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Skin Biostimulation With Biomimetic Peptides: Our Preliminary Clinical Experience

Gustavo González Zaldívar [1*], Yong Ji Chung[2], Gustavo Jiménez Muñoz Ledo[3], Enrique Obregón Moreno[4]

[1, 3]*Plastic and reconstructive surgeon, México.*

[2]*Molecular biologist, South Korea.*

[4]*General surgery resident, Mexico.*

Abstract

Introduction and Objective: Anti-aging treatments are often requested in our medical practice. According to statistics from the American Society of Plastic and Reconstructive Surgery, one of the treatment options is the use of fillers, which are second only to minimally invasive procedures. The aim of the study is to present the results of the application of biomimetic peptides and to demonstrate that this therapeutic option is useful and effective in the treatment of non-surgical facial and neck rejuvenation.

Material and Method: Through the subcutaneous application of biomimetic peptides in 10 patients, photographic documentation (pre-application and post-application of two sessions), and satisfaction survey of Helmy measurement (Annex 1 and 2), in addition, through our experience in the application of fillers we evaluate the results comparatively.

Results: After the satisfaction analysis, clinical and photographic results, based on our experience in the application of fillers; it was observed that after the application of peptides. In 100% of the patients, they presented an improvement of the cutaneous quality, in addition, in relation to hydration, the tension of the facial skin and neck as well as decrease of expression marks

Conclusion: In our experience, the application of biomimetic peptides included in a noncross-linked sodium hyaluronate as a slow and sustained release vehicle provides an adequate skin redensification option. In in vivo experiments, it manages to restore the collagen and elastin fibers of the extracellular matrix; achieving aesthetic results in our preliminary experience.

Introduction

It is very common that in the daily practice of the plastic surgeon, fast, reliable, and safe treatments are requested, moreover, without post-surgical recovery time, which is why the numbers of non-surgical procedures with aesthetic purposes have increased exponentially in recent years. With very little time to reach the health and wellness market, the anti-aging industry offers high-tech alternatives that include medicine, food, cosmetics, and health programs with the ultimate goal of prevention, treatment, improvement of quality of life, and coupled with the development of genomic medicine. According to a BBC (British Broadcasting Corporation) investigation, the global anti-aging industry is expected to grow to $420 billion by 2030 [1].

According to the ASPS (American Society of Plastic Surgeons), minimally invasive procedures have increased since 2000. Minimally Invasive has increased to 14. 2 million (this segment includes so-called fillers. According to IMCAS (International Master Course on Aging Science), in 2014 the market for injectables was 150 million Euros in 2012, with a growth of 220 million Euros in 2018 [1, 2].

One of the treatment options is the use of fillers, usually hyaluronic acid. A variation to these treatments is a new option based on non-reticulated hyaluronates as peptide complex vehicles that experimentally produce direct stimulation on the fibroblast with an increase in the proliferation of collagen and elastin fibers (1-2-3). In addition, without much clinical evidence of its usefulness and effect, since it is a relatively new product on the market.

The Extracellular Matrix (ECM) is the set of extracellular materials that form part of a tissue. It is a means of physiological integration about complex biochemical nature, in which the cells are immersed. The ECM is considered a component that fulfills several functions, such as cell survival, cell development, intracellular, immunological interactions, and changing the conception in which it was only considered as part of the connective tissue. Furthermore, the ECM is formed by Fibrous Proteins (Collagen and Elastin), Proteoglycans (polypeptide chain, glycosaminoglycans; the most important, hyaluronic acid), and Structural Glycoproteins (fibronectin and laminin) [3-5].

This three-dimensional network made up of 25% collagen and elastin fibers is a biophysical filter for cell protection, nutrition, and innervation, on the other hand, the ground for immune response, angiogenesis, fibrosis, and tissue regeneration. It represents the means of transmitting mechanical forces to the basement membrane, which through the integrins supports the tensional integrity system and activates the cellular epigenetic mechanisms [4, 5].

The alteration of the ECM means the loss of its function as an effective filter, nutrition, elimination, cellular denervation, loss of regeneration, and healing capacity. Consequently, aging and tissue degeneration are the alteration of mechanical transmission as well as the loss of the substrate for a correct immune response to the infectious, tumour, and toxic agents [3].

***Address for Correspondence:** Dr Gustavo Gonzalez Zaldivar M.D. PhD, Plastic and Reconstructive surgeon, Private practice Sanatorio Durango, Ciudad de Mexico, Mexico. Mail: drgglez@yahoo.com

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The aging process affects all the layers and structures of the extra-cellular matrix, affecting its functionality. One repair option is growth factors and cytokines, which assemble with specific fibroblast and keratinocyte receptors stimulating their effect and regulating gene transcription, however, they have the disadvantage of high cost and biochemical instability [8].

In 2002, Dr. Chung managed to isolate in synthetic form the so-called biomimetic peptides. They are oligopeptides of 10 to 15 amino acids that have a clinical effect similar to the growth factors that occur in the phenomenon of repair and healing and have a mimetic effect identical to parenteral molecules [7 -9].

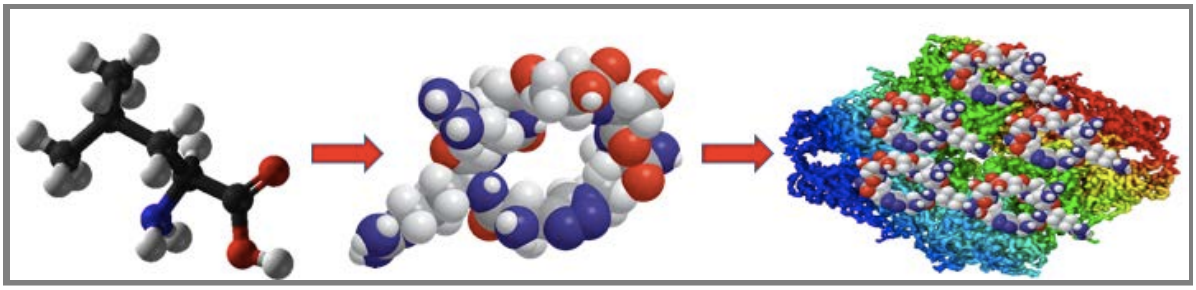


Figure 1: Structural difference between Amino Acid, Peptide and Protein.

Some peptides have specific actions as regulators of fibroblasts and keratinocytes, with a determining role in the components of the extracellular matrix altered in the aging process [10]. Other peptides are specific for hair growth, fat reduction as well as in inflammatory processes, opening the treatment options in a wide range of clinical applications, having the histopathological and clinical proofs of their effectiveness in a short term [8].

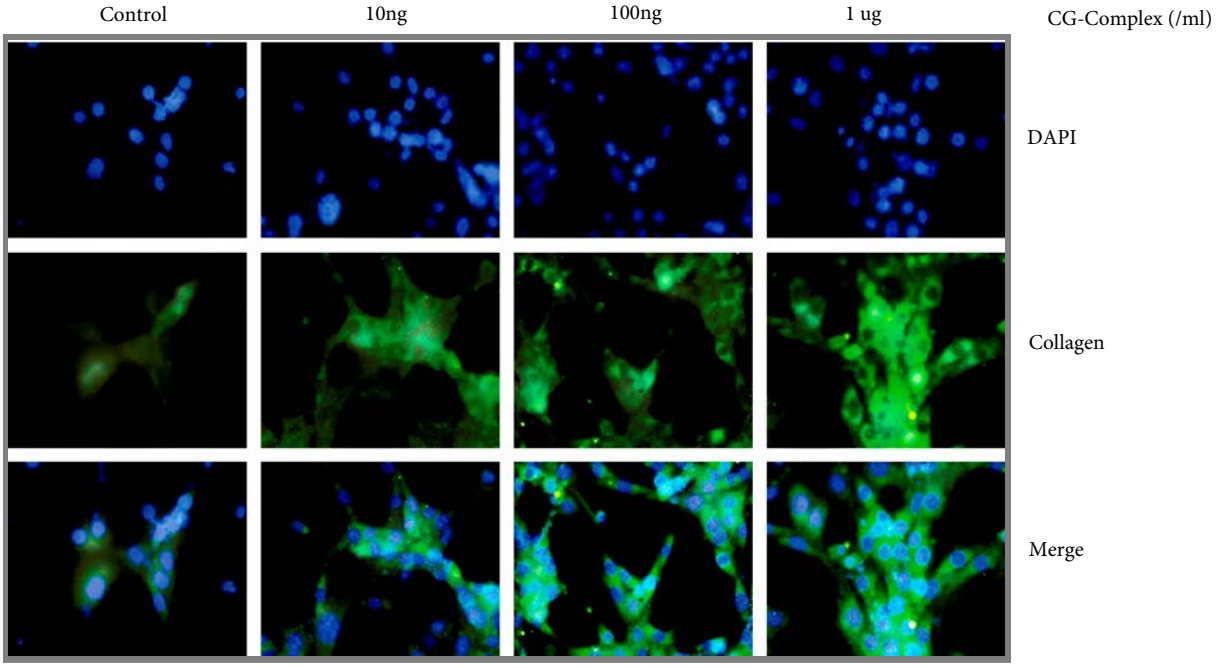


Figure 2: Pre-application and 48-hour post-application of biomimetic peptides. Showing effect on fibroblast and increase 169% of collagen fibers.

A corrective agent with biomimetic peptides developed in 2002 for skin hydration [9]. It was the basis for development in skin aging pathology. In 2014, the bioregenerative action of biomimetic peptides in non-reticulated sodium hyaluronate as a vehicle was demonstrated, giving rise to a new treatment option in skin redensification with new collagen fibers, in a period of 2 to 3 sessions with a space of 15 days between each one. This corrective agent contains 5 specific biomimetic oligopeptides (Oligopeptide 24, Decapeptide 36, Octapeptide 11, Oligopeptide 34, and Oligopeptide 92). The biocompatible vehicle of noncross-linked sodium hyaluronate that slowly degrades in the space of 2 weeks [10-12, 16], it is continuously and progressively releasing these biomimetic peptides directly onto the fibroblast.

Objective

The objective of the study is to present the results of the application of biomimetic peptides and to demonstrate that this therapeutic option is useful and effective in the treatment of non-surgical facial and neck rejuvenation; where classically fillers based on hyaluronic acid, hydroxyapatite, or polycaprolactone are applied to mention a few. However, at present, a variation on these treatments is a non-reticulated hyaluronate as a vehicle for peptide complexes produced within a laboratory. These products produce direct stimulation on the fibroblast with an increase in the proliferation of collagen and elastin fibers [1-3].

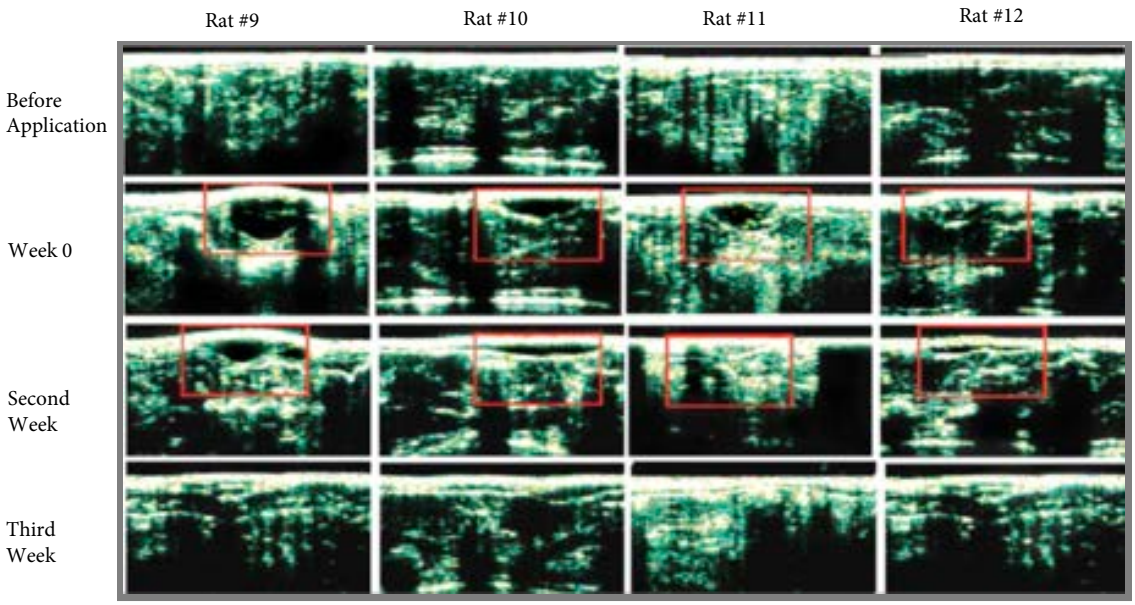


Figure 3: Ultrasonographic Measurement of Non-Reticulated Hyaluronic Acid.

A group of 10 patients was taken who are between the ages of 50 and 65, with an average age of 59, healthy, with indistinct sex (6 males, 4 females), with clinical evidence of middle third, lower and cervical facial photoaging, without previous surgery. Each patient is informed of the objective of the protocol as well as the characteristics of the study, which will consist of:

1. Signature of informed consent and assign rights to the authors of the article as well as the patient's treatment plan.
2. The biopeptide complex will be placed, immersed in a biocompatible sodium hyaluronate vehicle, in a 5ml presentation.
3. The application is made in 2 sessions with a space of 15 days; each session will consist of the injection of 6 ml of the product distributed in predetermined facial areas. Clinical photos were taken in a standard way, with the same light, white background, same distance, same focus (Front, three-quarters, and profile), Figures 5 to 14.
4. The biopeptide complex is administered in subdermal implantation, with a 45-degree angle and a rounded tip cannula, 22G caliber, retrograde.

At the second session (15 days after first application), a photographic control will be taken before the second session, the patient's opinion and satisfaction will be recorded using the Helmy Scale (Annex 1), which evaluates; complications throughout the follow-up period, degree of skin elevation in millimeters using the elevation score, and patient satisfaction during follow-up. One month after the second dose, photographs will be taken and a clinical and photographic analysis will be made of the evolution of the state of facial aging and the improvement of the cutaneous elastosis of each patient. In addition, again the dermatological survey will be completed.

Results

After the analysis of satisfaction, clinical and photographic results, based on our experience in the application of fillers, it was observed and measured that after the application of peptides, in 100% of patients, showed an improvement in skin quality. In relation to hydration, facial skin tension, and neck as well as reduced expression marks. In addition, it is to be a therapeutic and pre-surgical skin conditioning option for better results in patients who will undergo rhytidoplasty.

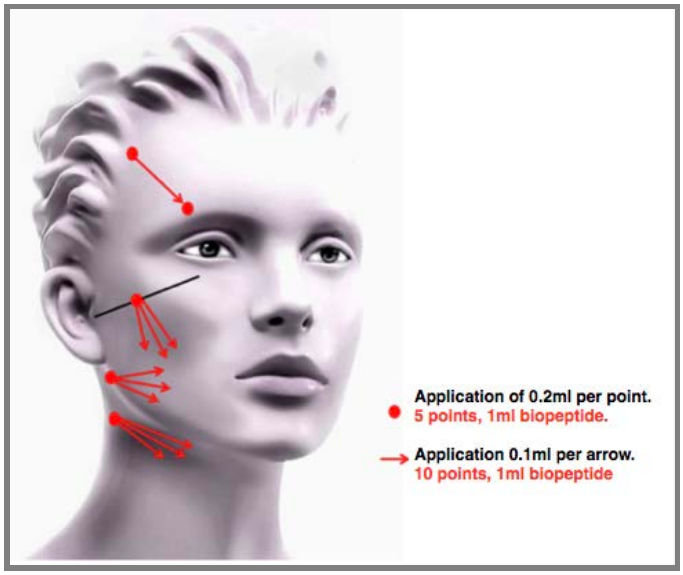


Figure 4. Main Application Sites.

Table 1: Patient demographics and Helmy's results. Pre and post aplication.

Sexo	Age	Pre aplication Helmy score	Post aplication Helmy score (2 weeks after)	Objective assessment of the degree of skin lifting
Male	61 years	Dissatisfied	Completely satisfied	Moderate
Female	54 years	Dissatisfied	Completely satisfied	Moderate
Male	61 years	Dissatisfied	Completely satisfied	Moderate
Male	54 years	Dissatisfied	Completely satisfied	Moderate
Male	62 years	Dissatisfied	Completely satisfied	Moderate
Female	64 years	Dissatisfied	Completely satisfied	Moderate
Female	55 years	Dissatisfied	Completely satisfied	Moderate
Female	59 years	Dissatisfied	Completely satisfied	Moderate
Female	55 years	Dissatisfied	Completely satisfied	Moderate
Male	55 years	Dissatisfied	Completely satisfied	Moderate

Figure 5. Male of 61 years.

Initial without treatment

Two months after the treatment

Figure 6: Male of 54 years.

Initial without treatment

Two months after the treatment

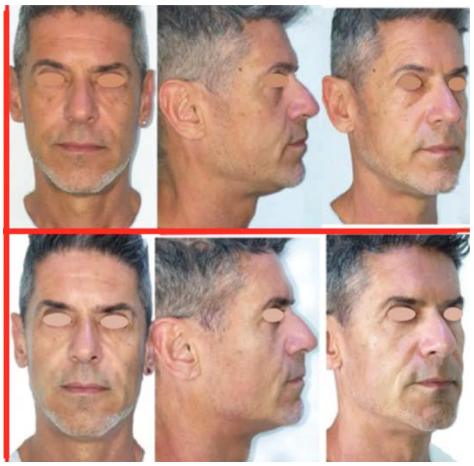


Figure 7: Male of 61 years.

Initial without treatment

Two months after the treatment

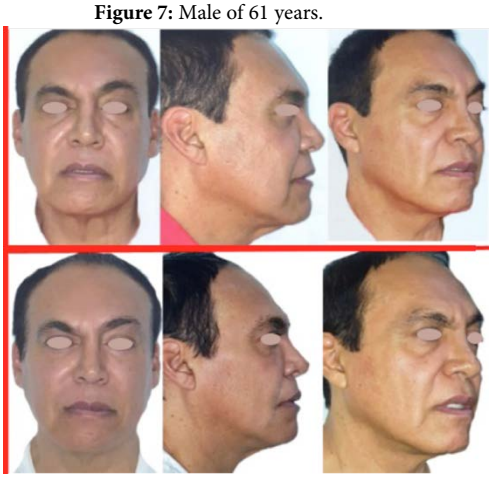


Figure 8: Male of 54 years.

Initial without treatment

Two months after the treatment

Figure 9. Male of 62 years.

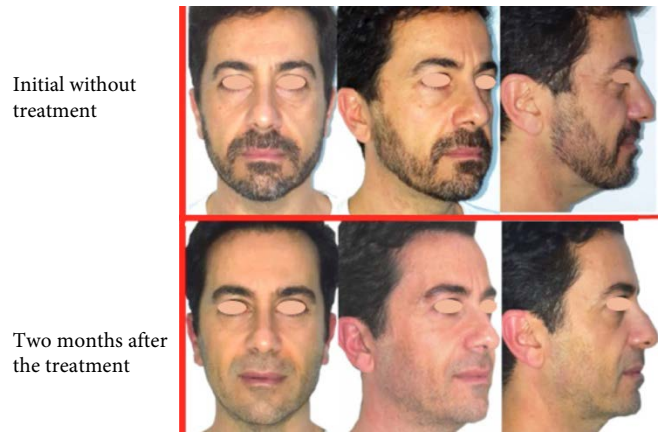
Figure 10: Female of 64 years.

Figure 11. Female of 65 years.

Figure 12: Female of 59 years.

Figure 13. Female of 58 years.

Figure 14: Male 55 years.



Discussion

Skin aging is a complex biological process influenced by a combination of endogenous or intrinsic and exogenous or extrinsic factors. Because of the fact that skin health and beauty are considered one of the principal factors representing overall "Well-being" and the perception of "Health" in humans, several anti-aging strategies have been developed during the last years [22].

Non-invasive treatments, according to ASPS (American Society of Plastic Surgeons) have increased since 2000. Skin aging is one of the most common conditions that request in the specialty of plastic surgery a treatment option, according to the WHO (World Health Organization) from a biological point of view, aging is the result of the accumulation of a wide variety of molecular and cellular damage over time, which leads to a gradual decline in physical and mental capacities, an increased risk of disease, and finally death [11]. In the skin, these processes affect all layers and structures producing a functional change of the extracellular matrix, advances in the knowledge of the molecular, and biochemical processes that lead to skin aging.

There are various in-office procedures, most of which are intended to 'resurface' the epidermis: to remove the damaged epidermis and replace the tissue with remodeled skin layers and sometimes spur the formation of new collagen. It is possible that the potential of GF, cytokines, and telomerase will eventually be harnessed via technological advancement and innovation in the burgeoning fields of tissue engineering and gene therapy in the nearest future [22].

Products injected within or beneath the skin to improve its physical features by soft tissue augmentation are known as fillers. There are autologous (fat, cultured human fibroblasts), collagen (bovine-derived, human-derived from tissue culture), HA (nonanimal stabilized or viscoelastic HA from bacterial fermentation), synthetic or pseudo-synthetic implants (silicone, polymethacrylate microspheres, poly-L-lactic acid, calcium hydroxylapatite microspheres suspended in aqueous polysaccharide gel, alkyl-imide gel polymer). These may be grouped into temporary, semipermanent (lasting between 1–2 y), or permanent materials (lasting longer than 2 y).

The goal of skin biorejuvenation is to increase the biosynthetic capacity of fibroblasts, inducing the reconstruction of an optimal physiologic environment, the enhancement of cell activity, hydration, and the synthesis of collagen, elastin, and HA (hyaluronic acid). The desired effect could be achieved by the microinjections in the superficial dermis of products containing only one active ingredient or cocktails of different compounds that are perfectly biocompatible and totally absorbable.

One therapeutic option is skin biostimulation with growth factors and cytokines, which are assembled with specific receptors of fibroblasts, keratinocytes stimulating their effect, and regulating gene transcription to regulate the integrity and functioning of the extracellular matrix. However, these growth factors have a very high production cost and are chemically unstable, making their use impractical, the biomimetic peptides [8, 9].

There are oligopeptides similar to growth factors (Biomimetic peptides) and have a mimetic effect on fibroblasts and keratinocytes, with laboratory and histopathological studies where the increase of the production of collagen and elastic fibers is proved. To these complexes, a molecule of non-reticulated hyaluronic acid was added as a vehicle of prolonged and sustained release, which is degraded in a time of 15 days, achieving this effect on the mentioned cells. Laboratory studies have demonstrated the increase in the proliferation of the fibroblast and consequently collagen fibers (19,20). These biomimetic peptides are synthetic compounds that are identical to amino acid sequence synthesized by an organism; it can interact with growth factor receptors and provide antiaging clinical effects [1].

A wide range of peptides have been developed and tested to solve these problems, the pioneers in this field are the growth factors with effects on keratinocytes and fibroblasts [12]. The objective is to stimulate a certain gene with a specific peptide hoping to modify the cellular response, these oligopeptides of approx. 15 amino acids have similar effects to growth factors, with lower production costs and chemical stability, they are protected by a double encapsulation of the denaturation of these peptides by endogenous proteases [13-16].

As it is known in the aging; the number, quality, quantity of collagen fibers, and the proliferative activity of the fibroblasts are diminished [10, 11]. Corroborating all these data with studies of very extensive, well documented and founded laboratories the diminished proliferation in quality and quantity of collagen and elastic fibers [9, 16-18].

Biomimetic peptides regulate the synthesis of proteins Ki-67, type I procollagen, AP-1, and SIRT6 in cell cultures of human fibroblasts. They contribute to the activation of regeneration processes and the initiation of mechanisms that prevent aging. Intradermal administration of complex biomimetic peptides produces a more dense arrangement of collagen fibers in the dermis and increased size of the fibers

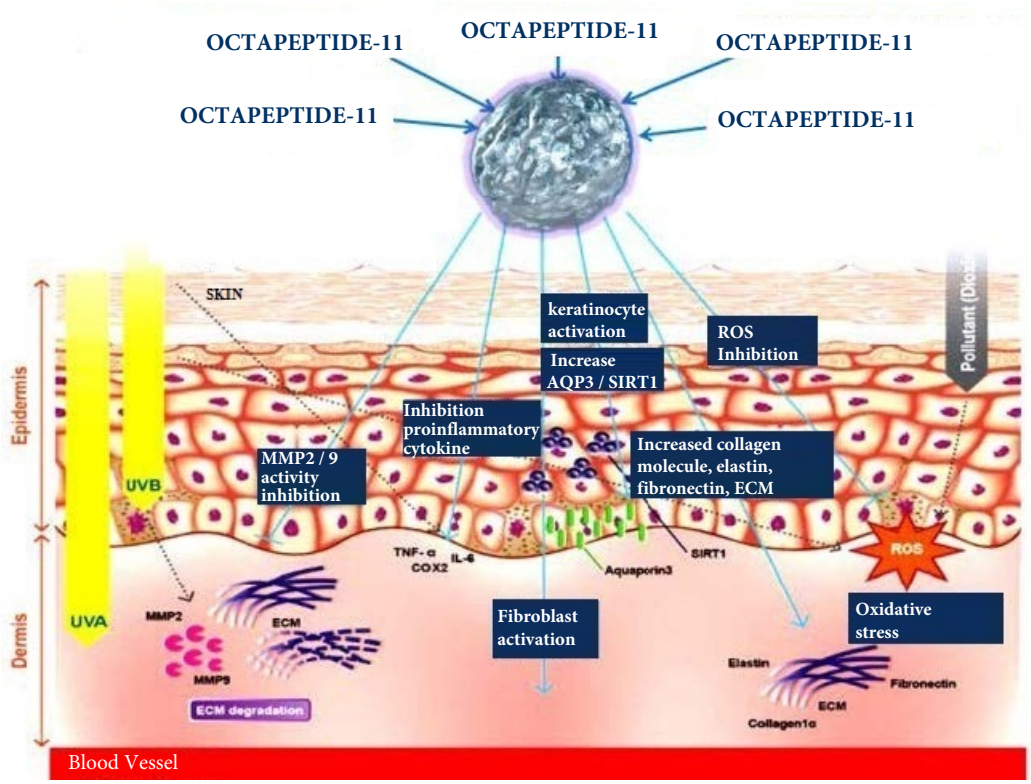


Figure 15. Biopeptide action mechanism.

A
Hyaluronic Acid

B
Cross linked Hyaluronic acid

C
Hyaluronic Acid
Not cross linked with
biostimulant biopetidics

Figure 16: Structural difference (Classic hyaluronic acid, reticulated and non-reticulated).

after 2 weeks. The complex of biomimetic peptides was effective in the in vivo experiments, where an increase in the proliferative and synthetic activities of fibroblasts was observed [1].

The clinical information as well as the photographic evidence and the level of satisfaction obtained in the patients treated with this complex, are very encouraging, pointing out in all, an evident improvement in the quality of the skin, being this one more firm, hydrated, luminous, and elastic, without contralateral effects in our preliminary study. However, the use and application of the product will have to continue, in order to increase the sample as well as a long-term follow-up (12 months) to corroborate the absence of side effects and the great benefits observed in the short term. As it is a new product in the market and carried out in the private practice, it is difficult to obtain skin biopsies to observe by spectrophotometry. However, it has been mentioned before, in experimental studies, the reintegration of the extracellular matrix is observed as well as the increase and quality of the collagen.

Conclusion

The application of biomimetic peptides, with the classic technique of facial fillers, we observe the results obtained in 10 patients on the characteristics of the skin in reference to hydration, firmness, elasticity as well as photographic follow-up and in relation to the level of satisfaction obtained in 100% of the patients studied, support the data obtained in an experimental manner from these biomimetic complexes on the production of collagen and elastin fibres.

The field of clinical applications with these biomimetic peptides opens up an enormous panorama in various human pathologies, above all an ideal field for application for cosmetic purposes.

Undoubtedly, there should be more studies, of scientific nature, to corroborate what has been described in relation to the reintegration of the extracellular matrix and the increase of collagen fibers, through the use of spectrography. However, this therapeutic option extends the weaponry available to the plastic surgeon within the spectrum of non-surgical treatments and even in combination with surgical procedures for facial and neck rejuvenation and repositioning.

Ethical Responsibilities

Protection of People and Animals

The authors state that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of Data

The authors state that they have followed their workplace protocols on publishing patient data.

Right to Privacy and Informed Consent

The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the author of the correspondence.

Annex 1 Helmy's score for subjective patient satisfaction.

Score	Description
0	**Dissatisfied.**
1	**Less satisfied**
2	**Moderate satisfied**
3	**Highly satisfied**
4	**Fully satisfied**

Annex 2 Helmy's score for objective assessment of the degree of skin lifting.

Degree of skin lifting in mm.	Score	Description
0	0	No lifting
1-2	1	Minimal
3-6	2	Moderate
6-10	3	Considerable
>10	4	Sensational

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