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A multidisciplinary approach to the comprehensive treatment of edentulous patients with perioral wrinkles of the skin

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Abstract

Objectives: The purpose of this study was to comparative analysis of effectiveness of isolated use of intradermal injections of modified hyaluronic acid (Hyalorepair 04) and its combination with platelet-rich autologous plasma in edentulous patients with perioral wrinkles of the skin.

Materials and Methods: A total of 56 patient’s presence of perioral wrinkles of the skin participate in the study after dental implant prosthodontics rehabilitations. They were randomly divided into 2 groups in accordance with the applied therapy method (29 isolated implementation of modified hyaluronic acid bio-repairing and 27 bio-repairing combined with autologic plasmotherapy). Treatment included implant-prosthetic rehabilitation followed by hyaluronic acid injections in order to correct cheek-zygomatic sulcus, nasolabial folds and marionette wrinkles. Preparations in an amount from 1 to 4 ml were injected into the face area, depending on the zones to be corrected at the request of the patients.

Results: The complex treatment restored the aesthetic profile of the face and oral cavity and increased the effectiveness of the chewing function. On M03 and M05, 2/3 of patients had significant improvement as assessed by physician and patient according to GAIS. Most of the patients also showed significant improvement at visit M12.

Conclusion: A multidisciplinary approach to the treatment of edentulous patients with perioral wrinkles increases the functional and aesthetic effect of the treatment. Implementation of combined of bioreparation and autologous plasmotherapy is significantly more effective comparatively to the isolated implementation of modified hyaluronic acid.

Keywords: Facial Esthetic; Implant-Prosthetic Rehabilitation; Hyaluronic Acid



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Introduction

Untreated caries in permanent teeth is the most common disease worldwide, affecting 35% of the world's population [1]. As a result of the progression of dental diseases, patients lose a large number of teeth. The most intense tooth loss is observed in patients over 40 years of age, reaching maximum rates in the age group over 60 years of age and can lead to edentulism [2,3]. Complete edentulism leads to functional chewing apparatus, this negatively affects the functioning of the gastrointestinal tract and the general health [4]. Complete loss of teeth causes not only significant functional disorders of the masticatory apparatus, but also leads to disharmony and deformation of the face, psychological impairment and social disability. The ongoing restructuring of the dento-jaw system is manifested in changes in the structure of the jaw bones, the development of changes in craniometric parameters, temporomandibular joints, and the muscular apparatus of the maxillofacial region. To the loss of support for these muscles, combined with weakening of the subcutaneous connective tissue and fat atrophy occurs due to facial aging. Loss of teeth affects the condition of the peri-maxillary soft tissues, namely the formation of skin folds - nasolabial, upper lip, excess skin in the infraorbital,

cervical areas [5,6] (Figure:1). Aging of the face as a result of a dynamic process characterized by degeneration of both soft tissues and bone structure leads to a change in the relationship between these components [7]. The nature of the anatomical, physiological and functional changes depends on the cause and duration of the loss of teeth, age, past diseases and other factors. A gradual increase in the number of persons with loss of teeth is noted not only among the elderly, but also among the working age. The problem of rehabilitation of patients with dentition defects is one of the urgent tasks of modern dentistry. Full treatment and prosthetics allow you to completely eliminate the cosmetic defect and restore the function of the dentition. It also restores the shape and function of the chewing apparatus, helps to normalize the function of the digestive system and delays the reduction of the facial skeleton. The use of dental implants expands the possibilities of the dentist in restoring the complete absence of teeth, since this method has a number of advantages over traditional complete removable prosthetics [8]. When using implants, jaw atrophy is sharply slowed down to the physiological level, which undoubtedly plays an important role in maintaining the overall proportions of the face and, accordingly, the aesthetic perception of a person [9].

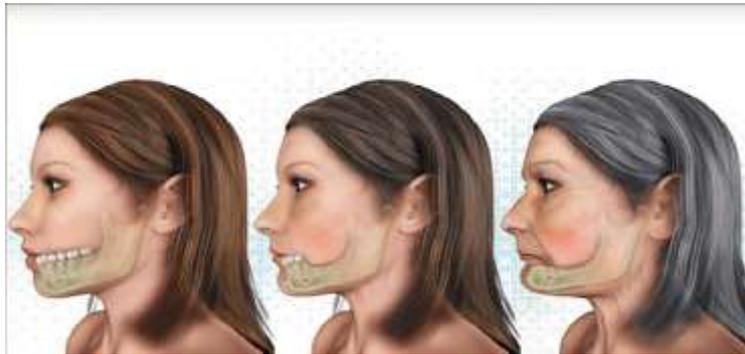


Figure1: Loss of teeth affects the condition of the namely the formation of skin folds - nasolabial, upper lip, excess skin in the infraorbital, cervical areas.

The rehabilitation of patients with edentulous is to restore chewing function and speech, prevent atrophy of jaw bones and perioral wrinkles. A global treatment plan aimed at restoring facial aesthetics in edentulous patients should include the rehabilitation of implant-retained prostheses to provide adequate deep support for perioral soft tissue, in edentulous patients, prostheses can improve the aesthetics of perioral wrinkles [10]. However, only by increasing the height of the alveolar arches, installing implants and dentures with support on them, it is impossible to completely eliminate the aesthetic defect, which the patient should be warned about. Currently, patients are demanding improvements not only in their dental (micro) aesthetics, but also in their overall (macro) facial aesthetics. Soft tissue augmentation with dermal fillers can be used to correct facial defects such as wrinkles caused by age, gravity, and trauma; thin lips; asymmetrical appearance of the face; depressions of the buccal fold; other. The appearance of perioral wrinkles often prompts patients to seek treatment. The number of requests for cosmetic procedures with permanent or temporary fillers to reduce the number and depth of wrinkles and to give lips the appropriate volume is growing with varying results. However, the number of less serious complications is also increasing, even with the use of safe molecules such as hyaluronic acid [11,12]. In these patients, the use of aesthetic

medicine techniques such as fillers can aid in dental rehabilitation [13,14]. According to statistics from the American Society for Aesthetic Plastic Surgery (ASAPS), dermal fillers (from English to fill; syn: dermal fillers) occupy a leading position among the most popular non-surgical aesthetic procedures [15].

The biorevitalization method is 100% safe and effective. Hyaluronic injections have become the gold standard for treating facial wrinkles over the past 10 years. Active hyaluronic acid injection is used to fill wrinkles and other voids on the face. HA was first described by Karl Meyer, the father of glycosaminoglycan (GAG) chemistry [16,17]. It was further developed by Endre Balasz, who established methods of production the first non-inflammatory, highly purified high molecular weight HA from the umbilical cords and rooster combs and n and application of the molecule in clinical medicine [18]. HA evenly fills the gaps between collagen fibers located in the spaces between cells, intensively moisturizes the skin, at the same time stimulating the synthesis of collagen (one of the most important proteins affecting elasticity), slowing down its breakdown, as a result, the skin begins to actively produce its own hyaluronic acid - thereby forming new skin fibers [19,20]. Plasmotherapy, in turn, stimulates the synthesis of main fibroblast cells, triggering the production of hyaluronic acid and inducing deep regenerative and



restorative processes in all layers of the skin [21]. It is important to emphasize that hyaluronic injections give a result with a natural effect - thanks to the injection, expression lines, deep wrinkles and folds are reduced and evened out, so the face looks younger and fresher. The search for optimal and safe combinations, scientifically grounded protocols for the correction of evolutionary changes in the skin of the face in edentulous patients is an urgent area of oral implantology and dermato-cosmetology. To date, no data reported on clinical indicators dynamic changes after combined by hyaluronic acid therapy and implant-prosthetic therapy in patients with perioral wrinkles of the skin. The purpose of this study was to conduct a comparative analysis of effectiveness of isolated use of intradermal injections of modified hyaluronic acid (Hyalorepair 04) and its combination with platelet-rich autologous plasma by comparison of these influence on clinical and functional parameters in edentulous patients with perioral wrinkles of the skin.

Material and Methods

A total of 56 patients (women aged 49 to 61 years old) presence of perioral wrinkles of the skin participate in the study after dental implant prosthodontics rehabilitations in the period 2017-2021. Inclusion criteria: healthy women aged 45-65; the patient's desire and ability to take part in the study and follow the doctor's prescriptions aimed at achieving the result of therapy and adherence to the protocol requirements; the presence of scales nazo-labial, lower and upper lips, marionette lines wrinkles of mild and moderate degrees according to the Merz Aesthetics Scale(MAS in the validated 5-point, where 0=no wrinkles, 1=mild wrinkles, 2=moderate wrinkles, 3=severe wrinkles, and 4=very severe wrinkles) [21,22]. Patients in front of a mirror independently assessed signs of aging on his face, comparing with the standard of the scale. The doctor, having his own subjective opinion

of the clinical picture on a visual scale (during consultation and analysis of photographs) exhibited the degree of severity wrinkles and folds in points, depending on the study design: either their subjective assessment. The following criteria were withdrawn from the study: the presence of somatic, endocrine, oncological, infectious and skin diseases, blood diseases, pregnancy, lactation, intolerance to Hyaluronic Acid (HA), the presence of permanent filler in the skin, peels, mesotherapy and surgery performed within 6 months prior to this study. Patients were informed of the purpose of the study and the use of any photographs obtained in which the patients could not be identified. All patients provided written consent to be included in this study and to use facial images for the purposes of the study. All patients underwent a thorough clinical laboratory, radiological examination according to a generally accepted scheme. To accomplish the assigned tasks, an X-ray examination of the teeth and jaws (orthopantomograms, CT) was carried out. After research and diagnosis, a treatment plan was drawn up, including an implant surgery followed by prosthodontics treatment. Surgical and prosthetic procedures used for all patients included: history and clinical examination, antibiotic prophylaxis, implantation surgery, underwater healing for 6-8 weeks, second surgery, dental impressions, prosthetics concept and final restoration. Indications for injections are wrinkles and folds, a decrease in the tone and hydration of the facial skin. A total of 56 women surveyed were randomly divided into 2 groups in accordance with the applied therapy method:

- 1) Group I - 29 women who had therapy with modified hyaluronic acid;
- 2) Group II - 27 women who had undergone combined administration of intradermal injections of platelet-rich autologous plasma and modified hyaluronic acid.



Microinjections

The course of injection therapy consisted of 3 procedures with a three-week interval. Each procedure consisted of the sequential implementation of microinjections of bioreparant/ platelet- rich autologous plasma (or combined).

Bioreparation therapy

Hyaluronic Acid (Hyalorepair 04 manufactured by Martinex) (HA concentration 14 mg / ml, Molecular weight 2 million Da in 1.5 ml syringes) was chosen as a bioreparant. This type of bioreparant contains hyaluronic acid modified with vitamin C, L-cysteine and L-glutathione, which stimulates the synthesis of its own collagen and elastin. The method of bio reparation with modified hyaluronic acid was based on the protocol of intradermal administration. The injection was performed to a depth of 1-2 mm until the appearance of papules with an interval of 1 cm.

Blood withdraw and microinjection of platelet-rich plasma

From the middle ulnar vein (v. Intermedia cubiti, v. Medianacubiti), a 21G needle collects 5 ml of blood into a vacuum test tube with an anticoagulant (3.8% sodium citrate), which is placed in a centrifuge and centrifuged twice at 3000 revolutions per minute for 7 minutes [4]. As a result of centrifugation, the contents of the tube are phased, divided into 2 parts. The erythrocyte mass settles at the bottom of the tube, and the platelet mass phase is formed at the top, which is aspirated, moved to another tube, and centrifuged again at 4000rpm for five minutes, after which the upper part (platelet-poor) is removed to allow only the platelet-saturated portion of the plasma to set in the tube as a result of repeated centrifugation. To activate the latter, a solution of calcium chloride in a ratio of 1: 9 with plasma is added to the tube. The introduction is carried out using microinjection needles 30G (0.4 x 12), dosage

of 1 ml on each side of the face. Preparations in an amount from 1 to 4 ml were injected into the face area, depending on the zones to be corrected at the request of the patients: cheek-zygomatic sulcus, nasolabial fold, labial fold. In order to correct nasolabial folds and marionette wrinkles, of 0.5 ml on each side was introduced by the cannula method.

Clinical assessment of treatment results (satisfaction by subject and investigator physician) was performed. The immediate results were assessed 1 month after the course, long-term results at the in 6-12 months of observation. Probable repeated preventive examination. Perioral wrinkles were assessed by comparing photographs at the beginning and at the end of the study for each case studied. The efficacy was assessed according to the International Global Aesthetic Improvement Scale (GAIS Table1)²³ on the 1st (M01), 2nd (M02), 3rd (M3), 6th (M06) month of complex therapy. Visual confirmation of clinical improvement was also obtained by Life Viz 3D camera pictures.

Statistical analysis

Statistical analysis was performed using the statistical software package SPSS 23 (Statistical Package for Social Science 23). When using the student test for independent samples, the calculation depended on the statistical significance of differences in the variance of the compared groups (Fisher's F-test was used to compare variances).

Results

The treatment was considered to be effective in patients with functioning implants who did not complain and were satisfied with the treatment outcome. Prosthetic rehabilitation with dental implants has improved the chewing function and facial aesthetics (Figure: 2A-2D). X-ray studies showed that the structure of the bone tissue and the state of the mucous membrane around the implants are close to normal, there are no signs of chronic inflammation and

pronounced atrophic processes in the tissues under study (Figure: 3). X-ray control showed a decrease in the height of the jaw bone tissue by 0.5-1 mm after 1-5 years in the area of implants in 28 patients (which, according to different authors, occurs in the first two years after implantation). The implant survival rates of implants were 9,7,2%. Evaluation of the effectiveness of the GAIS procedure on M03 and M05, 2/3 of patients had significant improvement as assessed by physician and patient according to GAIS. Most of the

patients also showed significant improvement at visit M12. Aesthetic improvement after courses with Hyaluronic acid were statistically significant on M03, and M06 in comparison with initial state ($p < 0.05$), (Table: 2, Figure: 4A-4D). The subjects and physicians clinical investigations results, a using the GAIS instrument in 2nd clinical group have indicated comparatively higher level of satisfaction with the treatment outcome ($p < 0.05$).

Table 1: Global Aesthetic Improvement Scale (GAIS) Degree Description.

SCORE	TREATMENT RESULT
1	Exceptional improvement Excellent corrective result
2	Very improved patient Marked improvement of the appearance, but not completely optimal
3	Improved patient Improvement of the appearance, better compared with the initial condition, but a touch-up is advised.
4	Unaltered patient the appearance substantially remains the same compared with the original condition.
5	Worsened patient the appearance has worsened compared with the original condition



Figure 2: Intraoral view of abutments upper jaw (2A), and lower jaw (2B) before prosthetic reconstruction. Final intraoral frontal view after prosthetic rehabilitation with non-removable monolithic zirconia restoration(2C,2D).



Figure 3: CT scan 4 month after surgery.

Visit	Group I patients		Group II patients	
	Doctor	Patient	Doctor	Patient
M01	2,5 ± 0,5	2,4 ± 0,52	2,6 ± 0,5	2,5 ± 0,51
M02	2,6 ± 0,5	2,5 ± 0,5	2,8 ± 0,46**	2,9 ± 0,31*
M03	2,1 ± 0,61*	2,0 ± 0,65*	2,7 ± 0,48**	2,5 ± 0,73
M06	1,3 ± 0,54*	1,2 ± 0,53*	1,8 ± 0,64*	1,7 ± 0,66*

Note: The value is statistically significantly different (p <0.05):*- from the indicator at the M01 visit.



Figure 4: Patient at baselin (4A,4B) and week 8 after after hyaluronic acid injections in the Nasola bial and marionette region 4C,4D).

Discussion

Skin aging is a gradual natural process and associated with changes in bones, muscles, ligaments, adipose tissue and skin, and in addition, it is associated with interactions between these types of tissues. Skin aging is classified as internal or external, and involves genetic, hormonal factors, and ecological mechanisms. Internal aging, also called chronological aging, can be influenced by exogenous factors such as smoking, alcohol consumption and exposure to ultraviolet radiation, which are considered major factors in external aging [24-26]. Normal facial appearance and skin tone depend on the correct position and functional length of the muscles

that attach to the orbicularis oris. These include the zygomatic, quadratus labii superior, caninus, mentalis, quadratus labii inferior, triangularis, buccinator and risorius. There is a close functional and aesthetic relationship between teeth, bones, gums and lips [27]. With age, the patient has a deepening of the nasolabial fold, drooping of the corners of the mouth and loss of the border of the lips. The wear of the occlusion and the loss of vertical dimension make the chin more visible. In turn, the contours of the groove and the mental sulcus change. Degenerative processes involving teeth (loss of teeth, poorly performed prosthetic rehabilitation, neglect of oral hygiene, etc.) also contribute to the aging of the facial appearance, both subjectively and objectively in relation to facial structures. In



fact, a face without a smile with full dentures looks older than a face with a full set teeth, both subjectively and objectively in relation to facial structures [28-30]. In edentulous patients esthetic deterioration may be associated with the loss of teeth and alveolar bone. The formation of wrinkles is a consequence of these processes. Wrinkles in the perioral region can detract from the overall esthetics of the face. Areas of primary concern for many patients are the “marionette lines,” and the nasolabial folds. One of the promising treatment options for these patients is soft tissue augmentation with skin fillers. Combined with intraoral aesthetics, skin fillers can provide the patient with a very aesthetic result as these materials have the ability to reduce the appearance of wrinkles and give the face a more youthful appearance. For the prevention or early treatment of superficial skin fine lines, options may include topical skin care (e.g. UV protection, antioxidants, retinoid, moisturizers, DNA repair enzymes), smoking cessation or smoking cessation, and also some anti-aging treatments on devices (e.g. intense pulsed light, radio frequency) [31]. Among non-surgical procedures according to statistics, fillers based on stabilized hyaluronic acid for the correction of evolutionary skin changes occupy a leading position. For patients with early static lines and folds (≤ 2 degrees of contraction and ≤ 1 degrees at rest according to rating scales) prophylactic injections are recommended. For rejuvenation, physicians have the right tools in their hands to prevent or slow down skin aging, which can be offered to an increasing number of patients. Injection procedures will be required to correct problems, and other methods, such as energy therapy, can be combined for optimal results. The prosthetic therapy also is an important in esthetic issue.

The effect of the skin bio revitalization procedure is provided by an increase in the body's production of its own hyaluronic acid, which helps to normalize the water balance. By filling the dermal layers of the skin, bio revitalization helps to smooth out fine wrinkles

[32]. Hyaluronic acid is used as a filler due to its ability not only to restore lost volume, but also to improve the quality of the skin, namely its elasticity, plasticity and hydration and the procedure itself is practically painless and easy to carry out [33]. By filling the dermal layers of the skin, bio revitalization helps to smooth out fine wrinkles. In addition, it has been proven that hyaluronic acid enhances the activity of fibroblasts - cells that are responsible for the synthesis of collagen, elastin and its own Hyaluronic acid, which is why a regular course of procedures contributes to a gradual increase in skin density and elasticity [34,35]. At the same time, all metabolic processes are improved, local blood flow is enhanced, which provides an increase in skin elasticity, a decrease in flabbiness, and an improvement in complexion. A competently performed technique evens out the relief of the skin, eliminates fine wrinkles, unwanted folds Due to the fact that bio revitalization is able to improve not only the external condition of the integument, but also to restore the internal structure, youth and health of the skin return, and the processes of wilting slowdown [36]. When carrying out any injection correction, a specialist must justify a differentiated approach to the depth of injection, the choice of drug concentration and volumes, as well as the staging of procedures in combination therapy [37]. The choice of drugs is carried out together with the patient, taking into account the individual mophotypological and age characteristics of his face, the area of influence. The combination of treatments with implant surgical procedures and fillers may help to forestall the facial aging process and provide more natural results than are possible with any of these techniques alone. This study presents results of a comprehensive method to address facial wrinkles and folds. 5 edentulous patient's with prominent nasolabial folds were treated and followed up for 12 months. The key components the reported study for improving facial cosmeses include, implant prosthodontics and treatment of wrinkles including Hyaluronic acid. Thanks to



implant-prosthetic therapy and course of Hyaluronic acid injections used in the protocols of this studio, mimic wrinkles and folds are reduced and smoothed, making the face look younger and fresher. This has been achieved by restoration of dentition and occlusion, improving stimulation of collagen and elastin after Hyaluronic acid injection procedures, increasing soft tissue and restoring facial volume. In patients received implant therapy and therapy with Hyaluronic acid of skin visual changes dynamics wrinkles and GAIS parameters' values had significant improvement comparison with initial state. The combined use of dental implantation and bio revitalization procedures with contour plastics improves the quality characteristics of the skin, increases satisfaction with aesthetic results for optimal esthetic results, the techniques presented in this study offer exciting options for edentulous patients who desire a younger and healthier appearance.

Conclusion

The results of the studies provide a basis for concluding that the combined of implant rehabilitation and bio reparation with Hyaluronic acid is effective wrinkles and folds. A multidisciplinary approach to the treatment of edentulous patients with perioral wrinkles increases the functional and aesthetic effect of the treatment. This method complex therapy will make contribution to solving the problem of ensuring skin aesthetic health and improving the quality of life of women in this age group. The results of the studies provide a basis for concluding that the implementation of combined of bio reparation and autologous plasma therapy is significantly more effective comparatively to the isolated implementation of modified hyaluronic acid regarding its effect on the clinical manifestations and skin functional parameters in women with wrinkles and folds.

References

1. Kassebaum NJ, Bernabe E, Dahiya M. 2015. Global burden of untreated caries: a systematic review and metaregression. *J Dent Res.* 94: 650-658. Ref.: <https://pubmed.ncbi.nlm.nih.gov/25740856/> DOI: <https://doi.org/10.1177/0022034515573272>
2. Jo E, Frencken. 2017. Global epidemiology of dental caries and severe periodontitis-a comprehensive review. *Journal Clinical Periodontology.* 44: 94-105. Ref.: <https://pubmed.ncbi.nlm.nih.gov/28266116/> DOI: <https://doi.org/10.1111/jcpe.12677>
3. Douglass CW, Shih A, Ostry L. 2002. Will there be a need for complete dentures in the United States in 2020? *J Prosthet Dent.* 87: 5-8. Ref.: <https://pubmed.ncbi.nlm.nih.gov/11807476/> DOI: <https://doi.org/10.1067/mpr.2002.121203>
4. Elham E, Raphael F, Marla K. 2013. The Impact of Edentulism on Oral and General Health. *Int J Dent.* 498305. Ref.: <https://pubmed.ncbi.nlm.nih.gov/23737789/> DOI: <https://doi.org/10.1155/2013/498305>
5. Manavpreet Kaur, Rakesh K, Sanjeev Singla. 2015. Analysis of facial soft tissue changes with aging and their effects on facial morphology: A forensic perspective. *Egyptian Journal of Forensic Sciences.* 5: 46-56.
6. Kahn DM, Shaw RB. 2010. Overview of current thoughts on facial volume and aging. *Facial Plast Surg.* 26: 350-355. Ref.: <https://pubmed.ncbi.nlm.nih.gov/20853225/> DOI: <https://doi.org/10.1055/s-0030-1265024>
7. Landau M. 2007. Exogenous factors in skin aging. *Curr Probl Dermatol.* 35: 1-13. Ref.: <https://pubmed.ncbi.nlm.nih.gov/17641486/> DOI: <https://doi.org/10.1159/000106405>
8. PJ Henry. 2000. Tooth loss and implant replacement. *Australian Dental Journal.* 45: 150-157.
9. KR Spencer. 2018. Implant based rehabilitation options for the atrophic edentulous jaw. *Aust Dent J.* 63: S100-S107. Ref.:



- <https://pubmed.ncbi.nlm.nih.gov/29574819/>
DOI: <https://doi.org/10.1111/adj.12595>
10. Nvon W, Gotfredsen K. 2001. Implant-supported overdentures, a prevention of bone loss in edentulous mandibles? A 5-year follow-up study. *Clin Oral Implants Res.* 12: 19-25. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/11168267/>
DOI: <https://doi.org/10.1034/j.1600-0501.2001.012001019.x>
 11. Lorenc ZP. 2012. Techniques for the optimization of facial and nonfacial volumization with injectable poly-L-lactic acid. *Aesthetic Plast Surg.* 36: 1222-1229. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/22926148/>
DOI: <https://doi.org/10.1007/s00266-012-9920-3>
 12. Wang Y, Kotsis SV, Chung KC. 2013. Applying the concepts of innovation strategies to plastic surgery. *Plast Reconstr Surg.* 132: 483-490. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/23897344/>
DOI: <https://doi.org/10.1097/prs.0b013e3182958c9a>
 13. Wilson YL, Ellis DA. 2011. Permanent soft tissue fillers. *Facial Plast Surg.* 27: 540-546. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/22205527/>
DOI: <https://doi.org/10.1055/s-0031-1298787>
 14. Sarosh FD, Carl EM, Hom LW. 2007. Dermal fillers for facial soft tissue augmentation. *J Oral Implantol.* 33: 191-204. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/17912960/>
DOI: [https://doi.org/10.1563/1548-1336\(2007\)33\[191:dfffst\]2.0.co;2](https://doi.org/10.1563/1548-1336(2007)33[191:dfffst]2.0.co;2)
 15. Statistics-American Society for Aesthetic Plastic Surgery. *Top 5 Procedures: Surgical & Nonsurgical.* 2018.
 16. Meyer K, Palmer JW. 1934. The polysaccharide of the vitreous humor. *J Biol Chem.* 107: 629-634.
 17. Weissman B, Meyer K. 1954. The structure of hyalobiuronic acid from umbilical cord. *J Am Chem Soc.* 76: 1753-1757.
 18. Balazs EA, Sweeney DB. 1968. In: *New and controversial aspects of retinal detachment.* McPherson A, editor. New York: Harper and Row.
 19. Eleni P, Michael R, George K. 2012. Hyaluronic acid: A key molecule in skin aging. *Dermatoendocrinol.* 4: 253-258. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/23467280/>
DOI: <https://doi.org/10.4161/derm.21923>
 20. Stern R, Maibach HI. 2008. Hyaluronan in skin: aspects of aging and its pharmacologic modulation. *Clin Dermatol.* 26: 106-122. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/18472055/>
DOI: <https://doi.org/10.1016/j.clindermatol.2007.09.013>
 21. Taihao Q. 2013. Enhancing structural support of the dermal microenvironment activates fibroblasts, endothelial cells and keratinocytes in aged human skin *in vivo.* *J Invest Dermatol.* 133: 658-667. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/23096713/>
DOI: <https://doi.org/10.1038/jid.2012.364>
 22. Enrica S, Alessandro DP. 2013. Standard Evaluation of the Patient: The Merz Scale. *Injections in Aesthetic Medicine.*
 23. Rzany B. 2012. Validated composite assessment scales for the global face. *Dermatol Surg.* 38: 294-308. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/22316186/>
DOI: <https://doi.org/10.1111/j.1524-4725.2011.02252.x>
 24. Miranda AF, KW Miller, Peter E. 2008. Intrinsic and extrinsic factors in skin ageing: A review. *International Journal of Cosmetic Science.* 30: 87-95. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/18377617/>
DOI: <https://doi.org/10.1111/j.1468-2494.2007.00415.x>
 25. Uraivan P, Gunya S, Natwarath R. 2016. Ultraviolet Radiation-Induced Skin Aging: The Role of DNA Damage and Oxidative Stress in Epidermal Stem Cell Damage Mediated Skin Aging. *Stem Cells International.*
 26. Lévêque JL, Goubanova E. 2004. Influence of age on the lips and perioral skin. *Dermatology.* 208: 307. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/15178912/>
DOI: <https://doi.org/10.1159/000077838>
 27. Ghassemi A, Prescher A, Riediger D. 2003. Anatomy of the SMAS revisited. *Aesthetic Plast Surg.* 27: 258-266. Ref.:



- <https://pubmed.ncbi.nlm.nih.gov/15058546/>
DOI: <https://doi.org/10.1007/s00266-003-3065-3>
28. Ozturk CN, Ozturk C, Bozkurt M. 2013. Dentition, bone loss, and the aging of the mandible. *Aesthet Surg J*. 33: 967-974. Ref.: <https://pubmed.ncbi.nlm.nih.gov/24023258/>
DOI: <https://doi.org/10.1177/1090820x13503473>
29. Martone AL. 1964. Effects of complete dentures on facial aesthetics. *J Prosthet Dent*. 14: 231-255.
30. McCartney JE. 1981. Prosthetic problems resulting from facial and intramural changes in the Edentulous patient. *J Dent*. 71-78.
31. Anthony VR, Thomas JS. 2013. The effect of a vitamin A palmitate and antioxidant-containing oil-based moisturizer on photodamaged skin of several body sites *J Cosmet Dermatol*. 12: 25-35. Ref.: <https://pubmed.ncbi.nlm.nih.gov/23438139/>
DOI: <https://doi.org/10.1111/jocd.12023>
32. Narins RS, Brandt F, Leyden J. 2003. A randomized double-Blind, multicenter comparison of the efficacy and tolerability of restylane versus zyplast for the correction of nasolabial fol. *Dermatologic Surg*. 29: 588-595. Ref.: <https://pubmed.ncbi.nlm.nih.gov/12786700/>
DOI: <https://doi.org/10.1046/j.1524-4725.2003.29150.x>
33. Peter Callan. 2013. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of midface volume deficiency: a 24 month study. *Clin Cosmet Investig Dermatol*. 6: 81-89. Ref.: <https://pubmed.ncbi.nlm.nih.gov/23687448/>
DOI: <https://doi.org/10.2147/ccid.s40581>
34. Joely KJ. 2019. Efficacy and safety of a new resilient hyaluronic acid dermal filler, in the correction of moderate-to-severe nasolabial folds: A 64-week, prospective, multicenter, controlled, randomized, double-blind and within-subject study. *J Cosmetic Dermatology*. 18: 1244-1253. Ref.: <https://pubmed.ncbi.nlm.nih.gov/31444861/>
DOI: <https://doi.org/10.1111/jocd.13100>
35. Syed N, Abbas B. 2018. Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. 120: 1682-1695. Ref.: <https://pubmed.ncbi.nlm.nih.gov/30287361/>
DOI: <https://doi.org/10.1016/j.ijbiomac.2018.09.188>
36. Sabrina F, Tatjana P, Loghem. 2017. Combined aesthetic interventions for prevention of facial ageing, and restoration and beautification of face and body. *Clin Cosmet Investig Dermatol*. 10: 423-429. Ref.: <https://pubmed.ncbi.nlm.nih.gov/29133982/>
DOI: <https://doi.org/10.2147/ccid.s144282>
37. Lefebvre VM, Trevidic P, Moradi A. 2015. Hand: clinical anatomy and regional approaches with injectable fillers. *Plast Reconstr Surg*. 136: 258-275. Ref.: <https://pubmed.ncbi.nlm.nih.gov/26441105/>
DOI: <https://doi.org/10.1097/prs.0000000000001828>