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REVIEW

Photoaging and the clinical utility of fractional laser

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Abstract: The description of atomic structure by Niels Bohr set the basis for the emergence of quantum physics. Based on these fundamentals, Einstein published in 1917 a paper on the amplification of energy by Stimulated Emission of Radiation as part of his quantum theories. In 1955, Townes and Gordon turned Einstein's theories into practice, creating a coherent and amplified microwave device using ammonia gas in an optical medium. But it was at the beginning of the 1980s, that Anderson and Parrish published an article about the selective photothermolysis model which revolutionized clinical practice. The use of laser in photoaging began with CO_2 (10,600 nm). In 1989, it was first used for resurfacing of a face with prominent photoaging. Ablative lasers have therefore had great popularity in the 1980s and 1990s, but prolonged postoperative time and significant risk of side effects have lowered the acceptance by patients. In 2004, the description of the fractionated radiation for the treatment of photoaging, by Mainstein, represented a great event. The stimulation of collagen occurred through fractional laser beams, which would reach the selected area while saving islands of sound skin. These islands accelerated the process of cicatrization of the treated tissue and shortened the postprocedure time. Furthermore, the fractionated radiation presented a smaller range of side effects, increasing the safety of the procedure. As mentioned earlier, as fractional lasers incise on the skin, they leave islands of healthy skin that accelerate recovery, while generating necrosis columns. Such necrosis columns remove damaged extracellular matrix material, allowing resettlement of fibroblasts. Such resettled fibroblasts, under the influence of a new tensile strength, restart to produce structures for extracellular matrix, such as collagen, elastin, and proteoglycans, in a more physiological way. Fractional lasers are considered by many dermatologists as the best choice in laser therapy for the treatment of photoaging.

Keywords: fractional laser, photoaging, collagen, elastin, hyaluronic acid

Lasers in dermatology

History

The description of atomic structure by Niels Bohr set the basis for the emergence of quantum physics. According to his theory, atoms existed in a state of inertia, in which they did not radiate any energy. However, in-between excitement and rest, they would be able to radiate energy (or quanta).[1] Based on these fundamentals, Einstein published in 1917 a paper on the amplification of energy by Stimulated Emission of Radiation as part of his quantum theories.[1]

In 1955, Townes and Gordon turned Einstein's theories into practice, creating a coherent and amplified microwave device using ammonia gas in an optical medium. The outcome, known as microwave amplification of stimulated emission of radiation

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was the prototype of lasers we know today.[2] The first light amplification of stimulated emission of radiation was created in 1955 by Maiman.[3] The amplification system used a ruby crystal with red light beam and a wavelength of 694 nm. Many other means were developed from this, either solid (eg, neodymium-doped yttrium-aluminum-garnet) or gaseous (eg, CO_2).[3]

The American doctor Leon Goldman was the first to explore the properties of laser use in clinical practice.[2] In 1965, he began to publish a series of papers concerning laser and skin. The first one describes the ruby laser in the treatment of tattoos.

Due to its great risk of potential and unacceptable complications, the continuous mode of light emission was soon replaced by the intermittent mode, which minimized the risks without abolishing them.[1] The absence of a specific target in the procedure still represented a lack of safety. Many of the earliest uses, after Goldman, aimed at the treatment of vascular lesions such as port-wine stains. However, used wavelengths (488–514 and 577–585 nm) were close to those of melanin, thus not very selective.[1] Acknowledging the undesired side effects due to great exposure time to which the adjacent sound tissue was subjected, Anderson and Parrish proposed a new model which revolutionized clinical practice.[4] At the beginning of the 1980s, they published an article in Science magazine about the selective photothermolysis model. Having developed a pulsed flash pulse, they suggested that by selecting a wavelength capable of delivering energy to a specific chromophore in a shorter time than its thermal relaxation time (the time needed for the tissue to cool down to half the temperature reached immediately after laser irradiation), the damage to the periphery would be minimized.[5]

The use of laser in photoaging began with CO_2 (10,600 nm). In 1985, the use of this device for the treatment of actinic cheilitis was reported for the first time.[6] In 1989, it was first used for resurfacing of a face with prominent photoaging and multiple actinic cheilitis.[7] The development of the CO_2 laser, however, dates from 1964.[8] The energy released was well absorbed by water and epidermis; and, used in a focused manner, worked like a scalpel. CO_2 pulsed lasers emerged in early 1990s as a way to vaporize the epidermis, limiting the thermal damage to the dermis. In 1991, it was approved by the US Food and Drug Administration for skin renewal, leading to its increased use for actinic keratosis lesions, as well as for the improvement of wrinkles and flaccidity.[9–12] The vaporization of the surface would remove the damaged epithelium, and the heating of the dermis would lead to a decrease and shortening of collagen, resulting in increased firmness.[12,13] The erbium laser (2,940 nm) dates from 1996,[14] and has been manufactured for the same purpose.

Ablative lasers have therefore had great popularity in the 1980s and 1990s, but prolonged postoperative time and significant risk of scarring and pigmentation have lowered the acceptance by patients.[1] The nonablative laser was then created in the quest of a treatment to improve photoaging with fewer side effects.[14–16] The goal was to stimulate collagen in the dermis without causing ablation of the epidermis. To this end, 800 nm diode lasers and neodymium-doped yttrium-aluminum-garnet 1064 nm long pulse were used. The results, however, were unsatisfactory and the procedure did not become popular as expected.[15]

In 2004, the description of the fractionated radiation for the treatment of photoaging, by Mainstein, represented a small revolution.[17] The stimulation of collagen occurred through fractional laser beams, which would reach the selected area while saving islands of sound skin. These islands accelerated the process of cicatrization of the treated tissue and shortened the postprocedure time. Furthermore, the fractionated radiation presented a smaller range of side effects, increasing the safety of the procedure.[15] From this point, nonablative fractional lasers have been developed with wavelengths higher (1440–1565 nm) than those of previously, less successfully tested lasers;[9] as well as ablative fractional CO_2 lasers (10,600 nm) and erbium (2,940 nm).[18–21] These lasers are still considered by many dermatologists as the best choices in laser therapy for the treatment of photoaging.[21]

Nonablative fractional lasers

The lasers in this category comprise wavelengths of 1,440, 1,540, 1,550, and 1,565 nm. Such lengths are well absorbed by water, being a logical choice for the stimulation of collagen remodeling.[22] By releasing energy, the lasers promote columns of coagulation in the skin, with the local epidermis being preserved, as there is no ablation. The dermis column, undergoing necrosis, releases its products from the dermis to the epidermis, leaving a dead space that will be filled by new collagen.[20]

The release of the rays, whose energy is usually measured in millijoules,[15] has variable fluency, this variation being what determines the treatment's penetration and depth. The results are adjustable: the collagen stimulation will be directly linked to increased fluency.[23] This treatment will be effective to remove vessels and pigmented lesions – even if these wavelengths do not have hemoglobin and melanin as targets, they are indirectly coagulated and therefore removed.[20]

There are two commonly used technologies. The first one, 1,540 nm (erbium glass laser rod) releases rays in a static manner, as is "stamping" the skin. The pulse lasts 10–100 milliseconds; and the fluences used vary from 20 to 100 mJ/cm^2. The average thermal damage caused is of 333 µm wide and 1 mm deep at high fluences. In the second type, 1,550 nm (erbium glass laser) releases the rays dynamically, as a "scanner". The treatment starts with the movement of the tip over the skin, with automatic control of rays' density, and the depth and width of the coagulation columns.[15] Both treatments imply edema and erythema lasting ~1 week. Used primarily for the treatment of photoaging, the technique can also be applied in any area of the tegument, and has been a controversial choice for the treatment of melasma.[24] Despite removing pigments, it does not alter the course of the disease, and the effects on rebound and relapse remain uncertain.[25]

Ablative fractional lasers

The ablative fractional technique was introduced in 2007.[26] The intention was to establish a safe procedure, in the same pattern of nonablative laser, and effective concerning the ablative techniques of CO_2 and erbium. The rays' fractioning reached, in fact, deeper levels, and healthy skin columns reduced the postprocedure time, as well as the risk of side effects. In that category, the lasers currently used are erbium of 2,940 nm and CO_2 of 10,600 nm.[15]

It is usually possible to achieve the same results as those obtained with nonablative fractional lasers with a smaller number of sessions.[15] The literature indicates that, in the treatment of photoaging, an average of three sessions of nonablative fractional laser will equal one session of ablative fractional laser.[27–29] Many authors recommend prophylaxis for herpes before the procedure, because an infection of this kind in the postprocedure period can deepen the created wound, with side effects like scars and dyschromia. It is also necessary to use a smoke aspirator by suspending the epidermis that undergoes ablation.[18]

Some fractional erbium lasers, unlike the purely ablative ones, are capable of causing CO_2 laser coagulation. The presence of a double pulse, in some machines, combines a more superficial short pulse and a long one, able to coagulate the tissue by reaching deeper levels. This modification allowed the ablation with erbium to reach 1 mm.[30]

Photoaging

The complaints of patients seeking treatment for skin aging vary from minor cosmetic problems such as wrinkles, spots, and flaccidity to bigger and more complex issues, often disfiguring and with high psychosocial impacts. Therefore, skin aging is considered a clinical entity with a broad spectrum of severity, ranging from wrinkles to malignant lesions.[31]

Human skin, like other body organs, heads toward aging. However, unlike these organs, the sink is in direct contact with the environment and, consequently, gets old due to additional environmental factors (radiation, smoke, wind, chemicals).[32] Therefore, there are two different processes that lead to skin changes associated with aging: the intrinsic and the extrinsic ones.[33] The first one is innate, the "biological clock", which affects the skin the same way as it happens to the other organs, in a slow, irreversible, and degenerative mode,[31] a result of the effect of gravity, facial expressions, hormonal changes, and genetic programming.[34] The second is a direct consequence of external elements, particularly of ultraviolet (UV) radiation, and hence being called photoaging.[35]

The intrinsic aging effects are observed throughout the skin, even in areas that are usually covered; as for exposed areas, especially the face and back of hands, photoaging exceeds degenerative changes.[31] Thus, changes in the skin of the face and the neck, the main complaints of patients, result from a combination of intrinsic and extrinsic aging; however, it has been suggested that 80% of facial aging is due to sun exposure.[36]

Exposure to UV radiation causes premature skin aging. The sun exposure is a cumulative process that affects mainly fair-skinned individuals.[37] The UV radiation-induced photooxidation is the main damaging factor for the connective tissue of the skin, yet there is evidence that intrinsic and extrinsic aging processes have, at least in part, common biological, biochemical, and molecular mechanisms.[38] The alterations associated with photoaging occur in both the epidermis and the dermis.[39,40] These changes are associated clinically with roughness, uneven pigmentation, telangiectasia, deep wrinkles, and neoplasia.[33,36,41,42]

Intrinsic aging

A number of theories have been proposed to explain the phenomenon of aging in general, and some of them also apply to skin aging.[31] One of these theories is related to the phenomenon of Hayflick,[43] who postulated that diploid cells, such as fibroblasts, have a finite lifetime when in culture medium. This observation, extrapolated to the tissues, where over time the depletion of dermal stem cells is observed, could be implicated in the senescence and cell degeneration.[31] One example of this is the repair in telomeric DNA. Telomeres are the sequences of nucleotide repetition present at the

end of chromosomes.[44,45] As the DNA polymerase cannot transcribe the final sequence of these bases in the DNA strand during replication, the telomeric size is reduced by each mitosis.[46] This reduction of telomere would be then associated with cell aging and with the finite lifetime described by Hayflick.[46–48]

Another theory concerns free radicals, and suggests that oxidative stress would damage not only the lipid layers of the cell membrane, but also the components of the dermis, especially collagen.[49] Through these free radicals, a process of nonenzymatic glycosylation of the collagen takes place, altering its primary functionality. This theory was developed through observation of diabetic patients with nonenzymatic glycosylation of crystallines and the blood vessels collagen, which are both signs of premature aging which present as cataracts and atherosclerosis, respectively.[50]

Finally, the skin aging is attributed to the differential gene expression. This theory suggests that, with the advance in aging, skin cells such as fibroblasts, alter their biosynthetic repertoire by expressing different genes. It has been shown that the elderly have a smaller biosynthesis of collagen than the neonates.[51] This would explain the greater difficulty of cicatrization or replacement of collagen fibers in older individuals. Similarly, if we measure the elastin mRNA in fibroblasts cultures of people as from the fourth decade, we will note a remarkable reduction.[51] Other studies showed that the degradation of oxidized products is carried out by the proteasome, a multicatalytic protease, whose activity also seems to decrease throughout life. In this way, there is an incomplete degradation of oxidized proteins, an increase of protein aggregates, and an acceleration of cell dysfunction, which ultimately leads to cell aging.[52,53] This situation, in which there is little capacity of the fibroblast to replace broken fibers, leads to a slow and continuous process of degeneration.[31]

Collectively, all the theories described for the aging of the dermal connective tissue suggest an imbalance between synthesis and degradation, with loss of repair capacity to stand up to progressive degeneration. This imbalance culminates in the loss of collagenic and elastic fibers, which manifests clinically by atrophy and loss of elasticity.[31]

Extrinsic aging

The main factor involved in the extrinsic aging is the exposure to UV. Thus, this is the most studied mechanism involved in senescence. The effects of exposure are cumulative, and they are worse in lower skin types. Radiation promotes an intricate cellular mechanism that leads to the aforementioned clinical features of photoaging.[53,54]

UV radiation involves the activation of cell surface cytokines and growth factor receptors (eg, epidermal growth factor, tumor necrosis factor-α, and interleukin-1) in the membrane of keratinocytes and fibroblasts in just 15 minutes of in vivo exposure. Such activated receptors induce a phosphorylation cascade that stimulates the production of matrix metalloproteinases (MMPs).[53]

MMPs are proteolytic enzymes involved in the tissue remodeling process related to illness or to normal tissue. They share structural and functional properties but differ in their substrate specificity.[55] Over 20 MMP have been described and can be divided into subclasses. Biochemical studies divide the main groups of MMPs in specific collagenase (interstitial), stromelysins, stromelysins-like (matrilysins), gelatinases, and membrane type. The main MMPs involved in photoaging are MMP-1, MMP-3, and MMP-9.[56]

MMP-1 initiates the cleavage of fibrillar collagen (types I and III) in its central triple helix structure. After it starts, new cleavage follows, led by MMP-3 and 9. These enzymes' action on collagen structure affects the integrity of the dermis, as the collagen cleaved is not replaced by new of proper fibers.[51]

Besides stimulating dermal collagen degradation through the action of metalloproteinases, UV radiation prevents new collagen formation. Its action inhibits the production of procollagen (collagen precursor) I and III, directly through apoprotein 1, which inhibits the formation of transforming growth factor-β. Transforming growth factor-β is a major profibrotic cytokine, which, besides the decrease in its synthesis, has a diminished production of its receptors because of UV radiation.[51]

Described as acute changes in radiation exposure, these mechanisms, if perpetuated, lead to a chronic reduction of procollagen production. However, the mechanisms that lead to a sustained reduction in collagen levels in the dermis are not well detailed. Fibroblasts in photoaged skin and in unexposed skin have the same ability, when cultured in vitro, of producing procollagen. Thus, it is assumed that the decrease in collagen production in photoaged skin is likely a result of an inhibition induced by the environment in which the fibroblasts is present (with cleaved and disorganized collagen fibers), instead of a change in the fibroblast itself.[57]

Just like collagen fibers, the elastic fibers also suffer from UV radiation action.[58] It is well documented that the more superficial the elastic fibers, the more they will suffer the action of UV radiation.[59] The normal elastic system consists of mature elastic fibers (in a deep layer), and elauninic and oxytalan fibers (near the epidermis).[60] Thus, elauninic and oxytalan fibers are the ones most susceptible to destruction

due to a greater proximity to the external environment, although the mature fibers also suffer the effects of UV radiation. The fibers are considered altered when, instead of the usual straight and elongated aspect, they present a thickened and tortuous one. Decreased oxytalan fibers and less dense elauninic plexus characterize slight modifications, while the dermal–epidermal junction rectified with no oxytalan fibers and still more irregular elauninic plexus, with coarse fibers and sometimes nodular arrangement, characterize significant changes.[61]

The product of the cleavage of collagen fibers, with subsequent accumulation and decrease in its production, and the presence of less dense and irregular elastic fibers promote a striking histopathological feature, called solar elastosis. The accumulation of "elastotic material", associated with actinic damage has been primarily attributed to elastin, the main component of elastic fibers, because of their positive staining by Verhoeff-van Gieson method.[57,62] However, it was shown that in addition to elastin, the material that accumulates comprises a variety of components of the extracellular matrix (ECM) of the dermis. As the normal elastic fibers, the material that accumulates in the solar elastosis is composed of elastin and microfibril proteins like fibrillin.[63,64] Despite the similar content to that of normal elastic fibers, the accumulated material in solar elastosis is highly modified in its supramolecular and functional organization.[65]

As a result of these observations, studies in the past focused mainly on the pathology and biology of the elastin and its microfibrillar components.[15] Uitto and Bernstein[31] demonstrated that the expression of the elastin gene is markedly stimulated in the photodamaged dermal cells; and Kawaguchi et al[66] demonstrated that free radicals too, induced by UV radiation, had an important role in the activation of the elastin gene. However, with the description of the action of metalloproteinases in collagen degradation, the metabolism of this protein became the major known factor in the photoaging mechanism.[67] As a result, the studies of the elastic fibers alteration process were left behind. The "elastotic material" was conventionally called basophilic degeneration of collagen, insofar as the accumulation of this material was associated with the replacement of mature collagen fibers by other fibers with basophilic aspect.

Even today, the scientific knowledge has not yet been able to establish the exact relation between elastic fibers and photoaging: whether once degraded they cannot regenerate or, being overexpressed they accumulate as "elastotic material".

In 2007, Muto et al[68] described a new possibility for understanding the mechanism of photoaging. They showed that elafin (a serine protease inhibitor formerly known as skin-derived antileukoproteinase) was produced by fibroblasts as a result of exposure to UVA radiation, and would bind to elastic fibers protecting them from the breakage mediated by elastase.

Immunohistochemical studies confirmed strong elafin marking in the elastotic material accumulated in photodamaged skin. Because of this observation, the author linked the accumulation of elastotic material to a drop in degradation, instead of an overproduction of elastin. Chronic exposure to UV radiation would lead to sustained production of elafin, which would bind irreversibly to the elastic fibers. However, if the resistance to degradation and the propensity to aggregate both increase the synthesis of tropoelastin by fibroblasts, it may also be inferred that the overproduction would cause the accumulation of elastotic material along with the nondegradation. The controversy aforementioned is an example that well illustrates photoaging as a mechanism that is still far from being fully understood.

From the histological point of view, the one thing concrete in the photoaging process is the morphology of the dermis. In the hematoxylin and eosin staining method, the elastosis in the dermo–epidermal junction is characterized by the presence of hyalinized collagen fibers with disorganized aspect. In the papillary dermis, it is characterized by basophilic material diffusely dispersed in the high dermis (slight elastosis) or with nodular arrangement or in amorphous material strip (established elastosis). Specific staining for collagen fibers, such as picrosirius, confirms the hyalinized and disorganized aspect of the collagen fibers in the grenz zone; and staining methods for elastic fibers, such as orcein, confirm the decrease in density or absence of the superficial plexus (oxytalan and elauninic) associated with the loss of usual morphology of the mature elastic fibers.

Finally, it is relevant to mention that the ECM is not only composed of collagen and elastic fibrous proteins. Carbohydrates exist either isolated or in association with proteins and play an important role in skin biology. The presence of glycosaminoglycans is recognized in the ECM that bind to extracellular proteins to form proteoglycans (protein core associated with the carbohydrate chain), formerly called dermal mucopolysaccharides.[54] With more than 95% of carbohydrates in their structure, the proteoglycans look more like polysaccharides as compared with proteins. The main known proteoglycans are hyaluronic acid, chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, and heparin.[56] They have multiple functions, but we can highlight the maintenance of hydration, the support of the connective tissue and its cellular elements, as well as its close relation

with growth factors and cytokines.[69] As the fibrous protein elements, proteoglycans suffer the action of UV radiation. Because of the photoaging, glycosaminoglycans (especially hyaluronic acid and chondroitin sulfate) disarrange and redistribute, contributing to the change in the ECM architecture.[69] Observing these proteoglycans, in 2011 Rock et al[70] cast new light on the ECM remodeling mechanism in photoaging. In their paper, they found out that collagen fragments derived from metalloproteinase cleavage by the action of UVB radiation inhibited to some extent the production of hyaluronic acid by fibroblasts; thereby some effects on the skin, such as wrinkles, loss of elasticity, and hydration, would also be associated with this. These findings were consistent with the experiment of Tzellos et al,[71] which associated the change in the expression of hyaluronic acid genes and its metabolic enzymes with an extrinsically aged skin. Hyaluronic acid is recognized as extremely important in cellular proliferation and migration, and its alteration therefore determines the inability in regeneration of a photodamaged skin, the same way changes in collagen and elastic fibers do.

Fractional lasers and photoaging

Photoaging is responsible for the alteration of collagen fibers, elastic fibers, and proteoglycans present on EMC. The altered arquiteture of the EMC modifies the tensile strength of fibroblasts more than its anatomy. An evidence of this fact is that photoaged skin fibroblasts, when cultured in a healthy environment, are capable of producing protein structures for the ECM, like a nonphotoaged skin fibroblast.[32]

As mentioned earlier, as fractional lasers incise on the skin, they leave islands of healthy skin that accelerate recovery, while generating necrosis columns.[15] Such necrosis columns remove damaged ECM material, allowing resettlement of fibroblasts. Such resettled fibroblasts, under the influence of a new tensile strength, restart to produce structures for ECM, such as collagen, elastin, and proteoglycans, in a more physiological way.

It is therefore considered that the effect of fractional lasers on photoaged dermis is a predominantly physical effect.[15] Restoring the deteriorated microclimate, the fibroblast may restore functions closest to those of a nonphotoaged skin.

Disclosure

The authors report no conflicts of interest in this work.

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