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# aesthetic medicine

Official Journal of the  
International Union of Aesthetic Medicine UIME



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aesthetic medicine

Official Journal of the  
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## Editorial

Francesco Romanelli

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# Guidelines for Authors

Aesthetic Medicine is a multidisciplinary Journal with the aim of informing readers about the most important developments in the field of Aesthetic Medicine.

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All articles in their final version - completed with name, surname, affiliation, address, phone number and e-mail address of the author (s) - must be sent in word format to the Editorial Committee at the following e-mail address:

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References must be cited consecutively in the text as superscript numerals and listed on a separate sheet in numerical order at the end of the text. The references must be cited according to the AMERICAN MEDICAL ASSOCIATION (AMA) CITATION STYLE.

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Rev. 11/1/2012

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<b>Journal article - in print - more than 6 authors</b>	<b>Fukushima H, Cureoglu S, Schachern P, et al.</b> Cochlear changes in patients with type 1 diabetes mellitus. <i>Otolaryngol Head Neck Surg.</i> 2005; 133: 100-6.
<b>Journal article - online*</b> *if there is no DOI, provide the URL for the specific article	Coppinger T, Jeanes YM, Hardwick J, Reeves S. Body mass, frequency of eating and breakfast consumption in 9-13- year-olds. <i>J Hum Nutr Diet.</i> 2012; 25(1): 43-49. doi: 10.1111/j.1365-277X.2011.01184.x
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<b>Websites</b>	Outbreak notice: Cholera in Haiti. Centers for Disease Control and Prevention Web site. <a href="https://www.cdc.gov">https://www.cdc.gov</a> Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012.
<b>Entire book - in print</b>	Modlin J, Jenkins P. <i>Decision Analysis in Planning for a Polio Outbreak in the United States.</i> San Francisco, CA: Pediatric Academic Societies; 2004.
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<b>Example Article</b>  1. Zoellner J, Krzeski E, Harden S, Cook E, Allen K, Estabrooks PA. Qualitative application of the theory of planned behavior to understand beverage consumption behaviors among adults. <i>J Acad Nutr Diet.</i> 2012;112(11):1774-1784. doi: 10.1016/j.jand.2012.06.368.	
<b>In-Text Citation Example</b>	<p><b>L</b>ARGE INCREASES IN AMERICANS' CONSUMPTION OF sugar-sweetened beverages (SSB) have been a topic of concern. Between 1977 and 2002, the intake of "caloric" beverages doubled in the United States, with most recent data showing that children and adults in the United States consume about 172 and 175 kcal daily, respectively, from SSB.<sup>1</sup> It is estimated that SSB account for about 10% of total energy intake in adults.<sup>2,3</sup> High intake of SSB has....</p>
<b>References Section Example</b>	<p><b>References</b></p> <ol style="list-style-type: none"><li>1. Duffey KJ, Popkin BM. Shifts in patterns and consumptions of beverages between 1965 and 2002. <i>Obesity.</i> 2007;15(11):2739-2747.</li><li>2. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. <i>Am J Prev Med.</i> 2004;27(3):205-210.</li><li>3. Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. <i>Am J Clin Nutr.</i> 2007;85(3):651-661.</li></ol>

Use commas to separate multiple citation numbers in text, like you see between references 2 and 3. Unpublished works and personal communications should be cited in the text (and not on the reference list).<sup>1</sup> Superscript numbers are placed outside periods and commas, and inside colons and semicolons. When citing the same source more than once, give the number of the original reference, then include the page number (in parentheses) where the information was found. See pages 41-44 of the AMA Manual of Style for more information.

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## Editorial

In modern years, aesthetics has become quite important in every aspect of everyday life: following the hundreds of journals, magazines, blogs and websites pointing their attention towards this interesting and fascinating topic, the request for aesthetic medicine has increased manifolds.

Aesthetic Medicine is a new field of medicine, in which different specialists share the aim of constructing and reconstructing the physical equilibrium of the individual. Treatment of physical aesthetic alterations and unaesthetic sequel of illnesses or injuries, together with the prevention of aging, are perhaps two of the most iconic areas of intervention for Aesthetic Medicine.

However, in order to prevent frailty in the elderly, a program of education is similarly important.

Furthermore, the line between health and beauty is extremely thin: psychosomatic disorders resulting from low self-esteem due to aesthetic reasons are frequent and cannot be ignored by a clinician.

It is therefore clear that there is no figure in the field of medicine which is not involved in Aesthetic Medicine: endocrinologists, gynecologists, angiologists, psychologists and psychiatrists, plastic surgeons, dermatologists, dieticians, physiotherapists, orthopedists, physical education instructors, massophysiotherapists, podologists, and rehabilitation therapists are just some of the specialists who are sooner or later going to have to answer their patients' needs for aesthetic interventions.

The involvement of all these specialists fits the description of health as defined by the WHO: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" for which, undeniably, a team of different physicians is required.

The number of patients requiring medical consultation for esthetic reasons is rapidly increasing: in order to be able to provide adequate feedback, medical and paramedical specialists should be trained and, more importantly, should be taught how to work together. Existing Societies of Aesthetic Medicine from different countries share the aim of creating such teams and provide constant updates to the literature: the creation of an international network of specialists from all around the world under the flag of Aesthetic Medicine represents a challenge, but at the same time it is the proof of the widespread interest in this topic.

The first issue of this Journal represents the results of the efforts of the many national Societies and of the Union Internationale de Medecine Esthetique, now together as one; it is our hope that in years to come this Journal might improve our knowledge in this field, and provide adequate scientific advancement in the field of Aesthetic Medicine.

**Francesco Romanelli**

*MD Editor-in-chief*

*Associate Professor at "Sapienza" University of Rome*

# Editors' notes

## Aesthetic Medicine, the booming medical activity

Aesthetic Medicine was born in France 40 years ago.

The French Society of Aesthetic Medicine was the first of its kind in the world, followed by Italy, Belgium and Spain. Starts were rather difficult as aesthetic procedures in those early years were only surgical.

At that time aesthetic doctors and cosmetic dermatologists had very few real medical procedures to offer to their patients for treating aesthetic problems on face and body.

At the beginning of the '80s, viable medical procedures started to emerge in Europe for aesthetic and cosmetic purposes. Mostly, at that time, they were imported from the United States: those included collagen injections for wrinkles (Zyderm by Dr. Stegman), and chemical peels (phenol by Dr. Baker, TCA by Dr. Oba- gi). But, subsequently, European research on Aesthetic Medicine gained momentum. Hyaluronic acid appeared on the market, as it was discovered that it could be used as a dermal filler for wrinkles. During the '90s, the use of lasers offered aesthetic doctors and cosmetic dermatologists new possibilities.

The "beam revolution" started with CO2 laser for facial resurfacing.

Today, CO2 resurfacing is not used as much anymore, because of the long and difficult postop. CO2 laser was replaced with the gentler Nd-YAG and Erbium lasers and more recently with non invasive photonic devices for facial rejuvenation, including IPL, US and radiofrequency. These new technologies allow today's aesthetic doctors and cosmetic dermatologists to offer their patients procedures with low risk of post- op complications. Then, Botulinum Toxin has "invaded" both sides of the Atlantic Ocean.

Today, Botox injections are the most popular treatment for facial expressive wrinkles.

Botox injections are now so common everywhere that many cosmetic surgeons have given up their bistouries for syringes. Last but not least, development in Aesthetic Medicine is shown by mesotherapy and adipolipolysis.

About lipolysis, new data and recent publications have explained that radiofrequency, ultrasounds and cryolyse could have positive action to dissolve fat and to improve some unaesthetic disorders like cellulite.

These non invasive procedures intend to replace the surgical liposculpture with success.

Nowadays, Aesthetic Medicine has the necessary tools to address all major disorders within the aesthetic field. After 40 years, Aesthetic Medicine is now active in 32 countries in the world (France, Italy, Spain, Belgium, Morocco, Poland, Russia, Switzerland, Kazakhstan, Algeria, Brazil, Argentina, Uruguay, Venezuela, Colombia, Chile, Mexico, U.S.A, Canada, South Korea, Ecuador, China, South Africa, Turkey, Ukraine, Georgia and recently Croatia, Portugal, India, Guatemala, Peru and Bolivia). All 32 national Societies are members of the Union Internationale de Médecine Esthétique (U.I.M.E.). Aesthetic Medicine is taught in 7 countries (France, Italy, Spain, Argentina, Mexico, Venezuela, Kazakhstan) in universities that deliver UIME's diplomas after 3 to 4 years of studies.

## What is the future of Aesthetic Medicine?

In the last few decades, patients' desires to look and feel younge, have fueled Aesthetic Medicine and Cosmetic Dermatology: many different procedures have been developed to satisfy the demands.

As life-span have increased, patients today are not only asking about aesthetic procedures, they are also asking for a way to stay in good physical conditions in the last decades of their lives. As a direct result, Anti-Aging Medicine, which covers skin aging and general aging, has recently emerged and expanded very quickly. Anti-Aging Medicine can offer senior patients better nutrition, dietary supplementation with vitamins, minerals, antioxidants, and eventually hormone replacement therapy, but only when needed.

Today, and in the near future, both Aesthetic Medicine and Anti-Aging Medicine will offer to our patients, who now live longer, better wellness with aesthetic treatments for skin aging and anti-aging treatments for general aging. Aesthetic Medicine is booming, but all medical practitioners should be correctly trained, so its future will be bright.

**Jean-Jacques Legrand**

*Former General Secretary and Honorary President of UIME*

## **Aesthetic Medicine: a bioethic act**

When in 1977 the Italian Society of Aesthetic Medicine published the first issue of the magazine “La Medicina Estetica” Carlo Alberto Bartoletti, the Founder, wrote an editorial in which traced the pathway of the discipline and of the Scientific Society, still valid and projected into the future.

Today from that Editorial Board arise an International Journal, which wants to be indexed, in order to give to the doctors practicing Aesthetic Medicine all around the world a solid basis of shared knowledge.

In the late ‘60s, what was called in Italy Aesthetic Medicine, moved its first steps thanks to “remise en forme and anti aging projects” imported from the experience the “Institutul de geriatrie Bucuresti”, directed by Dr. Ana Aslan.

For this reason, there is the bioethical imperative that the Discipline should be first prevention, then return to physiology and finally correction.

The worldwide diffusion and the efforts of Industries born on the wave of the phenomenon have often led to choose the fastest route to achieve and maintain the physical aspect in the myth of beauty at all costs, without considering that aesthetic is not synonymous of beauty, but it is a balance between body and mind, and the role of the doctor is to take care of the Person globally and not only focusing on the correction of “a badly accepted blemish”.

Faithful to the teaching of my Master had almost 50 years ago, this new journal will have the task of elevating the human resources, aligning and validating methodologies, but above all affirming the humanitas of the medical art in its purest sense to pursue the good and the graceful for the person who relies on it.

**Fulvio Tomaselli, MD**

*Honorary President of the Italian Society of Aesthetic Medicine*

## **Aesthetic Medicine needs science. All over the world**

All Aesthetic Doctors know that science is the basis for safety. Safety is the most important issue in our discipline.

Unfortunately, Aesthetic Medicine is more often surrounded by marketing than by science, despite the hard work done by Scientific Societies all over the World. And, too often doctors working in this field are dealing with sellers that promote products with insufficient scientific studies.

However, they sell it anyway. I think that doctors must learn that the first thing to ask about a medical device is the scientific background regarding that product: patients treated, follow up period, adverse events and, most of all, publications.

With this new International Journal completely dedicated to Aesthetic Medicine, proposed by the Italian Society of Aesthetic Medicine, endorsed by UIME and shared by all the National Societies of Aesthetic Medicine belonging to UIME, World Aesthetic Medicine wants to stimulate scientific production in this discipline to increase safety and quality in aesthetic medical procedures.

Another important goal of the Journal is to catalyze the proposal of new protocols and guidelines in Aesthetic Medicine, with the consensus of the entire Aesthetic Medicine Scientific Community.

What this Journal should achieve in the near future is to improve the number and quality of scientific production in Aesthetic Medicine, in order to allow this discipline to grow in the field of evidence based medicine, not only in the rationale field.

I hope this can be the start of a new era for Aesthetic Medicine, with the commitment of all Scientific Societies all over the world.

**Emanuele Bartoletti, MD**

*Managing Editor*

*President of the Italian Society of Aesthetic Medicine*

*General Secretary of UIME*

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# Hybrid cooperative complexes of high and low molecular weight hyaluronans for facial skin rejuvenation in the Oriental mongoloid face: a case series

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## Abstract

Chrono-aging, i.e. the cutaneous effects of senescence, results in dermal thinning, skin laxity and the formation of wrinkles and fine lines. It correlates with a series of metabolic and histological changes in the skin, notably the marked reduction in hyaluronic acid (HA) production in the extracellular matrix. HA has long been employed as a dermal agent in the field of aesthetic medicine for the correction of soft tissue defects, and IBSA Pharmaceuticals' Profhilo® is the first BDDE-free injectable formulation of stabilized cooperative hybrid HA complexes. Its *in vivo* efficacy and the specifically-developed 5-injection point technique (BAP technique) for the tissue remodeling of the malar and sub-malar areas have been positively evaluated in several independent published studies.

In this case report, Profhilo®'s efficacy for facial skin rejuvenation was tested on 10 individuals (9 females, 1 male) of the Central Eastern European ethnic subpopulation presenting with Oriental mongoloid features. Comparison before and after treatment and between the BAP technique group (5 participants) and diffuse Profhilo® injections group (5 participants) was performed via photographic evidence, Soft Plus and Antera 3D assessment systems.

Although no significant difference in terms of efficacy was identified between the two injection techniques, results revealed a significant amelioration in skin hydration and wrinkle overall size, and a clear, albeit non-significant improvement in skin elasticity, melanin levels and skin texture. Visual comparison also showed a macroscopic improvement in wrinkles, fine lines and skin brightness and tone. Lastly, two patients suffering from pre-existing dermatological conditions reported an amelioration of said complaints after treatment.

## Keywords

Hybrid cooperative complexes, hyaluronic acid, asian mongoloid face, bio aesthetic point, skin laxity

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## Introduction

Chrono-aging is the plethora of metabolic changes occurring in skin physiology as an effect of aging<sup>1</sup>. One well-known manifestation is skin laxity, which is due to both a decrease in collagen and elastin production and to changes in the extracellular matrix including reduction in hyaluronic acid (HA) synthesis<sup>2</sup>.

The glycosaminoglycan HA is widely distributed in epithelial and connective tissues and is a chief component of the extracellular matrix. Here it contributes to tissue hydrodynamics and viscoelasticity, protection from oxidative stress and, most crucially, tissue repair<sup>3-7</sup>. HA's regenerative action is due to its intrinsic anti-inflammatory and bio-stimulating properties, resulting in fibroblast proliferation and increased collagen production<sup>8-10</sup>. The aforementioned properties make HA a highly desirable dermal agent in the field of aesthetic medicine for the correction of soft tissue defects<sup>10</sup>. However, once injected in the dermis, native HA is rapidly degraded by hyaluronidase, making it non-viable for mid- to long-term results<sup>11</sup>. This led to chemically stabilizing HA via cross-linking, a process increasing the molecule's stability, rigidity and elasticity, but whose main drawback is the chemical alteration of HA's natural molecular structure<sup>12</sup>.

This issue was bypassed by Profhilo®, a 2015 product developed by IBSA Pharmaceuticals, whose innovative thermal production process yields stable, cooperative hybrid HA complexes without the need for BDDE or other chemical agents<sup>13</sup>.

The product formulation is a mixture of 32 mg of high molecular weight HA (110-1400 kDa) and 32 mg of low molecular weight HA (80-110 kDa), stabilized by a thermal process consisting of a high-temperature step followed by a low-temperature step. Profhilo®'s unique characteristics include high HA concentration, excellent manageability, low viscosity, optimal tissue diffusion, a low tissue inflammatory response and a duration comparable to weakly cross-linked gel<sup>6,13-15</sup>.

Profhilo®'s effectiveness has been proven in *in vitro* studies, where it demonstrated enhanced tissue repair<sup>6</sup>, extracellular environment remodeling and neofibrogenic and adipogenic properties, while maintaining optimal conditions for fibroblast, keratinocyte and adipocyte vitality<sup>15</sup>. Profhilo®'s clinical indications in the field of aesthetic medicine are in tissue remodeling and improvement of skin laxity of the face, neck and body, and its *in vivo* efficacy has been proven on 120 patients over the course of 4 independent published studies<sup>16-19</sup>. IBSA has furthermore developed the Bio Aesthetic Points (BAP) technique, a Profhilo®-specific injection procedure for the tissue remodeling of the malar and sub-malar areas<sup>16-19</sup>. The technique entails five 0.2 mL bolus injections in the superficial subcutaneous tissue compartment of each hemiface, localized in anatomically receptive facial areas identified for the lack of large vessels and nerve branches<sup>20</sup>: the zygomatic protrusion, the nasal base, the tragus, the chin and the mandibular angles (*Figure 1*). This minimizes the risks and maximizes the diffusion of the product in the lower third of the face.

- 1 **ZYGOMATIC PROTRUSION**  
at least 2 cm away from the external corner of the eye
- 2 **NASAL BASE**
  - draw a line connecting the nostril and tragus
  - draw a perpendicular line starting from the pupil
  - locate the injection point at the intersection of the 2 lines
- 3 **TRAGUS**  
1 cm anterior to the bottom of the tragus
- 4 **CHIN**
  - draw a vertical line in the center of the chin
  - draw a perpendicular line one third from the top of the vertical line
  - from the point of intersection move 1.5 cm towards the oral commissures
- 5 **MANDIBULAR ANGLE**  
1 cm above the mandibular angle

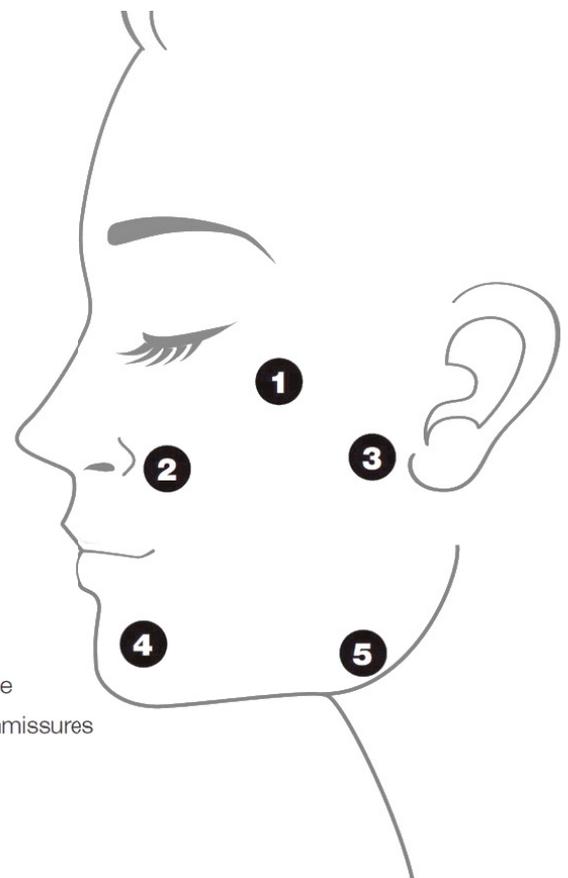


Figure 1 - The BAP (Bio Aesthetic Points) Technique for the treatment of the malar and submalar areas.

The BAP technique allows for highly satisfactory results with only 2 treatments performed 4 weeks apart<sup>21</sup>. Previously published clinical experience on Profhilo®'s efficacy in tissue remodeling prompted the current study, which focuses on an ethnic subpopulation of the Slavs, i.e. the Central Eastern European group. This ethnic group displays so-called Oriental mongoloid face features, which differ from the Caucasian craniofacial form in facial profile, shape of the orbits, cheekbones and mandibular angle. Specifically, the oriental face is wide and round or square, with a flattened facial profile, shorter forehead, and broad nasal bridge with wide nasal wings. The eyes are typically almond-shaped with an elongated intercanthal width, set in fuller upper eyelids with an absent supratarsal fold (so-called "single eyelid"). On the basis of gross histological findings, the single eyelid is due to the fusion of the levator palpebrae aponeurosis with the orbital septum closer to the eyelid margin than in non-Asians, hindering the aponeurotic fibers of the levator from reaching the subcutaneous tissues, which is responsible for the formation of a double eyelid crease<sup>22</sup>. Oriental mongoloid lips are fuller and more protuberant, and the chin more receded than in Caucasian individuals. Overall, the skull morphotype is roughly rectangular, compared to the trapezoidal Caucasian morphotype. Lastly, the mimetic and chewing muscles are active and well developed: it has been posited that the peculiar Oriental structural features of the zygomatic area and the malaris muscle, which is inconsistent in Caucasian anatomy, prevents soft tissue ptosis, with an overall anti-aging effect of the midface<sup>23,24</sup>.

Despite the numerical strength of the considered population, few studies have assessed facial skin aging in Asian populations. One such study highlighted an increase in transepidermal water loss (TEWL), denoting a loss in stratum corneum barrier function, coupled with a decrease of sebum content, due to a decrease in estrogen-induced sebaceous gland activity<sup>25</sup>.

### Materials and methods

Based on these observations, we investigated the efficacy of Profhilo® for facial skin rejuvenation in 10 individuals (9 females, 1 male) of Oriental appearance aged 26 to 62 (mean = 44 years). We included only participants compliant to the following criteria:

- No rejuvenation procedures performed 6 months ago or later.
- Relatively normal somatic health.
- Not during pregnancy/lactation period.
- No tendency to form cheloid scars.

Participants were requested to maintain the same habits on food, exercise, make-up, cosmetics, and detergent.

A comparative analysis was led between group 1 (5 participants), treated with Profhilo® following the BAP technique for injection points (29G needle) (Figure 1), and group 2 (5 participants), treated with diffuse injections of Profhilo®. The latter technique consisted of diffuse 0.05 mL injections 1 cm<sup>2</sup> apart in the subcutaneous layer of the right and left submalar areas (30G needle). Both groups were treated in two sessions at 4-week intervals, and efficacy was evaluated

pre- and post-treatment. Comparison was performed via photographic evidence, Soft Plus and Antera 3D assessment systems. The Callegari Soft Plus probe system was used to measure skin hydration (in terms of capacity measurement), elasticity (in terms of stress/deformation of the skin by suction application) and melanin (via a double wavelength reflectance photometer) at three points on the right side of the face: the center of the forehead, the outer corner of the eye (1 cm above the zygomatic arch and 2 cm laterally from the outer cantus) and the cheek (2 cm laterally from the labial commissure)<sup>26</sup>.

The Miravex Antera 3D macrophotography camera was employed for 3D topographical and chromophore analysis, specifically assessing overall wrinkle size, skin texture in terms of arithmetical mean roughness and average pigmentation concentration. Again, three areas of the right side of the face were assessed: the glabellar area, the outer corner of the eye and the cheek area near the labial commissure<sup>27</sup>.

Statistical analysis was performed using Fisher's angular transformation ( $\phi$ -method) to compare Group 1 (treated by diffuse injection) and Group 2 (treated by Bio-Esthetic Points). The  $\phi$ -method estimates the statistical significance between the percentages of two samples according to the null hypothesis (H 0): the percent of persons with apparent effect in sample 1 is no more than in sample 2.

### Results

Visual pre- and post-treatment comparisons showed a clear improvement in skin wrinkles and fine lines, with skin appearing brighter and more toned after completion of the procedure (Figure 2).



Figure 2 - Sample visual pre- and post-treatment comparison (patient treated with BAP technique).

Visual pre- and post-treatment comparisons showed a clear improvement in skin wrinkles and fine lines with skin subjectively appearing brighter and more toned after completion of the procedure. Though no objective measurements of volumetric changes or sebum changes were performed to support existing research, as this

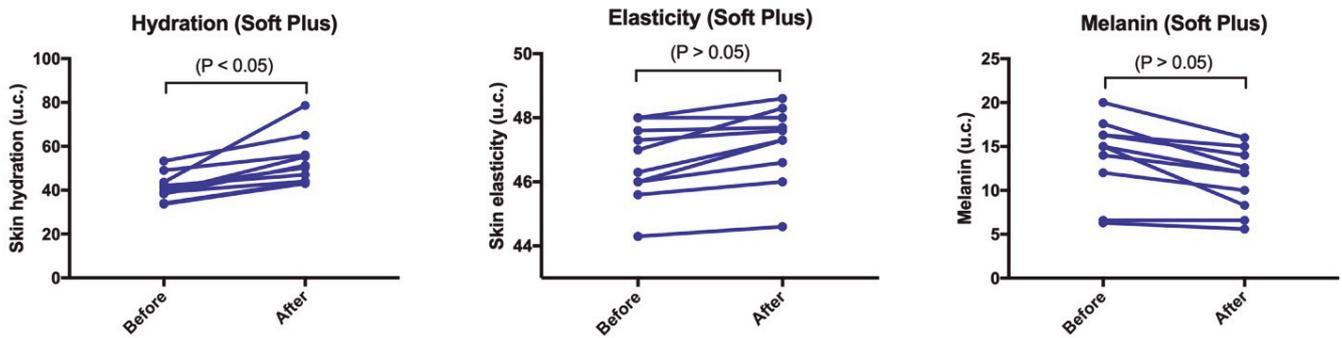


Figure 3 - Soft Plus assessment outputs: paired nonparametric two-tailed T test (Wilcoxon test).

was not within the focus area of this case study. The Soft Plus assessment outputs recorded a significant improvement (P-value 0,008) in skin hydration with an average increase of 12,13 u.c..

Skin elasticity and melanin levels also displayed an overall amelioration of an average 0,59 u.c. and 2,7 u.c. respectively, albeit non-significant (P-value 0,28 and 0,15 respectively) (Figure 3).

Macrophotographical evidence from the Antera 3D camera displays a clear improvement in topographical parameters (Figure 4).

### Wrinkles (Antera 3D)

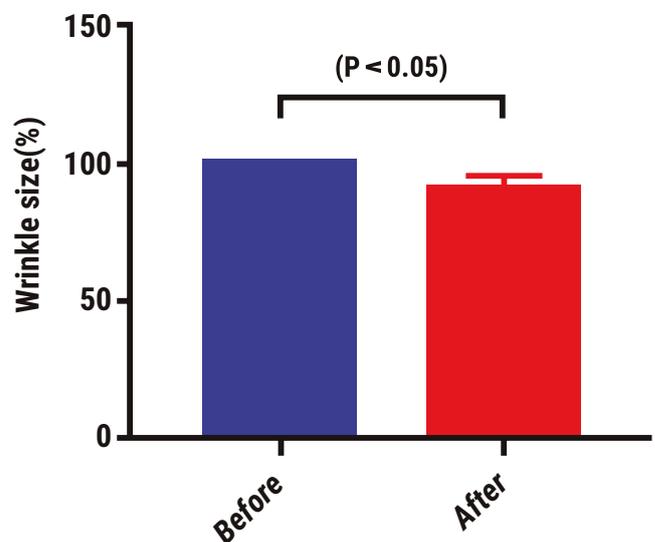


Figure 5 - Antera 3D assessment outputs: paired nonparametric two-tailed T test (Wilcoxon test).

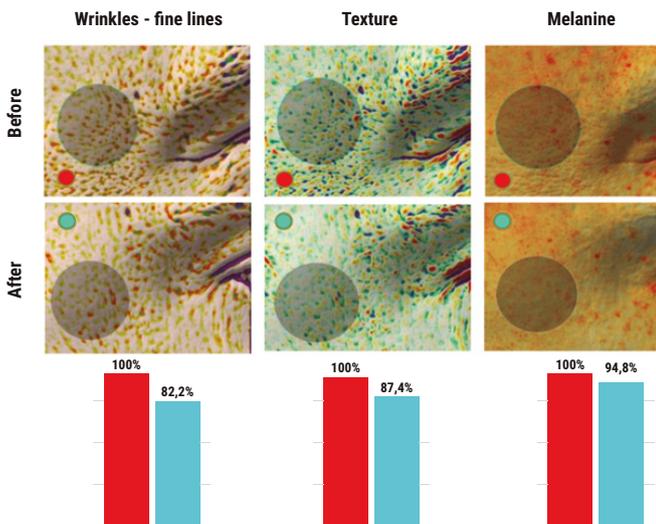


Figure 4 - Sample Antera 3D topographical analysis (patient treated with BAP technique).

Quantitatively, a significant improvement in wrinkle overall size (P-value 0,01) was measured, with an average 8,5% size decrease (Figure 5).

Skin texture was also positively affected, with an average arithmetical mean roughness decrease of 9,2% (P-value 0,002). Lastly, a 4,5% average decrease in skin pigmentation was measured (P-value 0,01).

Furthermore, two patients suffering from pre-existing dermatological conditions reported an improvement in their ailment after treatment.

Patient A (female, 26 years) (Diffuse Injections Group), who suffered from occasional eruptions of acne vulgaris, described a significant decrease in the rash after the second treatment sitting, and an overall reduction in the severity of stagnant post-acne stains.

Patient B (female, 36 years) (BAP Group), suffered from

facial atopic manifestations in wintertime such as skin reddening and peeling. Likewise, after the first treatment sitting the patient noted a significant improvement in her skin condition and claimed complete remission of peeling after the second sitting.

Regarding the injection technique, comparison between group 1, treated following the BAP technique, and group 2, treated with diffuse injections in the subcutaneous layer, revealed no significant difference in terms of efficacy in all the parameter measured.

No adverse events were reported during this study, except for some minor petechiae.

### Discussion

Facial aging is the product of cumulative effects of time on the skin, soft tissues and deep structural components of the face, and is a combined result of skin textural changes and loss of facial volume<sup>1,2</sup>.

Among the skin alterations, loss of tissue elasticity and skin laxity due to decrease in elastin, collagen and hyaluronic acid production strongly affects the phenotypic presentation of the face, causing superficial

textural wrinkling and alterations of its 3D topography. In recent years, there has been a steady increase in nonsurgical procedures for facial rejuvenation<sup>1,2</sup>.

Factors which make the nonsurgical approach so appealing are the immediacy of the cosmetic result and a short recovery time. Profhilo® is an exclusive skin bioremodeling treatment designed by IBSA Pharmaceuticals to treat loss of facial volume and elasticity. Profhilo®'s stabilized hybrid hyaluronic acid complexes stimulate the production of collagen and elastin, thus significantly improving the appearance of wrinkles and fine lines, while increasing tone and hydration across the face. Previous published clinical experience has tested the efficacy and tolerability of Profhilo® on 120 patients in 4 independent studies, with highly satisfactory quantitative results in terms of skin hydration, elasticity, trans-epidermal water loss (TEWL), validated clinical scales (WSRS, FVLS and Beagley and Gibson Scale) and patient and doctor satisfaction rates, with no relevant side effects<sup>17-21</sup>.

Based on Profhilo®'s success in the Caucasian ethnicity, the present report aimed to test the treatment's efficacy on a different ethnic subpopulation, i.e. the Central Eastern European group, which exhibits so-called Asian mongoloid face features. In this case report, 10 patients (9 female, 1 male) were treated with subcutaneous injections of Profhilo® 2,0 ml for facial skin rejuvenation. Photographic pre- and post-treatment comparison revealed a smoothing and lightening of the skin, with macroscopic improvement of wrinkles and fine lines. Quantitative analysis and topographical measurements further highlighted a significant increase in skin hydration and a slight improvement in skin elasticity, confirmed the improvement in skin texture and wrinkle severity, and recorded a decrease in skin pigmentation, probably due to the antioxidant activity of HA<sup>28</sup>. Furthermore, two patients with pre-existing dermatological conditions, namely acne vulgaris and atopic dermatitis, achieved remission after treatment. These results confirm the *in vitro* properties exhibited by Profhilo®: an increase in expression levels of collagen in fibroblasts and keratinocytes and of elastin in the extracellular matrix, combined with enhanced adipogenic differentiation and proliferation of adipose-derived stem cells (ASCs), resulting in excellent regenerative action.

The case report confirms Profhilo® as a unique product with polypotent properties, and as an effective and highly tolerable nonsurgical skin bioremodeling treatment in patients of diverse ethnicities.

#### Acknowledgments

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# Minimally Invasive Procedures for Nasal Aesthetics

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## Abstract

Nose has an important role in the aesthetics of face. It is easy to understand the reason of the major interest that has revolved around the correction of its imperfections for several centuries, or even from the ancient times. In the last decade, all the surgical or medical minimal-invasive techniques evolved exponentially. The techniques of rejuvenation and corrections of nasal imperfections did not escape this development that is much widespread in the medicine of the third millennium. In many cases, the techniques of surgical correction involve invasive procedure that necessitates, for the majority of cases, hospitalisation. The author, using a different approach, has developed mini-invasive techniques using botulinum toxin A (BTxA) and absorbable fillers for the correction of nasal imperfections. BTxA allows to reduce the imperfections due to hypertension of muscles, while the absorbable fillers allow to correct all the imperfections of the nasal profile from the root to the tip in total safety. The correction is based on the precise rules that allow avoiding the majority of side effects. Results are long lasting and well appreciated by patients.

## Abbreviations

Hyaluronic acid (HA), Botulinum Toxin A (BTxA)

## Keywords

Botulinum toxin, hyaluronic acid, medical rhinoplasty, aesthetic medicine, nonsurgical procedures

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**Introduction**

Absorbable fillers have become increasingly popular to reverse signs of aging on the face. Since bovine collagen fillers received Food and Drug Administration approval in 1981, these fillers gained popularity for more than a decade; however, bovine collagen had the potential for allergic reactions and required skin testing before the first treatment. Since then, non-animal-based hyaluronic acid (HA), which had been used for intra-articular joint injection and ophthalmologic procedures for many years with a very good safety profile, was introduced and has become the most commonly used facial filler over the past several years. HA fillers show excellent efficacy not only in correcting wrinkles but also in restoring tissue volume with minimal downtime. These fillers are easy to use, allergy-free, and enzymatically degradable using an injection of hyaluronidase in case of a bad result<sup>1</sup>. Botulinum toxin injection for treatment of facial wrinkles is the most frequently performed cosmetic procedure in the Treatment of frown lines and crow’s feet, which are the cosmetic indications approved by the U.S. Food and Drug Administration, and horizontal forehead lines, offers predictable results, has few adverse effects, and is associated with high patient satisfaction. Wrinkles are formed by dermal atrophy and repetitive contraction of underlying facial musculature. Botulinum toxin is a potent neurotoxin that inhibits release of acetylcholine at the neuromuscular junction. Injection of small quantities of botulinum toxin into specific overactive muscles causes localized muscle relaxation that smooths the overlying skin and reduces wrinkles. Botulinum toxin effects take about two weeks to fully develop and last three to four months. Dynamic wrinkles, seen during muscle contraction, yield more dramatic results than static wrinkles, which are visible at rest<sup>2</sup>. Minimally Invasive Procedures for Nasal Aesthetics rests its therapeutic base on two pillars: first, the control of the muscular activity at the base of the nose that provokes the rotation and the dropping of the tip, through the use of botulinum toxin A (BTxA), and second, the improvement of the nasal profile and ageing with the use of absorbable fillers. This article describes the procedure and clinical outcomes and discusses the indications of the treatment and possible mechanisms of the long-lasting effects.

**Patients and Methods**

The author successfully performed a Minimally Invasive Procedures for Nasal Aesthetics has developed mini-invasive techniques using botulinum toxin A (BTxA) and absorbable fillers hyaluronic acid (HA) for the correction of nasal imperfections. 48 carefully selected patients, between September 2017 and October 2018, with an eight - to twelve - months follow-up. Patient ages ranged from 21 to 39 years. All of the patients elected not to undergo any aesthetic nasal surgery but were requesting a slight improvement of their nasal shape. Monophasic Hyaluronic Acid (HA) gel with the presence of two different molecular weights: 1000 kDa and 2000 kDa (Figure 1). This is an advantage both from a biological and mechanical point of view. In fact, different

molecular weights allow the physician to act on different HA receptors, putting a number of mechanisms in place that are involved in the regeneration of skin tissue. Furthermore, there is a mechanical advantage; a high molecular weight HA fills larger spaces, while a low molecular weight HA fills smaller spaces, resulting in a complete filling action. Additional important features of product are its safety and manageability. For example, as with most volumising fillers, it is indicated for use at the supraperiosteal layer and deep tissue, but with Monophasic hyaluronic acid (HA) gel no problems arise if it is injected at the mid or deep dermal level (Figure 2). Therefore, it can be used safely throughout the nose area. The smoothness of the gel reduces the possibility of side-effects such as swelling and bruising, as well as the risk of over-correction. Monophasic hyaluronic acid (HA) gel is indicated in all patients who wish to create or redefine facial contour, in those who have lost subcutaneous tissue, and for correcting deficits following injuries<sup>3</sup>.

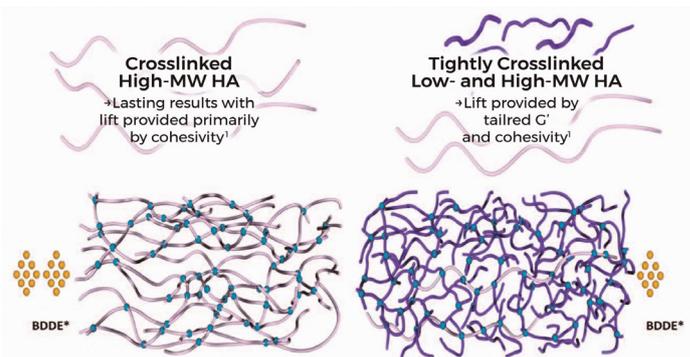


Figure 1 - Difference of crosslinked high molecular weight hyaluronic acid gel and crosslinked low & high molecular weight hyaluronic acid gel<sup>4</sup>.

**Hyaluronic acid**

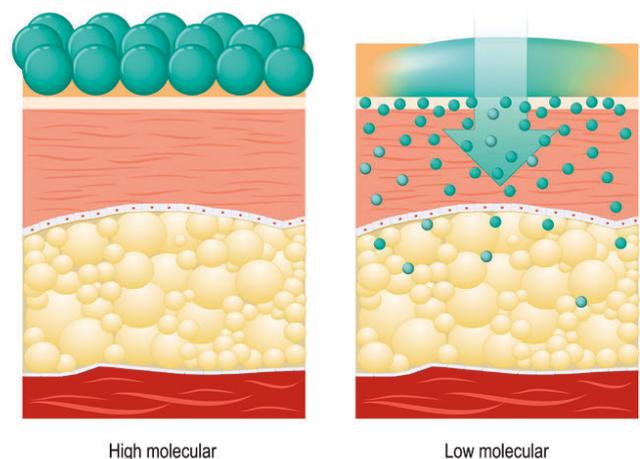


Figure 2 - Molecular weight of HA in a product, as well as the diameter of HA, make a difference in its efficacy<sup>5</sup>.

**Anatomy**

**Surface Appearance:** the external nose has a pyramidal shape (Figure 3). The nasal root is located superiorly, and is continuous with the forehead. The apex of the nose ends inferiorly in a rounded 'tip'. Spanning between the root and apex is the dorsum of the nose. Located immediately inferiorly to the apex are the nares; piriform openings into the vestibule of the nasal cavity. The nares are bounded medially by the nasal septum, and laterally by the ala nasi (the lateral cartilaginous wings of the nose). **Skeletal Structure:** the skeleton of the external nose is made of both bony and cartilaginous components: bony component - located superiorly, and is comprised of contributions from the nasal bones, maxillae and frontal bone (Figure 4). Cartilaginous component - located inferiorly, and is comprised of the two lateral cartilages, two alar cartilages and one septal cartilage (Figure 5). There are also some smaller alar cartilages present. Whilst the skin over the bony part of the nose is thin, that overlying the cartilaginous part is thicker with many sebaceous glands. This skin extends into the vestibule of the nose via the nares (Figure 6). Here there are hairs which function to filter air as it enters the respiratory system (Figure 7)<sup>6</sup>.

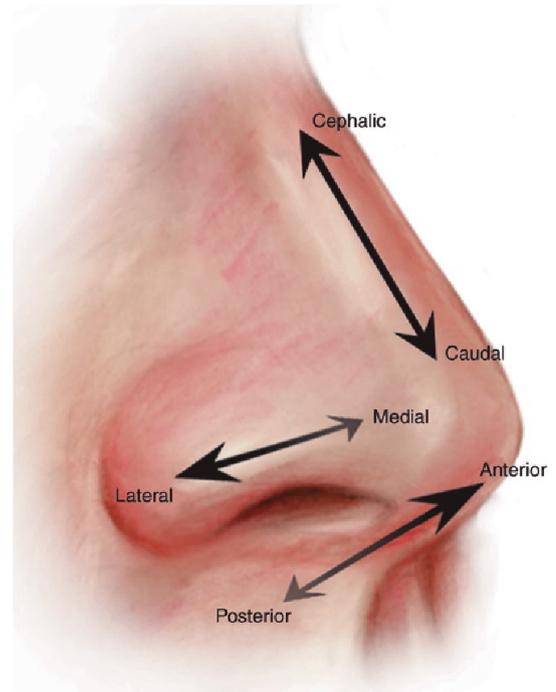


Figure 3 - Nasal anatomy physical appearance<sup>7</sup>.

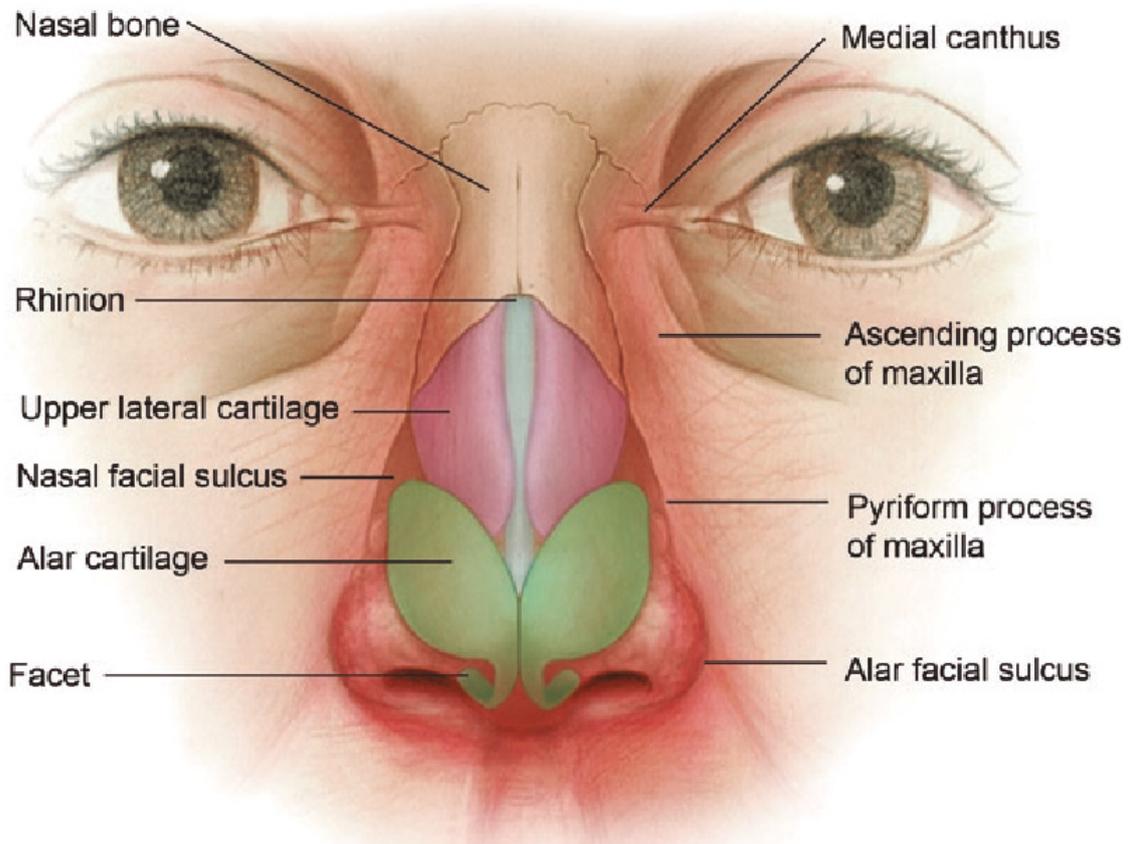


Figure 4 - Nasal anatomy physical appearance<sup>7</sup>.

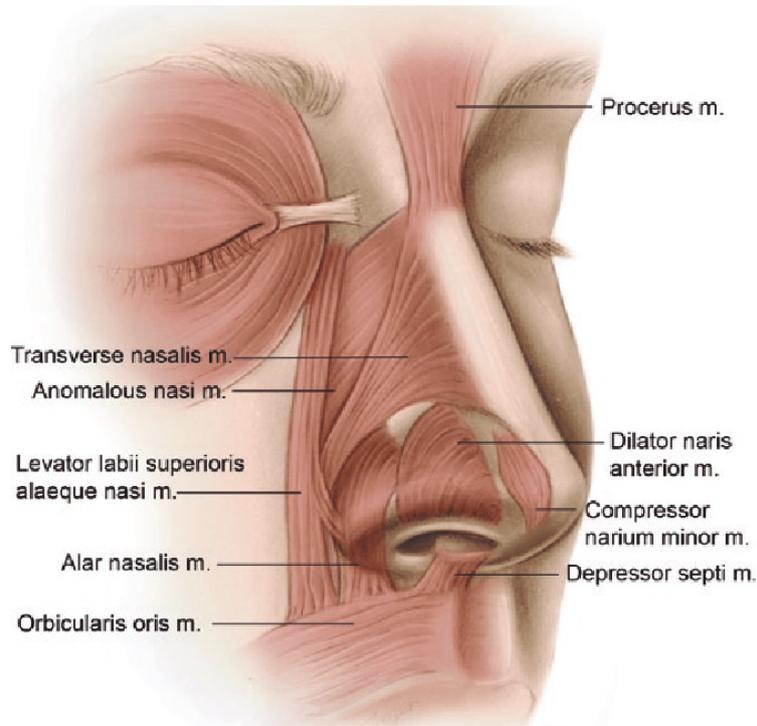


Figure 5 - Nasal anatomy muscle structure<sup>7</sup>.

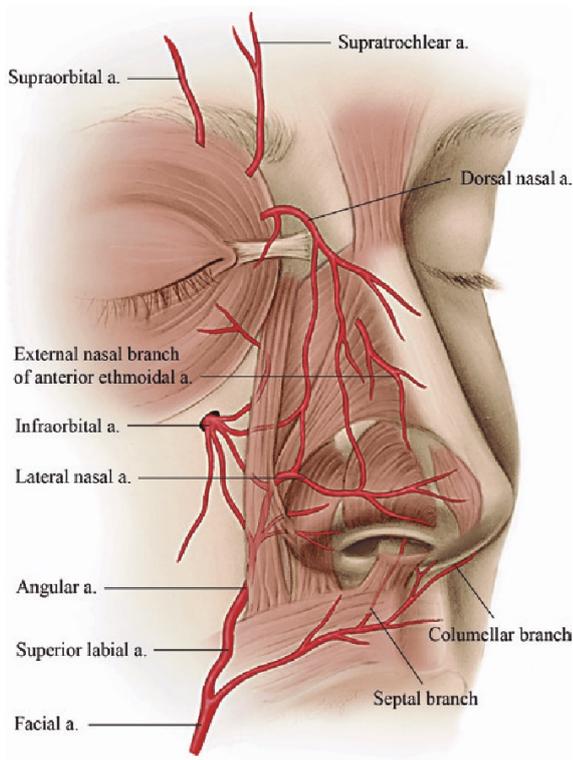


Figure 6 - Nasal anatomy vascular structure<sup>7</sup>.

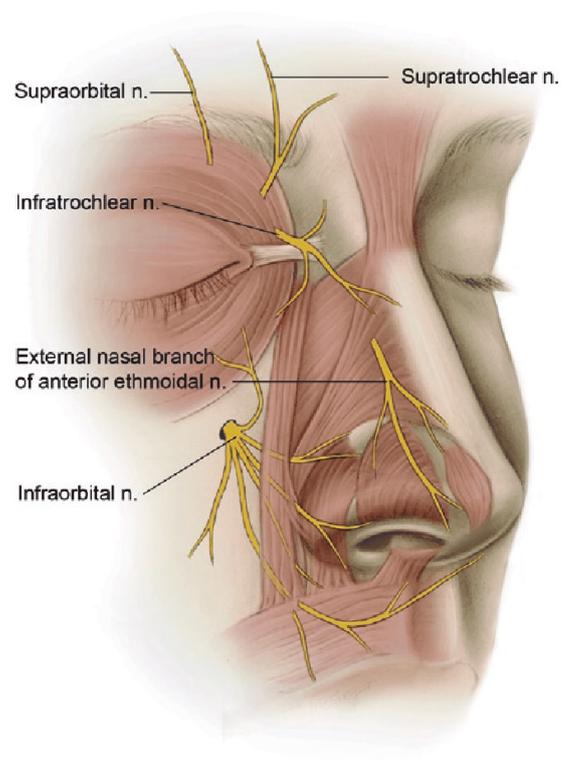


Figure 7 - Nasal anatomy nerve structure<sup>7</sup>.

**The Medical Approach With Botulinum Toxin and Dermal Filler**

**Correction of the nasal profile and elevation of the tip with Botulinum Toxin**

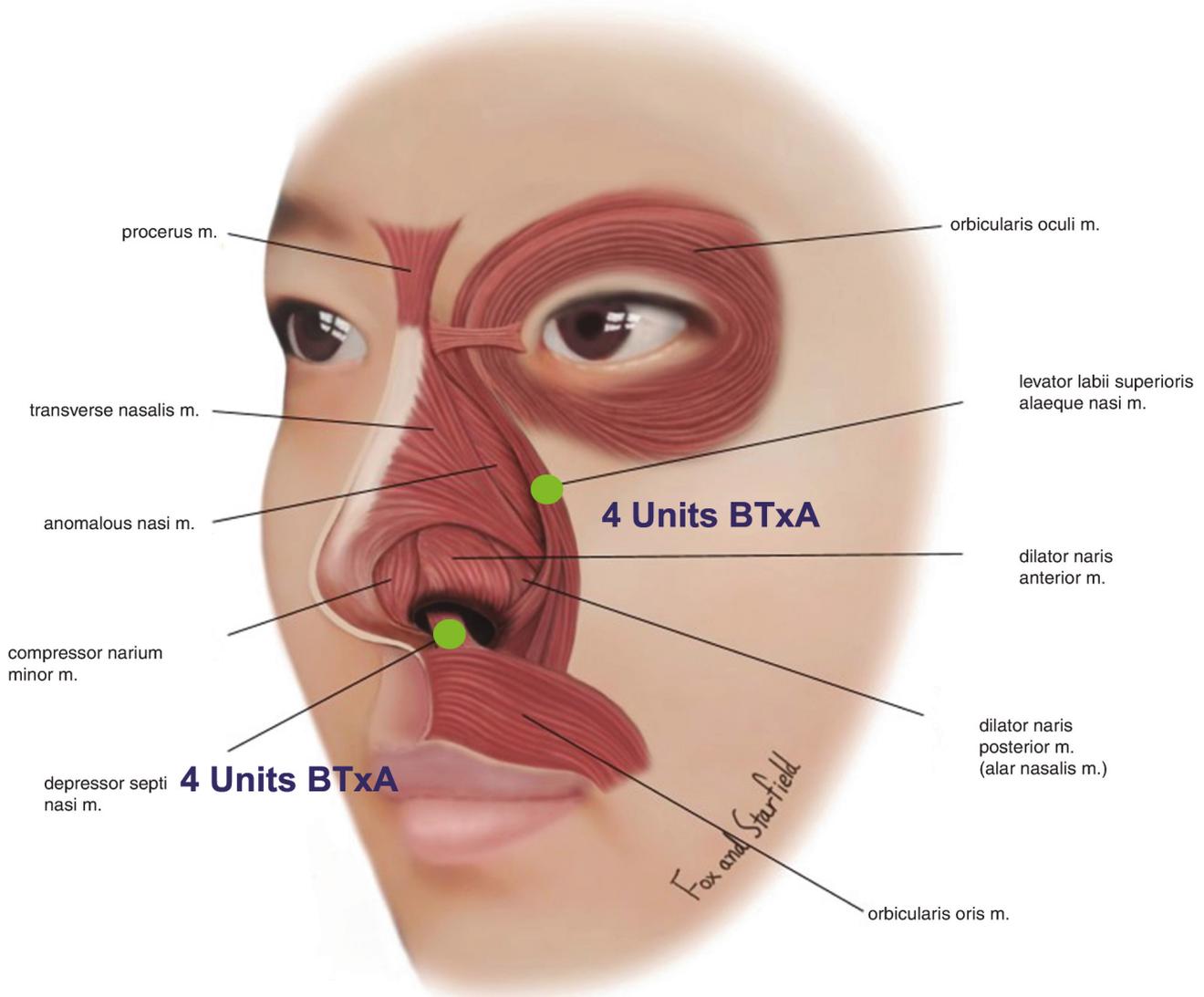
The muscles involved in the rotation of the nasal tip towards the maxillary bone, are the depressor septi nasi and levator labii alaeque nasi. Their treatment with BTxA is easy. The depressor septi nasi muscle can be injected along both its insertion above the columella and in the nasal spine. In this case, we use 4 Units Botulinum Toxin (Botox® Allergan).

If there is hypertonia of the levator labii alaeque nasi muscle with a clear lift of the nasal sides and rotation of

the tip downwards, we can give the injection of 4 Units Botulinum Toxin (Botox® Allergan) (*Figure 8*).

To appreciate the result, it is necessary to wait for 7 to 15 days. We always perform a retouch session after 15 days, both to evaluate the results and for possibly enhancing it with another injection of a few units.

It is important to be careful while treating the levator labii alaeque nasi muscle, since it is possible that the length of the upper lip can increase, getting ptosis. The risk is lower in young women with gummy smile, short lips (less than 1.5 cm) than in older people (over 60 years of age) with long lips. When the distance between the nasal spine and the apex of the Cupid’s arch is more than 1.8 cm, the treatment is strictly contraindicated.



*Figure 8 - The depressor septi nasi muscle inject 4 Units Botulinum Toxin. The levator labii alaeque nasi muscle (both side) inject 4 Units Botulinum Toxin (Botox® Allergan)®.*

**Correction of the nasal profile with monophasic hyaluronic acid dermal filler**

Normally use average cross-linked hyaluronic acids, and in particular: Aliaxin® EV.

The safety of materials is fundamental to obtain good results, and so the advice is to use well-known materials with a very high safety profile.

We always start with topical anaesthesia with an anaesthetic lotion for at least 30 min. Before the procedure, the midline and the most prominent spot of the nasal domes were marked. A Cannula guide needle was used through the nose tip to create the entry point (center of domes tip defining point) (Figure 9)<sup>9</sup>.

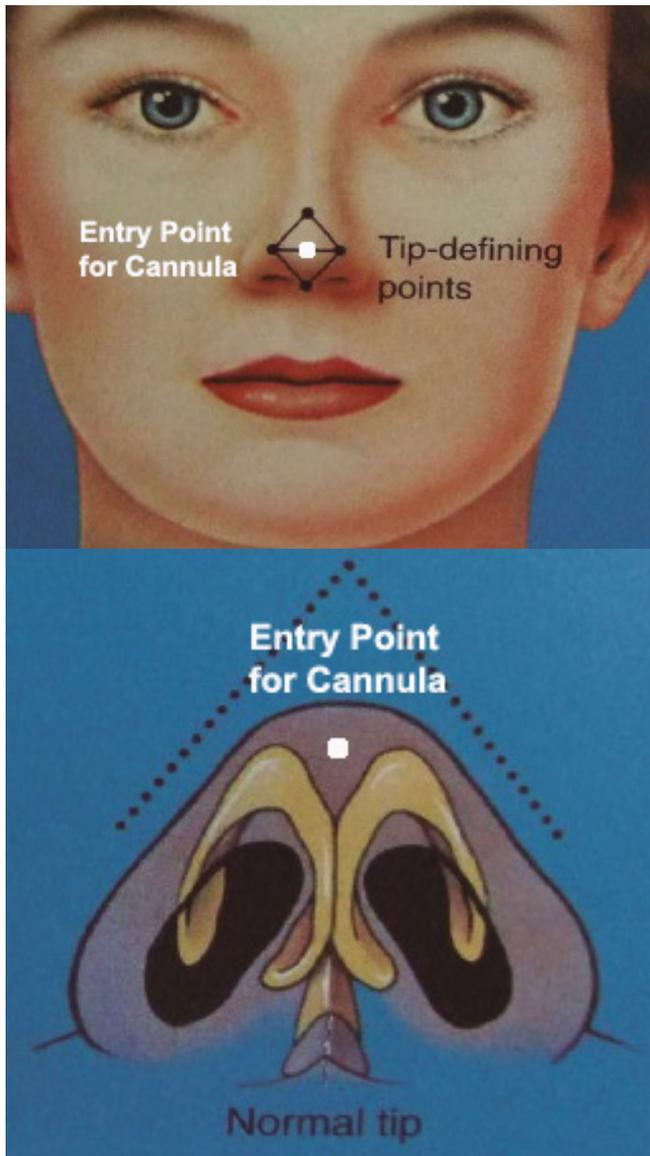


Figure 9 - Center of domes tip defining point for cannula inject the dermal filler<sup>9</sup>.

AliAxin® EV Dermal Filler: 1 ml or 2 ml Total  
 Injection Technique: Fan Technique  
 Injection Device: 23G x 50 mm Cannula  
 Target Area: Subcutaneous Layer  
 Attention: Avoid Columellar Artery and Lateral Nasal Artery

First Step: with the columella angle needs to be enlarged by moving the columella through the entry point and placing the Aliaxin® EV dermal filler into the nasal septal cartilage. The cannula is not removed at all during the procedure. Forward and backward maneuvering places the Aliaxin® EV dermal filler into the columella<sup>9</sup>.

Second Step: it is necessary to move along the nasal dorsum from the entrance point and to put the Aliaxin® EV dermal filler over the nasal periosteum and proceed to the glabella to lift the nasal bridge. The cannula is not removed at all during the procedure. Forward and backward maneuvering places the Aliaxin® EV dermal filler into the nasal dorsum<sup>9</sup>. The amount injected is variable depending on the imperfection to correct.

If the Nasolabial angle is also reduced (less than 90°), we proceed with an injection at the level of the nasal spine to open this angle that should be possibly more that 90°. This injection opens the Nasofrontal angle, so it is obvious that the best indication remains the one with a reduced angle, less than 115°. It is better not to exaggerate with the injection and reach the optimum result, We use fan technique and, again the best results are obtained step by step. References: (Figures 10 and 11)<sup>10</sup>

<http://www.healioswoundsolutions.com/dermatology/non-surgical-rhinoplasty-tips-tricks>.

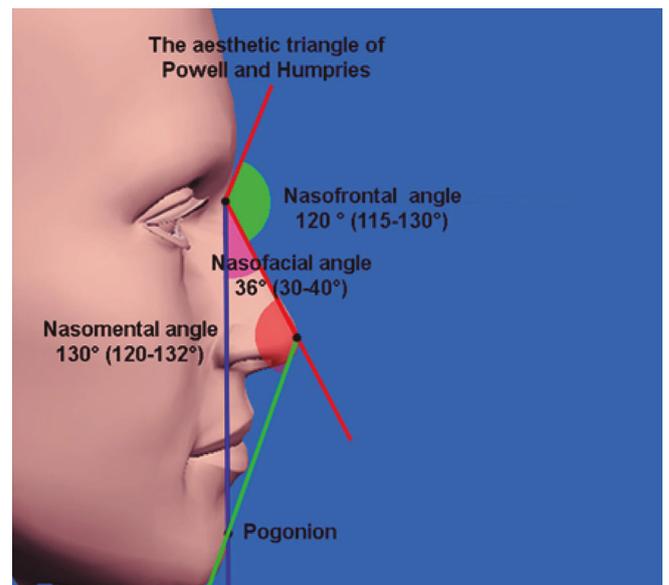


Figure 10 - The aesthetic triangle of Nose.

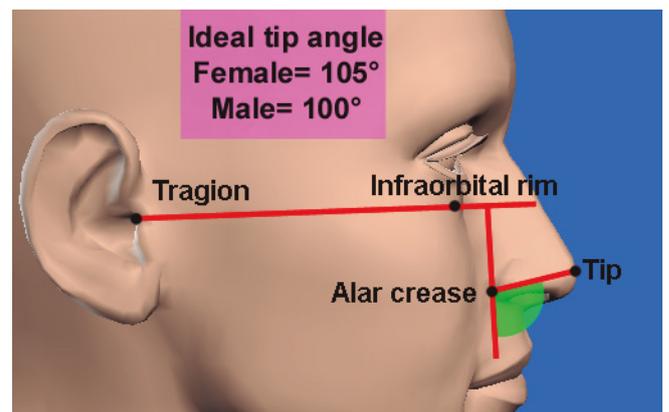


Figure 11 - The ideal Tip Angle of Nose for Female and Male.

**Results**

Between September 2017 and October 2018, 48 carefully selected patients, with an eight - to twelve - months follow-up. Patient ages ranged from 21 to 39 years.

The results were satisfactory in all but 42 of the 48 cases based on patient feedback (Table 1). Six patients found the results inadequate and those patients underwent normal rhinoplasty afterward.

The operation duration was under 30 minutes in all of the cases. Our longest follow-up was 12 months, during which we observed that the final outcome appeared after the third month and did not undergo any change afterward. No complication related to the Aliaxin® EV dermal filler and Botulinum Toxin (Botox® Allergan) (Figures 12, 13, 14, 15, 16, 17 and 18).

Satisfied Patients	Inadequate (Rhinoplasty Afterwards)	Total Patients
42	6	48

Table 1 - The results were satisfactory in all but 42 of the 48 cases based on patient feedback.

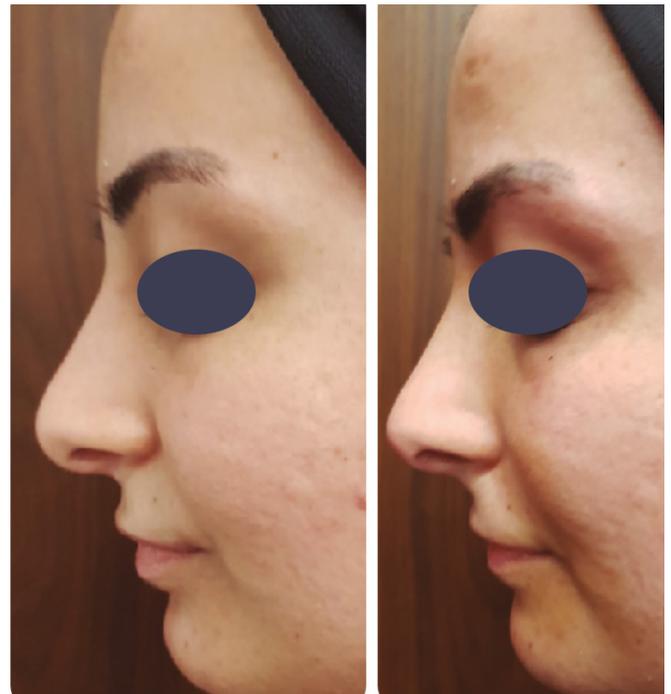


Figure 13 - Female patient 22 years old, Lateral view.

**Clinical Cases**

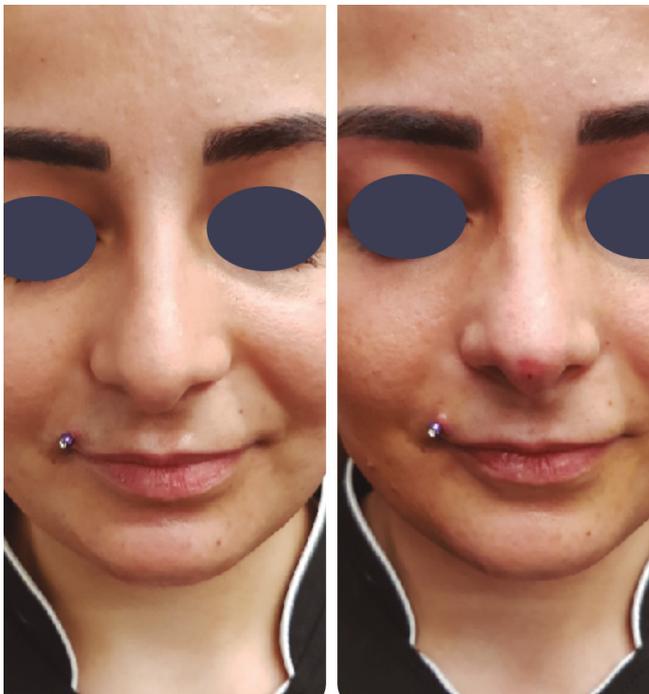


Figure 12 - Female patient 22 years old, front view. The depressor septi nasi muscle injected 4 Units Botulinum Toxin. The levator labii alaeque nasi muscle (both side) injected 4 Units Botulinum Toxin (Botox® Allergan).

AliAxin® EV Dermal Filler: 1 ml Total  
 Injection Technique: Fan Technique  
 Injection Device: 23G x 50 mm Cannula  
 Target Area: Subcutaneous Layer



Figure 14 - Female patient 22 years old, Lateral view.



**Figure 15** - Female patient 30 years old, front view. The depressor septi nasi muscle injected 4 Units Botulinum Toxin. The levator labii alaeque nasi muscle (both side) injected 4 Units Botulinum Toxin (Botox® Allergan).

AliAxin® EV Dermal Filler: 1.5 ml Total  
 Injection Technique: Fan Technique  
 Injection Device: 23G x 50 mm Cannula  
 Target Area: Subcutaneous Layer



**Figure 16** - Female patient 30 years old, front view. The depressor septi nasi muscle injected 4 Units Botulinum Toxin. The levator labii alaeque nasi muscle (both side) injected 4 Units Botulinum Toxin (Botox® Allergan).



**Figure 17** - Female patient 40 years old, Lateral view. The depressor septi nasi muscle injected 4 Units Botulinum Toxin. The levator labii alaeque nasi muscle (both side) injected 4 Units Botulinum Toxin (Botox® Allergan).

AliAxin® EV Dermal Filler: 2 ml Total  
 Injection Technique: Fan Technique  
 Injection Device: 23G x 50 mm Cannula  
 Target Area: Subcutaneous Layer



**Figure 18** - Female patient 40 years old, Lateral view.

## Discussion

Facial rejuvenation involves a spectrum of interventions, ranging from topical cosmetic products to surgical tissue manipulation. Botulinum toxin and Dermal filler injections fall somewhere in the middle of this spectrum. Used alone or in conjunction with other modalities, botulinum toxin and dermal filler products play an important role in achieving a youthful, aesthetically pleasing facial appearance. As demonstrated throughout this article, nonsurgical approaches to facial rejuvenation have become enormously popular among both patients and practitioners in recent years. Facial rejuvenation is comprised of a spectrum of interventions ranging from topical cosmetics to surgical restoration. Injectable products fall somewhere in the middle of the spectrum, offering dramatic aesthetic results for a moderate cost and require minimal posttreatment recovery time. The present article serves as a general conceptual outline regarding the use of injectable products to achieve facial rejuvenation. Certainly, every patient warrants treatment approaches tailored to their specific situation, and when questions arise, specific recommendations should be sought from one's more experienced colleagues<sup>11</sup>.

In the author's experience, injection of HA gel is a valuable tool for minimally invasive nasal reshaping. Experienced plastic surgeons can use HA injection as an alternative/complement to many indications for rhinoplasty because of its versatility.

In the author's opinion, this is infrequently considered by many surgeons. Benefits with HA injection include a quick and noninvasive method to change nasal features without need for general anesthesia. The procedure is associated with no/minimal downtime and with lower cost per treatment compared with rhinoplasty. Minor and sometimes time-consuming and risky secondary surgical procedures can sometimes be avoided with HA injection. In addition, HA gel injections are useful for preserving the height of the nose, which can be challenging with a surgical reshaping rhinoplasty. The nonpermanent nature of HA and reversibility with hyaluronidase are also favorable properties. Limitations include a relatively short duration of effect in some cases and thus need for retreatment. Although use of HA in aesthetic facial treatments is well established for treatment of wrinkles and folds, most patients are unaware of nasal indications. As a nonsurgical minimally invasive alternative to rhinoplasty, it would likely appeal to many patients who wish to modify the appearance of their nose. HA treatment may also serve as a door opener to surgery for patients who are reluctant to undergo rhinoplasty<sup>12</sup>.

Rhinoplasty is one of the most common cosmetic procedures performed by plastic surgeons. However, non-surgical nose jobs with a dermal filler are becoming increasingly popular in the world. Filler rhinoplasty has become an advantageous choice for patients that are afraid of surgery or general anesthesia. It is a fast, safe, simple, and effective method when compared with surgical rhinoplasty<sup>13</sup>.

On the other hand, HA filler rhinoplasty can be completely reversed with hyaluronidase when needed. Signorini et al. recommend an injection of 10 to 20 U hyaluronidase for areas less than 2.5 mm and two to four injections of 10 to 20 U hyaluronidase for areas greater than 2.5 mm<sup>14</sup>.

In some patients, the use of BOTOX® increases the distance between the columellar base and the vermilion border, creating the appearance of a fuller and voluminous lip. It can also correct the gingival smile. If the toxin diffuses laterally in the base of the columella, it can affect the levator labii superioris and the orbicularis oris, provoking an unaesthetic elongation of the superior lip, filtrum flattening, and labial sphincter incompetence when talking and drinking.

The use of high doses in the nasal tip can produce an exaggerated opening of the nostrils and a strong elevation of the tip, leaving an unattractive appearance in the frontal view. The clinical effect in this area usually lasts for a shorter time than other parts of the face. The first days after the injection, the patient can experience pain in the nasal tip<sup>15</sup>.

Nasal aesthetic problems are one of the few fields in which we are not able to offer our patients an acceptable, minimally invasive alternative. Furthermore, we have patients who are incapable of arranging their daily programs to accommodate the required recovery period or who do not wish to undergo such a significant operation because of their associated health problems or anxiety over an irreversible change in their facial characteristics.

The main objective of the technique we describe is to provide patients with a simple method for nose reshaping, which can be performed in the office under topical anesthesia in less than 30 minutes and is therefore with Botulinum toxin or Fillers in the patient's mind.

For selected patients, however, our method can be proposed as a simple, office-based procedure that can be performed under topical anesthesia in a matter of minutes with virtually no downtime<sup>9</sup>.

At the end of the session, we normally use a camphor cream to disinfect and reduce the oedema which is usually modest. The patient can immediately resume his or her daily activities. The main indication of these procedures is in all minor defects of appearance of the nose, particularly for the plunging tip.

A second important indication is the flat nose, frequently seen in black/brown and yellow skin people. In these cases it is also possible to achieve a reduction of enlarged nasal wings. Another useful indication is the correction of many post-surgical imperfections, which will be difficult to treat otherwise. Corrective surgery is not always so easy to perform.

The training of doctors, who want to engage with this easy technique that gives extraordinary results, is always necessary and essential. Rules, written long time ago and well documented, remain the best way to achieve good results and reduce to the minimum the incidence of side effects<sup>16</sup>.

## Adverse Effects

Potential major complications of injection rhinoplasty include infection, ischaemic necrosis from arterial embolism, pressure necrosis from overinjection of nasal tip and osteophyte from periosteal injection.

These risks may be reduced, with effective nasal analysis, meticulous injection technique, and a good understanding of nasal cartilaginous and vascular anatomy. Radix and

upper nasal third injections should be medially placed to avoid the dorsal and lateral nasal arteries.

Pre-injection palpation may aid identification, and aspiration before injection is mandatory. Intravascular filler injection can lead to arterial embolisation and subsequent skin necrosis or retinopathy.

Visual impairment following middle facial third filler injection mandates urgent ophthalmological review to exclude retinal embolism. Prompt anticoagulation and hyaluronidase injection may be a useful adjunct should complications arise<sup>17</sup>.

### Conclusion

Injection of HA gel is a valuable tool for plastic surgeons to consider for nasal reshaping. Small corrective refinements offered to patients may help achieve higher patient satisfaction and have in many cases had a surprisingly long duration of effect. The clinical experience gained with HA gel injections for nasal treatments over 15 years has also shown that HA gel can be used for correction of minor postrhinoplasty defects in appropriate patients<sup>12</sup>.

Minimally invasive procedures for nasal aesthetics described herein is one of very few minimally invasive alternatives for aesthetic nasal surgery. For selected patients, our method can be used as a simple, office-based procedure that can be performed under topical anesthesia without any significant morbidity, a very high patient satisfaction, and a recovery period of only two to three days. The reversibility of the result, at least for a short period of time, is also appealing to patients who are uncertain about the outcome of nasal surgery.

Injection rhinoplasty is not a substitution for surgical rhinoplasty. There are many indications where it will be insufficient to achieve the desired aesthetic outcome. Noses that are significantly overprojected, or overrotated, have a shallow radix, and tension noses are better suited to surgical correction. It is however a useful postoperative adjunct to surgery or in those patients contemplating rhinoplasty. The non-permanence and minimal morbidity of associated with degradable fillers is especially beneficial to those patients who seek cosmetic rhinoplasty but are discouraged by the risks and convalescence of surgery<sup>17</sup>.

### Conflicts of Interest

The author declare no conflict of interest.

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Review

# Novel concepts on the role of melatonin in aging and human female fertility

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The story of melatonin dates back to the beginning of the evolution process. In fact, this tiny molecule, known as a biogenic amine or indole (its molar mass is 232.278 g/Mol) appeared very early in living organisms and was then “conserved” throughout evolution; thus, the melatonin present in current living humans is identical to that present in cyanobacteria that have existed on Earth for billions of years. In 1958 it was officially discovered by Lerner and, since then, the interest in this substance has never faded and given rise to a huge amount of papers, trying to unravel the mystery of its meaning<sup>24</sup>. Initially thought to be produced by the pineal gland only, it is now known to be produced in many, and probably all, cells of the body. Its first-described actions linked melatonin to circadian (and circannual) rhythm regulation, however more recent studies validated the great number of functions of this molecule, which include actions at the molecular level that are able to modify the physiology of organs and organisms<sup>53</sup>. The initial idea that melatonin could be produced only in animals with the pineal gland, was lately modified since it was demonstrated that it could be synthesized in every living organism, including bacteria, unicellular organisms and plants. As far as melatonin signal transduction is concerned, the indole works via well-defined membrane receptors (MT1 and MT2)<sup>8</sup>, and also nuclear receptors (RZR/RORalpha)<sup>27</sup>. However, its actions far transcend these receptors, since binding sites have also been described in the cytosol and mitochondria. In addition, some of melatonin actions receptor-independent, due to its ability to permeate all barriers acting as a potent radical scavenger. The sense of the above is that probably no cell or function in plants and animal kingdoms escapes the impact of melatonin. In fact, it has a pivotal role in a bunch of different physiological processes, and it also may have a significant role in the etiology of many disorders<sup>2,37</sup>. Recently it has been postulated that the initial and primary action of melatonin in photosynthetic cyanobacteria, which appeared on Earth 3.5-3.2 billion years ago, was as an antioxidant. This is due to the fact that photosynthesis is associated with the generation of toxic free-radicals. The other functions came about much later in the evolution process<sup>26</sup>. Oxygen is an essential element for aerobic organisms because oxidative metabolism represents the main energy source. However, the partial reduction of O<sub>2</sub>, derived from the normal physiology of the organisms, results in Reactive Oxygen Species (ROS) formation. These molecules include two major groups: free radicals such as the superoxide anion and hydroxyl radical, and molecules such as hydrogen peroxide. As we know, oxidative stress occurs when an imbalance between pro-oxidant and anti-oxidant molecules takes place, due to an increase of ROS and of Reactive Nitrogen Species (RNS), and a decrease of the activity of the antioxidant defense mechanism. Melatonin has a major role in the antioxidant defense mechanism, in fact this multifunctional molecule, whose amphiphilic nature enables it to penetrate all morphophysiological barriers and all subcellular compartments, protects cellular membranes, the electron transport chain and mitochondria from oxidative injury<sup>47</sup>. As far as the latter are concerned, the measurement of

subcellular distribution of melatonin has shown that the concentration of the indole in the mitochondria greatly exceeds that in the blood. Melatonin presumably enters mitochondria through oligopeptide transporters (PEPT1 and PEPT2) and it seems to function as an apex antioxidant<sup>27</sup>. In addition to being taken up from the circulation, melatonin may be produced in the mitochondria as well, according to recent data, providing on-site additional protection as a powerful antioxidant<sup>18,38</sup>. Moreover, melatonin increases the permeability of membranes and acts as lipoxygenase inhibitor, helping in maintaining the efficiency of the local antioxidant system<sup>45</sup>. Therefore, melatonin's high concentrations and multiple actions as an antioxidant provide a potent antioxidant protection to these organelles which are commonly exposed to abundant free radicals. However, it is important to underline that the melatonin molecule, in order to display its own antioxidant activity, needs to be oxidized and cannot be reduced to its former state because it forms several stable products upon reacting with free radicals. For that reason, it is also called “terminal” or “suicidal” antioxidant and its concentration in physiological fluids decreases, as the scavenging process progresses. In addition, its metabolites also have antioxidant properties; thus, the protection exerted by melatonin against oxidative damage to cells and particularly to DNA is a continuous process<sup>14</sup>.

Health maintenance is strongly dependent by a proper internal organization which should be synchronized to the daily light/dark cycle of the external environment. This organization is provided by a complex mechanism that includes a master clock (located in the suprachiasmatic nucleus: SCN) that is able to demonstrate an autonomous circadian rhythm of a little more than 24 hours. At the cellular level, the macromolecular transcription-based oscillator is formed by the clock and the clock-controlled genes, which contribute to the rhythmic functions of the organism. However, as said, despite the fact that the cells have a circadian rhythm to ameliorate their ability to survive, it is essential that the rhythm is well synchronized to the external light/dark cycle, in order to align endogenous processes. This task is performed by melatonin (N-acetyl-5methoxytryptamine), the well-known tryptophan-derived indole of the pineal gland, that is produced and secreted according to a circadian rhythm that is connected to the light/dark cycle. At least four enzymes are involved in the synthesis of melatonin. Among them, arylalkylamine N-Acetyl-Transferase (NAT) is considered the rate-limiting enzyme in the regulation of melatonin biosynthesis. In fact, the NAT enzyme exhibits a robust daily rhythm, reaching concentrations that are 100 times higher during the dark phase, compared to daylight hours. Sympathetic nerve endings in the superior cervical ganglion release norepinephrine (NE) in accordance with a circadian rhythm, which is related to the light/dark cycle in the environment, increasing its secretion during the dark phase. NE induces melatonin biosynthesis from the pinealocyte and, in this view, tryptophan is first converted into 5-hydroxytryptophan by the enzyme tryptophan hydroxylase, which is then decarboxylated into serotonin. Serotonin is acetylated

into N-acetylserotonin (by NAT), which is finally O-methylated into melatonin by Hydroxyindole-O-Methyl-Transferase (HIOMT). Once released into the circulation, roughly 70% of melatonin is bound to albumin, and another 30% diffuses to the surrounding tissues. The main metabolic pathway of melatonin occurs in the liver where it is hydroxylated to form 6-hydroxymelatonin, then conjugated with sulphate or glucuronate and finally excreted in the urine. Daily light exposure that affects the retina, directly influences melatonin production, blunting its rhythm. This is due to a direct neural connection between the eye and the pineal gland, through which it receives information about light (or dark) conditions of the environment. In addition, melatonin travels throughout the body without limitations and, therefore, it is considered as a ubiquitous molecule. Finally, the chemical conservation of melatonin in all tested species makes it a candidate for a universal time messenger. Measures of melatonin are considered the best peripheral index of human circadian timing based on an internal 24-hours clock<sup>20</sup>. Plasma melatonin reflects the melatonin synthesized in the pineal gland, since no storage compartments for the pineal indole do exist. In humans, melatonin secretion increases soon after the onset of darkness, with a peak in the middle of the night (between 2:00 and 4:00) followed by a gradual decrease during the second half of the dark phase. Serum melatonin concentrations during nighttime also vary considerably according to age and among individuals, the highest amount being in the first years of life, falling immediately before puberty and then maintained throughout adulthood, followed by a progressive decrease during the aging process that leads to minimal levels with old age<sup>36</sup>.

According to its circadian rhythm, melatonin is mostly secreted during the night, with lowest plasma levels during the day. In this view, light is recognized as the most efficient stimulus to blunt melatonin secretion and, in fact, the exposure to light during the night determines chronodisruption that may have deleterious consequences on well-being and it is called light pollution (especially with short wavelength light in the 460-480nm spectrum: blue light). Unlike our ancestors, who lived in natural environments, the modern generations of people residing in developed Countries have self-selected their light-dark cycle. The most important differences between these two lifestyles, with respect to light exposure, are: a progressive general decrease in light intensity and regularity; a modification in light timing, with delayed and reduced exposure during the day and increased light at night; and finally, a shift in the light spectrum towards artificial light sources with a strong blue component. It has been demonstrated that light at night enriched with wavelength between 460-480nm can cause toxic effects to the eye inasmuch they can penetrate the cells and their organelles, inducing the generation of ROS in retinal epithelium mitochondria and even apoptosis. Thus, nocturnal lighting, and specifically that with a high short wavelength content (i.e. mobile phone and tablet screens), should be avoided also because blue light at night has a greater impact on retina cells, with respect to Sun-derived blue light during the day, due to retinal physiology changes between day and night<sup>41</sup>. Even though some applications

have been recently developed and released to reduce the negative effects of the use of electronic devices at night by adjusting the display color temperature according to the natural light/dark cycle (namely, reducing the blue light content during nighttime and increasing it during light hours), attention should be paid because the melatonin-inhibiting activity of light can be initiated at extremely low lux levels<sup>35</sup>. However, in order to maintain a good health of our circadian system, appropriate lighting levels during the day should also be recommended. Diurnal light should not be poor in short wavelength, since the maximum human circadian spectral sensitivity, in terms of melatonin suppression ability, occurs in this part of the spectrum<sup>29</sup>.

There are several situations in which individuals are particularly exposed to a chronodisruptive illumination, with significant effects on human health<sup>63</sup>. Among them, shift work is one of the most frequent in modern population. In fact, approximately 15 to 20% of workers in Europe and US participate in shift work, including work at night, and rises up to 30% when manufacturing, mining, transportation, health care, communications and hospitality sectors are considered. Epidemiological studies have demonstrated an increased risk of some cancers, namely breast, prostate, colorectal and endometrial cancers. The reason being the disruption of the circadian oscillator, with the consequence of melatonin circadian rhythm alteration, and the decrease of melatonin concentrations, due to light at night. In this view, a recent paper suggests that women with hereditary breast cancer predispositions should avoid using light at night<sup>28</sup>. Since the circadian oscillator is involved in the regulation of cellular division pathway, its disruption may be linked to disturbances of the cell cycle control, with the consequence of an acceleration of malignant growth. In addition, the concomitant decrease in melatonin concentrations may induce a decrease in its overall availability as antioxidant molecule, therefore increasing tumorigenesis and acceleration of malignant growth. This assumption is in line with the repeatedly observed increases in lipid peroxidation and decreases in glutathione peroxidase and superoxide dismutase in pinealectomized animals. In addition, the association of shift work with metabolic syndrome, cardiovascular diseases and type II diabetes has also been demonstrated<sup>41</sup>. In fact, altered food intake and obesity, eventually associated to high blood pressure, are shown to be induced, or aggravated by shift work which also acts causing sleep disturbances. Sleep deficit and interruption are also known to be associated to changes in eating behavior and obesity, however the relationship between the increased body mass index related to eating at night and the aspects of circadian rhythmicity in nutrient uptake is not simple to demonstrate. Recently, it has been shown that insulin resistance is promoted by circadian perturbation, under conditions of controlled sleep loss<sup>23</sup>. Importantly, the change in insulin sensitivity was associated with increases in inflammation markers in those subjects. One of the predictable consequences of the concomitant nocturnal shutoff of melatonin blood concentrations by light at night is, therefore, an increased oxidative damage to biomolecules. Moreover, circadian perturbations due to repeated phase shifts have also

been shown to increase oxidative damage, to reduce lifespan in animals and to increase the amount of 8-hydroxydeoxyguanosine (a product resulting from free radical damage to DNA) in the DNA of shift workers<sup>25</sup>. Another frequent situation that is capable to disrupt our internal circadian rhythm is the so-called jet-lag that depends on a rapid travel across multiple time zones, associated to the fact that the change is considered by the organism too drastic to allow the circadian system to adapt smoothly. In fact, melatonin rhythm is shifted and does not resemble the light/dark cycle of the external environment. Common symptoms are sleep impairment, anxiety, depressed mood, gastrointestinal complaints and dizziness. In recent years, the fact that many individuals (especially the younger ones) shift their sleep and activity times by several hours between workdays and the weekends gave rise to what is now called “social jet-lag”, which is comparable to jet-lag. In addition, as noted above, the internet, email, video games and television until late not only contribute to later bed times, but also induce a decrease of the physiological melatonin rise at nighttime, due to the exposure to modern LED screens which are known to blunt melatonin secretion because of their higher blue light content, with respect to white incandescent bulbs and compact fluorescent bulbs. As a result, adolescents experience a misalignment between biological and social rhythms which, added to sleep loss, results in fatigue, daytime sleepiness, behavioral problems and poor academic achievement, also opening the door to future problems as obesity, metabolic syndrome, diabetes, increased cardiovascular risk and infertility<sup>54</sup>. Epidemiological studies demonstrated that children sleep approximately 1.2 hours less than their counterparts of a century ago. In addition, the sleep of exposed adolescent becomes irregular, shortened and delayed in relation with later sleep onset and early waking time, which results in rhythm desynchronization. It is noteworthy that, according to several studies, among adolescents 47.8% of high school students in India, 25% in Japan, 22.8% in the US, 16.1% in China and 9.9% in Spain suffer from insomnia due to many causes, but probably as the result of disturbed habits and irregular lifestyles<sup>5</sup>. In this view, the expanding use of leisure technology seems to have substantially contributed to this sleep deficiency<sup>32</sup>. Therefore, the permanent social jet-lag resulting in clock misalignment and melatonin rhythm decrease and disruption experienced by a high number of adolescents should be considered as a matter of public health. In this view, very recent data obtained in preschool-age children indicate that this specific population is particular sensitive to evening light exposure, in terms of melatonin suppression, with the consequence of easily and rapidly disrupting the circadian rhythmicity<sup>1</sup>. On the other hand, melatonin treatment of these patients may have beneficial effects on sleep disturbances<sup>13</sup>.

It is well known that, inadequate timing, spectrum and intensity of retinal light input produced by nocturnal activities and sleep during daytime is a key factor to explain the incidence of chronodisruption, since it not only induces instability of the master internal pacemaker, but it also reduces melatonin synthesis. As noted above, this reduction, due to repeated light

exposure at nighttime (and the consequent decrease in melatonin production) may have an important role in the pathogenesis of a number of illnesses, such as breast cancer, cardiovascular problems, diabetes, cognitive dysfunctions, male and female reproductive problems, among others. As far as the latter is concerned, a strict link between melatonin and female reproduction has been already established. Since decades ago it has been demonstrated that melatonin is involved in the regulation of the reproductive system of both, males and females, and the most recent data of the literature confirms and ameliorates our knowledge in that field. In fact, melatonin is able to control the reproductive axis through a quite complex mechanism which includes the regulation of the secretion of Gonadotrophin-Releasing Hormone (GnRH), and of the activity of the gonadotrophin release-inhibitory hormone (GnIH), which has been recently shown to have a role in the mechanism that regulates male and female reproduction, acting directly on GnIH neurons through its receptors to induce (birds) or to inhibit (mammals) the expression and release of GnIH<sup>55</sup>. In this view, in mammals it is able to inhibit the activity of components of the Hypothalamic-Pituitary-Gonadal (HPG) axis, including a reduction of sexual behavior. The GnIH content of the brain is influenced by changes in day length and, on the other side, melatonin stimulates the release of GnIH from the hypothalamus of birds and mammals<sup>55</sup>. It is noteworthy that GnIH neurons express melatonin receptors, thus suggesting a strict regulatory connection between the pineal hormone and the GnIH action within the brain<sup>40</sup>. In addition, melatonin stimulates the secretion of progesterone from granulosa cells<sup>12</sup>. Another important melatonin target tissue is the pituitary gland and, in adult mammals, the dominant pituitary site of melatonin action is the Pars Tuberalis (PT), a thin layer of the anterior pituitary that surrounds the pituitary stalk and extends rostrally along the ventral surface of the median eminence. In fact, it is now believed that melatonin signal duration (long in winter and short in summer) drives the photoperiodic control over multiple aspects of neuroendocrine physiology, including the lactotrophic and reproductive axes, via the PT in adult mammals<sup>20</sup>. However, differently from seasonal breeders, human reproductive efficiency seems to be less dependent by seasonal day length variations, but this does not mean the melatonin has no effects on human reproductive organs. In fact, data from the last two decades indicates that the pineal indole has multiple effects directly at the level of the gonads and their adnexa in the human and other mammals<sup>36</sup>. In particular, both stable circadian rhythm and cyclic melatonin availability are critical for optimal ovarian physiology, gestation and parturition. In particular, as far as the latter is considered, light at night impedes regular uterine contractions in late term human pregnancy, reinforcing the importance of a correct melatonin rhythm in coordinating nocturnal myometrial contractions such that delivery of offspring more frequently occurs at night than during the day. On the other hand, women with higher nocturnal melatonin surges display more vigorous and coordinated uterine contractions at parturition<sup>36</sup>. In addition, chronodisruption during pregnancy has also

deleterious effects on the health of progeny, including metabolic, cardiovascular and cognitive dysfunctions. In this view, since light exposure after darkness onset at night disrupts the master circadian clock and suppresses elevated nocturnal melatonin levels, leading to pathophysiology and/or diseases, light at night should be avoided<sup>5</sup>. Melatonin is also produced in the peripheral female reproductive organs, including granulosa cells, the cumulus oophorus, and the oocyte. These cells, along with the blood, may contribute to follicular fluid melatonin content, which is higher than that in the blood by a three-fold factor<sup>6,39</sup>. The origin of melatonin in the follicular fluid was commonly thought to be the exclusive result of its uptake from the blood. However, there is a bunch of evidence indicating other ovarian cells (as indicated above) that are able to synthesize melatonin which could be appropriately released into the follicular fluid<sup>50</sup>. The fact that follicular fluid melatonin concentrations in humans are two times higher in large follicles just prior ovulation, with respect to those in smaller antral, immature follicles induces to speculate that because melatonin is such a potent antioxidant, the elevated concentrations in the follicular fluid at the time of ovulation could be physiologically advantageous. In this view, recent data demonstrates that there is a strong positive relationship between melatonin levels in the follicular fluid and the quality and quantity of oocytes and that melatonin concentrations in the follicular fluid can be considered as a marker of *in vitro* fertilization techniques and ovarian reserve<sup>52</sup>.

In addition, melatonin is able to reduce granulosa cells oxidative damage, in an animal mode<sup>17</sup>. The presence of the indole acting as a potent antioxidant molecule is so important because mammalian gametes and embryos are highly vulnerable to oxidative stress due to the presence of high lipid levels and the ovulatory processes have been linked to inflammation and high free radical production. Briefly, the inflammatory-like process identified in the ovary at the time of ovulation include augmented synthesis of prostaglandins and cytokines, increased activation of proteolytic enzymes and elevated capillary permeability, which are all associated to a higher production of damaging reactive oxygen species. In addition, it is known that macrophages, leucocytes and vascular endothelial cells residing in the vicinity of large follicles contribute to free radicals production at the time of follicle rupture<sup>57</sup>. Free radicals influence the balance between oxidation-reduction reactions, disturb the trans-bilayer-phospholipid symmetry of the plasma membrane and enhance lipid peroxidation. Therefore, in order to protect the ovum from oxidative damage during the ovulation process, the presence of melatonin would ensure that it escapes molecular damage, with the consequence of a healthy embryo and fetus. In this view, recent data indicates that melatonin is able to significantly improve the cytoplasmic maturation of bovine oocytes through the amelioration of organelles distribution, the increase of intracellular glutathione and ATP levels, the enhancement of antioxidant genes expression, and the modulation of the so-called fertilization-related events, all of which results in increased fertilization capacity and developmental ability<sup>61</sup>. Other Authors recently demonstrated that the

experimental damage of mouse oocytes induced by the administration of Bisphenol A (BPA, which is a known potent disruptor of mammalian oocytes quality) may be reversed by melatonin administration *in vivo*, increasing the fertilization rate by restoring the BPA-induced defects of fertilization proteins and events through the reduction of ROS levels and inhibition of apoptosis<sup>62</sup>. Additionally, a recent paper indicates that melatonin may be considered as a promising pharmacologic agent in the prevention of reproductive toxicity caused by endocrine-disrupting chemicals, as BPA<sup>60</sup>. Finally, melatonin has also been shown to modulate cell cytoskeleton, therefore ameliorating the physical cell resistance<sup>4</sup>. In this view, a recent paper demonstrated that melatonin could become an important tool in the management of ovarian and luteal diseases<sup>44</sup>.

Female fertility in humans is not constant throughout the reproductive period (from menarche to menopause), but it peaks at about 25 years and rapidly declines after 35 years. Nowadays, due to current cultural and social trends, many women around the world decide to delay their "pregnancy project". In fact, in recent decades maternal age has progressively increased from about 5% of women who became pregnant when older than 30 years old in 1975, to about 26% in 2010 and, therefore, many of them become exposed to infertility when they decide to conceive, due to the ovarian aging process<sup>15</sup>. More recent data obtained by an Indian study group confirmed the beneficial role of younger age in reproduction, emphasizing its importance especially when *in vitro* fertilization techniques are concerned<sup>11</sup>. From a biological point of view, the ovarian aging process is characterized by a decline in mitochondria function, in the integrity of the cytoskeleton and especially in telomere length (which is considered as a biomarker of cellular senescence and is highly sensitive to oxidative events), oocyte reserve as well as an obvious increase in the number of low-quality oocytes<sup>21</sup>.

In this view, mitochondria, which are the primary energy generators and are also the main source and target of free radicals, and mitochondrial oxidative stress in particular is considered a major factor in contributing to the aging process. Recent data of the literature clearly indicates that melatonin is able to significantly delay the fertility decline associated to reproductive aging by improving both the quality and the quantity of oocytes. In particular, melatonin is effective to either ameliorate mitochondria oxidative damage (preventing cardiolipin oxidation, which is known to be a key component of mitochondria membrane) and apoptosis, and to preserve optimal mitochondria function in the aging ovary, also contributing to maintain the length of the telomeres in aging mouse ovaries<sup>34,47</sup>. Therefore, acting on mitochondria seems to be an attractive perspective for health and lifespan, since rejuvenating aged mitochondria could be an interesting strategy to improve health<sup>51</sup>. In fact, a recent paper dealing with the aging process was able to demonstrate that melatonin may have beneficial effects at different levels of the anti-inflammatory network<sup>17</sup>. Since obesity in humans is associated to poor outcome across the reproductive spectrum, an obese animal model has been used to demonstrate that oral administration of melatonin is able to significantly reduce ROS generation and stimulate

sirtuins, to prevent chromosome abnormalities and meiotic defects in oocytes, with the result of healthier embryos<sup>16</sup>.

In addition, melatonin supplementation significantly improves oocytes mitochondria membrane potential, enhances their ATP production and induces a more uniform, granulated distribution of active mitochondria in maturing oocytes, which is an important index of oocyte quality. Of particular interest is the recent data that suggests a role for melatonin in protecting the endoplasmic reticulum (ER) of the cells from oxidation and damage and, therefore in preserving the reproductive organs from premature aging. For example, mice intraperitoneal lipopolysaccharide (LPS) injections during pregnancy retard intrauterine growth and induce fetal death. In addition, the placenta of pregnant mice displays an important ER stress, which is almost completely alleviated by previous melatonin administration, ultimately protecting fetuses<sup>59</sup>.

Poor oocyte quality is one of the major problems where Assisted Reproductive Techniques (ART) are concerned, even though the methodologies have greatly improved within the last two decades. This is generally believed to be the result of oxidative damage of the gamete. In this particular case, the presence of radical scavengers, as well as antioxidative enzymes which metabolize ROS to inactive products, is essential in protecting the ovum from oxidative damage. Since melatonin is considered to be either a direct free radical scavenger, and a stimulator of gene expression and activities of antioxidant enzymes, it seems reasonable to consider this indole to have a utility in improving the quality of human ova, both in normal conditions or to be used for ART. In fact, melatonin administration to infertile women who failed to become pregnant in previous ART trial, was able to induce a marked improvement of the fertilization rate, by reducing free radical damage and elevating the percent of oocytes that reached maturity<sup>48</sup>. In a more recent study, melatonin started before ART cycles and continued during pregnancy resulting in improved fertilization success (50% higher in melatonin treatment cycle, with respect to non-melatonin cycles), pregnancy rates and pregnancy outcomes<sup>56</sup>. In addition, recent data from a randomized, controlled, double blind study indicates that melatonin supplementation to PCOS patients undergoing in vitro fertilization for poor oocytes quality is able to ameliorate oocyte and embryo quality, acting synergistically with inositol, which is also known to have an important role in reproduction<sup>33</sup>. More recent data, obtained in a PCOS animal model, demonstrated that melatonin has the potential to induce oocyte nuclear maturation and guarantees the fertilization potential<sup>30</sup>. In this view, studies designed to evaluate the effects of melatonin administration to young female patients undergoing ART for reduced ovarian reserve are now on the way to be completed<sup>9</sup>. Again in the PCOS field, a very recent paper demonstrated that melatonin supplementation to PCOS women for a 12 week period resulted in a significant amelioration of hirsutism, total testosterone concentrations, while reducing oxidative stress and inflammation biomarkers<sup>19</sup>.

Once pregnancy is achieved, either naturally or through ART, maternal melatonin levels progressively increase until term, in order to transfer a high amount to the

fetus, due to its important role in brain formation and differentiation. In fact, serum melatonin concentrations reach a peak in the third trimester, with values that are more than the double of those in non-pregnant women, and rapidly decreasing to non-pregnant levels on the 2nd day postpartum. On the other hand, in pathological pregnancies, melatonin levels are lower after 32 weeks of gestations. Maternal melatonin provides the first circadian signal to the fetus and it is also important due to its well-known antioxidant protective effect<sup>10</sup>. Therefore, in presence of lower plasma melatonin levels or circadian rhythm disruption (i.e. light at night) during pregnancy an alteration of fetal brain programming may occur, with long-term effects. The pathophysiological basis of this outcome, besides cycle disruption, may also be the induction of high oxidative stress in compromised pregnancies (those with gestational diabetes mellitus, intrauterine growth retardation, preeclampsia, maternal undernutrition, maternal stress). In this view, suppression of maternal plasma melatonin circadian rhythm by continuous light exposure during the second half of gestation is able to induce several effects on fetal development as, among them, intrauterine growth retardation, altered a decreased corticosterone rhythm, altered brain development, in experimental animals. The shift work while pregnant is associated with a higher risk of prematurity and/or low for gestational age babies, spontaneous abortion<sup>58</sup>. Finally, recent data indicates that the administration of melatonin to women with pregnancy disorders has been established as an efficient therapeutic approach against fetal brain injuries<sup>42</sup>.

Antioxidant properties of melatonin may also be demonstrated in the placenta, where the indole is highly produced and protects against molecular damage and cellular dysfunction due to local oxidative stress. In fact, recent studies demonstrated that placenta owns the machinery to produce melatonin throughout pregnancy (from week 7 to term), with a maximal expression around the third trimester. In addition, the primary villous cytotrophoblast seems to be the main melatonin production site in the placenta and the in vitro melatonin treatment is able to induce an increase in human chorionic gonadotropin (hCG) secretion, probably mediated by MT1 and MT2 melatonin receptors, which contributes to the correct function of the placenta<sup>46</sup>.

In this view, since a precise balance between formation and degeneration of the syncytiotrophoblast syncytium, which is derived by the proliferating cytotrophoblasts, is necessary to prevent placental pathologies, melatonin may have a major influence in creating a stable villous cytotrophoblasts/syncytiotrophoblast homeostasis.

In fact, it is well known that the indole has a prominent regulatory effect on apoptosis, showing anti-apoptotic actions in normal cells, while being pro-apoptotic in cancerous cells and that these dual functions are believed to be utilized by the placenta cells to maintain the necessary balance between cyto- and syncytiotrophoblasts<sup>43</sup>. In a recent report, using a mid- to late-gestation animal model, the authors demonstrated that melatonin supplementation increased heifers umbilical arterial blood flow that was previously reduced by food restriction, suggesting that these specific responses on

umbilical arterial hemodynamics and fetal development may be partially mediated through vascular melatonin receptors<sup>22</sup>.

On the basis of the above considerations, it is easy to understand that melatonin can be used as a pharmacological agent, and in this view, the ability of exogenously administered melatonin to phase shift human circadian rhythms was firstly described in the mid '80s<sup>3</sup>. If given before the natural rise of endogenous melatonin, phase advances in sleep, core body temperature have been observed. On the other hand, if given in the early biological morning it can induce a phase delay in circadian timing. This ability of the indole to advance or delay clock timing depending on the biological time of administration has been used in the treatment of circadian rhythm disorders in which the sleep/wake cycle is desynchronized from the circadian timing system. In fact, appropriately timed melatonin (0.3-5mg p.o.) has been shown to alleviate symptoms of jet-lag (social jet-lag included) and night shift work. A great deal of effort has focused on trying to identify the optimal treatment regimen and, at the moment, it is widely accepted that melatonin, in order to synchronize the sleep/wake rhythm, should always be given at the same time, roughly at 22:00 and at a dosage that is dependent on the subject. In particular, due to the fact that melatonin night peak physiologically decreases with advancing age, the amount needed to obtain the effect is higher in the older population, with respect to younger people who need lower amounts. It is noteworthy that young and young/adults if treated with high amounts of melatonin may experience sleep disturbances like nightmares and hangover symptoms the next morning. Therefore, it seems that an amount of melatonin as low as 1-2mg per night is the most suitable to obtain the results without unwanted side effects in younger populations. Regarding the so called "social jet-lag" is concerned, which mainly involves the young and young/adult population, it is important to underline that it is able to induce a circadian rhythm disruption and a decrease of melatonin plasma concentrations, with the risk of reproductive, metabolic, cardiovascular and cancer problems. The administration of melatonin has been shown to ameliorate circadian rhythm synchronization, with the achievement, as far as reproduction is concerned, of higher fertility score. The increase of melatonin plasma concentration may also be achieved by endogenous stimulation. In fact, the overnight acupressure of the so-called wrist HT7 point resulted in an amelioration of sleep parameters in a number of insomniac patients<sup>31</sup>.

Despite the efficacy of exogenously administered melatonin as a synchronizing agent in circadian rhythm disorders, its use to exploit the potent antioxidant ability opens wide scenarios, especially as far as the reproductive system is concerned. In fact, it is quite evident that melatonin is an essential part of the mechanism that physiologically regulates the reproductive system, acting on every component and positively influencing them. In addition, not all melatonin is pineal-derived, since there is clear evidence that peripheral reproductive structures have the machinery to actively produce melatonin for their own use. The fact that mitochondria are able to produce

melatonin and that, therefore there is no cell that does not synthesize this important indole, added to the knowledge that melatonin's functions, both in terms of its receptor-mediated and receptor-independent actions, are ubiquitous, leads to suggest that the indole may be critical not only to maintain reproductive health, but health in general. Regular physiological rhythms are important to ensure a stable maternal environment which provides the fetus with a series of stimuli that facilitate prenatal perceptual learning and development of his/her internal and external environment. As a consequence, the occurrence of circadian rhythms that are already present during fetus life as regular repetitions of identical sequences (i.e. light/dark cycles), may help the fetus to develop the ability to adapt to change in an environment characterized by high regularity. In this view, melatonin, which plays a pivotal role in the regularity and synchronization of central and peripheral oscillators, allowing the development of harmonious internal functioning and adaptation of the internal milieu to the external environment, is generally considered to be the best peripheral biomarker of human circadian timing. For that reason, its use, alone or as adjuvant therapy, is highly recommended not only to preserve good health in general, but also in particular cases such as when female reproductive problems are concerned, in young and older females. As stated above, melatonin administration is able to induce a higher quality of oocytes and therefore to ameliorate ART outcomes, with the consequence of better embryos, fetuses and newborns<sup>49</sup>.

In conclusion, the story of melatonin as a therapeutic agent is far from being completed. On the contrary, it seems that the more the knowledge advances, the wider the clinical use of melatonin becomes, especially in the field of aging process and female reproduction where the main actors are the mother, the oocyte, the placenta and the embryo/fetus/newborn. All of them may benefit from the presence of adequate amounts of melatonin, in order to correct either circadian rhythm disruptions, and/or increased oxidative damage of very sensitive structures. In this view, the gold standard for the next years is to extend the use of melatonin in routine clinical practice, in the prevention and treatment of an increasing number of pathologies, considering that the utility of this essential biogenic amine is not only for reproductive well-being, but for the improved health of other tissues as well, and ensuring, in this view, that melatonin may be considered the most important endogenous compound that is able to display anti-aging activities, acting at different levels.

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# Oncological cosmetics: cosmetic selection criteria

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## Abstract

As a result of the increase in the number of cosmetic products aimed at oncological patients, and the lack of unified criteria of these products, there exists a need to determine and agree upon the characteristics required to add value to a cosmetic product for its use in oncology. The main aim of this work has been to define the criteria that a cosmetic product must complete for its use with oncological patients, with the aim of improving the health and quality of life of the patients.

The evaluation and development of these criteria has been carried out based on the bibliographic investigation compiled and the assessment, appraisal and safety evaluations from more than 500 materials amongst selected active ingredients and compounds in current cosmetics, obtaining guidelines of the composition of cosmetic products aimed at oncological patients.

It is believed that a cosmetic product for oncological patients must, as a minimum, preserve and not damage the skin, must be effective at relieving dryness, itching and sensitivity, must protect them from solar rays, and be safe, given the vulnerability of these patients.

## Keywords

Cutaneous toxicity, cosmetic ingredients safety, skin care in oncological patient, chemical composition cosmetic, oncology

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## Introduction

The oncological patient needs to adapt their cosmetic needs (hygiene, hydration, sun protection and make up) to their new situation. Their skin, mucous membranes and extremities (hair and nails), can be subject to changes and adverse effects either directly (radiotherapy, surgery), or indirectly (chemotherapy, directed treatments, immunotherapy, hormone therapy) produced by the treatments.

There exists evidence of the beneficial, and even therapeutic, benefits that cosmetics play in managing some of the adverse dermatological effects produced by antineoplastic therapies. A cosmetic product could be a very useful contributory therapeutic to: i) prepare and strengthen the skin before receiving a treatment, ii) reduce the skin toxicity produced by antineoplastic treatments (xerosis, itching, erythema, paronychia, fissures, rashes, hyperkeratosis, radiodermatitis, photosensitivity), iii) increase the oncology treatment adherence and iv) allow image recovery and improve the quality of life<sup>1,2,3</sup>. The cosmetic needs of an oncological patient start from before the beginning of the treatment: to prepare the skin, avoid irritation, sensitivity and allergenic substances. Later, during the treatment, it will be necessary to relieve the increased dryness, protect from the sun, and be covered by concealing make up. Finally, after treatment the skin will need regeneration.

When choosing a cosmetic product, the oncological patient must not only take into account personal care use but also those uses carried out during professional treatments, whether they are aesthetical, for illness or physiotherapy.

The main aim of this work is to define the criteria that a cosmetic product must complete for its use by oncological patients, identifying both the suggested ingredients and those that aren't recommended. So such we have focused our work on the following areas:

- Raise awareness of the importance of suitable oncological cosmetic products, both to medical professionals and to patients.
- Create a list of non-recommended ingredients that allow for avoidance protocols to be carried out, identifying inappropriate agents for oncological patients.
- Create a list of recommended ingredients, to maintain and improve skin qualities, and contribute to limit adverse dermatological effects caused by treatments. Assess the producers of these products
- Produce guides to therapeutic cosmetic products that improve the choice of ingredients for cosmetic products based on their different uses.

## Materials and Methods

The following bibliographic searches have been carried out:

- 1) A bibliographic review done through the following technical criteria: I): key words: cutaneous toxicity, cosmetic ingredients safety, skin care in oncological patient, chemical composition cosmetic, chemical composition cosmetic and oncology; II) thesaurus:

Pub med, Cochrane, Ovid; III) filters: reviews, full text articles, from the last 5 years.

- 2) Compilation of the information from cosmetic care before, during and after oncological treatment, cited in: i) specialist studies in oncology and aesthetics (Masters in Quality of Life and Medical Aesthetic Care edition I and II) and ii) in health institutions and scientific societies such as: ASCO (American Society of Clinical Oncology), SEOM (Spanish Society of Oncological Medicine), SEOR (Spanish Society of Oncological Radiotherapy), OMS (World Health Organisation), AEDV (Spanish Academy of Dermatology and Venereology), ADD (American Academy of Dermatology), SKF (Skin Cancer Foundation).
- 3) A review and adjustment of algorithms and criteria of cosmetic care for other at-risk group (immunocompromised, photosensitive, atopic, sensitive skin and altered dermal barrier patients).
- 4) A review of the profile of more than 500 ingredients: evaluation of their valuation, ratings and security analysed in the following databases: Scientific Committee on Consumer Products (SCCS) of the European Commission, Cosmetic Ingredient Review (CIR), Environmental Working Group (EWG), Cosing (database of cosmetic ingredients proposed by the European Commission). Note: SCCS and CIR emit judgements that direct legal changes in Europe and North America, respectively. The ingredients have been selected from current cosmetic products catalogued by their producers as "for oncological use and other ailments", such as sensitive and atopic skin and those suitable for children.

## Results

The three recommended cosmetic products with most consensus have been:

- Hydrating emulsions free of alcohol, perfumes and hypoallergenic
- pH neutral soaps
- high photoprotection

Of the ingredients analysed, there are approximately 40% with studies that show potentially harmful effects to oncological patients: irritation, allergic reactions, endocrine disruption, toxicity, photosensitivity, carcinogenicity, toxic effects on reproduction, mutagenic. This paper gives the conclusions taken from analysis of more than 100 ingredients selected according to their beneficial properties, prejudicial effects and/or frequency of appearance in current European cosmetic products (Table 1). The results of this complete work (analysis of 500 ingredients) will be published in the 1st edition of the Vademécum de Cosmética Oncológica, which will be presented at the 35<sup>th</sup> SEME Congress.

[CLICK HERE TO SEE TABLE 1](#)

*Table 1 - The most and least recommended ingredients have been represented in green and red respectively, catalogued according to the information obtained and adapted to the extra vulnerability of the oncological patient.*

## Discussion

The antineoplastic treatments reduce the skin's tolerance to cosmetic products, and this has been attributed to an imbalance in the corneal layer (modifications in the proliferation/maturity of the keratinocytes or keratinization mechanisms) which affects the functioning of the dermal barrier<sup>1,4,5</sup>. The use of appropriate cosmetic products can control the seriousness of the symptoms derived from this disruption. This still isn't an accepted definition of "barrier repair products". It is believed that use of cream moisturiser is an excellent therapy to counteract the disruptions in altered or diseased skin<sup>6</sup>.

The ingredients of a cosmetic product formulated to improve skin quality before, during and after oncological treatment must be: i) active ingredients, ii) auxiliary ingredients (water, moisturisers, emollients, firming oil, emulsifiers, gelling agents, surfactants and conservatives), iii) gentle and free of alcohol (colorants, perfumes, aromas and essential oils), iv) non-sensitising or hypoallergenic and v) non-blocking<sup>4,5,7</sup>.

According to European Parliament regulations regarding cosmetic products, it is possible to guarantee the safety of finished cosmetic products on the basis of the security of the knowledge relating to the ingredients that they contain.

Various active ingredients with antimicrobial, antioxidant, cleansing, deodorant, antiperspirant, emollient, hair conditioning, moisturising, keratolytic, hydrating, refreshing, skin conditioning, skin protecting, and calming cosmetic functions have been evaluated, such as those used in cosmetic products.

These ingredients can produce anti-inflammatory effects (alpha-bisabolol, vit. E, calendula, shea butter, etc.), antipruritic (dexpantenol, niacinamide, evening primrose oil), restoratives (rose hip oil, dexpantenol, alpha-bisabolol, vit. E, omega 3, omega 6, allantoin, Asiatic pennywort, marigold, niacinamide, vit F, growth drivers, etc.), and hydrators (Aloe Vera, hyaluronic acid, Urea, etc.) but in some products irritants, sensitizers, endocrinic disruptors, CMR (carcinogens, mutagenic and toxic for the reproduction) and nanomaterials have been found that could be counterproductive in the oncological patient.

Fragrances are the most common cause of allergies in cosmetic products, followed by conservatives and hair dyes; but all of the components must be considered potentially sensitizing<sup>8,9,10</sup>. The sensitivity to fragrances refers to those both of a synthetic and natural origin. According to the SCCS report on essential oils, it hasn't been demonstrated, in the scientific literature reviewed, that the compounds of natural fragrances are safer than synthetic ones<sup>11</sup>. Neither do they justify that it might be possible to establish the concentration in which it would be improbable that sensitivity is induced by the fragrance<sup>12</sup>.

A recent study on the presence and distribution of conservatives in more than a thousand products advised to prompt measures that lead to a restriction in the use of problem conservatives, and they consider that compiling cosmetic ingredients allows the creation

of "prohibited" product lists for sensitive people<sup>13</sup>.

The conservatives that are added to cosmetic products can cause the skin to become sensitized for the exposed user<sup>20</sup>. Cases of allergy to safe conservatives are increasingly frequent where they have made damaged skin more sensitive<sup>14</sup>. We must choose the least sensitizing conservatives with special attention to skin with an altered dermal barrier<sup>15</sup>.

It should be highlighted that the term natural is not synonymous with innocuous, and that the extracts of many plants are chemically complex<sup>16</sup>.

The cosmetic products are considered to be within the elements that can be exposed to humans and the endocrine disruptors<sup>17,18</sup>. These chemical substances are capable of altering the hormonal equilibrium and their exposition has been related to different endocrine disorders (obesity, diabetes, etc.), alterations in the reproductive functions and different types of cancer (breast, prostate, pancreas, brain)<sup>17,19,20,21,22</sup>.

The European Union REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) considers that chemicals of endocrine alteration are products of a similar risk as substances classed as "high concern" or SVHC (Substances of Very High Concern).

In 2018 the UN published a list prepared by the commission of The International Panel on Chemical Pollution (IPCP) of 45 chemical substances that have been identified as chemical substances of endocrine alteration (EDC) or potential EDC (until the end of July 2017). In it are found substances that could be present in cosmetics, such as: triclosan, parabens, phthalates, sun filters (benzophenone-3 (Oxybenzone), 4-Methylbenzylidene camphor (4-MBC), Ethylhexyl methylcinnamate (Octinoxate, OMC).

The intrinsic photoprotection mechanisms of the skin can become diminished and be insufficient to prevent photoaging and photo photocarcinogenesis<sup>23</sup>, making the skin of the oncological patient more vulnerable to sun exposure. The increased photosensitivity owing to treatments requires that the protection adequately covers the UVA spectrum, which causes the majority of the photosensitivity mechanisms, and the visible and infrared light because of the risk of hyperpigmentation<sup>24</sup>. Chemical solar filters can have photodegrading problems because of the action of sunlight. They can also cause the possibility of producing irritation and variable phototoxicity, presenting a higher risk of causing contact reactions compared with mineral screens<sup>23,25</sup>. For this reason there is a special risk of intolerance in sensitive skin after chemotherapy and/or radiotherapy.

EU legislation on the regulation of cosmetics establishes that they must be produced to the standards of best practice, which include an evaluation of safety for human health of the finished cosmetic product, before it is launched on the market. Even so, there are still concerns about the release and/or possible presence of trace contaminants during some manufacturing processes. For example, the CIR emphasized that the polymerization in benzene of carbomer and other acrylates must be avoided<sup>26</sup> and limits the impurities of heavy metals present in zinc salts. The SCCS recommends using amines for cosmetics that aren't easily nitrosated and/or give rise to non-carcinogenic nitrosamines. Some

publications have found that residues of ethylene oxide remain after the manufacture of some cosmetics<sup>18</sup>. Many compounds have received favourable reports from expert commissions on the grounds that they are manufactured in concentrations and dosages as “non-irritant”. The manufacturer must provide information if they are produced as non-irritant.

There are contradictory reports and studies<sup>27</sup> which has made it difficult to catalogue some ingredients.

Other ingredients have favourable reports when applied to healthy or intact skin or with sunburn, and these have been classed as apt. However because of their characteristics, such as size, it is not recommended to apply these on skin with an altered dermal barrier (nano titanium dioxide, nano zinc oxide), because of the risk of percutaneous absorption. The use of nano ZnO in cosmetic products must not imply a risk to the consumer in the absence of a substantial systemic exposure<sup>28</sup>.

### Conclusion

Oncological treatments can alter the functioning of the skin barrier, making it more permeable and sensitive to certain ingredients.

The terms of use of cosmetics can go further than hygiene purposes. Many of the ingredients of cosmetic products which are left on can accumulate with time and contribute to long term toxic effects which are hard to evaluate. The following composition recommendations are given for a cosmetic product for an oncological patient:

- It must not contain more ingredients than are strictly necessary. It must not contain substances (including impurities or traces) with the following properties: carcinogenic, mutagen, reproductively toxic properties (CMR), with disruptive endocrine activity, potentially allergic nor with criteria included in lists of substances subject to authorization. The legislation advises this for vulnerable people (children under three years old, the elderly, pregnant or breastfeeding women and people with altered immune responses).
- They must not contain substances under suspicion, which are included in credible lists such as VHCs (Very High Concern Chemicals) compiled by REACH. They must not contain substances which are being studied, as The Scientific Committee on Consumer Safety can take up to five years to emit judgements.
- Priority must be given to substances with reports compiled by expert commissions and which are supported in the scientific literature.
- Cosmetics destined for patients with skin diseases must have been clinically proved and have demonstrated a good tolerance profile.
- Studies are needed on absorption through skin with an altered dermal barrier.
- The production methodology must be of maximum security.

- Many new ingredients show highly allergenic properties with use and over time. For this reason, that the formulation of a cosmetic product aimed at altered skin should not only not contain potentially allergenic substances, but also contains those which have been proven to not be so.

- The evaluation of ingredients and the creation of lists must be open, reviewable, updateable and be subject to modifications according to judgements and evaluations published by expert commissions.

The oncological cosmetic criteria proposed by the authors of this work are the following:

#### 1 Low allergenicity

Free of sensitising substances allergenic, fragrances, perfumes, some sun screens, conservatives and colorants, etc.)

#### 2 Free of irritants

surfactants, acids, alcohols, formaldehydes, parabens, etc.)

#### 3 Free of endocrine disruptores

(resorcinol, 4-chloro methylphenol, DEP or diethyl phthalate, benzophenone 1, Oxybenzone, 4-Methylbenzylidene Camphor, Octinoxate, Methylparaben, Butylparaben, Ethylparaben, Propylparaben, Triclosan, Homosalate, etc)

#### 4 With recommended physical and chemical sunscreens

(Titanium Dioxide, Zinc Oxide, Drometrizole trisiloxane, etc.)

#### 5 With recommended active ingredients

(Alpha bisabolol, Vit. E, calendula, shea butter, Dexpanthenol, niacinamide, evening primrose oil, rosehip oil, Alpha- bisabolol, Vit. E, Omega 3, Omega 6, Allantoin, Asian pennywort, Calendula, Niacinamide, Vit F, Aloe Vera, hyaluronic acid, Urea, etc.)

#### 6 Adequate dosage form

(emulsions, lotions, pastes, ointments, cleansers without soap, etc.)

#### 7 Dermatologically tested

(good tolerance profile tested and clinically proven in patients with skin diseases and oncological patients)

#### 8 Free from potentially toxic substances and carcinogens

(octamethylcyclotetrasiloxane, nitrosamines, boric acid, phthalates, formaldehyde, etc.)

#### 9 Manufactured with a methodology of maximum safety

#### 10 Adapted to every patient and situation

### Conflict of interests

The authors declare that they have no conflict of interests.

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# Overview on biostimulation

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## Abstract

Skin biostimulation is an intradermal treatment indicated to prevent and/or reduce the effects of physiological and/or photoinduced skin aging and to restore firmness, turgor and elasticity to aged skin. The products used include: Platelet-Rich Plasma (PRP), Polydeoxyribonucleotide (PDRN), non-cross-linked hyaluronic acid (HA) (full-sized or fragmented) also in association with other active principles (amino acids, vitamins, antioxidants, etc.) as well as some weakly crosslinked hyaluronic acids.

Among these, HA, a polysaccharide (hyaluronan) chemically defined as a linear polysaccharide chain consisting of disaccharide units, plays an important role. It is classified among glycosaminoglycans (GAGs) and it binds to larger amounts of water than any other molecule of the ExtraCellular Matrix (ECM). The cellular effects obtained are mediated by specific membrane receptors including CD-44. The binding of CD-44 to HA appears to affect cellular adhesion, angiogenesis, cell proliferation, cell migration and cell-to-cell adhesion.

This article describes and analyzes the various factors that characterize skin biostimulation/biorevitalization and the characteristics of the wide range of available products, which allow to deliver a customized treatment based on patients' age, aging degree and area to be treated.

With regard to skin biostimulation, we will also discuss some recent – although preliminary – data that allow to define and discriminate bioregeneration as a process that physiologically promotes neocollagenesis, a feature of biostimulation, as well as elastogenesis when the injection area contains constituting amino acids such as L-alanine and L-valine that seem to regulate the biosynthesis of proteins of the extracellular matrix, especially elastin.

## Keywords

Biostimulation, bioregeneration, elastogenesis, hyaluronic acid (HA), neocollagenesis, polydeoxyribonucleotide (PDRN)

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### Facial skin biostimulation: state-of-the-art

Several studies have shown that skin can be stimulated by intradermal injection of biological substances that induce dermis revitalization, in order to prevent and reduce aging-related alterations<sup>1</sup>.

With regard to this, several products are used in Aesthetic Medicine to prevent and reduce skin aging. Among these products, Hyaluronic Acid (HA), which is often used alone or in combination with other substances, certainly plays a key role thanks to its natural stimulating and hydrating properties.

However, it is necessary to clarify the criteria underlying the choice of the different products currently available. Collagen is the main protein in human connective tissue accounting for 25% of the total mass and 6% of body weight.

The most stable molecular disposition and re-arrangement of collagen is proline-rich triple helix. Collagen structural unit is represented by *tropocollagen*, a protein with a molecular mass of approximately 285 kilodaltons made of three left-handed polypeptide chains that join to form a right-handed triple helix. For collagen Type I, there are usually two *alpha 1* chains and one *alpha 2* chain, while collagen Type III consists of three *alpha 1* chains<sup>2</sup>.

As previously said, our body produces a number of different collagens, the types involved in the biostimulation process being Type I and Type III<sup>3</sup>, the structural differences of which are responsible for their effects on the skin.

Besides structural differences, the two types of collagen have a strong expression of receptor sites to attack metalloproteases.

Although collagen Type I (fibrotic) is responsible for biological aging and characterizes mature age, it has been previously highlighted that its increase leads to aesthetic improvement<sup>2,3</sup>; while the presence of collagen Type III (reticular) characterizes young skin.

Although there is no recognized correlation between molecular structure, fibrotic collagen and reticular collagen, a review of the available data shows a different structural role of collagen Type III, characterized, within its  $\alpha 2$  chains, by the presence of an amino acid, cysteine, which is absent in other chains and appears to prevent the action of metalloproteases (MMPs) in the degradation of the collagen produced<sup>4,5,7</sup>.

Collagen Type I has been recognized to be a collagen of fibrotic nature; however, we should be noted that some studies have shown to argue this data, by recognizing that collagen Type I (fibrotic) is a fibrillar collagen with a different biochemical structure and does not necessarily result in biological aging<sup>6</sup>.

Zigrino P et al 2016 highlighted the role of fibroblasts in activating metalloproteases and regulating collagen homeostasis in adult skin. Fibroblasts produce several types of collagen based not only on patients' age but also on the stimulations they receive and the environment they live in (Extra Cellular Matrix-ECM). The difference in response is to be found both at receptor level, in stimulated fibroblasts, and at environmental level where procollagen is released. The reduced synthesis of collagen that characterizes adult age reflects two mechanisms: 1. Fibroblast aging, characterized by a reduction in their number; 2. Low mitotic activity,

resulting in reduced activation and production of collagen fibers, hyaluronic acid and elastin. Moreover, clinical studies show that the possible effect caused by mechanical stimulation of the skin and the alteration of cellular matrix would trigger the aging process with subsequent reduction in the production of collagen<sup>6,7</sup>.

The therapeutic use of hyaluronic acid in several clinical settings requires a few considerations on the possible interactions of this molecule with cells. This is certainly a new era for biological studies that will improve understanding of HA functions, properties and roles.

The crucial steps have been the following: 1. Identifying cellular receptors; 2. Identifying HA-synthetase; 3. Identifying intracellular HA.

It has been demonstrated that the different types of HA receptors, hyaladerins, are located on the cellular membranes, on the extracellular (pericellular) matrix and inside the cells. In particular, the membrane receptors are mainly located on the fibroblasts of isoform CD-44.

CD-44 receptors are stimulated by fragments of the dermal matrix, which suggests that this substance needs to be continuously formed, and by growth factors. CD-44 binding to HA appears to affect cellular adhesion, angiogenesis, cellular proliferation, cellular migration and cell-to-cell adhesion.

Moreover, it has been shown that the stimulus induced on CD44 receptors would induce the neoformation of reticular collagen.

Conversely, some authors highlight that the stimulation of CD39 and CD40 receptors leads to the neoformation of fibrotic collagen.

Fibrosis causes an increase in fibrotic Type I collagen that, by exerting a tensile action on the dermis, is responsible for the lifting effects on skin. This aesthetic improvement is actually caused by the implementation of an inflammatory process, responsible for the functional damage to tissue. The international literature confirms that inflammation includes the production of Transforming Growth Factor Beta 1, which in turn stimulates the production of collagen Type I and dermal fibrosis<sup>8</sup>.

In a recent review, Kavasi RM et al have highlighted some HA properties depending on its molecular weight. The analysis of the literature shows that the biostimulation treatment with free High Molecular Weight Hyaluronic Acid (HMWHA) is reported to stimulate the production of inflammatory cytokines. The subsequent fragmentation of hyaluronic acid is reported to produce fragments that in turn would be able to stimulate CD44 receptors with the consequent production of reticular collagen. This degradation process, resulting in the formation of fragments with increasingly low molecular weight, is reported to induce the production of inflammatory cytokines.

Therefore, the inflammatory reaction seems to be induced by any hyaluronic acids, regardless of whether their molecular weight is low or high. Hyaluronic acid has been shown to be produced by several cell populations located both in the dermal layer and in the epidermis, such as keratinocytes<sup>9</sup>. Although the authors have recognized that HA plays a key role in these processes and that the effects produced in the tissues

are determined by the size and concentration of HA, they concluded that the complexity of these processes makes it extremely necessary to further analyze these issues in additional studies<sup>9</sup>.

Quan T et al.<sup>10</sup> have highlighted that fibroblasts can maintain their functional activation capacity, but it is crucial to stimulate the extracellular matrix. Although it is commonly thought that non-crosslinked, non-reticulated hyaluronic acid (HA) in concentrations ranging from 0.8 to 2%, with molecular weight (MW) > 1.000.000 Dalton produces the lowest number of inflammatory cytokines, the fragments produced by degradation seem to maintain an inflammatory action. An important aspect to be highlighted concerns recommendations about contraindications to the biostimulation/biorevitalization treatment. A product that contains an association of more substances in the same mixture is more likely to produce adverse reactions, in particular if there is nickel which excludes its use by allergic patients. Biostimulation contraindications are: acute articular rheumatism; presence of previous non-resorbable fillers at the infiltration sites (this is a sufficient reason to avoid the use of other fillers); patients under anti-coagulant treatment (sodium warfarin); patients with cancer who receive chemo- and/or radiation therapy. For the treatment of patients with previous cancer diseases, who are not currently receiving any pharmacological treatment and/or radiation therapy, it is appropriate to reach a multidisciplinary case-by-case consensus.

### Classification of available hyaluronic acid-based products

Several preparations indicated for biostimulation/biorevitalization are available on the market with different characteristics in terms of molecular weight (MW), concentration and viscosity.

These products can contain:

- Free non-cross-linked HA;
- Weakly cross-linked or stabilized HA. These products require the activation of hyaluronidases and they undergo a prolonged degradation process;
- HA associated to glycerol. Glycerol has a protective action against HA and slows down the degradation process;
- HA associated to mannitol. Mannitol maintains homeostasis and allows HA to remain longer in the area where it has been injected;
- HA associated to amino acids (AAs). In these formulations, HA can be full-sized or fragmented;
- HA associated to amino acids and other substances.

One of the most important factors that plays a crucial role in the choice of a product for biostimulation treatment is HA concentration. The different HA concentrations can drive a targeted use based on the area to be treated and the desired result: prevention of skin aging and restitution of tissue integrity on mature skin.

The available concentrations are (Figure 1):

0.8% concentration: Indicated in particularly thin skin areas (periocular and perioral regions, neck region) and in prevention and maintenance treatments.

It is advisable to inject the product into the superficial

### Clinical practice recommendations

0.8% concentration: Indicated in particularly thin skin areas (periocular and perioral regions, neck region)

1.4-1.6% concentration: Indicated for the treatment of face, neck, décolleté, hands and body areas in prevention, restitution and maintenance treatments.

1.8-2% concentration: Indicated for the treatment of areas with thick skin, in restitution treatments and to obtain a temporary filler effect.

Figure 1 - Available HA concentrations and treatment indications.

and medium dermis, possibly with the picotage technique. The maintenance protocol includes monthly sessions.

1.4-1.6% concentration: Indicated for the treatment of face, neck, décolleté, hands and body areas in prevention, restitution and maintenance treatments. It is advisable to inject the product into the medium and deep dermis with linear technique and / or picotage technique. The protocol includes 3 fortnightly sessions, followed by monthly maintenance treatment.

1.8-2% concentration: Indicated for the treatment of areas with thick skin, in restitution treatments and to obtain a temporary filler effect. The protocol includes: 3 fortnightly sessions, followed by monthly maintenance treatment. It is advisable to inject the product directly into the deep dermis/superficial subcutaneous layer with linear technique and/or picotage technique.

2% concentration: Indicated only for face treatments in the restitution phase. It is advisable to inject the product into the medium and deep dermis / superficial subcutaneous layer with linear technique and / or picotage technique. The protocol includes 3 fortnightly sessions, followed by monthly sessions.

The association of stable hybrid cooperative complexes of high HA (1.100-1.400 KDa) and low molecular weight HA (80-100 KDa) is characterized by a concentration of 32 mg H-HA + 32 mg L-HA in 2ml (pre-filled syringes). The combined action of stable hybrid HA complexes allows to obtain a bioregeneration and remodeling action on the dermis. The treatment pattern includes two treatments at 1-month interval followed by a maintenance treatment at 2 months depending on the aging level<sup>11</sup>.

Among the hyaluronic acid-based products associated with amino acids there are several formulations.

A HA formulation with a concentration of 10 mg/ml, P.M. 200 - 400 Kd associated with lyophilized amino acids (glycine, l-proline, l-leucine, l-lysine) that are involved in the process of production of collagen is a Class 3 medical device and its administration is recommended in superficial and medium dermis of face, neck, décolleté. The protocol includes 4 fortnightly sessions followed by monthly sessions, possibly with administration of non-crosslinked HA between sessions. It is indicated in dehydrated skin with medium degree cutaneous relaxation.

In the formulations that include the association of fragmented HA with AA, HA is in micromolecular form (20-38 monomers) i.e. fragmented with MW from 1440 to 2736 kD; it is associated to amino acids (l-isoleucine, l-leucine, l-lysine hydrochloride, l-proline, l-valine,

l-glycine, l-serine, l-alanine). The protocol includes 4 weekly sessions, 2 fortnightly sessions, followed by monthly sessions. It is advisable to inject the product in the superficial and medium dermis of the face, neck, décolleté, back of hands. It is indicated in dehydrated skin with mild-degree skin relaxation.

Finally, a particular association of HA + AA with concentration of 10 mg/ml (3 ml) PM 200 Kd is an association with lyophilized amino acids (glycine, l-proline, l-leucine, l-lysine, l-alanine, l-valine), with L-alanine and l-valine being the amino acid constituents of elastin, making this product particularly active on the turnover of ExtraCellular Matrix proteins and in case of skin laxity of the face where the biostimulation treatment is indicated<sup>12</sup>.

The latter is a crucial element in the physiological promotion of neocollagenesis and elastogenesis through the migration of fibroblast in the injected area. A recent in vitro study conducted on human dermal fibroblasts showed the efficacy of extracellular matrix proteins, in particular elastin, on biosynthesis; it has been demonstrated that by changing the quality and quantity of amino acids in the mix, it is possible to increase the expression of elastin, at gene and protein level, while maintaining collagen stimulation<sup>12</sup>.

### Conclusions

In summary, several products are used to prevent or reduce damage caused by skin aging. Among these, the HA-based preparations play a crucial role. Available data show that HA is often used either free or in combination with other substances, thanks to its natural stimulating and hydrating properties. There are several HA-based preparations available for biostimulation that differ in terms of molecular weight, concentration and viscosity. Although the available scientific evidence supports an increasingly important role of HA in skin biostimulation, recent findings allow to define bioregeneration as a process that physiologically promotes neocollagenesis and elastogenesis through the migration of fibroblast chemotaxis in the injected area. With regard to this, the involved factor would be the presence, in the injected area, of constituting amino acids such as L-alanine and L-valine that seem to regulate the biosynthesis of proteins of the extracellular matrix, especially elastin. A final consideration, not to be forgotten, is that the wide range of available products allows to personalize the treatment based on the patients' age and degree of skin aging.

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# 22<sup>ND</sup>

## WORLD CONGRESS OF AESTHETIC MEDICINE



This year International Congress of Aesthetic Medicine and Anti-Aging will take place in Warsaw 26–29 September 2019. It is the largest meeting of physicians and key industry experts in aesthetic medicine and anti-aging. Held annually, this now four day event provides an excellent opportunity to meet distinguished scientists and practitioners from around the world who are working to develop this branch of medicine.

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2019

**26 - 27 April - Brussels (Belgium)**  
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**Belgian Society of Aesthetic Medicine**  
Radisson Blu Royal Hotel  
President: J. Hebrant  
Web: [sbmebveg.be/en](http://sbmebveg.be/en)

**17 - 19 May - Rome (Italy)**  
**40th SIME Congress**  
**Italian Society of Aesthetic Medicine**  
Rome Cavalieri Congress Center  
President: E. Bartoletti  
E-mail: [congresso@lamedicinaestetica.it](mailto:congresso@lamedicinaestetica.it)  
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**14 - 15 June - Basel (switzerland)**  
**16th Congress of the Swiss Society of Aesthetic Medicine**  
**7th Congress of the Swiss Society of Aesthetic Surgery**  
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**15 - 16 June - Opatija (Croatia)**  
**2nd Congress of the Croatian Society of Aesthetic Medicine (HUEM)**  
Hotel Milenij Opatija  
President: E. Bunar  
Web: [huem.eu/congress2019](http://huem.eu/congress2019)

**13 - 14 September - Paris (France)**  
**40th National Congress SFME**  
**French Society of Aesthetic Medicine**  
Palais des Congrès de Paris  
President: J.J. Legrand  
Email: [info@sfme.info](mailto:info@sfme.info)  
Web: [www.sfme.info](http://www.sfme.info)

**26 - 29 September - Warsaw (Poland)**  
**22nd World Congress of Aesthetic Medicine**  
**Organized by: Polish Society of Aesthetic and Anti-Aging Medicine**  
Hilton Warsaw Hotel and Convention Center  
President: A. Ignaciuk  
Web: [www.icaam.pl](http://www.icaam.pl)

**4 - 6 October - Lima (Peru)**  
**1st Scientific Congress of Aesthetic and Anti-Aging Medicine**  
**Scientific Association of Aesthetic Medicine (ASOCIME)**  
San Isidro District, Lima  
President: I. Ogata Matayoshi  
Email: [info@asocime.com.pe](mailto:info@asocime.com.pe)  
Web: [www.asocime.com.pe](http://www.asocime.com.pe)

**25 - 26 October - Toronto (Canada)**  
**CAAM 16th Annual Conference**  
**Canadian Association of Aesthetic Medicine**  
Hilton Toronto / Markham Suites Conference Centre  
President: J. Carroll  
Web: [www.caam.ca](http://www.caam.ca)

**31 October - 2 November - Cascais, Lisbon (Portugal)**  
**4th National Congress of Aesthetic Medicine**  
**Portuguese Society of Aesthetic and Anti-Aging Medicine**  
Hotel de Oitavos  
President: J. P. Vale  
Web: [www.spme.pt](http://www.spme.pt)

**6 - 8 November - La Paz (Bolivia)**  
**2nd Bolivian Congress of Aesthetic Medicine**  
**Bolivian Association of Aesthetic Medicine (ASOBOME)**  
Hotel Atix La Paz  
President: D. Hurtado Terrazas  
[Facebook page](#)

**8 - 10 November - Long Beach California (USA)**  
**16th AAAM Congress**  
**American Academy of Aesthetic Medicine - AAAM**  
President: M. Delune  
Email: [delegate@aaamed.org](mailto:delegate@aaamed.org)  
Web: [www.aaamed.org](http://www.aaamed.org)

**28 November - 1 December - Belek (Turkey)**  
**3rd National Medical Aesthetic Congress**  
**Turkish Association of Medical Aesthetic Medicine**  
Kaya Palazzo Golf Resort Hotel, Belek - Antalya  
President: H. Subasi  
Email: [mestder@opteamist.com](mailto:mestder@opteamist.com)  
Web: [mestder2019.org](http://mestder2019.org)

2020

**2 - 3 May - New Delhi (India)**  
**International Congress of Indian Society of Aesthetic Medicine**  
President: A. Rana

**15 - 17 October - Quito (Ecuador)**  
**XIII Pan American Congress of Aesthetic Medicine - UIME**  
Organised by: Ecuatorian Society of Aesthetic Medicine  
President: V. Tinoco Kirby  
Email: [medesticapanam2020@gmail.com](mailto:medesticapanam2020@gmail.com)  
Web: [www.seem.com.ec](http://www.seem.com.ec)



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