Facial regeneration: current status and perspectives

Gabriela STOLERIU[1,2], Cătălina Maria VOICU[3], Daciana Elena BRĂNIȘTEANU[1], Nicuța MANOLACHE[2], Lucreția ANGHEL[4], Florina Mihaela FILIP-CIUBOTARU[5], Vasile Valeriu LUPU[6]

1 University of Medicine and Pharmacy "Grigore T. Popa", Iași, Faculty of Medicine, Department of Dermatology

2 "Dunărea de Jos" University of Galați, Faculty of Medicine and Pharmacy, Department of Pharmaceutical Sciences

3 = Derma Clinique, Iași

4 "Dunărea de Jos" University of Galați, Faculty of Medicine and Pharmacy, Department of Medical Clinic

5 University of Medicine and Pharmacy "Grigore T. Popa", Iași, Faculty of Medicine, Department of Family Medicine

6 University of Medicine and Pharmacy "Grigore T. Popa", Iași, Faculty of Medicine, Pediatrics Department

stoleriugabriela@yahoo.com

Abstract

Skin aging is a complex biological processes influenced by endogenous and exogenous factors. The primary aim of all skin anti-aging strategies is to reverse the dermal and epidermal signs of photoaging and chronological aging. Healthy and normal functioning skin barrier is an important protector against dehydration, penetration of various microorganisms, allergens, irritants, reactive oxygen species and radiation. The skin barrier may be specifically adjusted to allow penetration of desired substances.Regenerative medicine is the science of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal form and function. It uses cells, tissues, drugs, synthetic biomaterials and devices to help patients heal or regeneration. The reason of different methods of skin regeneration is to increase skin regeneration, elasticity, smoothness, density, macroscopic and microscopic aspect, changing the skin condition. It is necessary to slow down ageing processes on a cellular level concomitantly. We can provide to the skin primary structural constituents, such as collagen, elastin, to prevent the formation of wrinkles, but some products and techniques do promote the natural synthesis of these substances except elastin enhancing. Simultaneously it is necessary to prevent wrinkle formation by reduction of inflammation (topical or systemic antioxidants) in combination with sunscreens and retinoids to enhance their protective effects. An important attention must be accorded to Transforming Growth Factor-β family, other TGF-β-based approaches (Decorin and Mannose 6 Phosphate), modulation of Smad3/Smad7 Signaling, Epidermal Growth Factor family, Fibroblast Growth Factor family, Platelet-Derived Growth Factor family, Granulocyte Macrophage-Colony Stimulating Factor, Connective Tissue Growth Factor, Interleukin 10, Connexins, other approaches under investigation for scar reduction, collagen, fibronectin, laminin, elastin, glycosaminoglycans and other natural biomaterials. Regenerative Aesthetic Dermatology is focused on innovative treatments to support the skin in restoring and regenerating old and/or damaged tissue and thus improving overall skin quality, promoting faster healing while minimizing downtime and side effects for patients. The onset of effects could be instantly after procedure or can be observed gradually increasing over the time (weeks or monthes), as we are determining the skin to help itself. The regenerative treatments are encouraging the skin to build more collagen and elastin itself by bio-stimulation: resurfacing the epidermis (topical drug application, ablative LASERs, Laser radiofrequency resurfacing, ablative radiofrequency, microneedling, plasma skin resurfacing, crystal-free microdermabrasion), the formation of new collagen (IPL, Lasers, radiofrequency, infrared, Jett Plasma Medical, medical needling, mesotherapy, platelet-rich plasma, fillers as hyaluronic acid, ***HydraFacial MD, Oxygen facial, chemical peels,*** *hormone replacement therapy, autologous and allogeneic stem cells, gene therapy), slow down the visible aging process by helping in the management of certain dynamic facial lines and wrinkles (Botulinum toxin).*

Resurfacing the skin could be considered as a cancer prophylaxis and aesthetic dermatology is contributing to slowly, healthy, gracefully aging.

Keywords: *prevention anti-aging, antioxidants, regeneration, rejuvenation, laser, IPL, peeling, fillers, botulinum toxin, plasma, therapy, hyaluronic acid*

Introduction

Skin aging is a complex biological processes influenced by endogenous (genetics, cellular metabolism, hormone and metabolic processes) and exogenous factors (chronic light exposure, pollution, ionizing radiation, chemicals, toxins). These factors lead together to cumulative structural and physiological alterations and progressive changes in each skin layer as well as changes in skin appearance, especially, on the sun-exposed skin areas.In contrast to thin and atrophic, finely wrinkled and dry intrinsically aged skin, premature photoaged skin typically shows a thickened epidermis, mottled discoloration, deep wrinkles, laxity, dullness and roughness. Gradual loss of skin elasticity leads to the phenomenon of sagging. Slowing of the epidermal turnover rate and cell cycle lengthening coincides with a slower wound healing and less effective desquamation in older adults. This fact is important when esthetic procedures are scheduled. On the other side, many of these features are targets to product application or procedures to accelerate the cell cycle, in the belief that a faster turnover rate will yield improvement in skin appearance and will speed wound healing.

Three primary structural components of the dermis, collagen, elastin and GAGs have been the subjects of the majority of anti-aging research and efforts for aesthetic-anti-aging strategies pertaining to the skin, from ”anti-wrinkle creams” to various filling agents. The primary aim of all skin anti-aging strategies is to reverse the dermal and epidermal signs of photoaging and chronological aging.

Chronic photodamage of the skin manifests itself as extrinsic skin aging (photoageing). DNA photodamage and UV-generated reactive oxygen species (ROS) are the initial molecular events that lead to most of the typical histological and clinical manifestations of chronic photodamage of the skin. Wrinkling and pigmentary changes are directly associated with premature photo-aging and are considered its most important cutaneous manifestations. The strategies aimed at preventing photo-aging include sun avoidance, sun protection using sunscreens to block or reduce skin exposure to UV radiation, retinoids in order to inhibit collagenase synthesis and to promote collagen production, and anti-oxidants, particularly in combination, to reduce and neutralize free radicals.

Healthy and normal functioning skin barrier is an important protector against dehydration, penetration of various microorganisms, allergens, irritants, reactive oxygen species and radiation. The skin barrier may be specifically adjusted to allow penetration of desired substances.

Regenerative medicine is the science of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal form and function. It uses cells, tissues, drugs, synthetic biomaterials and devices to help patients heal or regeneration.

Materials and methods

The reason of different methods of skin regeneration is to increase skin regeneration, elasticity, smoothness, density, macroscopic and microscopic aspect, changing the skin condition. It is necessary to slow down ageing processes on a cellular level concomitantly. We can provide to the skin primary structural constituents, such as collagen, elastin, to prevent the formation of wrinkles, but some products and techniques do promote the natural synthesis of these substances except elastin enhancing. In the following, we will describe the methods that help us to obtain this kind of results.

Chemical peels

A chemical peel involves the application of toxic chemical solutions to the skin in a controlled manner, producing controlled tissue death. The desired depth of the wound is dependent upon the condition to be treated. After the peel, the skin regenerates. The damaged skin likely regenerates through the growth of cells from deeper layers of the epidermis or from undamaged hair follicles.

Chemical peels are broadly defined by the depth of damage in the skin that they produce. They are categorized as superficial, medium, and deep. Superficial peels do not damage skin below the epidermis, the most superficial skin layer. Medium peels may reach to the superficial layer of the dermis, the deeper layer of the skin. Deep peels generally reach the deeper layers of the dermis. The depth of damage depends on the nature and concentration of the chemicals in the peeling solution and the length of time they are permitted to interact with the skin. Popular chemicals in peeling solutions include retinoids (tretinoin dissolved in propylene glycol), alpha-hydroxy acids (lactic acid and glycolic acid), beta-hydroxy acids (salicylic acid), trichloroacetic acid, and phenol (carbolic acid). Jessner's solution, a combination of resorcinol (14 g), salicylic acid (14 g), and lactic acid (85%) in ethanol (95%), is also an excellent peeling agent.

The indications for a chemical peel, since it is largely a cosmetic procedure, depend on the patient's tolerances and wishes for correcting skin textural problems. Treatments vary with the severity of the condition and the wishes of the patient. Indications for aesthetic concerns are as follows: photoaging, fine superficial wrinkling, dilated pores, superficial scars.

Physical peeling

Cryotherapy with liquid nitrogen or dry ice it is recomanded to obtain a tighter and a healthier skin, to increase metabolic and caloric burn, and also to product collagen.

Crystal-free microdermabrasion

Microdermabrasion has remained a popular method for skin resurfacing and rejuvenation. This modality effectively exfoliates the outer layers of the epidermis using the propulsion of a mechanical medium, such as aluminum oxide microcrystals, at the skin through a handpiece. As the skin is exfoliated, the handpiece suctions the skin debris and microcrystals away through an accompanying vacuum. This modality has been used to treat light scarring, discolored and photodamaged skin, enlarged pores, and has been helpful in reducing the appearance of stretch marks and fine lines. This method also stimulates papillary dermis thickening. Despite its effectiveness, microdermabrasion is not recommended for all skin types and is used cautiously in persons with Fitzpatrick skin types IV–VI, rosacea, sensitive or thin skin because of the increased risk of irritation and hyperpigmentation. Though complications of microdermabrasion are minimal, patients' largest complaints post-procedure are temporary dryness and photosensitivity. Newer methods of microdermabrasion have moved toward microcrystal-free modalities exemplified by diamond tip microdermabrasion and hydradermabrasion.

The diamond tip microdermabrasion system is a handset with a contact point composed of diamond fragments that are adjustable for size and abrasiveness enabling treatment of a large variety of skin types and thicknesses. This method functions with a polishing motion to wear down the epidermal layers while the vacuum suctions away the debris and dead cells. Treatment is reliant on the operator's skill with the handpiece and the manual pressure applied to the epidermis along with the level of suction being used. Advantages of the diamond tip can be seen with treatments on areas around the eyes and mouth that can be treated without risk of microcrystals causing irritation, damage, or being ingested. Also, the tips are reusable reducing the cost of consumable microcrystals, with treatment times being shorter due to more effective clearance of debris and dead cells.

The second developing method is hydradermabrasion. It works in the same manner as microdermabrasion but instead of exfoliating with propelled microcrystals, hydradermabrasion uses a combination of oxygen and aqueous solutions at supersonic speeds to remove debris and dead cells that are then suctioned away. This new modality is novel because as the treatment is exfoliating the epidermis, it is also hydrating the skin within the same treatment pass. This supersonic micro-droplet jet results in a pressured widening of micro-canals in the outer skin layers that facilitate greater hydration and cleansing of the skin. This moisturizing component allows for less irritation, reduced discomfort, and quicker recovery. Solutions and serums can also be formulated allowing better cleansing, extraction, and exfoliation while possessing antioxidant properties targeting specific skin types, textures, and conditions which cannot be delivered with traditional microdermabrasion. Hydradermabrasion has the same indications for use as microdermabrasion making it an excellent choice for persons with darker skin tones, aging skin, sensitive skin areas, oily, and dry skin complexions.

Further histological examination saw a replacement of elastic dermal tissue, collagen hyalinization, and fibroblast density correlating with a decrease in the appearance of fine lines, pore size, and hyperpigmentation in hydradermabrasion treated areas 6 weeks post-treatment with no patient complications. With its ability to add hydration, oxygen, and antioxidants to the exfoliated skin, this study demonstrates that hydradermabrasion treatment is effective at improving skin quality and should be considered an alternative to microdermabrasion.

LASER

Nonablative skin rejuvenation or "subsurfacing" comes as a low risk and short downtime technology which can improve aging structural changes without disruption of cutaneous integrity. The mechanism of action is supposed to be a selective, heat induced denaturalization of dermal collagen that leads to subsequent reactive synthesis. Nonablative skin rejuvenation is not a precise term since rejuvenation is a controlled form of skin wounding aimed at achieving a more youthful appearance after the wound heals.

Treatment of photoaged skin has been divided into treatment of ectatic vessels and erythema, irregular pigmentation, and pilosebaceous changes and into the improvement of the dermal and subcutaneous senescence. The epidermis and superficial dermis can be selectively damaged by two basic mechanisms: (a) by targeting discrete chromophores in the dermis or at the dermal-epidermal junction or (b) by utilizing mid infrared (IR) lasers.

The devices for treatment of vascular and/or pigment irregularities include lasers emitting light at 532-, 585-, 595-, 755-, 800-, and 1064-nm wavelengths as well as filtered light generated by IPL systems equipped with different cut-off filters. Lasers emitting 1,320, 1,450, and 1,540 nm using interstitial and intracellular water as target chromophores and pulsed dye lasers (PDL) using oxyhemoglobin as the primary chromophore are now employed for Type II photo rejuvenation only. The clinical efficacy of these nonablative modalities are weaker than that of the ablative methods, however, new collagen formation and clinically observable improvement in wrinkles can be observed. Reduction of facial wrinkles by using IPL devices has shown less effect comparing to laser technology, but for type I photo rejuvenation, IPL systems have in general shown considerably better results than laser systems operating at subpurpuric energy levels. Ultrastructural and histological analysis confirmed effectiveness of absorption of light (532, 585, 595, with or without 1064-nm Nd:YAG laser) in the blood vessels of the superficial dermis, resulting in the release of inflammatory mediators and growth factors into the interstitium followed by stimulated fibroblast activity and initiation of tissue repair and enhanced collagen and elastin neoformation replacing the originally damaged elastic tissue. The increase in dermal collagen has also been confirmed by noninvasive ultrasonographic analysis and radioimmunoassay.

Nonablative skin rejuvenation should not yet be considered an alternative for laser resurfacing. However there are interesting data showing comparative histological changes between the ablative and nonablative modalities.

Histological sections of skin before and after treatment with the different IPL devices have shown the formation of new collagen in the papillary and reticular dermis, as well as an increase in the number of fibroblasts and proportional decrease in the amount of solar elastosis is also usually found. If vascular and/or pigment disturbances improvement are immediate, the collagen remodeling response is delayed and maximum results are seen only between 3 and 12 months after treatment.

Laser resurfacing has been shown to be effective in counteracting photoaging through entire epidermal ablation, collagen shrinkage, stimulation of neocollagenesis, extensive dermal remodeling, regeneration of cellular organelles and intercellular attachments but parallelly, results in long recovery time are associated with risks of severe long lasting side effects, such as persistent erythema, hypo- or hyperpigmentation, infection or scarring.

Recently, fractionated CO_2-, erbium glass or erbium-YAG lasers have been introduced to reduce downtime and side effects. These devices emit light in a pixilated fashion onto the skin, producing an array of microthermal zones in the dermis. The controlled thermal stress to the epidermis and the dermal compartment is followed by a wound healing response ultimately leading to re-epithelization and dermal remodeling.

Although the underlying molecular changes induced by different ablative and non-ablative as well as thermal and non-thermal skin rejuvenation treatments are not fully understood, there are investigations suggesting important roles of heat shock proteins (HSP), transforming growth factor β (TGF-β), different MMPs, synthethases, hyals and hyaluronic acid (HA). Type I and type III procollagen mRNA was also elevated for at least 6 months.

Monopolar RF is a noninvasive way to obtain skin tightening and immediate collagen contraction with a single treatment. Unlike lasers, the RF technology produces electric current, which generates heat through resistance in the dermis and as deep as the subcutaneous fat. Unfortunately there is a lack of long-term studies of efficacy and analysis of side effects for the skin using this method of skin rejuvenation.

It is obvious that different treatment modalities using visible light devices have resulted in varying clinical effects and allow to select individual treatment parameters for different indications. For this reason, careful simultaneous evaluation of any pigment disturbances, vascular abnormalities, wrinkles, and cutaneous sagging as skin layers are all linked is highly recommended.

Mesotherapy

Mesotherapy, commonly known as “biorejuvenation” or “biorevitalization”, is a non-surgical method of correction of different aesthetic skin problems. The word “mesotherapy” comes from the Greek word “meso-“, which means “middle” and “therapeia” – to treat medically. In other words, this is a multiple injection introduction of different pharmaceutical, homeopathic or plant extracts, but also vitamins or microelements, in the dermato stimulate the biosynthetic ability of fibroblasts and facilitate interaction between cells and is intended to increase collagen and elastin production.

It appeared that mesotherapy could help for many aesthetic problems: it fights baldness, removes marks and scars, corrects cellulite, stops the process of skin-aging. It works successfully after plastic surgery intervention for faster recovery of the skin of the face and body, after peeling, after laser resurfacing by decreasing the recovery period. It can be wonderfully combined with introduction of botox, hyaluronic acid for wrinkles and all other non-surgical manipulations. By a series of mesotherapies the skin of the face becomes smooth, it tightens and revitalizes. It has new

radiance and hydration. It is applied to face, décolleté, back side of hands and body. It takes 3 to 6 treatments, depending on the products introduced.

Different injection techniques can be used in mesotherapy: the intra-epidermal technique; thepapular technique, in which reagents are injected into the dermo–epidermal junction; the nappage method, in which injections penetrate to a depth of 2–4 mm and are delivered at an angle of 30-60°; point-by-point injection into the deep dermis.

Mesotherapy is used to: remove fat in areas like the stomach, thighs, buttocks, hips, legs, arms, and face, reduce cellulite, fade wrinkles and lines, tighten loose skin, recontour the body, lighten pigmented skin, treat alopecia, a condition that causes hair loss. The technique uses very fine needles to deliver a series of injections into the middle layer of skin. The idea behind mesotherapy is that it corrects underlying issues like poor circulation and inflammation that cause skin damage.

'Vampire'/ 'Dracula' Lift (PRP – platelet rich plasma)

Platelet Rich Plasma (PRP) therapy of the skin, also known as the 'Vampire facelift' or 'Dracula facelift' is a revolutionary regenerative aesthetic treatment that encourages the skin to build more collagen and elastin and thus renew and rejuvenate itself. The treatment involves taking a blood sample from the patient, from which we then isolate a certain fraction of the blood, which is particularly rich in platelets. After application of a numbing cream for pain relief, this fraction of the patient's own blood is injected back into the skin using a special technique.

Platelets contain many beneficial growth factors. Upon reinjection the platelets release these growth factors, which trigger surrounding skin cells to proliferate and stimulate collagen production, thus helping to repair and regenerate damaged tissue.

Growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), are secreted from the α-granules of concentrated platelets activated by aggregation inducers. These factors are known to regulate processes including cell migration, attachment, proliferation and differentiation, and promote extracellular matrix (ECM) accumulation by binding to specific cell surface receptors. It has been shown that PRP may induce the synthesis of collagen and other matrix components by stimulating the activation of fibroblasts, thus, rejuvenating the skin.

PRP therapy is a great addition or in some cases even alternative to other non-surgical cosmetic treatments such as 'botox' and fillers. It's considered a very natural treatment, as it uses the patient's own cells and growth factors to stimulate tissue repair, rather than injecting synthetic substances. The molecular mechanisms underlying PRP-inducing wound healing processes are still largely unknown and experimental studies confirming the effects of PRP on aged fibroblasts are very limited.

'Vampire'/ 'Dracula' PLUS (Advanced PRP)

The 'Vampire'/'Dracula' PLUS lift is a combination of platelet rich plasma (PRP) with infusion of a high-grade cell nourishing cocktail. In this advanced PRP treatment, it can be mix the patient's own platelet rich plasma with a sterile solution containing more than 50 key skin optimization ingredients, before reinjecting it back into the skin. Apart from hyaluronic acid, the revitalizing solution used contains 12 vitamins, 23 amino acids, 6 coenzymes, 5 nucleic acid bases, 6 minerals and 1 special antioxidant, proven to protect and stimulate skin cells.

Dermal Fillers

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 which are perfectly biocompatible and totally absorbable: HA, vitamins, minerals, nutrients, hormones, GF, amino acids, autologous cultured fibroblasts, homeopathic products, etc. The distinct formulations can induce strikingly divergent molecular and cellular processes in fibroblasts in vitro. However, more detailed studies are required to elucidate whether and how the cellular and molecular processes are involved in facial skin rejuvenation in vivo, whether these processes are similarly efficient, independent of the age of the patients. The proof of concept, including long-term efficiency, optimal injecting protocols are still lacking too.

Dermapen

The Dermapen microneedling is a device that looks like a pen, that uses sterile, individually-sealed, disposable needle cartridges for optimal patient safety and comfort. Every Dermapen needle tip is actually made up of 12 smaller needles, which use proprietary technology to penetrate vertically into the skin. This creates small, micro-skin channels, while stimulating the skin's natural ability to heal itself and increasing the production of new collagen — which is the formation of strong, insoluble fibers that serve as connective tissue between cells.

These micro-skin channels carry up to 80% more topical nutrients, allowing penetration deep into the dermis fibroblasts, feeding the cells found in the dermis and basal layers. This increases the absorption of active ingredients into the skin, stimulating repair at a cellular level and accelerating the regeneration of the skin's epidermal cells. This treatment is similar to laser treatments, but without the severe side effects or the long recovery time. Adding to that benefit, studies have shown that Dermapen treatments are more effective than traditional microdermabrasion and chemical peels, due to how the disposable needles reduce the risk of cross-contamination. The adjustable needle depth also allows treatment that adapts to individual client's needs.

Microneedling being the advanced skincare treatment will reduce the appearance of wrinkles, fine lines, scarring, sun damage, improves the skin tone and texture, and give you plumper and smoother skin. As the treatment improves your skin's ability to self-repair by producing new collagen and elastin, you will see the exceptional results with minimal downtime. You will have the firmer skin and more youthful skin with this safe, chemical free treatment.

The microneedling procedure is easily tolerated by almost every patient and it can be tailored by going deeper in the specific areas where skin damage needs a stronger approach. When you start this treatment, after one or two treatments, you will see the reduced signs of the following: wrinkles and fine lines, scarring, enlarged pores, acne scars, stretch marks, skin sags, hair loss, burn scars, pigmentation marks from sun damage or acne, improve skin tone, stimulate the production of collagen and elastin.

Jett Plasma Medical it is method that use the result of the physical agents, like ions, electrons, neutrals, photons, nitric oxide, hydrogen peroxide on plasma. It is recomanded for improving the skin color and structure, increasing its tone, elasticity, flexibility, for activation of the process of production of collagen fibers, which continues for 12 months after the procedure, and for smoothing age wrinkles of different depth. The result is a pronounced visual lifting effect and the observed reduction of the number of wrinkles of neck, legs, arms, hands, feet, including those around the lips and eyes. Jett Plasma Medical is a safe method because the superficial layers of the skin are not injured.

Botulinum toxin (BTX) has no effect on skin texture and cannot discontinue the skin aging process. However, regular BTX injections can slow down the visible aging process by helping in the management of certain dynamic facial lines and wrinkles. Current treatment options of exaggerated frown lines, glabellar lines or crow feet such as surgery or implants, do not address

the underlying cause of these lines, namely the excessive nerve stimulation. The mechanism of action of BTX makes it an ideal agent to target the major cause of these dynamic lines.

Results and discussion

The desired therapeutic anti-aging effect of the skin is a continuous, step-by step process, which combines various methods of the skin bio-revitalization and rejuvenation, augmentation, restoration of each skin layer individually and in the light of many other factors—from a style of the life to the immune, genetic, emotional and health status in general.

Simultaneously it is necessary to prevent wrinkle formation by reduction of inflammation (topical or systemic antioxidants) in combination with sunscreens and retinoids to enhance their protective effects. An important attention must be accorded to Transforming Growth Factor-β family, other TGF-β-based approaches (Decorin and Mannose 6 Phosphate), modulation of Smad3/Smad7 Signaling, Epidermal Growth Factor family, Fibroblast Growth Factor family, Platelet-Derived Growth Factor family, Granulocyte Macrophage-Colony Stimulating Factor, Connective Tissue Growth Factor, Interleukin 10, Connexins, other approaches under investigation for scar reduction, collagen, fibronectin, laminin, elastin, glycosaminoglycans and other natural biomaterials.

Conclusions

Regenerative Aesthetic Dermatology is focused on innovative treatments to support the skin in restoring and regenerating old and/or damaged tissue and thus improving overall skin quality, promoting faster healing while minimizing downtime and side effects for patients. The onset of effects could be instantly after procedure or can be observed gradually increasing over the time (weeks or monthes), as we are determining the skin to help itself.

The regenerative treatments are encouraging the skin to build more collagen and elastin itself by bio-stimulation: resurfacing the epidermis (topical drug application, ablative LASERs, LASER radiofrequency resurfacing, ablative radiofrequency, microneedling, plasma skin resurfacing, crystal-free microdermabrasion), the formation of new collagen (IPL, LASERs, radiofrequency, infrared, Jett Plasma Medical, medical needling, mesotherapy, platelet-rich plasma, fillers as hyaluronic acid, *HydraFacial MD, Oxygen facial, chemical peels,* hormone replacement therapy, autologous and allogeneic stem cells, gene therapy), slow down the visible aging process by helping in the management of certain dynamic facial lines and wrinkles (Botulinum toxin).

While natural aging is genetically determined, extrinsic aging can be prevented. Aesthetic dermatology should contribute to "healthy aging" not only in cosmetic means by trying to erase time vestiges in skin but by also playing a significant part in prevention, regeneration, and delaying of skin aging combining knowledge of possible local and systemic therapy, instrumental devices and invasive procedures, filling the lack of scientific investigations and becoming one of the important focuses of the aging research.

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