# Assessment of Laser Effects on Skin Rejuvenation

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**Abstract**
Laser skin resurfacing has changed the approach of facial skin rejuvenation over the past decade. This article evaluates the laser effects on skin rejuvenation by the assessment of laser characteristics and histological and molecular changes, accompanied by the expression of proteins during and after laser-assisted rejuvenation of skin. It is important to note that different layers of skin with different cells are normally exposed to the sun's UV radiation which is the most likely factor in aging and damaging healthy skin. To identify the expression of proteins, using validated databases and reviewing existing data could reveal altered proteins which could be analyzed and mapped to investigate their expression and their different effects on cell biological responses. In this regard, proteomics data can be used for better investigation of the changes in the proteomic profile of the treated skin. Different assessments have revealed the survival and activation of fibroblasts and new keratinocytes with an increase of collagen and elastin fibers in the dermis and the reduction of matrix metalloproteinases (MMPs) and heat shock proteins (HSPs) as a result of different low-power laser therapies of skin. There are a wide range of biological effects associated with laser application in skin rejuvenation; therefore, more safety considerations should be regarded in the application of lasers in skin rejuvenation.
**Keywords:** Rejuvenation; Scars; Laser; Skin aging; Laser therapy.

## Introduction

Laser applications in medicine have been promoted in different fields such as dermatology, dentistry, ophthalmology, and surgery.[1-4] There are many documents about the widespread use of lasers in skin treatment, especially in skin rejuvenation.[5-7] Skin aging is a natural process that occurs as people age. However, it could be accelerated by such factors as sunlight, stress, and chemicals. Skin aging is affected by numerous genetic and environmental factors that can appear as wrinkles, abnormal pigmentation, skin weakness, and telangiectasia.[8] Researchers are increasingly looking for different ways to rejuvenate skin. Recently, the use of laser radiation for skin rejuvenation has become commonplace and has apparently been effective. The expansion and application of lasers and light for medical procedures based on the selective principle of photothermolysis have increased exponentially over the past two decades. The fundamental principle of this procedure is that selective heating is attained by preferential laser light absorption and heat manufacture in the target chromophore, with heat being localized to the target by pulse duration shorter than the thermal relaxation time of tissue.[9] This study examines the effect of the laser beam on skin rejuvenation in different aspects and reviews the published articles in this field to present a new perspective of laser application in skin rejuvenation. The study includes the research method, skin aging phenomena, skin photoaging histology, skin aging treatment, laser features and skin aging treatment, ablative lasers, nonablative lasers, fractional lasers, Photobiomodulation (PBM) lasers, laser effects on tissues, photothermolysis, molecular aspects of laser effects in cell biology, and conclusion parts.

## Methods

The search engines of Scopus, Google Scholar, and PubMed were applied to search such keywords as "Skin", Laser therapy", "Rejuvenation", "Skin Aged",

and "Proteomics". The titles in English were identified and studied in such a way that the relevant articles were selected for more evaluation and assessment. The abstracts of 155 documents were investigated and the full texts of 134 articles were selected. After the review of 134 articles, 84 documents were chosen to be included in this study.

## Skin Aging Phenomena

The clinical signs of skin aging include thinning skin, cigarette paper-like wrinkles, elasticity loss, and benign overgrowth or vascular formations such as keratosis or angioma.[10] These clinical signs appear by genetic factors of aging. UV irradiation induces photoaging and gravity, leading to ECM matrix changing to appear wrinkles. Therefore, these aging processes are accompanied by the phenotypic exchange in cutaneous cells as well as structural and functional changes in extracellular matrix components such as collagen, elastin, and proteoglycans, which are necessary to provide tensile strength, elasticity, and hydration to skin respectively.[11] Also, they cause laxity and fragility of skin with reduced collagen syntheses and enzymatic degradation.[12] The degree of skin photoaging could be classified by Fitzpatrick skin types I to IV according to its severity from few wrinkles to deep wrinkles. We should also mention the vascular pattern changes as telangiectasia.[13]

## Skin Photoaging Histology

The chronology of histological change in skin aging indicates that events such as epidermal atrophy and reduced collagen amount and fibroblasts of dermis along with the epidermal atrophy, mainly with regards to the spinosum layer of epidermis according to prolonged cell cycles are happened.[14] The number of melanocytes and Langerhans cells decreases per decade after the age of thirty.[15] Subsequently, the amount of collagen and elastic fibers and also fibroblasts decreases in chronologically aged skin compared to younger skin.[16,17] In postmenopausal subjects, collagen synthesis is reduced by 30%.[18] However, the heterogeneity and thickness alteration of epidermis in photoaging are reported.[19] An increase in melanocytes and different keratinocytes and the regulation of the expression of free radicals are other consequences of photoaging histology.[20] It can be generally stated that changes in the aged skin occur in the dermis and between the epidermis and the dermis. It leads to the accumulation of glycosaminoglycans and proteoglycans in the area. However, it may be due to the accumulation of metalloproteinases in hypertrophic fibroblasts and it is in contrast to the photoaged skin in which the number of inflammatory cells such as eosinophils, mast cells, and other mononuclear cells increases.[21,22] Wrinkle formation may cause a reduction in collagen fibers. Mostly prominent histological feature of skin photoaging is the accumulation of elastic amorphous fibers and also

thicked fibers in dermis named Solar Elastosis.[23]

Several biological pathways and risk factors related to skin aging are determined as; telomerase shortening,[24,25] Matrix metalloproteinases (MMPs), signal transduction,[26,27] oxidative stress,[28,29] vascular alterations,[30] cytokines alterations[31] and UV radiation.[32]

## Skin Aging Treatments

Skin aging is affected by various factors including genetics, environmental exposure (UV, xenobiotics and mechanical stress), hormonal changes, and metabolic processes (production of reactive chemicals such as reactive oxygen species, sugars, and aldehydes). All factors work together to transform the skin, its function and appearance. However, solar UV is undoubtedly a major factor responsible for skin aging. Skin aging may cause psychological side effects, leading patients to seek a suitable solution.[33] Public desire to look good and young is inevitable and more than 8 million cosmetic treatments were performed in the United States in 2017.[34] The treatment of photoaged skin may be classified into two categories: one is the removal of pigmentation, erythema, irregular vessels, and sebaceous changes and the other one is the improvement of skin senescence.[35] The process of skin rejuvenation has been associated with aggressive elements such as peeling in the past, but in recent years the demand for non-invasive treatment of skin rejuvenation has increased dramatically. Public demand for faster healing treatments with better natural state maintenance has increased, leading to a shift in skin rejuvenation techniques at public requests.

## Laser Features and Skin Aging Treatment

One of the techniques for rejuvenating the skin is to use lasers and other light beams. Lasers have been used for skin rejuvenation since 1980.[36] Different wavelengths of lasers have been used to treat skin aging (see Table 1). The use of high-power lasers and skin peeling by heat generation is one of the methods for skin rejuvenation. Since this process is accompanied with side effect; the adjacent damaged tissues recover with the same mechanism of wound healing, but recently the use of low-power lasers has become commercial. Different types of lasers for skin rejuvenation are ablative lasers, non-ablative lasers, and fractional lasers (Figure 1).

## Ablative Lasers

These kinds of lasers have been used to treat scars, pigmentations, and rhytides by removing the epidermis and heating dermis (Table 2). Ablative lasers are generally used for skin resurfacing and rejuvenation.[39] Ablative lasers evaporate tissue and hence are more aggressive, in contrast with the mild non-ablative lasers that leave the skin intact. However, ablative lasers reduce time of treatment and cause a more difficult recovery process, they stay the lasers that create the most dramatic
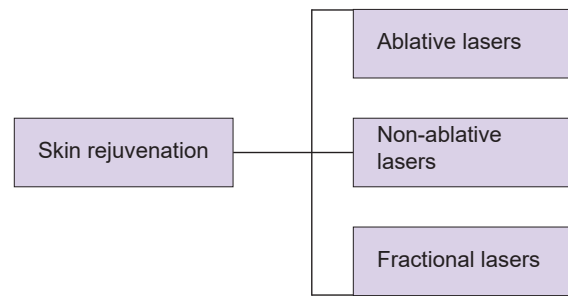
**Table 1.** Two Types of Lasers With Different Wavelengths Used for Skin Rejuvenation[37,38]

| Laser Wavelength | Type 1(Vascular or Pigment Treatment) | Type 2 (Skin Rejuvenation) | Special Targeting |
|---|---|---|---|
| 532 nm | * | | General |
| 585 nm | * | | General |
| 595 nm | * | | General |
| 755 nm | * | | General |
| 800 nm | * | | General |
| 1064 nm | * | | General |
| Intense pulsed light lasers | * | | General |
| 1320 nm | | * | Target water |
| 1450 nm | | * | Target water |
| 1540 nm | | * | Target water |
| Pulse dye lasers | | * | Target oxyhemoglobin |



**Figure 1.** Different Types of Lasers Involved in Skin Rejuvenation.

impressive. For severe facial wrinkles, pigmentation, and skin challenges, ablative lasers are often the preferred treatment.[33] Non-ablative lasers penetrate into the dermis and heat the dermis without heating epidermis. These types of lasers denature dermis proteins such as collagen, and stimulate collagen synthesis and finally tighten the skin bed (Figure 2).[39] The most common ablative lasers used for skin rejuvenation are $CO_2$, erbium-doped yttrium aluminium garnet (Er:YAG), and erbium doped yttrium scandium gallium garnet.

## Non-ablative Lasers
Non-ablative laser resurfacing demonstrates one of the main developments in procedural dermatology over the past decade and has become the treatment of selection for a broad range of aesthetic indications. However,

safety concerns related to their use in darker skin types have remained.[40] These lasers are less destructive than ablative lasers and stiffen the skin by stimulating collagen production in the dermis; the epidermis is protected through skin cooling. This type of laser is less aggressive than the optical laser and due to the stimulation of collagen in the dermis, it makes the skin firm (Table 2). The epidermis remains cool when using this laser because the waves penetrate the dermis layer. The heat generated in the dermis coagulates the collagen and then begins the wound healing process. As a result, new collagen synthesis is performed on the substrate of the skin and extracellular matrix.[41] The side effects of these lasers, such as scars and infections, have decreased[42]; however, the efficiency of non-ablative lasers is less than ablative ones and they have been used for patients with moderate photoaging.[43]
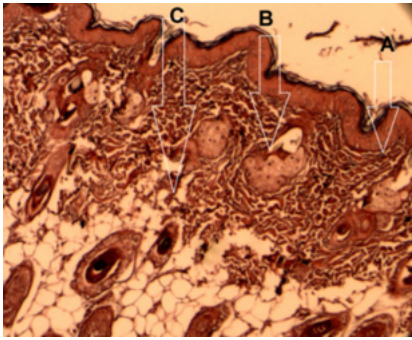
## Fractional Lasers
Fractional lasers including non-ablative and ablative fractional lasers generally provide columns at the depth of 1 and 2.5 mm into the skin, respectively.[34] Non-ablative lasers influence dermis and leave epidermis with no

**Table 2**. The Characteristics of 3 Types of Lasers Used for Skin Rejuvenation: Er:YAG, Er:DYSGG, PPTP and Nd:YAG[51,52]

| Type of Laser | Source of Laser | Wavelength | Action |
|---|---|---|---|
| Ablative lasers | $CO_2$ Er:YAG | 10600 nm 2940 nm 2790 nm | Thermally ablate and vaporize epidermis & upper region of dermis |
| Non-ablative Lasers | ILP, High dose PDL Low dose PDL PPTP Nd:YAG Diode Lasers Erbium glass lasers Alexandrite lasers | 500-1299 nm 585-595 nm 589-598 nm 532 nm 1032 & 1064 nm 1450 nm 1540 nm | Tighten the skin by collagen synthesis stimulating by the wound healing process. Less destructive than ablative lasers. Heat dermis. |
| Fractional lasers Ablative Non-ablative | Er:YAG $Co_2$ Erbium glass | 2940 nm 10600 nm 1540,1550 nm 1440,1540,1550,1556 nm 1440-1540-1550-1556 nm | Create columns of beam at the depth of skin without injuries to spaces between columns. Ablative fractional heat epidermis & upper dermis. Columns of Non-ablative fractional lasers heat deep dermis columns |
| PBM | LEDs, lasers, broad lights waves | Red & Near infra-red wavelengths | Treat with no thermal reactions as photophysical or photochemical reaction |

Abbreviations: Er:YAG, erbium: yttrium aluminum-garnet; Er:DYSGG, erbium-doped yttrium scandium gallium garnet; PPTP, pulsed potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet; PBM, photobiomodulation; ILP, intense pulsed light; PDL, pulsed dye laser.

**Figure 2.** Penetration of Different Lasers Into the Skin for Rejuvenation (A) Ablative; (B) Non-ablative; (C) Fractional lasers.[39]

effects (Table 2). A comparison between the action of fractional ablative lasers and that of non-ablative ones on facial skin revealed clinical improvements in both techniques; however, collagen and elastin formation and edema in skin treated by the ablative fractional erbium laser were more than non-ablative one.[44]

Lasers resurfacing of skin as peeling could remove fine wrinkles of skin although, however potentially have the advantages to treat deep wrinkles by collagen making stimulation.[45] Skin healing in deep peeling and laser resurfacing is known as like wound healing mechanism and depends on the depth of the lesion.[46]

### Photobiomodulation Lasers

PBMs lasers mainly utilize red and near-red light spectra to activate biological processes used in a wide range of medical applications (Table 2). Low-power sources as LEDs, broadband lights and lasers are the sources of the photochemical and photophysical phenomenon without thermal reactions.[47] Photon energy is converted to stimulate biological reactions as collagen synthesis.[48] Near-infrared irradiation assists fibroblasts in making collagen to increase the consistency of skin.[49] The PBM technique without thermal reactions has been able to dramatically increase patients' satisfaction with skin rejuvenation.[50]

### Laser Effects on Tissues

Laser–skin interaction can be categorized as: photochemical, photothermal and photoplasmal pheromones. Photochemical reactions happen when the energy of photons made by the laser in the molecules of the cells causes chemical reactions in the molecules without changes in temperature.[53] In photothermal reaction, photon energy absorbed in a cell and converted to heat causes an increase in the temperature of the cell, associated with denaturation and necrosis.[53] Photoplasmal reaction occurs when irradiance energy is high enough ($10^8$ or $10^9$ w/cm) to form plasma accompanied by high electric fields, dielectric reactions, shock waves, and tissue rupture.[54]

### Photothermolysis

This is a technique that targets tissue in a specific area without damaging other neighbor tissues. Different chromophores such as oxyhemoglobin, melanin, water, tattoos absorb different wavelengths.[34] Longer wavelengths can penetrate in deeper parts of skin. Chromophores absorb photon energy to heat and destroy targets; however, surrounding tissues need to be cool (Thermal relaxation time). For example, the target tissue cooling time is 3 to 10 ms for the epidermis and 1 μs for melanosomes.[39] Thus the properties of radiation and relaxation time between the periods of radiation are important for skin rejuvenation.[55]

### Molecular Aspects of Laser Effects in Cell Biology

Several factors are proposed to illustrate the molecular basis for skin aging, including the theory of cellular senescence, decrease in cellular DNA repair capacity and loss of telomeres, point mutations of extranuclear mitochondrial DNA, oxidative stress, increased frequency of chromosomal abnormalities, single-gene mutations, reduced sugar, chronic inflammation, and so on.[56] Some scientists have argued that most influences are caused by extrinsic factors and that only 3% of aging factors have an intrinsic background.[57] Researches have demonstrated that low-power laser therapy can deliver lower energy to the tissues.[58] The energy of low-power laser therapy could be absorbed by mitochondria and cytochrome C.[59] The energy of the red-NIR (Near-infrared) laser could primarily be absorbed by mammalian cells cytochrome C oxidase.[60] Excited electrons in cytochrome C oxidase lead to more electron transfer and subsequently more ATP production.[61] Investigations have revealed that NO can inhibit cytochrome C oxidase activation;[62] on the other hand, low-power lasers can inhibit NO activity, resulting in more oxidative activities of the cells.[62,63] More activation of the cells causes more production of ROS.[62,64] It is considered that ROS displays a necessary role in dermal extracellular matrix alterations of both intrinsic aging and photoaging. ROS can be made from various sources including the mitochondrial electron transport chain, peroxisomal and endoplasmic reticulum localized proteins, the Fenton reaction, and such enzymes as cyclooxygenases, lipoxygenases, xanthine oxidases, and nicotinamide-adenine dinucleotide phosphate oxidases. Low-power lasers are useful for the treatment of skin disorders like wrinkles, scars, and burns because low-power lasers could positively affect cell proliferation and remodeling, DNA repairing, ion channels, and membrane potentials.[65-67] Low-power lasers could change the expression of different genes as the Er:YAG laser upregulates the expression of IL1B, IL8, keratin16, MMP3, and MMP1.[68] In this regard collagen synthesis increases. Picosecond infrared laser application leads to a reduction in neighbor's tissue damage, a decrease in beta-catenin

and TGF b signaling, and more cell viability to accelerate the wound healing process.[69] Ablative CO2 resurfacing skin revealed the upregulation of different MMPs.[70] In a large-scale study of skin aging and skin rejuvenation proteins, proteomics is efficient. Proteomics has less technical limitations on protein identification and a large number of proteins could be identified by this technique.[71] Proteomic analysis of foot skin compared to breast skin demonstrated the presence of 50 ECM common proteins in both skins, but there was a difference between the expressions of tenascin-x in breast skin and serum amyloid p component in foot skin.[72] By examining the proteomic profile of elderly epidermis, it was found that interferon-stimulating polypeptides expression increased, causing the stimulation of phosphatidylinositol 3-kinase and manganese superoxide dismutase.[73] The skin irritation proteomics approach demonstrated the upregulation of HSP27 and suggested it as the skin irritation marker.[74] Laser skin proteomics evaluation suggested a balance between skin cancer and laser irradiation.[75] Aging leads to a reduction in skin collagen and elastic fibers with MMPs upregulation; however, UV causes skin aging effectively.[76,77] A study on mouse skin exposure to the Er:YAG laser revealed skin water epidermal loss and the upregulation of p21 & p53 to repair DNA and skin survival.[78] Low-power laser therapy could downregulate the expression of cytokeratin and antigens related to proliferation.[79,80] Proteomics assay revealed the downregulation of Rho GDI 1 expression following by low-power laser therapy and the adjustment of Rho protein activities could disrupt actin cytoskeleton and kill keratinocytes following by new keratinocytes migration to replace the old ones.[81] Laser therapy could reduce HSP26 protein and cause surface cell death of skin after 24 hours of treatment.[81] In one study, low-level Er:YAG laser irradiation to gingival fibroblast cells caused galectin 7 wound healing protein upregulation and suggested reduced cell proliferation after laser therapy in gingival fibroblast cells.[82] Lee et al reported the long-pulsed 1064-nm neodymium-doped (Nd): YAG laser treatment of mouse skin. The results of their study indicated an increase in collagen and TGF-B and decreased expression of MMPs.[83] Findings from a study by De Filippis et al revealed an interaction between keratinocytes and fibroblast and overexpression of filaggrin, aquaporin, TGase, HSP70 with a reduction in MMP-1 and an increase in elastin and procollagen type1 with the use of the 1064 nm Nd:YAG non-ablative laser.[84] It can be generally assumed that non-invasive lasers are effective in enhancing the activity of fibroblasts and keratinocytes with the synthesis of collagen, elastin, and decreased expression of some metalloproteinases.

## Conclusion

As the assessment of skin rejuvenation and laser therapy demonstrated, many proteins related to collagen synthesis, fibroblasts and keratinocytes proliferation,

and apoptosis activities were introduced. However, more investigations into the proteomic and genomic analysis are required to interpret laser effects on the molecular biology of skin rejuvenation. It is recommended to provide a comprehensive genetic and protein map which will be suitable to find out different biological pathways of laser traded skins to improve better ways to rejuvenate aged skin because many proteins and genes are still unknown. On the other hand, the improvement of lasers for the treatment of different skins and sooner cooling of skin layers is suggested. The wide range of biological events which are accompanied by laser application in skin rejuvenation implies that more safety points should be considered in the therapeutic guidelines.

## Ethical Considerations
Not applicable.

## Conflict of Interests
The authors declare no conflict of interest.

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