



SUMMARY

Ageing is a generalised process that affects all organs; however, it is common to refer to the skin when talking about biological ageing. Psychological experience, chrono- and photo-ageing, and skin are closely related. Stress, which is at the root of the alterations in the systems, leads to a chronic inflammatory state that disrupts the balance of organs, particularly the skin, resulting in the appearance of blemishes and wrinkles.

The skin is the largest organ in the human body and is in close connection with the Autonomic Nervous System: muscular tightening, which constricts the blood vessels resulting in less O₂ supply to the skin Tissues, and the excessive production of cortisol, correlate to the occurrence of pathologies and kinesthetics.

Unlike classic aesthetic medicine, which only treats the blemish without considering the person as a whole, the integrated multi-systemic and multi-level approach places the underlying causes of the blemish at the centre, acting mainly on the basic chronic inflammation to recover, reactivate and maintain the 'youthfulness', health and quality of the skin.

– The multi-systemic approach involves the use of biological drugs that can 'talk' to the cells and bioregulate them, allowing a state of global well-being to be achieved along with the aesthetic result and to enhance all the other treatments in the therapeutic protocol.

– Twenty female patients aged between 35 and 70 years were enrolled and underwent several multilevel steps: bio-detoxification (by means of an oral drainage and hydration therapy of the extracellular matrix, a systemic anti-ageing therapy and a body detoxification); biostimulation (by means of a local infiltrative therapy), accompanied in some cases by radiofrequency intradermal needle therapy, the application of biorevitalising acids and carboxytherapy. Both steps involve solutions acting at multiple levels due to the effect of BrSM natural multi-components capable of modulating the physiological mechanisms regulating ageing and Made, Guna-Collagen, and MD-Tissue. The effects of the therapy were assessed by means of a self-assessment questionnaire by the patients and with photographs.

KEY WORDS

AGEING, INFLAMMAGEING, WRINKLES, GUNA-COLLAGEN, MD-TISSUE

DERMOAESTHETIC FACIAL MEDICINE – INTEGRATED THERAPY

“One does not become old because a certain number of years have rained down upon us: one becomes old because one has abandoned one's ideals.

You will stay young as long as you stay receptive.

Receptive to what is beautiful, good and great.

Receptive to the messages of nature, of man, of the infinite”.

Gen. Douglas A. McArthur (1880-1964)

INTRODUCTION

The skin is a constantly changing organ that performs numerous functions:

- coating and protection from external agents
- regulation of body temperature
- sending tactile and pain information to the Nervous System
- immune defence
- production of vitamin D
- elimination of toxic substances.

The skin microbiome, which is in continuous communication with the gut microbiome, is dynamic and changes over time; its stability is lower than the intestinal one, probably due to the greater exposure to extrinsic varying factors as genotype, gender, age, environment, climate, geographic area, lifestyle, work activity, personal hygiene, concomitant diseases, immune activity, and inflammation.

– The skin is a very complex organ that acts as a protective barrier against the external environment.

It is the largest organ in the human body; its average surface area is between 1.6 and 1.85 square metres; the skin surface is characterised by the presence of folds, ridges and orifices.

The pattern of the texture of the palmar lines is genetically determined (arcs, loops, swirls). During embryonic development they begin to take shape before the onset of hand movements (around week 11 of gestation), do not change throughout life, have a high discriminating power and uniqueness and serve as a clinical-diagnostic aid in certain Syndromes due to chromosomal aberrations.

The **Extracellular Matrix (ECM)** of the dermal connective Tissue contains glycosaminoglycans (hyaluronic acid,

DIFFERENCES BETWEEN INTRINSIC AND EXTRINSIC SKIN AGEING		
CHARACTERISTICS	INTRINSIC AGEING	EXTRINSIC AGEING: PHOTO-AGEING
SKIN APPEARANCE	smooth surface, deepening expression lines, moderate loss of elasticity	knotty and thickened surface with spots tending to yellow, deep wrinkles, significant loss of elasticity
EPIDERMIS	soft and radiant	marked acanthosis, cellular apathy
ELASTIC TISSUE	increased, normal appearance	increased, degenerated into amorphous clusters
COLLAGEN	thickened, non-parallel bundles	decrease in collagen bundles and fibres: transformation from soluble to insoluble collagen
GLUCOSAMINOGLYCANS, PROTEOGLYCANS	slightly smaller	markedly increased
RETICULAR DERMIS	softer, decreased and inactive fibroblasts, decreased mastocytes, inflammation absent	thickened with elastosis phenomena, increased fibroblasts, hyperactive, mast cells markedly increased, infiltrated with mixed inflammation
PAPILLARY DERMIS	absent in the border areas with the dermis	solar elastosis

TAB. 1

chondroitin sulphate and dermatan sulphate); hyaluronic acid is distributed throughout the connective fibres in the spaces between the fibres.

– These molecules contribute to the elastic properties of the skin.

The subcutaneous Tissue (hypodermis) is the deepest layer and is connected to the dermis by septa of fibrous connective Tissue; it consists of adipose Tissue and collagen; there are also larger blood vessels, lymph vessels and nerves.

– With age, the skin becomes pale and thin with less tolerance to solar radiation exposure due to a decrease in the number of melanocytes; the decline in sebaceous and glandular activity leads to dryness and the appearance of wrinkles due to the loss of elastic fibres, reduced vascular supply and lower sexual hormones.

There is the onset of solar lentigo, seb-

orrhoeic and actinic keratoses and telangiectasias.

There is a chrono- and photo-ageing (TAB. 1); the latter mainly affects areas exposed to sunlight.

– Ultraviolet rays act, partly directly and partly mediated by the production of free radicals, on RNA, DNA, proteins, cell membrane and cytoplasmic enzyme phospholipids.

– Free radicals attack collagen and determine cross-linking bonds between fibres in the dermis, making them less elastic; they also attack hyaluronic acid, lowering its quality and functions.

Certain types of wrinkles are classified as:

- linear
- graphic
- creases
- naso-labial.

The state of health of the stomach, in-

testines, kidney, liver, etc., can be ‘read’ from the particular signs on the face; this proves that a comprehensive, integrated anti-ageing medicine is required, considering not only local problematic issues, but also the person in his or her entire ‘being’.

“Every problem you recognise is but a tiny dot on the radar screen of your well-being. Every time you experience a difficulty, homeostasis is working for you to bring you back into perfect balance. Your role is simply to relax and allow nature to take its course”.

(Alan Cohen - writer)

Stress, underlying the alteration of the organic systems, leads to a chronic inflammatory state that causes cortisol levels to rise in an attempt to manage and extinguish Chronic Low Grade Inflammation.

Furthermore, of great importance is the Gut-Brain Axis, in which the gut microbiota is considered the second brain that is subsequently in close communication with the skin’s microbiota.

The skin’s microbiota actively participates in the dual protective function of the skin, as a physical and immune barrier that hinders the development of harmful bacteria, generating an environment which is hostile for their development; with its activity of degrading skin surface lipids, it also protects against the immunosuppressive action that UV radiation causes in the skin.

It is important to maintain a balanced composition of the microbiota in order to avoid the colonisation of harmful bacteria; when this balance is disrupted, inflammatory problems, infections, allergies and autoimmune diseases emerge.

– Recent studies have shown that the imbalance and destruction of skin microbial populations correlates with the worsening of existing pathological conditions (e.g. Atopic Dermatitis, Acne, Psoriasis).

– Based on this evidence, scientific re-

search has started to focus on the study of new cosmetic products containing bacteria which is useful in combating the skin disorders caused by pathogens.

When talking about PNEI regulatory Systems, it is possible to understand how stress is at the basis of alterations in these systems and the cause of Chronic Low Grade Inflammation, and how adaptogenic substances reduce the load caused by stress and are a valuable aid for an organism seeking a balance of health.

Due to its function as a protective interface between the inside of the body and the highly contaminated external environment, the skin is densely colonised by a diverse and active microbiota, a complex and dynamic ecosystem inhabited by bacteria, viruses, fungi and archaea. – These, collectively referred to as the ‘skin microbiota’, are fundamental to skin physiology and immunity. Interactions between skin microbes and the host can ‘fall’ anywhere along the *continuum* between mutualism and pathogenicity.

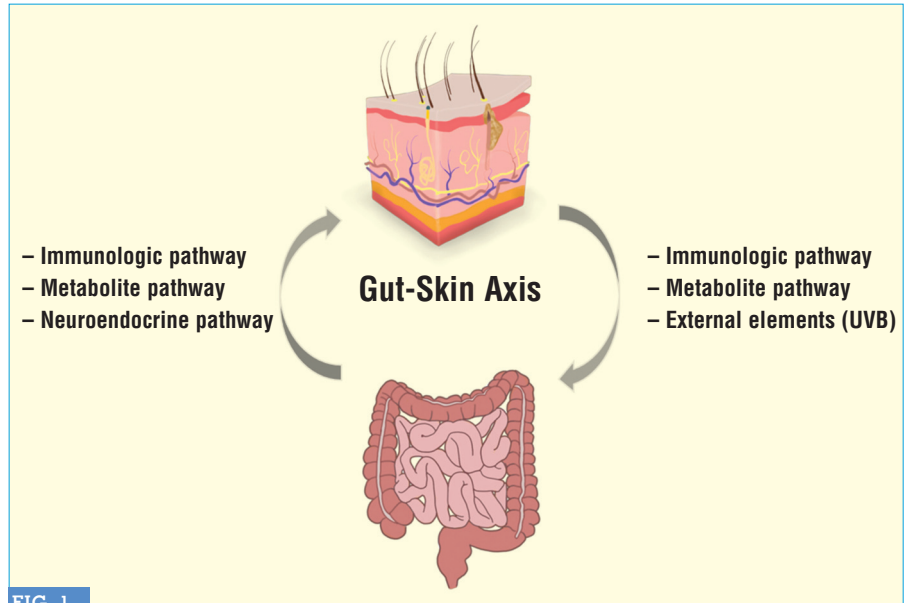


FIG. 1

Gut-Skin Axis.

Park D.H. et Al. – Comparative Analysis of the Microbiome across the Gut-Skin Axis in Atopic Dermatitis. Int. J. Mol. Sci. 2021, 22, 4228. <https://www.mdpi.com/1422-0067/22/8/4228>

Although cause and effect are generally difficult to determine with certainty, changes in the skin microbiota clearly play a role in the pathobiology of multiple skin diseases and aesthetic disorders.

The skin microbiota is of great importance for human health and wellbeing; it is involved in several skin diseases such as Psoriasis, Eczema, Contact Dermatitis, food Allergies, Seborrheic Dermatitis, Acne rosacea and it plays an im-

FIG. 2 Multi-systemic medicine.

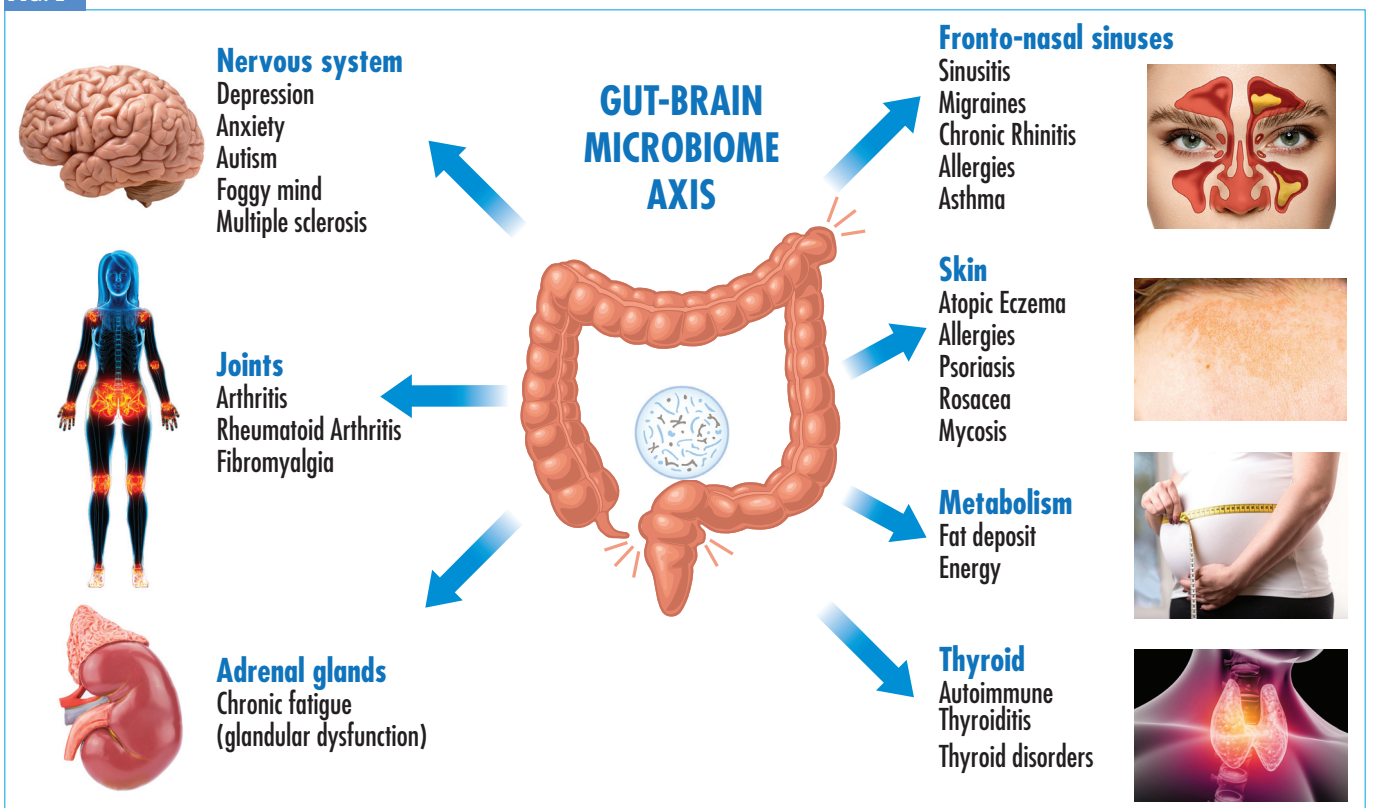




FIG. 3

Female, 40 years old. Slight skin laxity in the neck and “Venus rings” wrinkles; the patient underwent 4 sessions of biostimulation with Made (micro-injections); each session was performed every 2 weeks.

portant role in wound infections; it also plays an essential role in skin ageing, hence the importance of a **comprehensive** and **integrated therapeutic approach** that will act both topically and systemically with more physiological and natural methods.

– A crucial role in the onset of Acne, for example, is certainly played by *Propionibacterium acnes*, whereas atopic dermatitis involves *Staphylococcus epidermidis* and *Staphylococcus aureus*.

– Several ongoing studies aim at restoring the balance of the skin’s microbiota and the subsequent well-being of the individual by means of skin therapies with prebiotics or probiotics and the use of thermal waters in subjects with Psoriasis.

For some dermatological diseases, a

link has been shown with **intestinal dysbiosis** characterised by poor microbial biodiversity which is quite similar to that seen in patients suffering from Irritable Bowel Syndrome (IBS).

In many cases, the administration of certain strains of probiotics led to a lessening of intestinal and systemic inflammation and, subsequently, an improvement in skin symptoms.

– Such evidence demonstrates the existence of a true ‘**Gut-Skin Axis**’ (FIG. 1). The visceral brain presides over the vital functions of survival and is able to store stress and emotions, while the CNS regulates cognitive and relational function.

The gut produces neurotransmitters and psychoactive substances that influence moods (serotonin, endorphins) and the Gut-Brain Axis; consequently, the skin comprises direct links between these or-

gans with reciprocal influences.

It is essential to rebalance the gut microbiome to achieve positive, enhanced and long-lasting effects on the skin.

The connection between gut and brain is via the vagus nerve and the release of serotonin (secreted mainly in the gut), melatonin, tryptophan, GABA, and Peptide YY*.

Oxytocin is also produced in the brain, but its formation can be favoured, via the vagus nerve, by a balanced microbiota and in particular by *Lactobacillus reuteri*.

Performing the function of support, union and protection between the different Tissues are the connective Tissues, within which ECM is present in abundance.

– To put it simply, the ECM has the fundamental purpose of connecting the various cells in the body. Its most abundant component is **collagen**.

Another of the components of the ECM is the so-called **Fundamental Substance (FS)**, a colloidal gel-like structure that is deposited in the interstices of the fascial structure or ‘Fascial System’.

A particular feature of the FS is that inside there are structural elements such as lymphatic vessels, fibroblasts and fibrocytes, axons and arterio-venous capillaries. It is particularly the presence of all these elements that gives the ECM the articulated capacity to communicate at a distance between organs and apparatuses, albeit very different ones.

When an acid-base imbalance occurs, the composition of the FS is modified, becoming less fluid, reducing some of its most important functions, including its lymphatic drainage capacity, venous-capillary interchange and the plasticity of the Fascial System.

– In addition, it should be noted that the ECM also contains toxic metabolites.

The latter, together with the different state of FS and its ionic concentration, de-

* **Editor’s note:** Peptide YY is a hormone produced by the L-cells of the mucosa of the ileum and colon.

termine both the reactive modes and the development of certain characteristics of the individual, as well as ageing and the involvement of the Immune, Hormonal and Vegetative Nervous Systems.

- It is mainly the Lymphatic System that ensures the efficiency of the ECM.

Not all of the capillary transudate fluid re-enters the vessels: 10% of it (≈ 3

L/day), is deposited in the Tissues, turning into interstitial fluid.

- Therefore, it is essential that the Lymphatic System is able to operate at its best in the re-circulation of proteins and fluids: only in this way can correct homeostasis be maintained and fluids be prevented from accumulating in the ECM.

– When the excretory organs fail to adequately eliminate acidic waste, it accumulates in the ECM, which reacts through a general detoxification action, like a *metabolic sponge*.

The accumulation of acidic residues, resulting from catabolism, will however take place at the expense of the transformation of colloidal substances from the sol to the gel state; the functions of



FIG. 4

Females, 65-67 years old. Severe degree of skin ageing.
 – Six multilevel biostimulations were carried out on a weekly basis with Made + Guna-Collagen in a cocktail, followed by MD-Tissue; patients were then subjected to laser CO₂ treatment fractionated with double-pass and radiofrequency intradermal needling to complete the therapeutic procedure.
 Maintenance with multi-level biostimulation, 2/month.



FIG. 5

Female, 65 years old. Increased evidence of advanced ageing in the middle-lower third with pronounced perioral micro-wrinkles and deep wrinkles in the nose-genius area; 3 sessions of biostimulation with MD-Tissue every 2 weeks were carried out.



FIG. 6

Female, 53 years old. Skin laxity on the inner side of the arm; 3 biostimulations every 2 weeks with Made + Guna-Collagen in a cocktail preceded by carboxytherapy.
 – The patient continued with multi-level biostimulation and without needles in the same session, maintaining carboxytherapy, 1/month.

the ECM, together with the exchanges between cell and matrix, will tend to slow down.

The centrifugal force produced by the blood circulation pushes all the denser and heavier substances towards the periphery of the organism; skin changes caused by external irritation are rarer than those caused from within due to toxemia.

– The skin is thus to be considered as a draining organ that comes to the aid of the kidney, liver and lymphatic system.

Lymphatic drainage, liver detoxification, the functionality of the ECM, intestinal microbiome, and acid-base rebalancing are therefore fundamental.

The studies of Candace Pert, author of *“Molecules of emotion. Why you feel the way you feel”* have been able to ascertain the link between emotions and physiology, so much so that they claim that: *“this more holistic approach complements the reductionist view, expanding it rather than replacing it, and proposes a new way of understanding health and disease, not only to us scientists but also to laymen. We could define the entire system as a psychosomatic network of information, linking the psyche, comprising all that is non-material in nature, such as mind, emotions and soul, to the soma, which is the material world of molecules, cells and organs. Mind and body, psyche and soma”.*

▶ Unlike classical aesthetic medicine in which we intervene by directly treating the imperfection, without considering the person as a whole, **the multi-systemic approach** mainly targets the causes at the origin of the blemish, acting on the chronic inflammation to recover, reactivate and maintain the “youthfulness”, health and quality of the skin (FIG. 2).

– This innovative approach for the patient acts on cellular vitality and restores the physiological balances that sustain them.

Blemishes are considered the reflection of an imbalance in the entire organism; by acting on the real causes of ageing and related phenomena, a state of global well-being can be achieved.

We are aiming for a person’s harmony and psycho-physical well-being; **nutrition, nutraceuticals, water and exercise** play a very important role.

– There are two distinct therapeutic steps that can be applied successively or in parallel.

STEP 1: bio-detoxification, through systemic oral therapy, aimed at draining toxins from the ECM, systemic anti-ageing therapy and body detoxification, when necessary;

STEP 2: biostimulation through local injection therapy, aimed at biostimulating cellular turnover processes.

Both steps provide solutions that act at multiple levels through the effect of multi-component/multi-target natural medicines capable of modulating the physiological mechanisms that regulate ageing, without side effects.

STEP 1 can be enhanced by low-dose signal molecules capable of stimulating Tissue trophism.

STEP 2 is multi-layered through **low-dose multi-component/multi-target drugs** and **Collagen Medical Devices**, which are able to modulate the physiological mechanism leading to ageing; the latter act as scaffolds of the ECM, able to replace a structural vacuum.

– For a customised therapeutic strategy, they can be used individually or both, at several levels.

MATERIALS AND METHODS

- Systemic therapeutic protocol:
 - **Proflora**, 1 sachet/day; it is a symbiotic food supplement containing 6 different probiotic bacterial strains that promote the natural well-being of the intestinal microflora;
 - **Guna-Matrix**, 20 drops x 2/day + **Guna-Lympho**, 20 drops x 2/day x 2 consecutive months.
- Repeat Guna-Matrix cyclically throughout the year.
- **Lipidic Vitawin C**, 3 capsules/day to be taken at main meals x 2 consecutive months.

- Local therapeutic protocol:
 - **Guna-Collagen**, 1 fl + **Made**, 1 fl; weekly infiltrative therapy for at least 5 consecutive weeks, in a mesotherapeutic mode by means of an injector with the needle depth controlled by a computerised system, or by means of manual mesotherapy injections.
 - In some patients where the ageing process needed **deeper action**, **MD-Tissue** was injected in the same way.

The infiltrative technique is the micro-injection technique, which is very suitable for reaching the dermal layer.

– The 30G needle is inserted very slowly

ly and constant pressure is applied to the syringe plunger until a small white intradermal papule appears.

Depending on skin ageing, these treatments were accompanied by sessions of **carboxytherapy** [preceding biostimulation (STEP 2) and performed in the same session], with **needle-free biostimulation** and more invasive techniques such as the **fractioned CO₂ laser** and **intra-dermal needle-assisted radiofrequency**.

– Carboxytherapy consists in the subcutaneous administration of medical CO₂ in a gaseous state; it produces vasodilation and reactivation of the microcirculation, improves blood flow and skin metabolism, and increases tissue oxygenation.

– Needle-free biostimulation by means of peeling based on 33% trichloroacetic acid, kojic acid and hydrogen peroxide preceded by skin microneedling was generally carried out after micro-injections of the multi-level medicine products to enhance their effects.

– Treatment with the fractional CO₂

laser involves the execution of many tiny (a few microns) holes by means of a laser beam that reaches the dermis; it causes heating that generates the formation of young collagen.

The presence of new collagen results in the rejuvenation of the skin surface, from which corneous cells are removed, and the dermis, which thus acquires greater lustre and tone.

– Biostimulation treatments generally precede laser sessions to make the surface fertile and healthy in order to enhance their effects.

– Intradermal needle radiofrequency is the new generation microneedling device that offers immediate and long-term results, with well-tolerated sessions and very short recovery times. This minimally invasive treatment helps stimulate natural collagen production and is effective in improving facial and neck wrinkles and acne scars.

Collagen synthesis stimulation and induction treatments, better known as



FIG. 7

The patient underwent 5 sessions of biostimulation with **Made** (micro-injections) on a weekly basis using the needle gun and 1 session of fractioned CO₂ laser in “soft” mode: thanks to the BrSM medication, an optimal result was achieved, maintained and enhanced with the CO₂ laser, using parameters far below classical non-surgical blepharoplasty treatments.



FIG. 8

Female, 53 years old. The patient underwent 5 sessions of carboxytherapy followed by biostimulation on a weekly basis; there was a significant decrease of micro- and macro-wrinkles, especially in the periocular area; texture healed.

skin resurfacing, are among the safest and most popular.

Skin microneedling requires the use of disposable needles that gently penetrate the dermal-epidermal Tissue at specific depths; it stimulates the release of multiple growth factors that induce neo-collagenesis and neo-elastogenesis in the treated area via a cascading effect. It is a dermo-epidermal renewal treatment that does not damage the epidermis, is not selective on melanocytes and does not cause post-inflammatory pigmentation.

Biostimulation can precede radiofrequency by a few weeks or can be performed in the same session, after letting the Tissues cool down with a soothing mask; the multilevel treatment acts as an aid in recovering the discomfort produced by radiofrequency and 'educating' the tissues to a rapid functional recovery with an enhanced effect.

- All these multilevel treatments result in different effects:

 - 1) anti-inflammatory action
 - 2) local circulation stimulation
 - 3) Tissue stimulation
 - 4) collagen production stimulation
 - 5) wrinkle reduction
 - 6) skin firming
 - 7) bioscaffolding action.

At the end of each treatment, approximately 1 ml of a beauty gel was applied *in situ* with a gentle manual massage to penetrate the product.

– The evaluation of the results was based on the patients' satisfaction using the PAIS scale (Editor's note: The Psychosocial Adjustment to Illness Scale) and photographs.

RESULTS

This study shows that BrSM therapy, nutraceuticals and the multi-system approach are effective and highly efficient



FIG. 9

Female, 50 years old. Medium to severe chrono- and photo-ageing on the neck. – Four biostimulation sessions were carried out followed by multi-layer application with manual acid massage (needle-free biorevitalisation) on a weekly basis.

in both the prevention and treatment of skin ageing.

– Patients report markedly improved well-being and general psycho-physical health compared to the start.

The total absence of adverse reactions and the results obtained ensured excellent compliance with both outpatient and home therapy.

– The study shows that the protocols applied are effective and safe in treating skin ageing (FIGG. 3-10).

DISCUSSION

Patients maintain their results through some basic daily activities: a proper diet, calorie restriction, macronutrient allocation, customised nutraceuticals, hormones, anti-free radical antioxidants, average aerobic and anaerobic exercise, stress management, self-care, sexual performance and socialising.

– Human beings are constantly changing; the processes of growth and ageing are the most striking examples of this reality.

Becoming aware of one's own evolution, of the rhythms and interconnections that keep a body alive, means learning to understand and to take care of oneself in order to achieve inner and outer harmony.

From the above, it is easy to understand the importance of a comprehensive and patient-friendly approach: doctors must not limit themselves to a single blemish, but... must look beyond the skin.

The secret to staying 'young' and healthy is to provide the body with the necessary tools to activate the regeneration and functional recovery processes. ■



FIG. 10

Female, 53 years old. The patient underwent 3 sessions of biostimulation, 1 session every 2 weeks; at the last session, needle radiofrequency was also used.

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Fig. 2: (recomposed)

Source: Manera S. – *Cervello intestino, un legame indissolubile*. p. 94. Macro Edizioni, 2021.

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