Clinical evaluation of efficacy and tolerance of a skin reconditioning compound for anti-aging

A. Scarano[1], A. Sbarbati[2], F. Deriu[3], F. Inchingolo[4], D. Amuso[3], E.L. Iorio[3], R. Amore[2], C. Mortellaro[5], S. Bartolini[6], A. Greco Lucchina[2] and K. Gkritzalas[2]

[1]Dean of Master course in Aesthetic Medicine, Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Italy; [2]Department of Neurosciences, Biomedicine and Movement Sciences, Anatomy and Histology Section, University of Verona, School of Medicine, Verona, Italy; [3]Aesthetic Medicine and Wellness, University of Verona, School of Medicine, Verona, Italy; [4]Department of Interdisciplinary Medicine, University of Medicine Aldo Moro, Bari, Italy; [5]Research Laboratory in Regenerative Medicine and Tissue Engineering Saint Camillus International University of Health Sciences Rome Italy; [6]Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Italy

Facial aging involves all facial structures located at different levels: bones soft tissues and skin with a reduction of the extracellular matrix. The aim of the study was to evaluate the efficacy of the injectable solution antiaging complex composed by non-reticulated hyaluronic acid (HA) and amino acids vitamins and antioxidants conveyed with mesotherapy technique in subjects with different expressions of aging. 114 patients with different expressions of aging were enrolled in this study with mean age (49±6). HA and amino acids vitamins and antioxidants complex solution Neofound (Love Cosmedical, Castagneto, Italy) was injected on the dermal plane or superficial subdermal plane. Among the various imperfections, fine roughness surface irregularities skin firmness brightness/discoloration cutaneous hydration were those with the greatest response to therapy. The clinical data showed that the medical device Neofound is effective and safe to treat various skin signs of chrono and photoaging thanks to its ability to protect tissues from oxidative stress and hydrate the skin.

Environmental damage, intrinsic factors, and ultraviolet radiation from the sun are responsible for skin aging and the consequential age-related modifications in the dermis and face. Modern concepts of facial aging are based on the fact that this involution process affects all structures located at different levels: bones soft tissues and skin (1-4). Each layer is responsible for different blemishes. Those related to the surface of the skin such as wrinkles discoloration skin loss of firmness smoothness and brightness are very common and responsible for an unattractive look (5-7). During aging processes there is a reduction of the extracellular matrix (ECM) that can cause deep modifications and mechanical properties variations due to the reduction of the ECM density and enzymes in matrix degradation (8-10).

Many treatments are available today to reduce the appearance of surface defects such as: home topical therapy (11, 12) radiofrequency (13, 14) high frequency ultrasound (15) chemical peels (16-18) needling (7, 19, 20). Several approaches have been proposed for soft tissue augmentation using injectable materials for lip and soft-tissue augmentation due to their physical and biological properties (21).

Key words: Neofound, facial aging, mesotherapy, non-reticulated hyaluronic acid, amino acids vitamins, antioxidants

Corresponding author:
Prof. Antonio Scarano
Department of Medical Oral and Biotechnological Sciences
University of Chieti-Pescara Chieti Italy.
e-mail: ascarano@unich.it

0393-974X (2020)

Hyaluronic acid represents a natural component of the connective tissues related to wound healing and skin regeneration.

Previous study investigated the clinical and histological effectiveness of cross-linked hyaluronic acid for lip augmentation after a period of 60 days. After this period, a histological evaluation was performed to evaluate the healing of the treated regions. The healing phase reported no inflammatory response tissue contractions and no local inflammatory evidence in the treated areas where the filling volume appeared maintained. The 60 days histological evaluation showed evidence of filler resorption with few infiltrated inflammatory cells. The clinical and histological findings suggested that cross-linked hyaluronic acid represents a safe and effective tool for lip augmentation (22) mesotherapy (23-25) phototherapy (26, 27) filler injections (28, 29) botulinum toxin injections (30, 31).

The interest in maintaining a young and attractive appearance in an era in which the rhythms are increasingly hectic due to continuous growth of the average lifespan in the population (32) and the increasing availability of this type of treatments have greatly increased the use of rejuvenation procedures making them commonly used (33) especially those characterized by a short down time and low invasiveness. Intradermal injections were used for delivery biological substances for induce a revitalization of the dermis can stimulate quantitative and qualitative ECM and improvements in aging skin alterations. Non-cross-linked hyaluronic acid (HA) was used most frequently as substance recently was used with success the HA enriched with ammino acid through intradermal injection (25).

The aim of the study was to evaluate the efficacy through Global Aesthetic Improvement Scale of the injectable solution antiaging complex composed by non-reticulated HA and amino acids vitamins and antioxidants conveyed with mesotherapy technique in subjects with different expressions of aging.

MATERIALS AND METHODS

The study was a multicentric non-controlled national clinical trial, in accordance with the Standards of Good Clinical Practice of the European Union and the ethical principles expressed in the Declaration of Helsinki. The study began on 01-10-2019 and lasted until 28-02-2020. One-hundred-and-fourteen patients, 91 women and 18 men, with different expressions of aging were enrolled in this study with a mean age of 53 years. Patients were recruited from 01-09-2019 to 30-09-2019. The recruitment involved an initial interview in which the doctor evaluated the characteristics of the area to be treated to verify if they would satisfy the inclusion criteria of the study and provided information about the study. In case of interest on behalf of the candidates, the doctor moved on to the information regarding the adverse events and filled in the forms (information sheet, informed consent, personal data management sheet. At the end of the initial interview, in case of participation to the study, the recruited subjects to read the forms carefully at home and if necessary, request additional information or ask additional questions. After an interval lasting not less than 7 days. the adequately informed consenting patient returned the completed forms. From that moment on the subject was assigned an alphanumeric identification code and considered to be effectively recruited in the study.

Study inclusion criteria: people with different signs of photo and chrono aging both in terms of quality (such as fine wrinkles elastosis loss of skin tone skin laxity radiance) and quantity (degree extension and number of lesions) (Table I). Study exclusion criteria: psychological problems (indecisive or immature personalities anxious dysmorphophobia with factitious disorders or with family disapproval) minors, pregnancy or breastfeeding, known allergies to one or more of the active ingredients, severe or skin-related autoimmune diseases, current acute infections, immunosuppression, haemorrhagic, diathesis, oral anticoagulant therapy, platelet disorders, hormonal metabolic and organ diseases in acute phase or with functional deficiency patients who tend to develop hypertrophic scars keloids or skin inflammation. The contraindications relating to the area to be treated are represented by acute pathologies in progress (inflammation, burns, continuous solutions, acute dermatological lesions) infections, (including herpetic reactivations) skin tumours, prosthesis foreign bodies or permanent fillers in the involved area.

Medical device used in the study was Neofound (Love Cosmedical Srls, Castagneto Carducci, Italy). Neofound

is a solution for biorevitalization with 8 ingredients: Hyaluronic Acid with different molecular weights, Niacinamide, Acetyl, Cysteine Glycine, Proline Arginine and Resveratrol Hexapeptide-8. The device is indicated for the treatment of damages from aging via an injection into the dermis or superficial soft tissues.

Patients were treated through the modality and in accordance with the following protocol and technique: the sessions were performed 2 weeks apart for a total of 3 sessions; a quantity of 1.5 ml of solution for each treated area (face neck décolleté or hands) was used; during the entire period of the study the recruited subjects did not perform any concomitant therapy and aesthetic treatment (34)placed in definite anatomic areas, building up an alteration of the body silhouette. The aim of the present study was to investigate the effectiveness of reconditioning compound for anti-aging of skin tissue.

Before carrying out the treatment the skin of the area to be treated was carefully cleansed and any make-up was removed. The area to be treated has been thoroughly disinfected with hydrogen peroxide (H_2O_2) (35, 36). The infiltrative technique involved the inoculation of approximately 0.01 ml of solution at each injection site on the dermal plane (determined by the transient local onset of a papule with ischemic bleaching) or superficial subdermal plane. The infiltrations were performed from 5 mm to 10 mm away from each other. Subjects were asked to avoid strenuous physical activities, prolonged exposure to sunlight and tanning beds or extreme weather conditions for 24 h after the treatment, in order to reduce redness edema and irritation. Recruited subjects were re-evaluated before each session following the 1st and at 2, 4, and 8 weeks from the third and last treatment. The inclusion and exclusion criteria, the protocol and the method of use, minimized the factors that could have compromised the results. These are all represented by the management of the recruited subject such as:

- concomitant aesthetic therapies. Recruited subjects who during the period of the study performed medical and non-medical aesthetic treatments (e.g., fillers, botulinum toxin, biostimulation, laser, facial scrub cleansing) were excluded from the study.

- concomitant topical therapies. Recruited subjects who during the period of the study have used cosmetic products or topical medical devices in the treated were excluded from the study. Recruited subjects who interrupted the study were not replaced.

The clinical evaluation aimed to detect the efficacy and tolerance of the solution and its protocol. The efficacy was evaluated:

- by 2 doctors who had not performed the treatment and whom had not been provided with any additional information regarding the individual treated with photographic comparison before and after treatment at 2, 4 and 8 weeks from the third and last session. The two doctors evaluated the improvement of brightness, skin hydration, stains, fine wrinkles, surface irregularities (dilated pores small scars and other irregularities) and firmness of the skin, expressing an improvement value according to the Global Aesthetic Improvement Scale (GAIS) (37) ranking between 1 and 5 (Table II).

- subjectively by the treated patient through an anonymous self-evaluation test for results and their level of satisfaction at 4 and 8 weeks from the third and

Table I. *Correspondence in the aging process between the involved layer responsible process shown defect.*

LAYER	AGE RELATED INVOLUTION PROCESS	BLEMISH
BONE	reabsorption distortion	alteration of facial proportion disharmonious face
LOOSE CONNECTIVE TISSUE	reabsorption increase ptosis	beauty triangle reversal shadow furrow
SKIN	photoaging chronoaging	wrinkles elastosis, texture alterations and skin tone dark spots vascular anomalies benign neoplasms or tumors

last session. The self-evaluation was carried out in the waiting room and collected anonymously by non-medical staff. They were also asked to express an improvement value according to the Global Aesthetic Improvement Scale (GAIS) ranking between 1 and 5 and to fill out the effectiveness evaluation form for the patient.

The data deriving from the two different categories (doctors and treated individuals) were then collected and statistically evaluated in order to obtain the percentages of each of the 5 GAIS classes (1 optimal improvement, 2 good improvement, 3 moderate improvement, 4 no improvement and 5 worsening). Safety was evaluated using an adverse event onset form.

RESULTS

The study recruited 114 subjects across three different centres, among these 109 completed the study. Two subjects left the study for personal reasons, two for protocol violation (have performed aesthetic treatments concomitant to the study), and one for the onset of respiratory disease which involved taking symptomatic and antibiotic therapy. The subjects that completed the study were 91 women and 18 men (average age 53 years) they performed a total of 327 treatments and were evaluated both from an efficacy and a tolerance point of view.

The following adverse events occurred during the study: bruising in 85 subjects out of 327 sessions (25.99%), numbness of the treated area in 6 subjects in the first 12 hours post treatment (1.83%) and edema of the lower eyelids in 1 subject (0.28%). The edema self-resolved within 2 days of application. The relationship between the subject and adverse event was evaluated with an intradermal injection test of a small quantity in the forearm of the subject. The test result was negative proving that the adverse event was probably related to an excessive quantity injected into the delicate sub-eyelid region. Furthermore, the same subject did not manifest similar events in the other sessions (the edema occurred at the second session).

Common possible adverse events with anti-aging injection treatments such as erythema edema pain and itching did not occur in this study. Other rare adverse events described in literature after injecting aesthetic treatments (38-54) such as seroma fibrosis hypo-hyperpigmentation inflammatory reactions infections allergic reactions nodules and granulomas did not occur.

Effectiveness

The 109 patients who completed the study attributed an average score of 1.95. (Fig 1). The percentage of therapeutic failure judged with a score equal to or greater than 4 or 5 was 0%. The average best score (1.85) occurred in elderly subjects (Table III). The medical evaluation reported an average score of 1.89. The percentage of therapeutic failure again was 0%. Similarly to the evaluation of patients, the average best score was found in elderly

Table II. *Global Aesthetic Improvement Scale (GAIS).*

Degree of improvement	Description
1 Excellent	Excellent result
2 Good	Marked improvement of the appearance, but not completely optimal
3 Sufficient	Improvement in the appearance, better compared to the initial condition
4 No improvement	The appearance remains substantially unvaried compared to the original condition
5 Worsening	The appearance has worsened compared to the original condition

subjects (1.80) while the less satisfactory occurred in the younger group (2.00) (Table IV). The two evaluations (patients and physicians) did not show significant differences.

Though not relating to the purpose of the study, for information purposes, patients were asked to submit an evaluation regarding the aspect that showed the most evident improvement. Among various imperfections, fine roughness, surface irregularities, skin firmness brightness/discoloration (Fig. 2-5) and cutaneous hydration were those with the greatest response to therapy.

DISCUSSION

The study demonstrated therapeutic success judged as sufficient, good or excellent in all subjects who completed the entire protocol, demonstrating the effectiveness of injection therapy.

The combination of the solution injected with specific mesotherapy technique with the dosage and protocol used in this study proved to be valid and safe. While the difference between the two sexes was not significant, we saw major results (objective and subjective) with the increase of age. The subjects who benefited most were the age group between 58 and 77 years (Fig. 3), demonstrating that the effectiveness of the therapy is proportional to the degree of aging. The effectiveness was

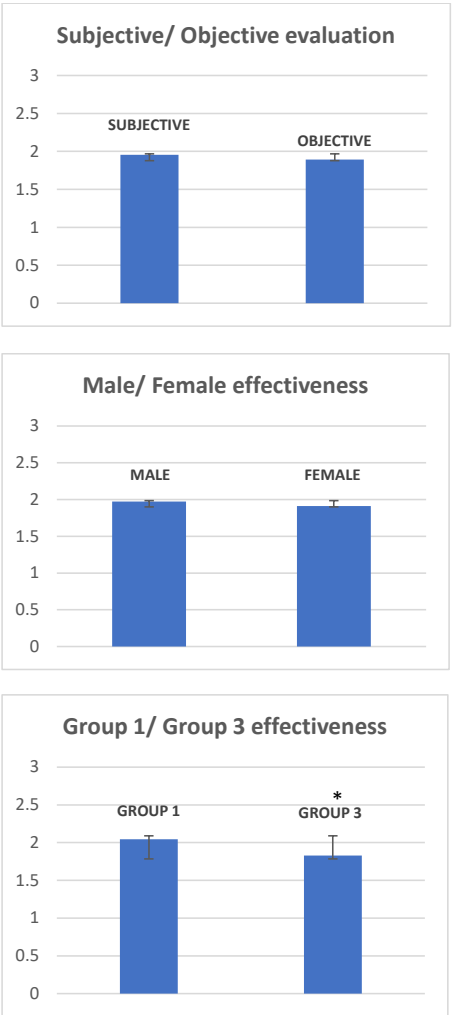

Fig. 1. *Evaluation of the patients.*

Table III. *Evaluation of the patients on the efficacy of the treatment.*

Degree of improvement GAIS	Number of subjects	Male	Female	Group 1 Age 18-37	Group 2 Age 38-57	Group 3 Age 58-77
Total	109	18	91	22	46	41
1 Excellent	16 (14.68%)	3 (16.67%)	13 (14.29%)	3 (13.64%)	6 (13.04)	7 (17.07%)
2 Good	82 (75.23%)	12 (66.66%)	70 (76.92%)	14 (63.64%)	35 (76.09%)	33 (80.49%)
3 Sufficient	11 (10.09%)	3 (16.67%)	8 (8.79%)	5 (22.72%)	5 (10.87%)	1 (2.44%)
4 None	0	0	0	0	0	0
5 Worsening	0	0	0	0	0	0
Average Score	**1.95±0.49**	**2.00±0.59**	**1.94±0.48**	**2.0±0.61**	**1.98±0.49**	**1.85±0.42**

observed not only on the face but also in the other treated skin areas without significant quantitative differences. The proposed protocol based on the clinical experience of the authors for similar medical devices already on the market and based on their use instructions (23-25, 55-61)vitamins, amino acids, minerals, coenzymes, and antioxidant substances; formulation B with hyaluronic acid and idebenone. Fifty participants were enrolled in the study and divided in two groups. Group 1 (50-65 years proved to be valid and effective and of good compliance, however, new future trials could evaluate variations to the used protocol, making it more efficient based on the characteristics of the subject to be treated.

Mesotherapy is a technique that has been in use for many years, and it determines an effect in the dermis through the release of minimal quantities

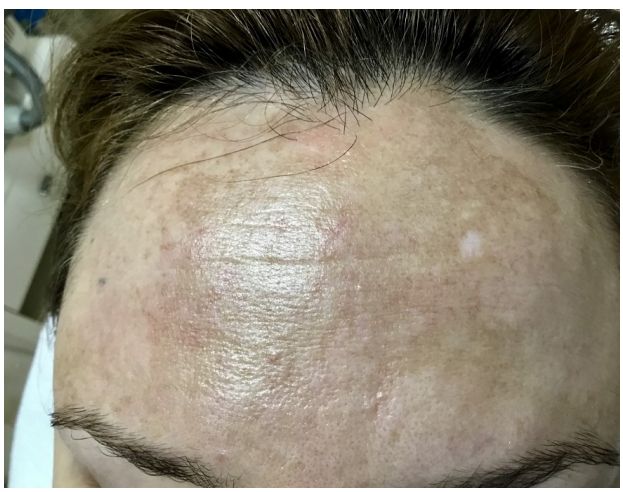

Fig. 2. *Surface irregularities and discoloration of forehead area.*

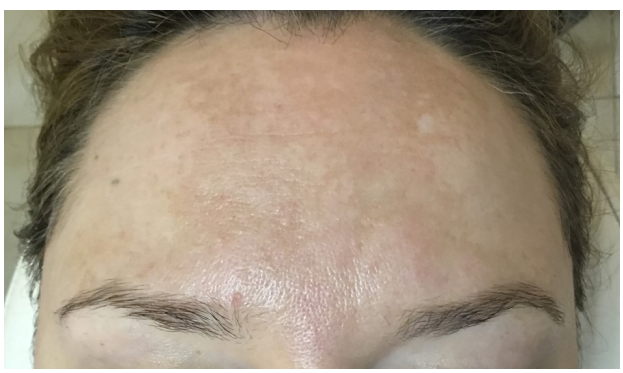

Fig. 3. *Before treatment there is an improvement irregularities and discoloration of forehead area.*

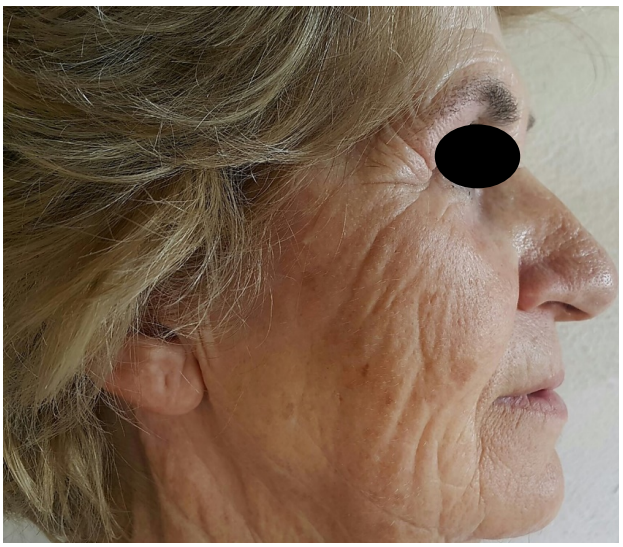

Fig. 4. *Mink cheek very extensive wrinkles.*

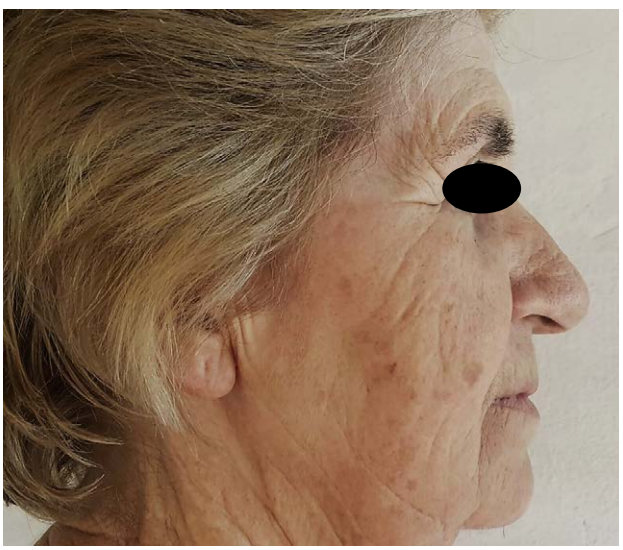

Fig. 5. *Before treatment there is a reduction of wrinkles mink of cheek area.*

of ingredients. There are numerous antiaging formulations on the market used in mesotherapy. Neofound is a biorevitalizing solution which aim is to improve the skin quality (epidermis dermis subdermic superficial loose connective tissue) that improves skin texture, and the level of hydration reduces fine imperfections (dilated pores fine wrinkles superficial scars) and discoloration.

The application of Neofound via injection, created evident changes in the skin through the following mechanisms:

Table IV. *Medical evaluation on the efficacy of the treatment.*

Degree of improvement GAIS	Number of subjects	Male	Female	Group 1 Age 18-37	Group 2 Age 38-57	Group 3 Age 58-77
Total	109	18	91	22	46	41
1 Excellent	16 (14.68%)	4 (22.22%)	12 (13.19%)	3 (13.64%)	5 (10.87%)	8 (19.51%)
2 Good	89 (81.65%)	11 (61.11%)	78 (85.71%)	16 (72.73%)	40 (86.96%)	33 (80.49%)
3 Sufficient	4 (3.67%)	3 (16.67%)	1 (1.10%)	3 (13.64%)	1 (2.17%)	0 (0.00%)
4 None	0	0	0	0	0	0
5 Worsening	0	0	0	0	0	0
Average Score	**1.89±0.41**	**1.94 ±0.64**	**1.88±0.36**	**2.00±0.53**	**1.91±0.35**	**1.80±0.40**

1) Fights oxidative stress by reducing damage induced by free radicals (antioxidant activity). The antioxidant activity also displays as photoprotection (62). The photographic documentation has showed a clinically relevant reduction of age spots, not only in the treated areas. The hyperpigmented macule is a common component of photoaged skin (63) caused by ROS which deplete and damage the non-enzymatic and enzymatic antioxidant defense systems (64). This evidence suggests that the injected product could interfere at different points in the skin pigmentation process by activating a photoprotective mechanism that improves the quality of the cutaneous pigmentation with a lightening action on melanin aggregates.

2) Water restrain providing firmness to the tissues (hydration). The results showed a positive difference in skin hydration which is partly due to the interaction between injected hyaluronic acid and water and partly to the improvement of the epidermal barrier function which generally decreases progressively with the aging process.

The clinical data evaluations emerging from this study showed that the medical device Neofound is effective and safe to treat various skin signs of chrono and photoaging thanks to its ability to protect tissues from oxidative stress hydrate and promote extracellular matrix synthesis reorganizing it (neofibrillogenesis neoangiogenesis). The protocol used in this study proved to be valid, effective, safe and of good compliance by patients. In future investigations it will be interesting to extend the follow-up to a longer time interval and to instrumentally evaluate the quantitative variations of specific parameters such as hydration, colouring, layer thickness and presence of wrinkles.

REFERENCES

1. Shaw Jr RB, Katzel EB, Koltz PF, Kahn DM, Girotto JA, Langstein HN. Aging of the mandible and its aesthetic implications. Plast Reconstr Surg 2010; 125(1):332-42.
2. Matros E, Momoh A, Yaremchuk MJ. The aging midfacial skeleton: implications for rejuvenation and reconstruction using implants. Facial Plast Surg 2009; 25(4):252-59.
3. Binder WJ, Kim BP, Azizzadeh B. Aesthetic midface implants. In Azizzadeh B Murphy MR Johnson CM eds. Master techniques in facial rejuvenation. Philadelphia: Saunders; 2007. pp. 197-216.
4. Schultz KP, Raghuram A, Davis MJ, Abu-Ghname A, Chamata E, Rohrich RJ. Fat grafting for facial rejuvenation. Semin Plast Surg 2020; 34(1):30-37.
5. Fink B, Grammer K, Thornhill R. Human (Homo Sapiens) facial attractiveness in relation to skin texture and color. J Comp Psychol 2001; 115(1):92-99.

6. Samson N, Fink B, Matts PJ, Dawes NC, Weitz S. Visible changes of female facial skin surface topography in relation to age and attractiveness perception. J Cosmet Dermatol 2010; 9(2):79-88.
7. Scarano A, Carinci F, Candotto V, Lorusso F. Eradication of benign skin lesions of the face by voltaic arc dermabrasion (atmospheric plasma): Postoperative pain assessment by thermal infrared imaging. Aesthetic Plast Surg 2020; 44(6):2277-85.
8. West MD. The cellular and molecular biology of skin aging. Arch Dermatol 1994; 130(1):87-95.
9. Peres PS, Terra VA, Guarnier FA, Cecchini R, Cecchini AL. Photoaging and chronological aging profile: understanding oxidation of the skin. J Photochem Photobiol B 2011; 103(2):93-97.
10. Varani J, Dame MK, Rittie L, et al. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol 2006; 168(6):1861-68.
11. Ho ET, Trookman NS, Sperber BR, et al. A randomized double-blind controlled comparative trial of the anti-aging properties of non-prescription tri-retinol 1.1% vs. prescription tretinoin 0.025%. J Drugs Dermatol 2012; 11(1):64-69.
12. Ogden S, Samuel M, Griffiths CE. A review of tazarotene in the treatment of photodamaged skin. Clin Interv Aging 2008; 3(1):71-76.
13. Alhaddad M, Wu DC, Bolton J, et al. A randomized split-face evaluator-blind clinical trial comparing monopolar radiofrequency versus microfocused ultrasound with visualization for lifting and tightening of the face and upper neck. Dermatol Surg 2019; 45(1):131-39.
14. Scarano A, Mortellaro C, Mavriqi L, Di Cerbo A. Evaluation effectiveness of the voltaic arc dermabrasion in perioral rhytides eradication. J Craniofac Surg 2016; 27(5):1205-08.
15. Friedmann DP, Bourgeois GP, Chan HH, Zedlitz AC, Butterwick KJ. Complications from microfocused transcutaneous ultrasound: case series and review of the literature. Lasers Surg Med 2018; 50(1):13-19.
16. Truchuelo M, Cerdá P, Fernández LF. Chemical peeling: a useful tool in the office. Actas Dermosifiliogr 2017; 108(4):315-322.
17. Starkman SJ, Mangat DS. Chemical peels: deep medium and light. Facial Plast Surg 2019; 35(3):239-47.
18. Scarano A, Amodeo V, Leonardi V, et al. Evaluation of the effectiveness and safety of peppermint peel (pmp) soft peeling for skin ageing. J Biol Regul Homeost Agents 2019; 33(6 Suppl 2):93-101.
19. Chung HJ, Cheng J, Gonzalez M, Al-Janahi S. Factors affecting depth of penetration in microneedling- and laser-assisted drug delivery: the importance of timing of topical application. Dermatol Surg 2020; 46(12):e146-e153.
20. Iriarte C, Awosika O, Rengifo-Pardo M, Ehrlich A. Review of applications of microneedling in dermatology. Clin Cosmet Investig Dermatol 2017; 10:289-98.
21. Scarano A, Carinci F, Piattelli A. Lip augmentation with a new filler (agarose gel): a 3-year follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 108(2):e11-15.
22. Scarano A, Puglia F, Cassese R, et al. Hyaluronic acid fillers in lip augmentation procedure: a clinical and histological study. J Biol Regul Homeost Agents 2019; 33(6 Suppl 2):103-108.
23. Savoia A, Landi S, Baldi A. A new minimally invasive mesotherapy technique for facial rejuvenation. Dermatol Ther (Heidelb) 2013; 3(1):83-93.
24. Prikhnenko S. Polycomponent mesotherapy formulations for the treatment of skin aging and improvement of skin quality. Clin Cosmet Investig Dermatol 2015; 8:151-157.
25. Scarano A, Sbarbati A, Amore R, et al. The role of hyaluronic acid and amino acid against the aging of the human skin: a clinical and histological study. J Cosmet Dermatol 2020.
26. Karrer S, Kohl E, Feise K, et al. Photodynamic therapy for skin rejuvenation: review and summary of the literature: results of a consensus conference of an expert group for aesthetic photodynamic therapy. J Dtsch Dermatol Ges 2013; 11(2):137-48.
27. Rhie JW, Shim JS, Choi WS. A pilot study of skin resurfacing using the 2790-nm erbium: YSGG laser system. Arch Plast Surg 2015; 42(1):52-58.
28. Lee BM, Han DG, Choi WS. Rejuvenating effects of facial hydrofilling using restylane vital. Arch Plast Surg 2015; 42(3):282-7.
29. Kerscher M, Bayrhammer J, Reuther T. Rejuvenating influence of a stabilized hyaluronic acid-based gel of

nonanimal origin on facial skin aging. Dermatol Surg 2008; 34(5):720-26.
30. Ong AA, Sherris DA. Neurotoxins. Facial Plast Surg 2019; 35(3):230-38.
31. Satriyasa BK. Botulinum toxin (Botox) A for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect. Clin Cosmet Investig Dermatol 2019; 12:223-28.
32. Ortman J.M, Velkoff V.A, Hogan H. An aging nation: The older population in the United States; United States Census Bureau 2014; P25-1140. pp. 1-28.
33. American Society of Plastic Surgeons. 2014 Plastic Surgery Statistics Report.
34. Scarano A, Sbarbati A, Amore R, Iorio E.L, Ferraro G, Amuso D. A new treatment for local adiposity with ascorbic acid and ascorbyl-palmitate solution: clinical and histological study. Aesthetic Plast Surg 2020; 44(5):1604-12.
35. Scarano A, Inchingolo F, Lorusso F. Environmental disinfection of a dental clinic during the covid-19 pandemic: a narrative insight. Biomed Res Int 2020; 2020:8896812.
36. Scarano A, Inchingolo F, Lorusso F. Facial skin temperature and discomfort when wearing protective face masks: thermal infrared imaging evaluation and hands moving the mask. Int J Environ Res Public Health 2020; 17(13):4624.
37. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized double-blind multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003; 29(6):588-95.
38. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers. Dermatol Surg 2005; 31(11 Pt 2):1626-33.
39. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Late-onset inflammatory adverse reactions related to soft tissue filler injections. Clin Rev Allergy Immunol 2013; 45(1):97-108.
40. Lemperle G, Gauthier-Hazan N. Foreign body granulomas after all injectable dermal fillers: part 2. Treatment options. Plast Reconstr Surg 2009; 123(6):1864-73.
41. Lemperle G, Gauthier-Hazan N, Wolters M, Eisemann-Klein M, Zimmermann U, Duffy DM. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. Plast Reconstr Surg 2009; 123(6):1842-63.
42. Monheit GD, Rohrich RJ. The nature of long-term fillers and the risk of complications. Dermatol Surg 2009; 35(Suppl 2):1598-604.
43. Narins RS, Coleman 3rd WP, Glogau RG. Recommendations and treatment options for nodules and other filler complications. Dermatol Surg 2009; 35(Suppl 2):1667-71.
44. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. Facial Plast Surg 2011; 27(1):23-28.
45. Bjarnsholt T, Tolker-Nielsen TIM, Givskov M, Janssen M, Christensen LH. Detection of bacteria by fluorescence in situ hybridization in culture-negative soft tissue filler lesions. Derm Surg 2009; 35(Suppl 2):1620-24.
46. Hirsch RJ, Narurkar V, Carruthers J. Management of injected hyaluronic acid induced Tyndall effects. Lasers Surg Med 2006; 38(3):202-04.
47. Douse-Dean T, Jacob CI. Fast and easy treatment for reduction of the Tyndall effect secondary to cosmetic use of hyaluronic acid. J Drugs Dermatol 2008; 7(3):281-83.
48. Rousso JJ, Pitman MJ. Enterococcus faecalis complicating dermal filler injection: a case of virulent facial abscesses. Dermatol Surg 2010; 36(10):1638-41.
49. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. Dermatol Surg 2009; 35(Suppl 2):1672-80.
50. Griepentrog GJ, Lucarelli MJ, Burkat CN, Lemke BN, Rose Jr JG. Periorbital edema following hyaluronic acid gel injection: a retrospective review. Am J Cosm Surg 2011; 28(4):251-54.
51. Pessa JE, Garza JR. The malar septum: the anatomic basis of malar mounds and malar edema. Aesthet Surg J 1997; 17(1):11-17.
52. Van Dyke S, Hays GP, Caglia AE, Caglia M. Severe acute local reactions to a hyaluronic acid-derived dermal filler. J Clin Aesthet Dermatol 2010; 3(5):32-35.
53. Geisler D, Shumer S, Elson ML. Delayed hypersensitivity reaction to Restylane®. Cosmet Dermatol 2007; 20(12):784-86.
54. Arron ST, Neuhaus IM. Persistent delayed-type hypersensitivity reaction to injectable non-animal-stabilized hyaluronic acid. J Cosmet Dermatol 2007; 6(3):167-71.
55. Sparavigna A, Tenconi B, De Ponti I. Antiaging

photoprotective and brightening activity in biorevitalization: a new solution for aging skin. Clin Cosmet Investig Dermatol 2015; 8:57-65.
56. Sparavigna A, Tenconi B. Efficacy and tolerance of an injectable medical device containing stable hybrid cooperative complexes of high-and low-molecular-weight hyaluronic acid: a monocentric 16 weeks open-label evaluation. Clin Cosmet Investig Dermatol 2016; 9:297-305.
57. Stellavato A, Corsuto L, D'Agostino A, et al. Hyaluronan hybrid cooperative complexes as a novel frontier for cellular bioprocesses re-activation. PLoS One 2016; 11(10):e0163510.
58. Deglesne PA, Arroyo R, Fidalgo López J, Sepúlveda L, Ranneva E, Deprez P. In vitro study of RRS® Silisorg CE Class III medical device composed of silanol: effect on human skin fibroblasts and its clinical use. Med Devices (Auckl) 2018; 11:313-20.
59. Brandi C, Cuomo R, Nisi G, Grimaldi L, D'Aniello C. Face rejuvenation: a new combinated protocol for biorevitalization. Acta Biomed 2018; 89 (3):400-405.
60. Deglesne PA, Arroyo R, Ranneva E, Deprez P. In vitro study of RRS HA injectable mesotherapy/biorevitalization product on human skin fibroblasts and its clinical utilization. Clin Cosmet Investig Dermatol 2016; 9:41-53.
61. Morganti P, Palombo P, Palombo M, et al. A phosphatidylcholine hyaluronic acid chitin-nanofibrils complex for a fast skin remodeling and a rejuvenating look. Clin Cosmet Investig Dermatol 2012; 5:213-20.
62. Bast A, Haenen GR. Lipoic acid: a multifunctional antioxidant. Biofactors 2003; 17(1-4):207-13.
63. Šitum M, Bulat V, Buljan M, Puljiz Z, Šitum V, Bolanča Ž. Senile lentigo-cosmetic or medical issue of the elderly population. Coll Antropol 2010; 34(Suppl 2):85-88.
64. Wlaschek M, Tantcheva-Poór I, Naderi L, et al. Solar UV irradiation and dermal photoaging. J Photochem Photobiol B 2001; 63(1-3):41-51.