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HETEROLOGOUS SKIN REGENERATION

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Premise

Today, medicine, physiology and cosmetic medicine, in the renewal of treatment for skin aging, are turning to an industry evolving: regenerative medicine. The scientific approach which today must follow the doctor is to regenerate the biological status of skin tissue through autogous or heterologous actives .
The **skin regeneration** requires the use of **autogous** patient's substances, such as:

- Platelet Growth Factors
- plasma rich in platelets
- Fibrin plasma
- Support Autogous Biological Tissue

With the goal of inducing regeneration of the dermis and epidermis which would bring the skin in a youthful state.

The **heterologous skin regeneration** always involves the activation of regenerative biological processes, however, made by Medical Device certified for this function. The regeneration heterologous replaces the generic term of biostimulation to indicate biological activity useful in functional improvement of skin.
Indeed, the generic term biostimulation indicates a generic biological activity, of course, will be included with this term positive and negative results.
Undoubtedly the products proposed as biostimulants are accepted by the physician and the patient for a possible hit on the skin. But in reality, all products sold are biostimulants (activators of skin biology), but not all, lead to an improvement of the physiological skin, often show a positive response on the aesthetic result, but with a skin biological damage .
But what we mean as physiological improvement of the skin? The physiological normalization of biological functions of the body and thus improve the skin indicates the physiological homeostatic optimization of biochemical reactions that must maintain our functional and trophic skin.

To program, therefore, a proper biostimulation, or rather a skin regeneration with Medical Device, we must first understand the biological mechanisms relevant to the biology of the skin.

Skin Physiology

Recall that our skin is made from epidermis and dermis.

The epidermal tissue is consists of several cell layers with different functions and other structures with specific activity. The process of differentiation of epidermal cells is very complex and is regulated by a variety of information that are provided both from outside and by complex enzyme systems that function as second intracellular messengers.

Among the external reporting should be mentioned, principle, the "cholinergic brokers" (acting on guanilciclasi with a stimulation of activity c-GMP training). Other factors that regulate differentiation kerotinocitaria are the Epidermal Growth Factor (EGF), estrogen and among the intrinsic factors regulating the Calones, hormone-like substances activities. The epidermal keratinocytes calones were produced by an advanced stage of proliferation and would function to inhibit cell mitosis of cells of the basal layer.

Therefore, we must highlight that a **correct epidermal functioning** is not possible without a proper function of:

- Growth factors
- The mediators cholinergic
- The epidermal calones

Under the skin we have the dermis. The dermis develops under the epidermis and consists mainly of cells, collagen and elastic fibers embedded in a colloidal matrix. The cells are represented mainly by fibroblasts.

The matrix is formed by colloidal ground substance (glycosaminoglycans and proteoglycans) and by fibrous proteins such as collagen and elastin. Collagen, elastin, glycosaminoglycans (GAGs) are produced by fibroblasts.

The matrix, a colloidal solution, is normally present in a state of sol, in pathological situations solidifies through the gel state and loses its capacity to metabolic exchange. The state of colloidal sol solution of the matrix is allowed by the dissociation of protein molecules that compose it. At physiological pH of 7.4 is the radical dissociated acid, leading to a negatively charged macromolecule. The common negative charge of macromolecules leading to repulsion of the same by creating a solution to the state of colloidal sol, which allows a free exchange metabolic pathway.

The inflammation or the suffering of a tissue leads to acidification of the matrix with release of hydrogen protons. Protons bind to the negative radical of macromolecules, with saturation and elimination of the electric repulsion. For the lost of electrostatic repulsion, the molecules are stacked on each other, transforming the colloidal solution in a gel . The variation of colloidal matrix is highlighted with an alteration of metabolic exchange and an suffering of the tissue. The sol state allows

the normal dermis metabolic exchange, the gel state alters the matrix function . This makes us understand that if we want a better function and aesthetic dermal matrix we must avoid acidifying processes.
The most important cell in the dermis is the fibroblast. This is capable, based on its age and the environmental situation (state of the matrix), to produce: proteoglycans, elastin and collagen.
Proteoglycans are macromolecules which constitute the basic structure of the matrix. They consist of glycoproteins consisting of a base of hyaluronic acid with the attached protein molecules associated with other sugars. This constitution allows the chemical bond with water molecules.
Elastin is a protein capable of maintaining the elastic structure of the dermis. This is enabled by a special hinge formed by desmosina which makes the structure similar to a spring.
The fibroblast also produces various types of collagen in the dermis. The majority of collagen type III and type I °. The fibroblasts produce collagen I ° or type III based on various receptor stimuli received. Ratio in young skin collagen type III / type I is much higher than in adults. This ratio tended to decrease with age.
The production of collagen is partly inside and partly outside the cell. The procollagen is formed in the fibroblast and is secreted in the external environment. Here peptidase cut portions of terminals (N-and C-terminal) allowing tropocollagene then assembled in the first, into fibrils and then eventually fiber. The assembling of tropocollagene underlying the formation of the first type I collagen or type III and is determined by the terminal residues (amino or carboxyl terminal).
Based on the type of collagen produced, we can distinguish two subsets of fibroblasts, NF and FF, the latter is characteristic of inflamed tissues.
In the dermis we have an ongoing reshuffle of biological components. The metalloproteinase hydrolyze skin macromolecules and the fibroblast reform. The metalloproteinases are present in the dermis in an inactive form and are activated at the time to act to remove a residue of cystine.
In the dermis, the fibroblast receives information on the matrix degradation from the fragments of this. The fibroblast build new components of the dermis and particularly proteoglycans, elastin and collagen type III (reticular).
Maintaining a **proper functioning of the dermis**, cannot do without:
• Keep the colloidal state of the array (to reduce inflammation and acidification)
• Activate the fibroblast
• Stimulating the growth matrix, elastic fibers and collagen type III
. Reduce the activation of metalloproteinases

Heterologous Skin Regeneration
From what we have stated, the dermo-epidermal regeneration obtained with the use of medical devices should lead to the skin:

• An action of stimulation of receptor tyrosine kinase normally activated by growth factors necessary to enable the growth both of the germinative epidermal layer, both the fibroblast
• Action mimetic that improves the epidermal cholinergic system
• useful buffer action to reduce the states of acidification induced by inflammation and help to maintain the colloidal state of the matrix
• action to stimulate new formation of matrix components (proteoglycans, elastic fibers and collagen type III)
• actin to block the activation of metalloproteinase responsible of the dermis catabolization.
And finally, reduce the processes of skin aging caused by oxidative stress of free radicals of oxygen.
The pharmaceutical industry, a long time, has provided us with a Medical Device Type III certificate for a biostimulation dermo-epidermal. This product contains:
- Hyaluronic Acid Fragments of 20-38 monomers capable of activating the CD (Cluster of Differentiation) 44. These receptors, once activated induce a metabolic activation and dermal-epidermal regeneration with multiplication. In particular lead to the synthesis, by the fibroblasts, of the matrix new components and collagen lattice.
- Amino acids precursors of matrix components, according to the Endomodulation principles, trigger biochemical reactions anabolic allowing a growth of the dermis.
- Amino acid cysteine, zip closing of the active site of metalloproteinases. The excess of this amino acid competes with the removal of the same to level of metalloproteinases, reducing the activation of these and the breakdown of the dermis.
- Bicarbonate buffer system that inactivates the release of H + ions induced by inflammation of the skin, keeping constant the pH value of 7.4. This allows the separation of anionic macromolecules that compose the matrix, keeping the electrostatic repulsion necessary for the maintenance of the matrix.
The actions of this second of III type device Medical undoubtedly good, omitted, however, two points set out above, namely:
• The mimetic action of epidermal cholinergic system
• The reduction processes of skin aging caused by oxidation of oxygen free radicals.
This forced us to treat these two points with different drugs, not approved for this treatment (glycerate choline and reduced glutathione). Recently, the same pharmaceutical industry has proposed new type III Medical Device containing the starting material described above with the addition, in one case, of choline, and in the another, of antioxidants.
The choline is the precursor of the acetyl-choline and, in turn, in its synthesis is stimulated by DMAE (dimethylaminoethanol), already known in cosmetics. Its addition in the Base Medical Device type III takes, according to the Endomodulation principles, a improvement of the acetyl-choline synthesis and an activation of the epidermal cholinergic system. In fact,, Kurzen, Wessler, Kirkpatrick, Kawashima e

Grando, say in Hormonal Metabolic Research del febbraio 2007: The non-neuronal cholinergic system of human skin is involved in basic functions of the skin through autocrine, paracrine, and endocrine mechanisms, like keratinocyte proliferation, differentiation, adhesion and migration, epidermal barrier formation, pigment-, sweat- and sebum production, blood circulation, angiogenesis, and a variety of immune reactions.
The antioxidants (vitamin C and glutathione) act by inactivating oxygen free radicals, escaped from electron transport chain. Vitamin C reactivates with its reversible passage by ascorbic acid to dehydro-ascorbic acid, vitamin E oxidized in its function block of the superoxide radical. Glutathione converts hydrogen peroxide, formed as a result of SOD (superoxide dismutase)action on the superoxide radical, in water preventing thus the damage of Fenton Reaction.

Conclusion

This evolution of the means at our disposal for the biostimulation, allows us to review, for the better, our protocol on the heterologous regeneration, incorporating these two new medical devices.
From this, we differentiate our protocols on the basis of results of evaluation of our patient's skin. In particolar:

- In the young patient who does not have excessive skin damage, we keep the classical treatment using the Base Medical Device . The time are those based each mesoterapy treatment: one session a week for four times, a fortnightly meeting twice, and finally a maintenance session once a month.
- In the patient with damage of biological aging (photo-aging or crono-aging) we substitute the Medical Device Base with one with antioxidants, keeping the protocol.
- In the patient with epidermal damages replace the Medical Device Base with one with Choline, always maintaining the same protocol.

Finally, in patients at older ages where they often add up all the needs, the our current protocol provides:

- A session with Medical Device Base week for four times.

Then:

- One session every fortnight with the Medical Device with Colina. Introduced to carpet across their face.
- One session every fortnight with the Medical Device with antioxidants. Introduced to carpet across the face.

Treatment should be maintained over time and supplemented with autologous regeneration.

Bibliography

Ceccarelli M., Curcio B.C., Biostimolazione e Bioristrutturazione della Cute .The Physiological Medical Letter Vol. 1 Num. 1 (17-30) Gen 2010

Eglen RM. Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. Auton Autacoid Pharmacol. 2006 Jul;26(3):219-33. Review.
Grando SA, Pittelkow MR, Schallreuter KU. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance. J Invest Dermatol. 2006 Sep;126(9):1948-65. Review.
Grando SA. Cholinergic control of epidermal cohesion. Exp Dermatol. 2006 Apr;15(4):265-82. Review.
Kirkpatrick CJ, Bittinger F, Unger RE, Kriegsmann J, Kilbinger H, Wessler I. The non-neuronal cholinergic system in the endothelium: evidence and possible pathobiological significance. Jpn J Pharmacol. 2001 Jan;85(1):24-8. Review.
Korkina L, Pastore S. The role of redox regulation in the normal physiology and inflammatory diseases of skin. Front Biosci (Elite Ed). 2009 Jun 1;1:123-41. Review.
Kurzen H, Wessler I, Kirkpatrick CJ, Kawashima K, Grando SA. The non-neuronal cholinergic system of human skin. Horm Metab Res. 2007 Feb;39(2):125-35. Review.
Palmer DM, Kitchin JS. Oxidative damage, skin aging, antioxidants and a novel antioxidant rating system. J Drugs Dermatol. 2010 Jan;9(1):11-5. Review.
Pedersen MØ, Larsen A, Stoltenberg M, Penkowa M The role of metallothionein in oncogenesis and cancer prognosis. Prog Histochem Cytochem. 2009;44(1):29-64. Epub 2008 Dec 1. Review.
Sykiotis GP, Bohmann D. Stress-activated cap'n'collar transcription factors in aging and human disease. Sci Signal. 2010 Mar 9;3(112):re3. Review.
Zhao W, Robbins ME. Inflammation and chronic oxidative stress in radiation-induced late normal tissue injury: therapeutic implications. Curr Med Chem. 2009;16(2):130-43. Review.