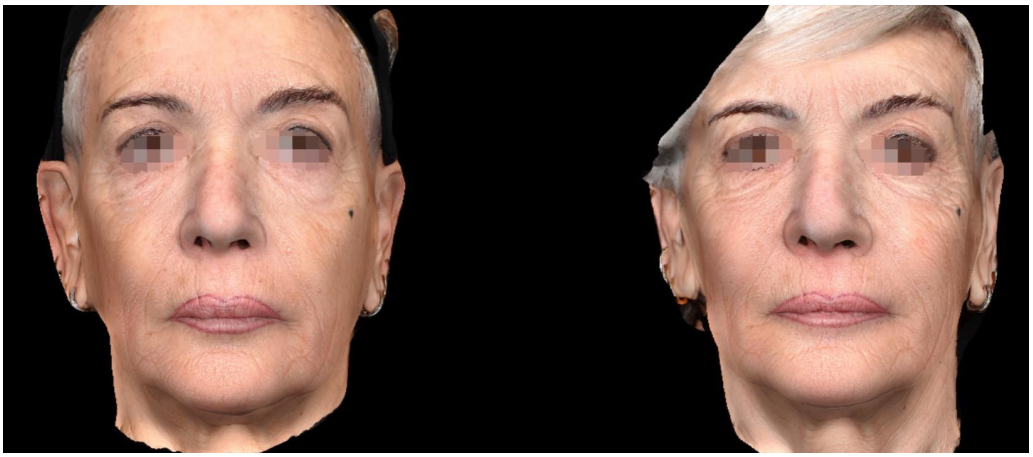

Figure 11. Frontal view before and after injection therapy—patient 2.

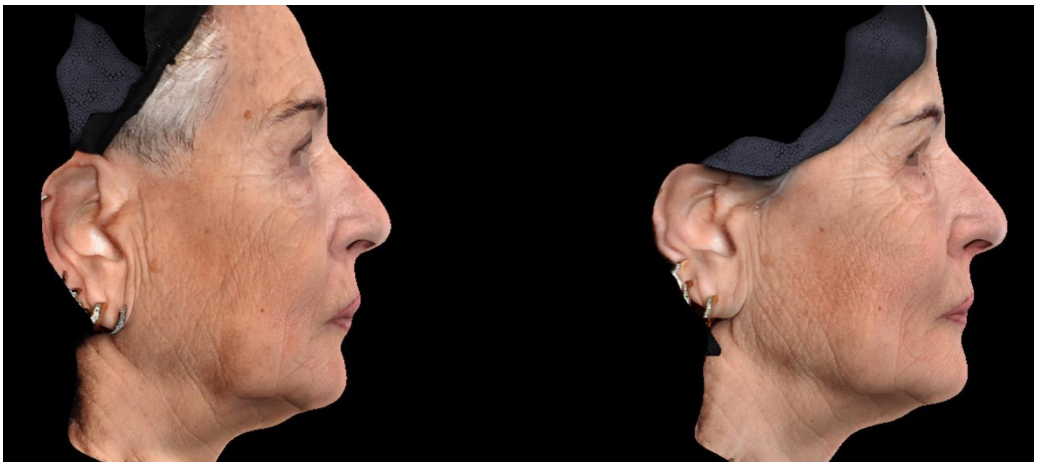

Figure 12. Oblique view before and after injection therapy—patient 2.

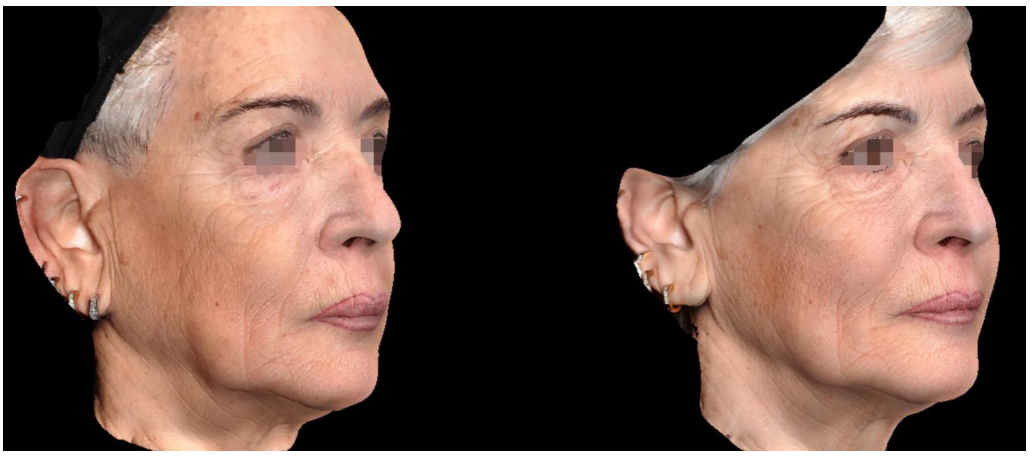

Figure 13. Profile before and after injection therapy—patient 2.

Consequently, the use of large injection volumes in a single session should be approached with caution and, whenever feasible, deferred to optimize clinical outcomes. Much has been discussed within the scientific community regarding the phenomenon of overfilling and the tendency of practitioners to administer excessive product volumes [20–23]. This article, for the first time, provides a quantitative and empirical basis supporting these prudent recommendations.

The authors hypothesize that this observation is attributable to the use of a multi-layer injection technique, which takes advantage of the rheological properties of the filler products in relation to the clinical characteristics of the study population. This technique effectively restores both deep and superficial volumes, both of which are diminished due to the aging process [24,25].

Thus, this is not a corrective therapy aimed at reshaping facial contours but rather a treatment that targets the effects of aging, which, as previously noted, are predominantly driven by volumetric deflation and ptosis in the mid-facial region.

The superficial suspension of mid-facial tissues using absorbable sutures aids in the restoration of ptotic volumes without any additional volumetric increase when performed under conditions of moderate gravitational ptosis [26]. The outcomes presented align with the indirect volumetric effect of the injected filler.

It is, therefore, conceivable that combining injectable techniques with suspension methods could offer clinicians a highly effective approach for non-surgical mid-facial rejuvenation, thus expanding the potential patient demographic eligible for this treatment.

The selection of an appropriate filler volume and its precise placement, tailored to volumetric loss due to aging and the depth of this loss within the mid-facial tissue layers, should, in light of the presented evidence, be regarded as a fundamental principle of the injection technique and clinical practice.

The reported results suggest that the rejuvenation of the middle third of the face can be effectively achieved through the injection of HA-based fillers, provided there is alignment between the rheological properties of the product and the appropriate injection plane, as corroborated by the published literature [26–31]. The injection protocol outlined demonstrates both safety and reliability, with optimized product performance, as evidenced by the outcomes.

However, this study has certain limitations that warrant careful consideration. The mean age of the study population was adults (42.1 years): in our experience, when this rejuvenation technique is employed in younger patients, the use of a single ampoule of product injected into the hypodermis should be considered.

The aging process does not cease after injection therapy, and any changes that occur during follow-up, given the study's duration, must be viewed within this context.

The optimal use of three-dimensional photographic devices requires a learning curve. However, once familiar with the software, the process becomes user-friendly and time-efficient when integrated into daily practice.

Future studies involving larger patient cohorts, stratified by the degree of aging, would allow for a more objective evaluation of the effectiveness of these procedures based on the preliminary results observed.

5. Conclusions

The results of this study indicate that rejuvenation of the mid-facial region through volumetric restoration with an HA filler leads to an indirect volumetric effect that is clinically more pronounced than the actual injected volume and similarly long-lasting. This article cautions that the volume chosen for injection should, therefore, be carefully considered and not excessive, as the tissues will exhibit a clinically more significant volumetric increase, as quantitatively assessed.

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Institutional Review Board Statement: Ethical review and approval were waived for this study due to the prevailing legislation DIRECTIVE 2001/20/EC: the HA-based dermal fillers are already approved and available on the market, injected according to techniques of proven safety and efficacy presenting a negligible risk of harm or discomfort and not being a new treatment.

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

Data Availability Statement: Restrictions apply to the availability of these data. Data was obtained from Dr. Diaspro and Prof. Sito. and are available from the authors.

Conflicts of Interest: The authors declare that this study received funding from Uniderm Farmaceutici S.r.l. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

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