Clinical Approaches and Procedures in Cosmetic Dermatology

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Bhertha Tamura *Editors*

Lasers, Lights and Other Technologies

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Clinical Approaches and Procedures in Cosmetic Dermatology

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The series Clinical Approach and Procedures in Cosmetic Dermatology intends to be a practical guide in cosmetic dermatology. Procedures in cosmetic dermatology are very popular and useful in medicine, indicated to complement topical and oral treatments not only for photo-damaged skin but also for other dermatosis such as acne, rosacea, scars, etc. Also, full-face treatments using peelings, lasers, fillers, and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries. Altogether, these techniques not only provide immediate results but also help patients to sustain long-term benefits, both preventing/treating dermatological diseases and maintaining a healthy and youthful skin. Throughout this series, different treatments in cosmetic dermatology will be discussed in detail, covering the use of many pharmacological groups of cosmeceuticals, the new advances in nutraceuticals, and emerging technologies and procedures.

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With 279 Figures and 25 Tables

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Foreword

When I received the invitation from Maria Claudia Issa, M.D., Ph.D., and Bhertha Tamura, M.D., Ph.D., to write one of the chapters of this marvelous book, I was very happy. Later, upon receiving the mission to write the prologue of this book, whose editors, with numerous publications in the international scientific field of cosmetic dermatology, dignify the Brazilian dermatology, left me extremely honored. In this book, some of the leading medical doctors and research scientists from Brazil and from all over the world present their professional experience in the cosmetic dermatology area.

Cosmetic dermatology is constantly evolving. Procedures for rejuvenating the skin are actively sought by people, nowadays. As dermatology grows as a specialty, an increasing proportion of dermatologists will become proficient in the delivery of different procedures. Even those who do not perform cosmetic procedures must be well versed in the details to be able to guide their patients.

Numerous major advances in the field of the cosmetic dermatology area, including botulinum exotoxin, soft tissue augmentation, chemical peels, cutaneous lasers, light source–based procedures, and the state of the art of dermatologic and cosmetic prescriptions, have been developed and enhanced by dermatologists and plastic surgeons.

Lasers, lights, and related energies are routinely used in cosmetic dermatology. These are very important tools in the armamentarium of the dermatology. Very interesting results in the treatment of photoaging, rosacea, scars, and stretch marks, among others, can be obtained with these procedures. However, accuracy in its management as well as the knowledge of possible complications and their management are of extreme importance. In this volume, different types of devices are thoroughly discussed.

The series Clinical Approach and Procedures in Cosmetic Dermatology offers a wonderful and embracing text. It was a pleasure to contribute in this unique book with so many well-renowned authors.

This work project is a text certainly of inestimable value for those who wish to deepen their knowledge in the field of cosmetic dermatology.

Hoping that you will enjoy learning a lot from this book!

Mônica Manela Azulay, M.D., Ph.D.

Preface

Nowadays, life expectation had increased and for a better quality of life, people are looking for beauty, aesthetics, and health. Dermatologists and plastic surgeons who work with cosmetic dermatology can help patients to maintain a healthy and youthful skin. Topical and oral treatments associated with full-face procedures using peelings, lasers, fillers, and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries.

This series of book is very special among other ones already published as it encompasses all subjects related to this area of dermatology. All authors are experts in the field of cosmetic dermatology. Literature review and its correlation with authors' experience is a differential feature of this work.

This work had been divided into four volumes due to the breadth of the subjects, which cover skin anatomy and histopathology, physiology, patient's approaches, common cosmetic dermatosis, topical and oral treatments, and cosmetic procedures.

Over the last decades, laser technology had great improvement. This volume on *Lasers, Lights and Other Technologies* was designed to bring a basic structural framework of the use of lasers, lights, and related energies in cosmetic dermatology. Here, Prof. Maria Issa, Prof. Bhertha Tamura, and collaborators discuss different types of devices with their indications, parameters to achieve better results, and management of possible complications. Some particularities including the use of lasers for different phototypes and body areas are also described.

The *Clinical Approach and Procedures in Cosmetic Dermatology* was prepared to be a guide in cosmetic dermatology. It can be considered a complete encyclopedia in the field of cosmetic dermatology and, for this reason, it is extremely useful for those who already work with cosmetic dermatology as well as for beginners in this field. This is a new reference work project, and we are delighted to have you on board.

Maria Claudia Almeida Issa, M.D., Ph.D.
Bhertha Tamura, Ph.D.

Acknowledgments

When we were invited to write a book about cosmetic dermatology, we could not imagine the dimension of this work project.

After drawing the program content, we realized that a comprehensive handbook series in this field would be built. Nevertheless, it would not be possible without the efforts and experience of our invited partners. They deserve our acknowledgment and our deep appreciation.

To all collaborators, our very special thanks.

Maria Claudia Almeida Issa
Bhertha Tamura

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About the Editors

Maria Claudia Almeida Issa is among the leading dermatologists in Brazil and Latin America, especially in what regards to cosmetic dermatology. Dr. Issa holds a Ph.D. in Dermatology from the Federal University of Rio de Janeiro (2008) and an M.Sc. in Dermatology from the Fluminense Federal University (1997). Dr. Issa is currently an Associate Professor within the Department of Clinical Medicine – Dermatology, at the Fluminense Federal University, Brazil. Her research focuses on photodynamic therapy, nonmelanoma skin cancer, lasers, photoaging, and dermal remodeling. Finally, Dr. Issa has an extensive clinical experience in cosmetic dermatology, being registered as a dermatologist at the Brazilian Society of Dermatology since 1995 and member of the American Academy of Dermatology.

Bhertha Tamura has M.Sc. and Ph.D. degrees in Dermatology from the Hospital das Clínicas de São Paulo – Universidade de São Paulo. Specialist in general surgery and dermatology. Counselor for the Brazilian Society of Dermatologic Surgery and for the Brazilian Society of Dermatology. Member of the Scientific Commission of the Brazilian Society of Dermatology. Chief of the Department of Dermatology at the Complexo Hospital Heliopolis (São Paulo, Brazil). Member of several international dermatological societies.

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Part I

Biophotonics, Lights, Ablative and Non-ablative Lasers

Biophotonics

Álvaro Boechat

Abstract

Light is one of the most beautiful forms of pure energy, we know some of its therapeutic properties, but there is still much to be explored. The aim of this chapter is to provide a better understanding of the best known light tools used in modern medicine, such as laser, intense pulsed light, the advent of fractional systems, radio frequency, and hybrid systems, which combine light and radio frequency, how they work, how to select which device will be better for your application, and how light and RF interact with the skin. Thus, this will enable the improvement of current treatment techniques as well as broaden the horizons of applications of these devices.

Keywords

Dermatological laser • Laser physics • Types of lasers • Pulsed light • IPL • Treatment platforms • Light-tissue interaction • Selective photothermolysis • Relaxation time • Radio frequency • Fractional lasers • Penetration depth • Ablative laser • Non-ablative laser • Sublative • Fractional radio frequency • ELŌS

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Introduction

The laser and pulsed light are simply sources of natural light. The visible light that we experience in our day to day is only one facet of a much broader physical phenomenon known as "electromagnetic radiation."

As shown in Fig. 1, the electromagnetic spectrum (Siegman 1986) includes several well-known phenomena, such as TV and radio waves, microwave, infrared, and, on the other side of the spectrum, ultraviolet and X-ray. However, our eyes are sensitive to only a very narrow range of the spectrum, which forms the visible light from violet to red. It is important to realize that each visible color or each emission spectrum is associated with a frequency or wavelength.

Thus, the differentiation between blue and green, for example, is related to their frequencies. It is similar to the musical notes; the difference of the note "do" (C) from the note "sol" (G) or "fa" (F) is their frequencies; one is low pitched and the other high pitched. Drawing a parallel with them, we can see that, in the light spectrum, the higher frequencies correspond to blue and violet and, on the other side of the spectrum, the lower frequencies correspond to red. As light frequencies are very high, of the order of millions of hertz, they are characterized by their wavelength or the distance between two adjacent peaks in the wave illustrated in Fig. 2 (Siegman 1986; Arndt et al. 1997).

Light radiation may be defined as the point-to-point power transmission in space, regardless of the medium in which it is being propagated. Light or electromagnetic radiation propagates at a high speed in the open space independent of the transmission medium in the form of waves that can travel in the vacuum or in spaces containing matter, such as gases, liquids, or solids. As it enters, or moves from, a different medium, it will suffer changes in direction and speed of propagation.

Lasers are sources of electromagnetic radiation, or light, with some special characteristics that are different from other light sources, such as a car headlight or a lamp.

The word **laser** is an acronym for **light amplification by stimulated emission of radiation**. We can divide this acronym into two well-defined parts: the stimulated emission phenomenon and the light amplification.

Stimulated Emission

Light is a form of energy generated, emitted, or absorbed by atoms or molecules. To emit energy, the atom or molecule is raised to an excitation energy level, above its natural resting state (in which there is excess energy to be discharged). Atoms cannot maintain the excitement for long periods of time. Consequently, they have a natural tendency to eliminate the excess energy in the form of emission of particles or packets of light waves called photons (Fig. 3a). This phenomenon is called spontaneous emission of light. The wavelength (λ), or the frequency of the emitted photons, is related to the photon energy through the relationship:

$$\mathbf{E_{photon} = hc/\lambda}$$

h – Planck universal constant $= 6.6260693 \times 10^{-34}$ J.s
c – Speed of light = 300,000 km/s
λ – Wavelength of the light (nanometers – nm)

We can draw an important conclusion from this equation: long wavelengths of light, such as red, carry less energy than shorter wavelengths, such as blue, which is at the other end of the spectrum.

Each atom or molecule in nature has different energy levels of excitement. Consequently, each element emits photons with different energies and different wavelengths (frequencies). All these primary radiations are monochromatic. The fact that the sunlight is polychromatic indicates that it is composed of a mixture of several distinct elements.

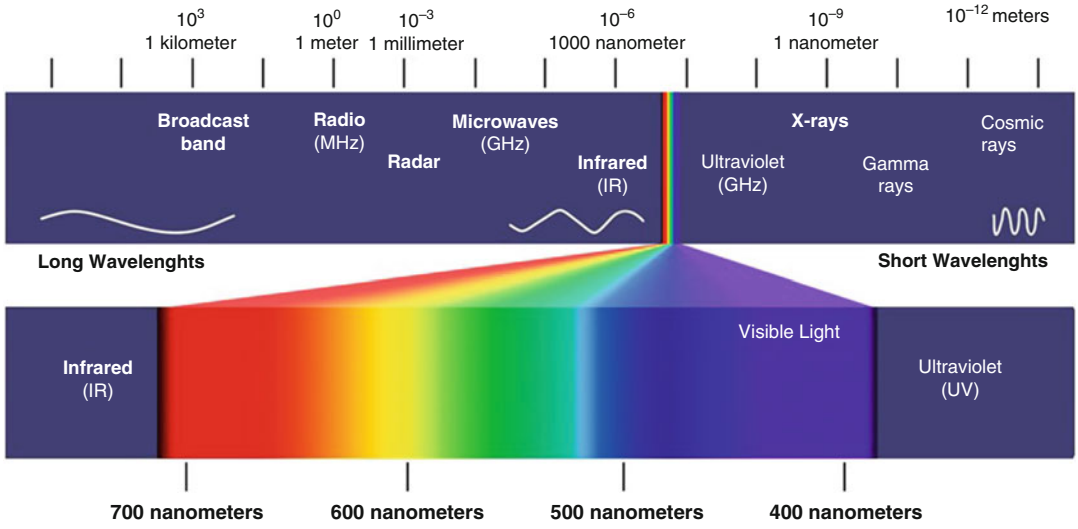

Fig. 1 The electromagnetic spectrum

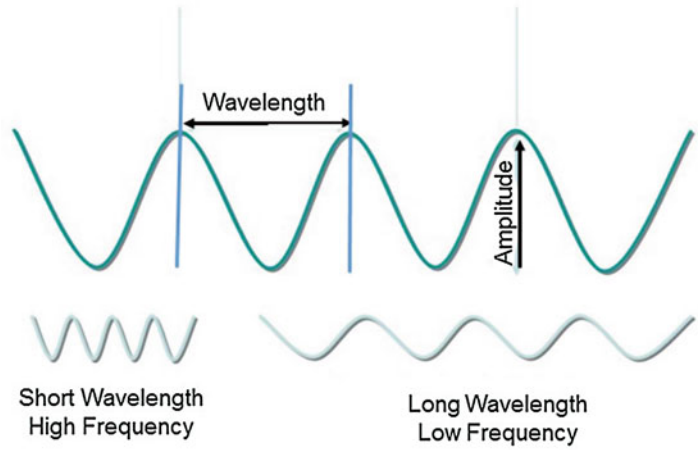

Fig. 2 Electromagnetic waves of photons that transport energy

Another important relationship is the frequency with wavelength (Siegman 1986):

$$\mathbf{f} = \mathbf{c}/\boldsymbol{\lambda}$$

f – Frequency of the light wave (Hz)
c – Speed of light = 300.000 km/s
λ – Wavelength of the light (nanometers – nm)

We see that these two quantities are inversely proportional; that is, the higher the frequency, the smaller the wavelength. For example, the frequency of visible light, which is very high of the order of Terahertz, has a very small wavelength, being the size of a molecule. As an analogy, a FM radio wave, of the order of Megahertz, has a wavelength the size of a two-story house.

Atoms can be excited by different mechanisms: heat, mechanical shocks with other particles as an electrical discharge (collision with electrons), or when they selectively absorb electromagnetic radiation energy from other photons. This is a natural process that occurs all the time around us, but as its magnitude is very small and

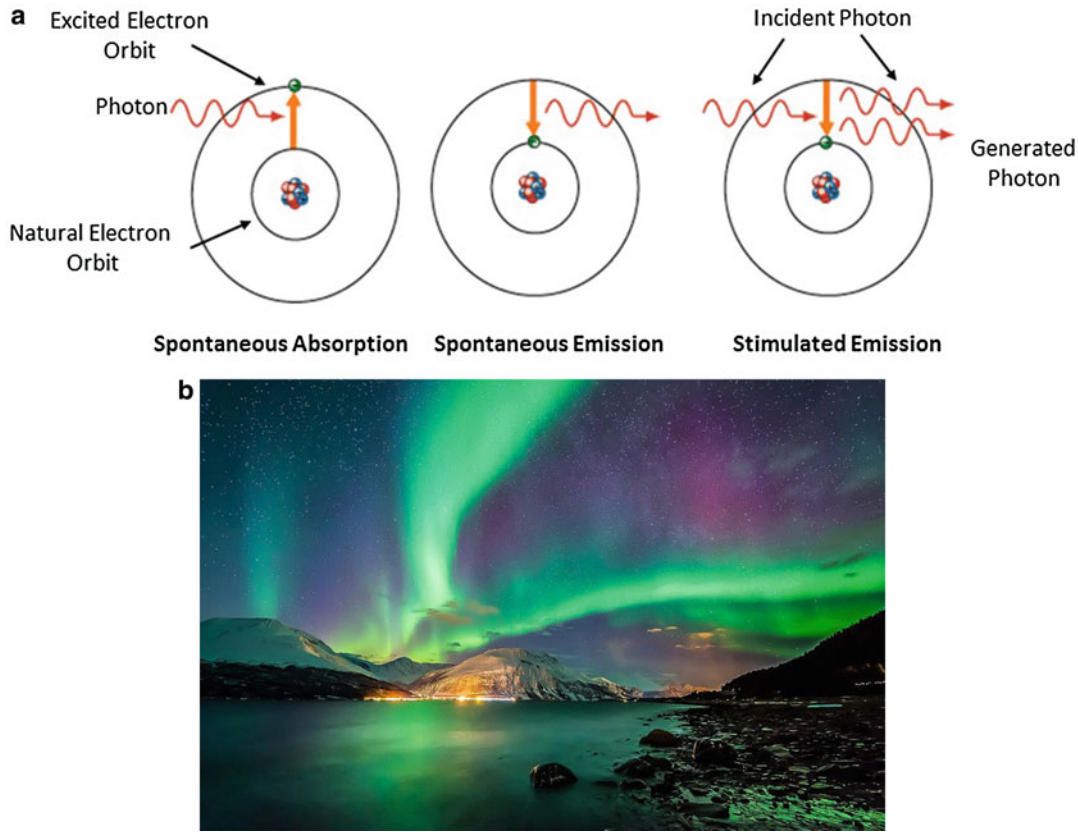

Fig. 3 (**a**) Spontaneous emission of light. (**b**) Northern Lights, or *aurora borealis*, an example of spontaneous emission of light

very narrow in the visible spectrum, we cannot see it. The location on Earth where we can more easily observe this phenomenon is, for example, near the North Pole, with the famous Northern Lights or auroras. It is produced by the impact between air molecules and cosmic particles from the Sun that constantly bombard Earth, producing a phenomenon of luminescence in the upper atmosphere (Fig. 3b).

However, atoms can also decay producing light radiation in a stimulated form. In 1917, Albert Einstein postulated and proved the existence of this mechanism (Siegman 1986; Wright and Fisher 1993; Arndt et al. 1997). When an excited atom collides with a photon, it instantly emits a photon identical to the first (Fig. 3a). This stimulated emission follows the following basic laws:

(a) The stimulated photon travels in the same direction of the incident.
(b) The stimulated photon synchronizes its wave with the incident; in other words, the waves of the two photons align their peaks adding their magnitudes and thereby increasing the intensity of the light. Photons with aligned peaks produce a coherent (organized) light. In a coherent beam, light travels in the same direction, in the same time, and with the same energy.

The end result of a stimulated emission is then a pair of photons that are coherent and that travel in the same direction. The stimulated emission of light is the working principle of a laser, invented more than 50 years after the discovery of Einstein.

Light Amplification

To illustrate the generation of light inside a laser, let us first imagine a rectangular box or a tube, as a straight cylinder, with a large amount of identical atoms or molecules, as an example, a fluorescent lamp tube with its gas. At each end of the tube, we place mirrors, which because of the construction will be parallel to one another. At one end, the mirror is totally reflective (100 % mirror), and at the other end (the exit window of the light – output coupler), the mirror is partially reflective (80 % mirror), so that part of the light is reflected back to the tube and part is transmitted through the mirror to the outside (Wright and Fisher 1993; Kulick 1998; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

Let us also imagine that the atoms are excited to a higher-energy level by an external source (a light source or an electrical discharge), as if we had activated the switch turning on the lamp. Through the mechanism of spontaneous emission, which takes place completely randomly, the atoms emit photons that begin traveling in various directions within the tube. Those hitting against the tube wall are absorbed and lost as heat, disappearing from the scene. In the case of a lamp, they leave the tube into the environment, illuminating the room. On the other hand, the emitted photons traveling parallel to the tube axis are likely to find other excited atoms and thus stimulate the emission of additional photons, which are consistent with the stimulating photon and travel in the same direction – i.e., along the longitudinal axis of the tube. These two photons continue their journey, again with the likelihood of stimulating, through a similar process, two additional photons – all consistent with each other and traveling in the same axis. The progression continues indefinitely and 8, 16, 32, 64, etc., photons are produced, all traveling in the same direction, as illustrated in Fig. 4.

It is clearly established a light amplification process that generates a large luminous flux in the longitudinal direction of the tube.

The mirrors perpendicular to the tube axis reflect the photons back intensifying this effect of amplification. Each of these reflected photons traveling along the axis in the opposite direction contributes to the chain reaction effect generating a stream of coherent photons. When they reach the partially reflecting mirror, 80 % of the photons return to the tube continuing the amplification effect. The remaining 20 % goes out forming the laser beam (Fig. 5a, b). They represent in absolute terms a very intense beam of photons produced by the amplification effect. The tube and its excited medium, together with the mirrors, are called the resonator (or oscillator) which is the basic components of a laser in addition to the excitation source.

Characteristics of a Laser Light

As described above, the laser light has unique properties that make them different from other light sources (Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kaminsky Jedwab 2010; Sardana and Garg 2014):

(a) **Monochrome**: it is generated by a collection of identical atoms or molecules; thus, all photons emitted have the same wavelength, a single frequency. This feature is important because of the selective absorption of the human tissue, which will be presented in the next section.
(b) **Coherent**: because of the stimulated emission and the way the light is amplified, which is only in the longitudinal direction inside the resonator, the photons are organized, as soldiers marching in a military parade. This is called spatial and temporal coherence. At any point of a laser beam, the photons (or light):
    (a) Have the same power
    (b) Travel in the same direction
    (c) Travel at the same time

Being coherent, light from a laser is called collimated. Traveling parallel to the tube axis, the laser beam has a very small divergence angle, i.e., the light does not spread; the photon beam is collimated (parallel). The small

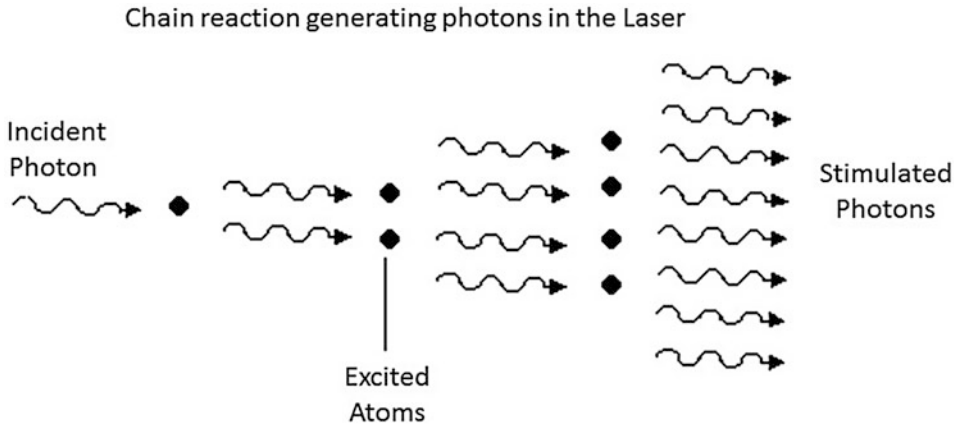

Fig. 4 Chain reaction producing photons inside the laser resonator

divergence allows the use of a lens system to concentrate all the energy of the laser in a precise way on a small focal spot (spot size), achieving a greater concentration of light energy or brightness. Optical laws tell us that the smaller the divergence, the smaller the focal point. When we focus a common light source such as a lamp, of incoherent light, the focal point will be too large and imprecise, whereas when using a laser, we have a very fine and extremely precise focal point and therefore a much more intense effect on the tissue.

Energy, Power, and Fluency

The increase of temperature or the effect of treatment on the tissue depends on the amount of energy that it receives. The energy, power, and fluency (energy density) are the physical parameters that control the treatment effect and determine the eventual increase in temperature.

Energy	Is measured in Joules (J)
Power	Is measured in Watts (W)

These are different parameters and they are related trough the following equation:

$$\mathbf{Energy(J)} = \mathbf{power(W)} \times \mathbf{time(s)}$$

Thus, energy is the amount of power delivered to the tissue in a given time or the laser pulse duration. The thermal effect of the laser is highly localized. In this way, the physical quantity that governs the thermal response of the tissue is the amount of energy delivered to a certain area, the overall size of the application area or the "spot size" produced by the laser handpiece. Thus, the energy density or fluency is measured in J/cm^2 (Boechat et al. 1991):

$$\mathbf{Fluency}\left(\mathbf{J/cm^2}\right) = \mathbf{Energy(J)/Area}\left(\mathbf{cm^2}\right)$$

The higher the fluency, the faster the temperature increases in the tissue and consequently the intensity of the desired effect. The effect of the treatment is achieved both by varying the laser output energy and the laser pulse duration, at the tissue application area. All commercial lasers allow us to change easily and continuously the energy.

For a fixed operating power, we can vary the fluency in the tissue by changing the application area (spot size – changing the lens that focus the laser beam in the handpiece) or by varying the distance of the handpiece from the tissue in a "focused" handpiece.

When we work with light in focus (Fig. 6), the power density is at its maximum because all the energy of the laser is concentrated in a small focal point (usually of the order of 0.1–1 mm), called "spot size." At the focal point, it is possible to precisely cut the tissue, and the application has its maximum effect. When we move the handpiece away from the tissue to a defocus, or out of focus

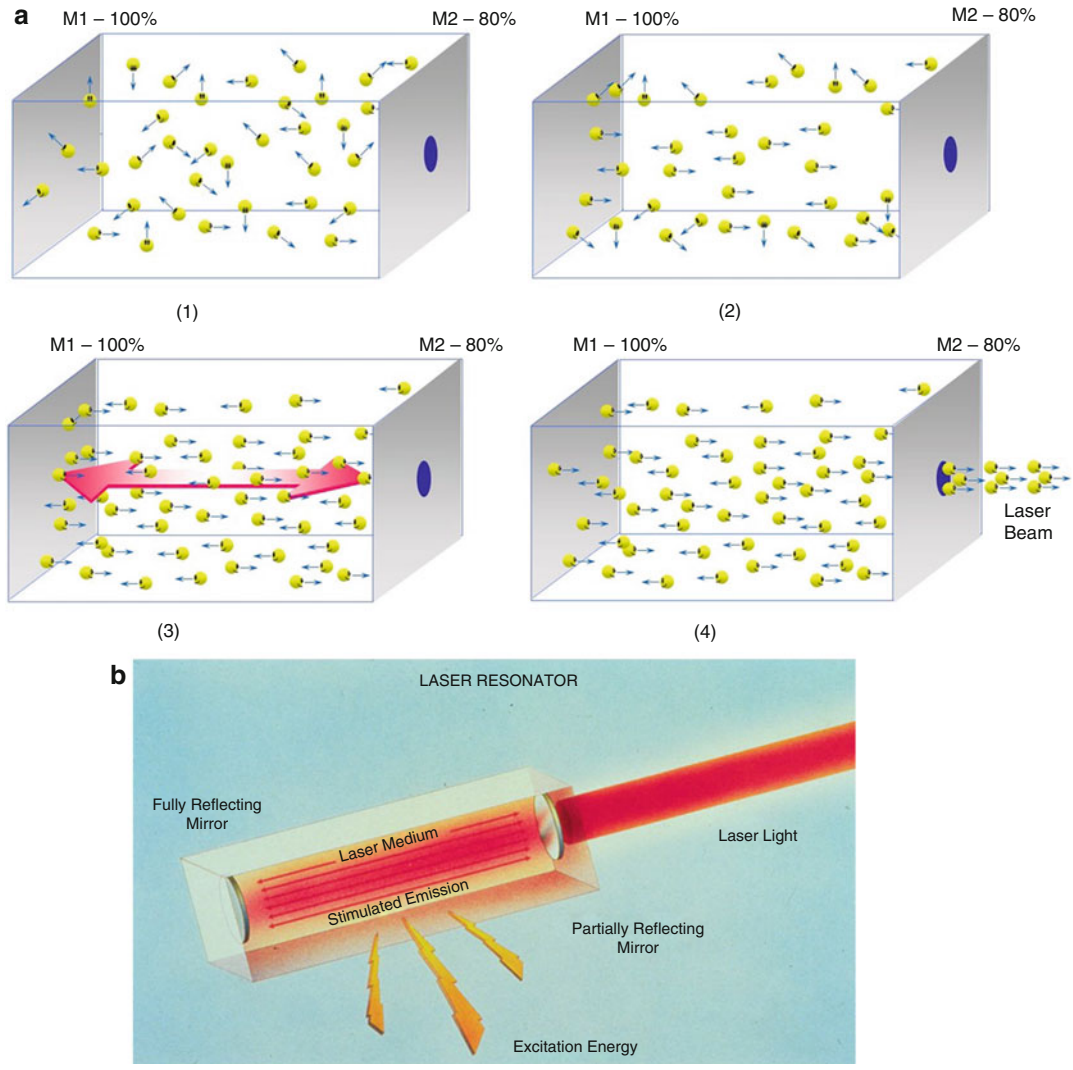

Fig. 5 **(a)** Light amplification and laser beam formation inside a laser resonator. M1 is the 100 % reflection mirror and M2 is the 80 % partial reflection mirror. The (1) and (2) are excited atoms that produce photons that begin to travel longitudinally along the resonator between the mirrors. The (3) and (4) are the photons traveling parallel to the axis of the resonator that stimulate new photons, producing the laser beam. (**b**) Schematic of the laser operation

position, the application area becomes larger reducing the power density (fluency) and increasing the temperature in the tissue. At this position, the effect becomes milder, producing a superficial effect of vaporization and coagulation (used in skin rejuvenation – skin resurfacing).

Another widely used laser handpiece is called "collimated." Here the laser beam remains parallel (collimated) and constant regardless of the distance from the tissue. It is used in hair removal systems and various types of skin treatment, such as tattoo and melisma removal (Fig. 7).

It is important to note how the cutting effect is controlled when using a laser. The surgeon is used to control the depth of the cut by the pressure exerted on the blade against the tissue. In the laser, as there is no mechanical contact with the tissue, the cut is determined by two factors:

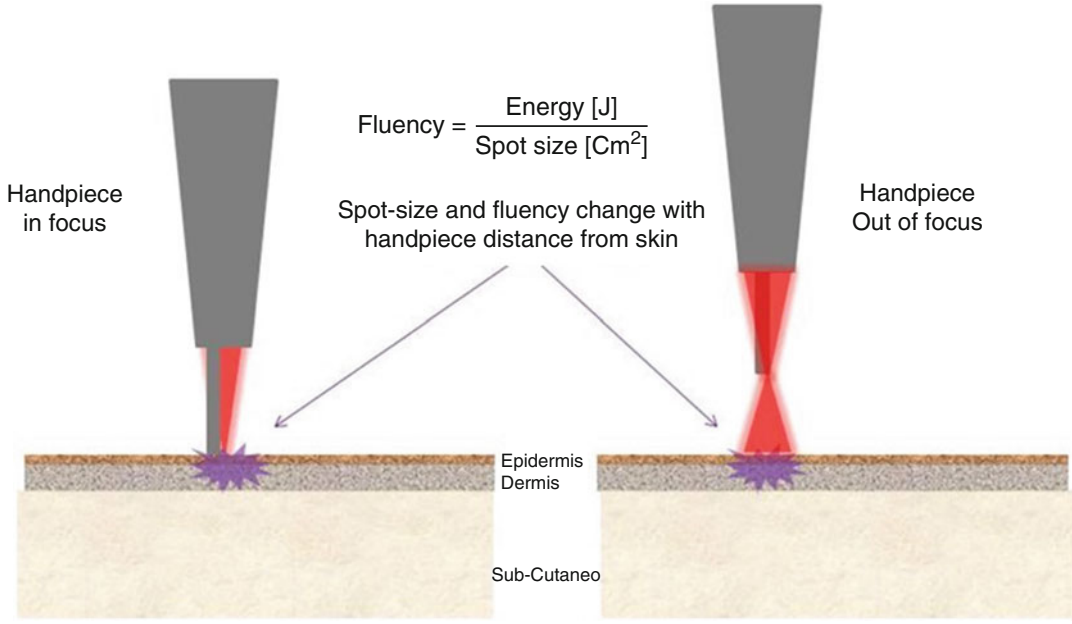

Fig. 6 Focused headpiece. Laser in focus: power density is at its maximum (vaporizing, cutting). Out of focus: power density is reduced (coagulation, milder treatment)

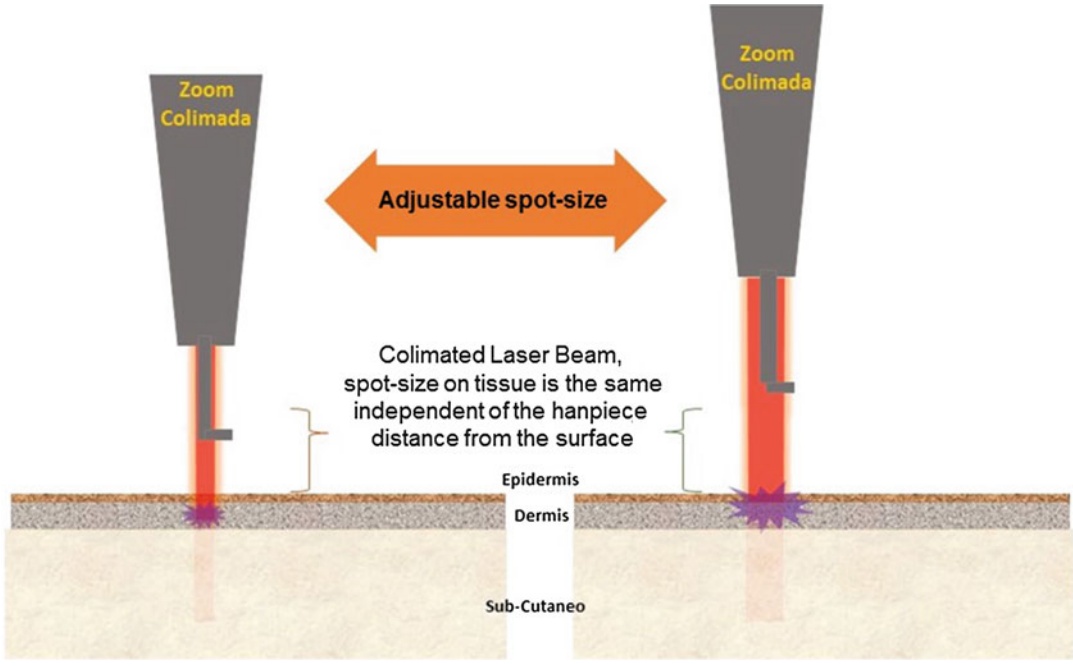

Fig. 7 Collimated handpiece. Regardless of the distance from the skin (touching or moving away), the spot size and fluency remain the same. Some handpieces have a zoom effect that allows the adjustment of the spot size

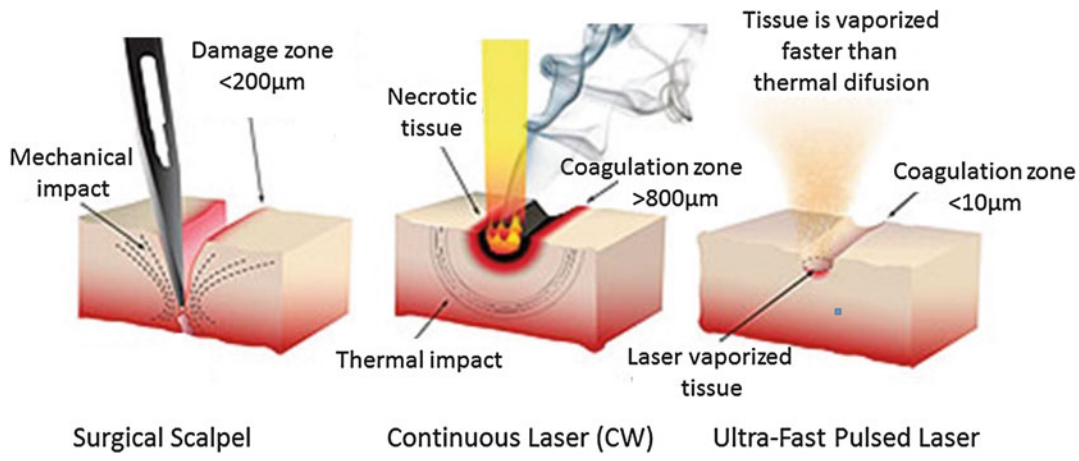

Fig. 8 Comparison of tissue laser cutting, showing continuous wave (CW) and ultrafast pulses that minimize the thermal damage to adjacent tissue

1. Hand movement speed
2. Laser energy

The speed is linked to tissue exposure time, because if we keep the laser acting on a point indefinitely, it begins to vaporize layer upon layer of tissue increasing the depth of the cut. Thus, for a constant power, if the surgeon moves the hand slowly, he or she will produce a deep cut. Likewise, for a movement with constant speed, the cutting will be deeper for a greater energy.

The laser exposure time also governs the amount of adjacent tissues which may be affected. Modern laser systems have mechanisms that quickly deliver energy to the tissue minimizing the thermal effect in adjacent areas. These mechanisms can be through ultrafast pulses ("ultrapulse" laser) or computerized rapid laser beam scanning systems (fractional scanners), used in skin rejuvenation treatments and more recently in fractional treatment systems. The "scanner" divides and moves the laser beam at high speed to position it over the skin minimizing damage to adjacent tissues. They are controlled by computer and can execute different types of scanning, with great precision and control over the amount of tissue being vaporized (Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kulick 1998; Alster and Apfelberg 1999; Alster 1997).

Operating Modes of a Laser

Depending on the effect of the treatment we want to obtain on the tissue, laser systems can operate in the following modes (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014):

1. **Continuous mode – CW**: In this mode of operation (also known as continuous wave), the laser stays on, just as a normal lamp, and emits a light beam of constant energy, as long as we keep the system powered by the foot switch or the power button on the handpiece (available on some devices). It is widely used in surgeries for coagulation or vaporization of tissue.
2. **Pulsed mode**: This mode works as if we turned a lamp on and off; the laser is pulsed electronically with the times and the intervals between pulses controlled by the equipment computer and selected via the panel. The repetition rate or frequency (given in Hz) of the laser pulse can also be programmed. Most lasers used in dermatology work with ultrafast pulses to vaporize the tissue faster than the thermal diffusion time of the skin in order to minimize damage to adjacent tissues, resulting in safe and effective treatments (Fig. 8).

According to the laser pulse duration, pulsed systems can be classified into:

(a) **Long pulses** – 0.001 s, millisecond (ms) 10^{-3} s
   (i) Hair removal, varicose veins
(b) **Quasi-CW** – 0.000001 s, microsecond (μs) 10^{-6} s
   (i) Skin rejuvenation, onychomycosis, inflammatory acne
(c) **Q-Switched** – 0.000000001, nanosecond (ns) 10^{-9} s
   (i) Treatment of melasma, tattoo removal
(d) **Mode-Locked** – 0.000000000001, picosecond (ps) 10^{-12} s
   (i) Tattoo removal and pigmented lesions
(e) **Femto** – 0.000000000000001, femtosecond (fs) 10^{-15} s
   (i) Refractive surgery in ophthalmology

Q-Switched: Nanosecond Laser

This mode is achieved by placing an optical accessory inside the resonator, at the side of the laser crystal, whose goal is to pulse optically the light (Siegman 1986; Goldman 1967; Raulin and Karsai 2011). It is generally used in crystal lasers such as ruby, alexandrite, and Nd:YAG, described below. The goal is to accumulate the laser energy at very high levels and release it at extremely rapid pulses. The result is a very high-peak-power laser pulse (often higher than the common pulse), which can penetrate deep into the tissue, with minimal side effects. Then a shockwave-induced mechanical action caused by the impact of the laser pulse onto the target tissue causes its fragmentation. In the long and Quasi-CW pulsed modes, the effect is purely thermal.

The Q-Switch can be **passive**, when using a crystal called "saturable absorber" that produces rapid pulses, or **active**, when using an electronic modulator crystal called "Pockels cell."

Passive systems using the saturable absorber are generally simpler and more compact resulting in smaller portable devices or systems installed into handpieces incorporated to a platform. They are more limited as it is not possible to control efficiently the stability of the fast pulse; the crystal is sensitive to higher energies, which limits the maximum working energy; and the application spot size is limited to a few millimeters (1–3 mm). They also fail to achieve high repetition rates of pulses (high frequencies), working in a maximum of 2–3 Hz.

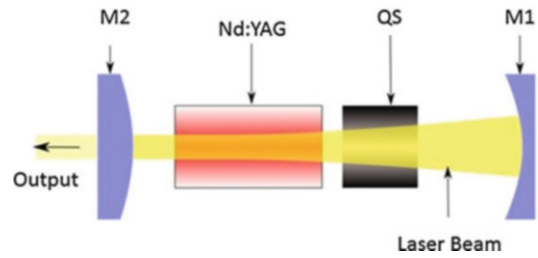

Fig. 9 Diagram of a Nd:YAG laser with Q-Switch (QS). M1 is the 100 % mirror; M2 is the output coupler

The active Q-Switch uses a Pockels cell which is a crystal subjected to a high electric frequency and is electronically controlled to produce a very fast and stable light switching effect. The result is faster pulses with very high peak powers that are not possible with passive systems. Thus, they can handle high energy, larger spot sizes (10 mm), and faster repetition frequencies of 2–20 Hz. Equipment with active Q-Switch allow the device to be turned off, and thus the laser can also work in the Quasi-CW mode, with micropulse, giving greater flexibility to the system (Fig. 9).

The classic application is in tattoo removal and the treatment of pigmented skin lesions such as dark circles, postinflammatory hyperpigmentation, and melasma (Goldman 1967; Reid and Muller 1978; Raulin et al. 1998; Chang et al. 1996; Shimbashi et al. 1997; Reid et al. 1983, 1990; Stafford et al. 1995; Ogata 1997; Chan et al. 1999; Jeong et al. 2008; Mun et al. 2010) (Fig. 10).

Mode-Locked: Picosecond Laser

To achieve picosecond pulses, a technique called "mode-locking" is used (Siegman 1986; Raulin and Karsai 2011; Sardana and Garg 2014). The base is a Q-Switch system as described above, in which nonlinear effects of the Q-Switch crystal are

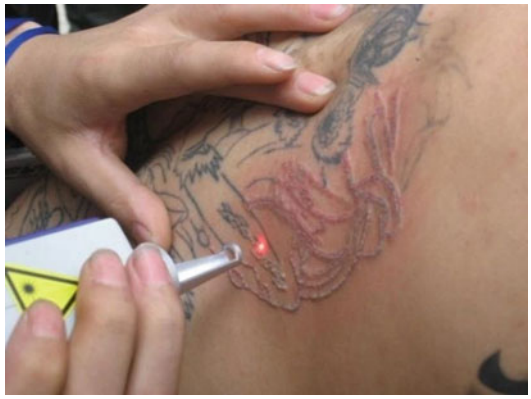

Fig. 10 Laser tattoo removal

stimulated and modulated inside the resonator in order to create faster pulses with a technique in which only they are amplified. It is more commonly used in crystal lasers as alexandrite and Nd:YAG.

There is the passive, with the saturable absorber, and the active mode-locking, with the Pockels cell electronically controlled. The limitations and benefits of each are the same as in the Q-Switched systems.

The picosecond lasers for dermatology provide pulses ranging from 375 to 760 ps.

To understand the picosecond laser advantages over a nanosecond device, we need to go back to the relationship between energy, power, and pulse duration, described above. We see that the peak power is inversely proportional to pulse duration. In other words, faster (shorter) pulses generate higher powers for the same energy:

$$\textbf{Power}(\textbf{W}) = \textbf{Energy}(\textbf{J})/\textbf{Duration of the Pulse}(\textbf{s})$$

A picosecond laser generates a very high peak power, making the photomechanical fragmentation of the target tissue and consequently the treatment more efficient. It also does not need high-energy levels. Working with very low energy results in milder treatments and faster recovery time. For example, in tattoo removal, a picosecond laser needs fewer sessions than a nanosecond system, and applications can be performed every 15 days, while in nanosecond systems, sessions are 45–60 days apart. The faster the system is, the milder and more effective is the treatment. That is why the industry has been investing in the development of these ultrafast devices (Fig. 11).

Fig. 11 Picosecond Laser PicoWay™ Nd:YAG/KTP (Syneron Candela)

As we will see in the following chapter, the pulse duration governs the way in which light interacts with the tissue (selective photothermolysis), and by varying the pulse duration, we can completely change the laser application in dermatology.

Laser Types

All laser devices consist of the following parts (Siegman 1986; Goldman and Fitzpatrick 1994; Boechat 2009; Kaminsky Jedwab 2010):

1. The resonator/oscillator – with mirrors (total and partial reflectors) and active medium, which, when excited, produces the light and thus determines the wavelength
2. The excitation source (also called pumping) – which delivers power to the active medium producing the photons

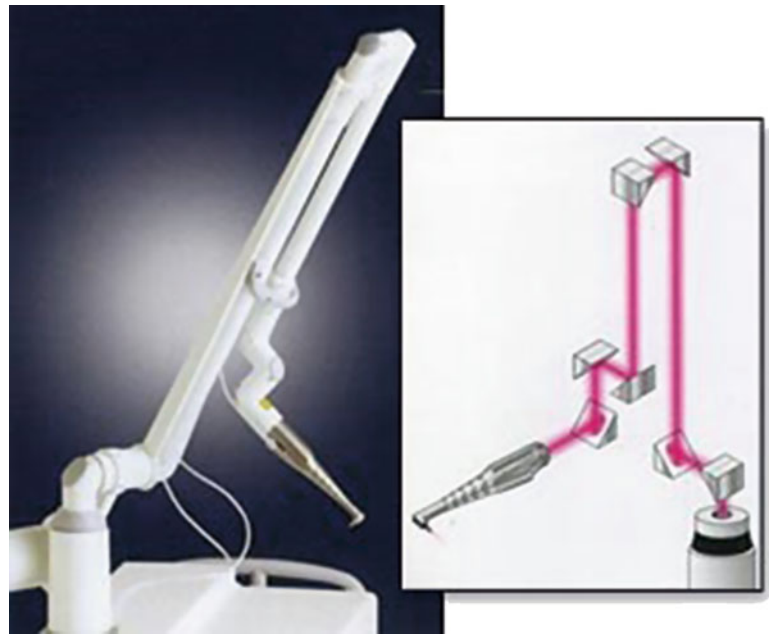

Fig. 12 Diagram of an articulated arm

3. Laser beam delivery system from the source to the hand of the operator
4. Handpiece, with focusing lens or a scanning system

The industry uses various elements in the manufacture of laser sources in order to cover a growing range of electromagnetic wavelengths. Today, we have ultraviolet lasers, visible light, and infrared. For this end, gases, liquids, crystals, fiber optics, and semiconductors (electronic components) are used.

The pumping of each element also varies; thus, electrical discharges, radio frequency, and light sources such as flash-lamps or even other lasers are used.

To carry the laser light from where it is generated in the resonator to the hand of the user who is making the application, various mechanisms are used depending on the wavelength and energy of the equipment. The most common are:

Articulated arm – a set of multiple mirrors positioned at the corners of articulated pipes to allow the freedom of movement in all directions (Fig. 12).

Optical fiber – thin waveguide with a core made of quartz covered with a thin layer called cladding, which is made of a slightly different material and encapsulated with plastic and metal coatings to give it flexibility. It delivers the laser beam by multiple internal reflections; that is, light enters the fiber, reflects on the core/cladding interface and keeps moving until it exits the optical fiber. Note that at the output of the fiber the laser beam has a wide divergence and is no longer collimated. In other words, the beam spreads, losing part of its coherence (Boechat et al. 1991, 1993) (Figs. 13 and 14).

A handpiece is placed at the end of the beam delivery system for either an articulated arm or an optical fiber. It contains the lens system which focuses the laser light on the working area facilitating the handling of the laser during treatment, as already described above. In fractional laser devices, described below, the handpiece holds the scanning systems, or scanners, in addition to the lenses.

Bellow we describe some typical commercial laser systems used in medicine, grouped according to the laser medium (Alster and

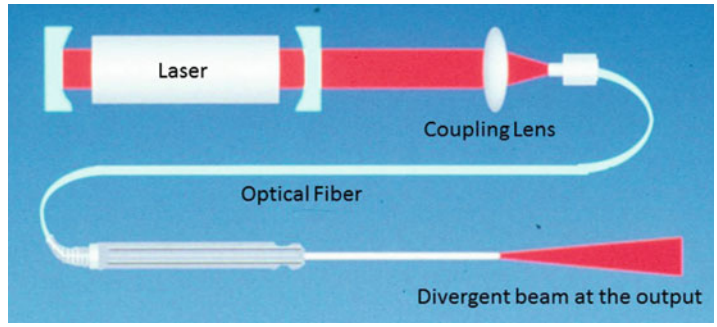

Fig. 13 Diagram of an optical fiber showing the beam divergence at the output

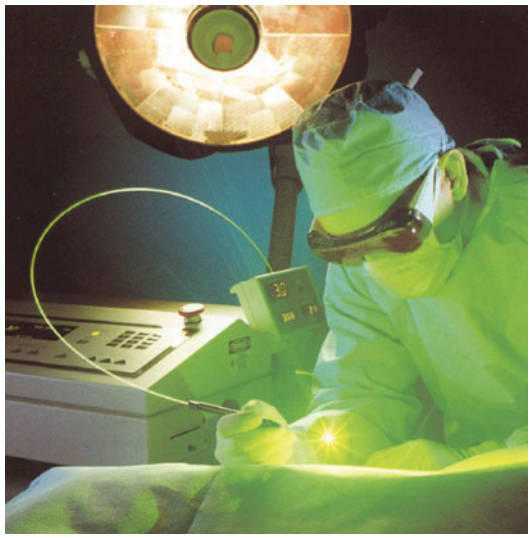

Fig. 14 Surgical laser with optical fiber

Apfelberg 1999; Alster 1997; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

Gas Lasers

Excimer

Gas molecules that exist only in the excited state, called "dimers," form the excited medium; examples are molecules such as halogens combined with noble gases (ArF, KrF, XeCl, Xef). The word "excimer" is an abbreviation of the term "excited dimer." The emission covers some wavelengths in the ultraviolet range such as 193 nm ArF, 222 nm KrCl, 248 nm KrF, and 308 nm XeCl. The pumping is usually made by electric discharge or the shock of electrons with gas molecules. Quartz optical fibers are used as beam delivery system. Since the wavelength is very small and carries a high energy, these lasers are widely used for high precision incisions or tissue ablation, such as in ophthalmic refractive surgery (myopia). In dermatology, this system has shown excellent results in the treatment of psoriasis and vitiligo (Zelickson et al. 1996; Guttman 2000).

Fig. 15 RF-pumped CO_2 laser with articulated arm, eCO2™ (Lutronic Inc.)

Argon Ion

The excited ionized argon gas, Ar^{+}, forms the laser medium. Pumping is made by electrical discharge. The wavelength can vary between 488 nm (blue) and 514 nm (green). It uses quartz optical fiber as the delivery system (Siegman 1986; Boechat 2009).

Helium-Neon (He-Ne)

The excited medium is a mixture of helium and neon gases. It is also pumped by electrical discharge. The wavelength is in the visible range, 632.8 nm, i.e., red. These systems are generally used for low-power applications such as cell stimulation and laser pointers or aiming systems for infrared invisible lasers. It uses quartz optical fibers (Siegman 1986; Boechat 2009).

Carbon Dioxide (CO_2)

The CO_2 is still one of the most used lasers in surgery, dermatology, and industrial applications. Its power may vary from a few KW up to MW in a continuous or pulsed manner. The laser medium is a mixture of gases including N_2 (nitrogen – 13–45 %), He (helium – 60–85 %), and CO_2 (1–9 %). Pumping is achieved by high-voltage electric discharge or radio frequency (RF). The molecule of CO_2 is excited by mechanical shock with electrons, of the N_2 and He molecules. The wavelength is in the infrared range at 10,640 nm. This is a relatively efficient laser (30 % of electro-optical conversion), and because of that, it has low-power consumption and maintenance. It uses an articulated arm and special dielectric coated flexible hollow waveguides (Siegman 1986; Kulick 1998; Alster and Apfelberg 1999; Alster 1997) (Fig. 15).

Liquid Laser

Dye Laser

It uses a liquid Rhodamine solution (R6G), which is a fluorescent dye, as the laser medium. It is pumped by a flash-lamp or another laser. The wavelength may vary continuously from 300 to 1,000 nm, and the resonator can be tuned. It is most commonly used in yellow (585–600 nm). Its main application is the treatment of vascular lesions and inflammatory processes of the skin. It uses quartz optical fiber (Siegman 1986; Reichert 1998; Mcmillan et al. 1998; Reyes and Geronemus 1990) (Fig. 16).

Fig. 16 Flash-lamp-pumped dye laser, Vbeam Perfecta™ (Syneron Candela)

Solid-State Laser (Crystal)

Figure 17 shows the schematics of the most common solid-state laser systems in the market. The mirrors, the laser rod (the crystal), and the flash-lamp, used for the pumping inside a cavity made of a coated elliptical reflecting material – usually ceramic or a large resistance metal such as gold – compose the resonator (Siegman 1986; Boechat 2009).

Ruby: $Cr^{3+}:Al_2O_3$

It was the first laser developed by Maiman in 1961 (Siegman 1986; Goldman and Fitzpatrick 1994; Arndt et al. 1997) (Siegman (1986) *Lasers*), but it was some time before this system started to be used

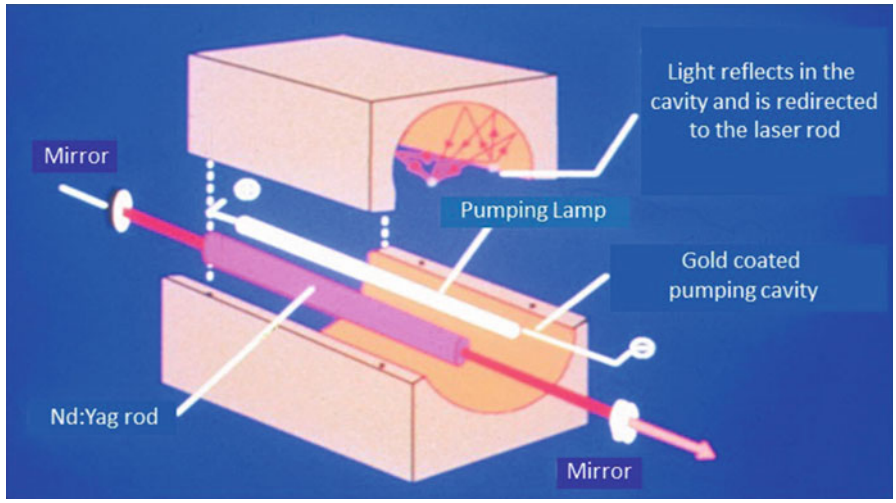

Fig. 17 Schematics of a typical laser using a crystal rod

in medicine. The medium is ionized ruby crystal. It is pumped by a flash-lamp. The wavelength is in the red range of 694 nm. The nature of the crystal requires high energy for pumping or high-power flash-lamps. It uses fiber optics and articulated arm for laser delivery. It is generally used for the treatment of pigmented lesions and hair and tattoo removal (Goldman 1967; Reid and Muller 1978; Raulin et al. 1998; Chang et al. 1996; Shimbashi et al. 1997; Yang et al. 1996; Ono and Tateshita 1998; Reid et al. 1983, 1990) (Fig. 18).

Alexandrite: $Cr:BeAl_2O_4$

The gain medium is chromium-doped chrysoberyl, the semiprecious stone alexandrite ionized. It is pumped by a flash-lamp. The wavelength is at the end of the red range (755 nm). It uses flexible optical fibers or an articulated arm. This crystal has better optical properties, which enables a faster and more efficient operation in a smaller device than the ruby. It is widely used for hair removal and treatment of pigmented lesions (Siegman 1986; Finkel et al. 1997; Stafford et al. 1995; Chan et al. 1999; Alster 1997) (Fig. 19).

YAG Family

The YAG abbreviation is short for yttrium aluminum garnet, which is a synthetic crystalline structure serving as host to the ion that will produce the radiation with the desired wavelength. It is pumped by laser diodes or a flash-lamp, and it works in the near-infrared spectrum. It uses optical fiber and in some cases the articulated arm

Fig. 18 Ruby laser with an articulated arm (Asclepion Laser Technologies)

(high-energy pulsed laser – Q-Switched) as the beam delivery system. The most common are (Siegman 1986; Goldman and Fitzpatrick 1994; Kulick 1998; Wong and Goh 1998; Ogata 1997; Chan et al. 1999; Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010):

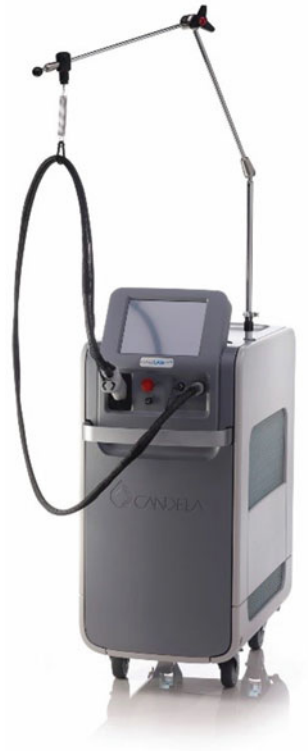

Fig. 19 Alexandrite Laser, GentleLASE™ (Syneron Candela)

- ***Nd*:*YAG*** – it uses the neodymium ion, with wavelengths of 1064 nm and 1320 nm, which is used for non-ablative skin rejuvenation (Muccini et al. 1998; Goldberg 1999, 2000b).
- ***Nd*:*YAG*/*KTP*** – by placing a second crystal in the laser resonator, in general the "famous" potassium-titanium-phosphate (KTP), it generates the frequency-doubled Nd:YAG laser with a green wavelength at 532 nm. It is used for removal of superficial pigmented and vascular lesions (Figs. 20 and 21).
- ***Nd*:*YAG*/*KTP* + *handpiece with crystal dye*** – a solid-state fluorescent dye handpiece can still be added to these lasers in order to obtain different wavelengths, such as 595 nm (yellow) and 650 nm (red), thus making the machine extremely versatile for the treatment of pigmented lesions and the removal of light color tattoos at different depths (Fig. 22).
- ***Ho*:*YAG*** – it uses holmium ions, with wavelength of 2,100 nm. It is excellent for treatments in bone and cartilage and for the fragmentation of kidney stones.
- ***Er*:*YAG*** – it uses erbium ions, with wavelength of 2,940 nm. It is well known for its use in "skin resurfacing" (skin rejuvenation) (Fleming 1999; Weinstein 1998).
- ***Tm*:*YAG*** – it uses thulium ions, with wavelength of 1,927 nm. It is used for non-ablative skin rejuvenation with a more superficial action (Fig. 23).

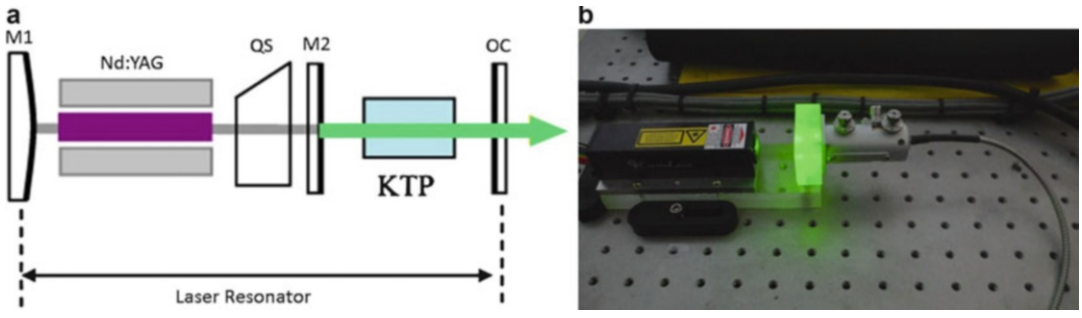

Fig. 20 (**a**) Schematics of a KTP laser pumped by a Q-Switched Nd:YAG laser. M1 is the 100 % reflector mirror; M2 is the partial reflector output coupler for the Nd:YAG pumping laser; QS – Q-Switch; KTP – the KTP crystal; OC – output coupler and wavelength selector for 1,064 nm and 532 nm. (**b**) Laboratory prototype of a Nd:YAG pumped KTP laser with optical fiber output connection

Nd:YAP

It uses neodymium ions in yttrium aluminum perovskite crystal, with wavelength of 1,340 nm. It is used for non-ablative skin rejuvenation and chronic inflammatory diseases such as hidradenitis (Milanic and Majaron 2013; Antonio et al. 2015).

Fig. 21 Laser system Spectra XT™ with two wavelengths: Nd:YAG (1,064 nm) and KTP (532 nm), Lutronic Inc.

Er:Glass

The gain medium is changed for crystal glass, which serves as host for the erbium ion. The wavelength shifts to 1,540 nm, in the near infrared. It is used for deeper skin rejuvenation and employed in fractional laser systems (Mordon et al. 2000) (Fig. 24).

Er:YSGG

The gain medium is similar to the YAG crystal, and it uses the erbium ion in an yttrium scandium gallium garnet (YSGG) host. The wavelength is also in the near infrared, 2,790 nm, used in the Pearl™ handpiece of Cutera. The main application is fractional skin rejuvenation. It is an alternative to the Er:YAG laser skin resurfacing.

Semiconductor Laser

– **Diode** – the laser medium is a semiconductor, i.e., an electronic component. It is pumped by electric current. The changing of the semiconductor achieves a wide range of wavelengths ranging from the visible, 450 nm, to the near infrared, 1,400 nm. The most common are aluminum gallium arsenide (AlGaAs) with wavelengths from red to near infrared, 620–900 nm, and gallium arsenide (GaAs) in the near infrared, 830–920 nm. It has a very efficient electro-optical conversion (greater than 50 %); thus, generally it is a small and greatly simplified operation system. It uses optical fibers or simply free, handheld devices. Some equipment manufacturers provide systems with one or more laser diodes with different wavelengths, increasing the

Fig. 22 Crystal dye handpieces, Laser Spectra XT™ (Lutronic Inc.)

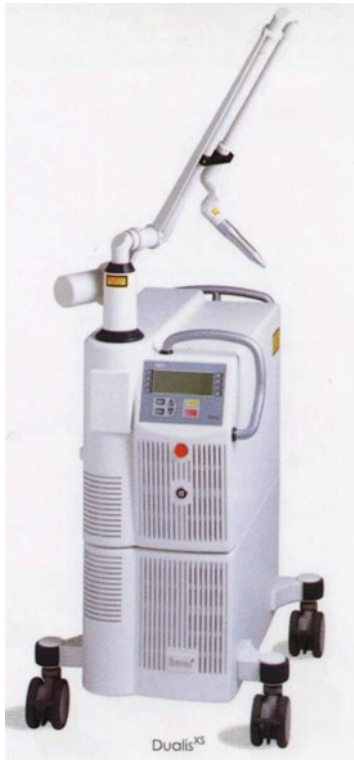

Fig. 23 Er:YAG laser system, with articulated arm for ablative skin rejuvenation (Fotona)

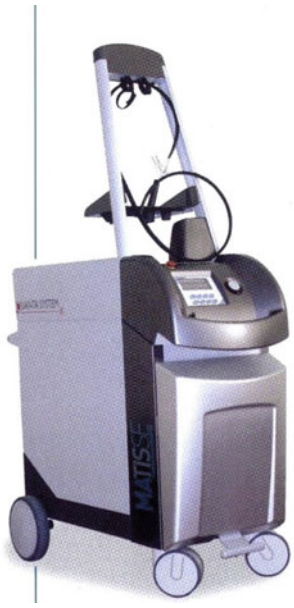

Fig. 24 Fractional Er:Glass laser system, Matisse™ (Quanta System)

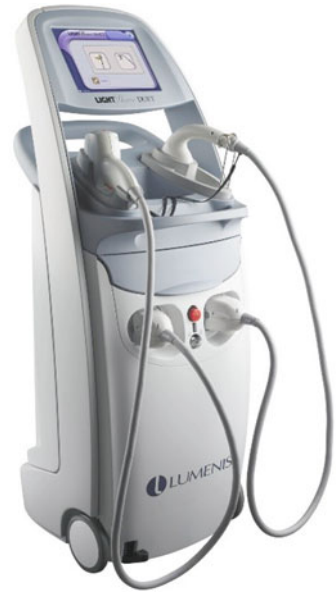

Fig. 25 LightSheer Duet diode laser, 810 nm (Lumenis)

flexibility of the system. It is widely used for hair removal, non-ablative skin rejuvenation, and treatment of vascular lesions. It is also used for pumping other lasers such as Nd:YAG, Nd:YAG/KTP, and fiber-optic lasers, as we will see below (Siegman 1986; Goldberg 2000a; Ross and Hardway 2000; Lou et al. 2000) (Fig. 25).

Optical Fiber Laser

Extremely robust, long-lasting, and highly reliable, this technology employed in undersea optical telecommunications cables has found an application in medicine in the development of fractional lasers (Manstein et al. 2004; Geronemus 2006; Raulin and Karsai 2011).

– **Y, Er:FIBER** – the gain medium is a quartz optical fiber measuring only 150 μm in diameter, containing erbium and yttrium ions. It is pumped by laser diodes. The wavelength is 1,550 nm. The system does not need optical components such as mirrors, output couplers, flash-lamps, and cooling system, which significantly reduces the need and cost of maintenance. This new technology produces microscopic focal points on the skin of the order of 100 μm (approximately the thickness

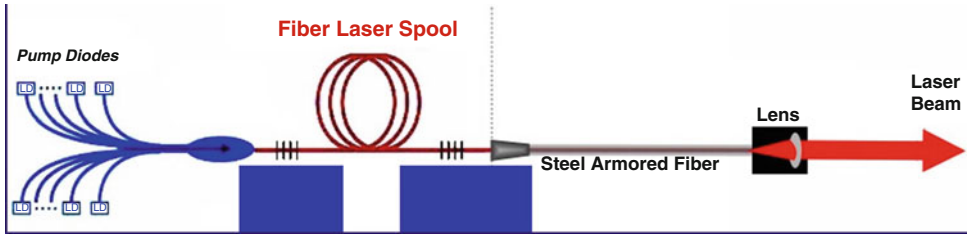

Fig. 26 Schematics of a laser diode array pumped, fiber laser

Fig. 27 Optical fiber laser, Mosaic™ (Lutronic Inc.)

of a human hair), since the light source is also a microscopic fiber, leading to the advent of fractional skin treatment (Figs. 26 and 27).

LED: Light-Emitting Diode

LEDs are electronic components, or semiconductor diodes, that emit light when stimulated by electric current. They may be considered as relate

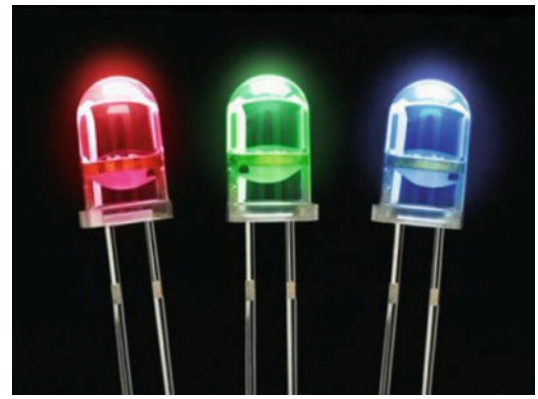

Fig. 28 Example of LEDs

to laser diodes, since they are manufactured with the same materials, as GaAs, GaAlAs, GaInPAs, and thus provide the same wavelengths. However, they do not have the light amplification effect produced by a laser resonator system. In this way, an incoherent monochromatic light is produced that diverges in various directions just as a lamp of low intensity (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

In order to concentrate and direct the emitted light, they are manufactured with a parabolic plastic housing, which functions as a small lens (Fig. 28).

LED treatment systems use panels made of 1,000–2,000 components in order to extend and optimize the application area. Depending on the application or treatment, it is possible to change the panel to a different wavelength. Some manufacturers have integrated LEDs with different wavelengths on the same panel thus avoiding the need to change them (Fig. 29).

Some of the most common applications are in the bio-modulation of cells, described below and in the following chapters, such as anti-inflammatory

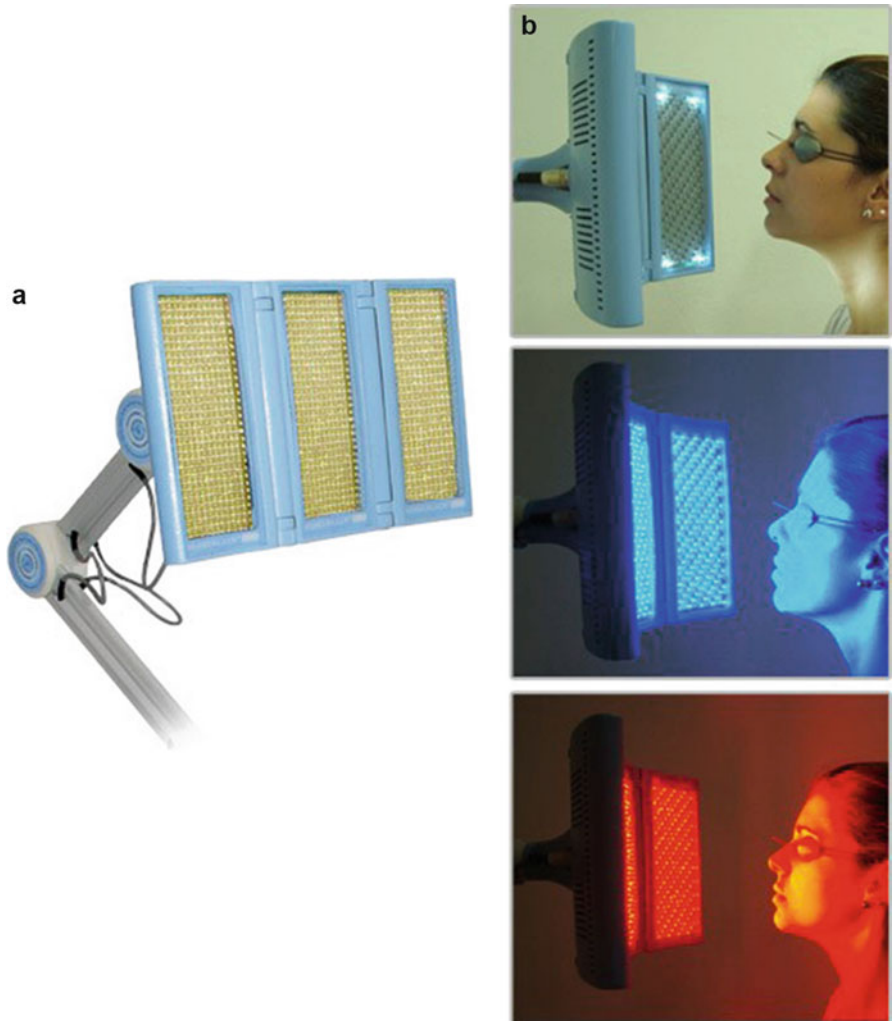

Fig. 29 (**a**) LED Panel, Hygialux™ (KLD). (**b**) LED Panels with different wavelengths (KLD)

effects and improved wound healing. It is also used in photodynamic therapy and teeth whitening.

Intense Pulsed Light

It is a system that employs a flash-lamp for many applications, but it is not a laser light source, pulsed light, or intense pulsed light – IPL. Dr. Shimon Eckhouse at ESC Medical in Israel developed this concept, in the 1990s (Boechat 2009; Raulin and Karsai 2011; Kaminsky Jedwab 2010).

It uses an electronically controlled intense flash-lamp. For this reason, it has distinct characteristics from a laser source:

(a) **Polychromatic**: it emits a broad spectrum of wavelengths, generally in the range from 400 to 1,200 nm. It uses band-pass filters placed in front of the lamp for wavelength selection. These filters remove a band of wavelengths, in general those below the filter specification, letting through all the wavelengths above it. Some machines use a

more complex filter, which narrows the emission at a range of wavelengths, as illustrated in Fig. 30. Even with a narrow emission spectrum limited by the filters, the emitted energy disperse within several wavelengths, that is those that will be absorbed by the tissue to be treated and others that will have no effect. Thus, the selectivity and effectiveness of the treatment is reduced as compared with a laser that has 100 % of the energy concentrated in a single wavelength (monochromatic).

(b) **Incoherent**: different from a laser source, the IPL energy is emitted in all directions; it spreads. Mirrored surfaces placed behind the lamp, similar to reflectors used in car headlights, concentrate and direct the light. It will have a more superficial and mild effect on the tissue because it is less intense than laser light. The application will also be less painful.

The multiplicity of emitted wavelengths makes these systems very versatile, being able to perform several applications such as in hair removal, pigmented lesions, non-ablative rejuvenation, and vascular lesions, by simply changing the filter and pulse duration (Fig. 31).

These systems generally have a fixed pulse duration already set by the manufacturer depending on the application. To change the pulse duration, in general, it is necessary to change the entire handpiece. Pulse duration is restricted to the range of milliseconds because of the lamp characteristics; however, it suits most skin applications.

Figure 32 illustrates an IPL with various application filters. To change the spot size, it is necessary to change the handpiece for one with a smaller application area or use physical filters, such as a plate with a hole of different sizes placed in front of the lamp, as shown in Fig. 33. The plate limits the application area but significantly reduces the treatment energy. In this way, they differ from lasers, in which a lens system located in the handpiece changes the spot size in a more versatile manner, preserving the total energy of the laser beam.

Treatment Platforms

Following the trend of the market to produce increasingly compact systems, which provide various applications, the laser industry has developed the concept of multi-application platform. These systems consist of a base (platform) that carries the energy source and cooling system. Then several handpieces can be connected to the base providing different applications. Each handpiece may contain an IPL or a laser system. The most frequent applications are hair: removal, skin rejuvenation, treatment of pigmented and vascular lesions, and tattoo removal (Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

These treatment platforms became very popular because of the excellent cost/benefit and versatile combination of intense pulsed light and laser in the same equipment. There are also platforms that have only lasers, or only IPL, and others that added a RF handpiece for skin tightening.

On the other hand, one of the limitations of this design is that it does not allow simultaneous treatments. For example, we need to finish the hair removal treatment to perform the skin rejuvenation. For busy clinics performing several applications at the same time, the choice of equipment with separate applications would be a better alternative to increase revenues.

Another important point is that when using a laser as a platform handpiece, it suffers from energy and versatility limitations. For example, an Er:YAG laser equipment with its articulated arm can provide more power, versatility, spot size application, and pulse duration than when installed in a platform handpiece. The same happens with a Q-Switched laser, as it is very difficult to adapt an active Q-Switch in a simple handpiece. Therefore, on a platform, Q-Switched devices usually are limited to the passive design (Fig. 34).

After becoming familiar with these technologies and their operating principles, a question comes to mind: when and how to use each of these systems?

The application of each laser, IPL, or LED in dermatology will depend on the response of the tissue to the wavelength being used.

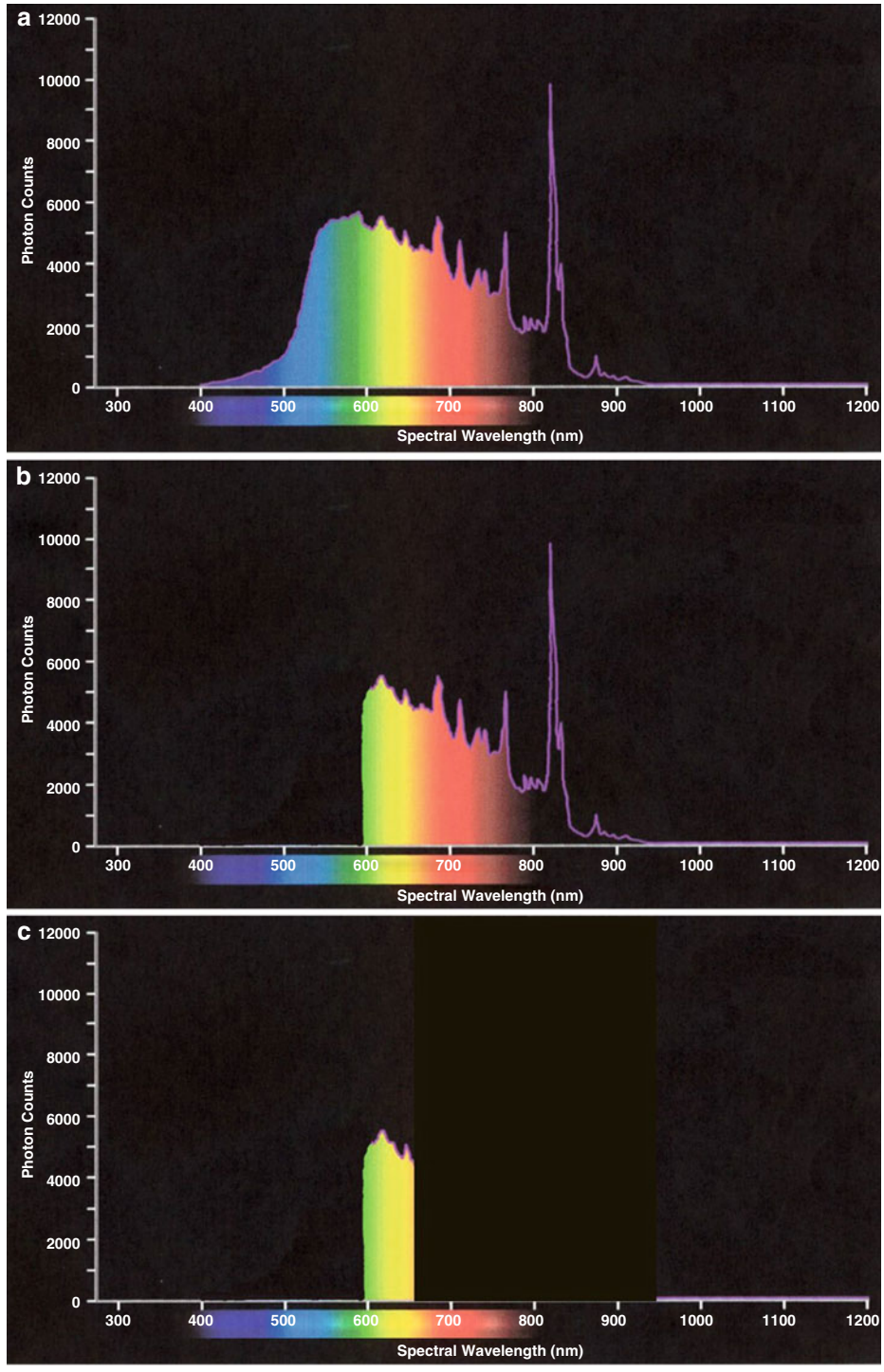

Fig. 30 (**a**) General output spectrum of an IPL, (**b**) with a single 570 nm cut filter and (**c**) with a band-pass filter that limits even further the output spectrum

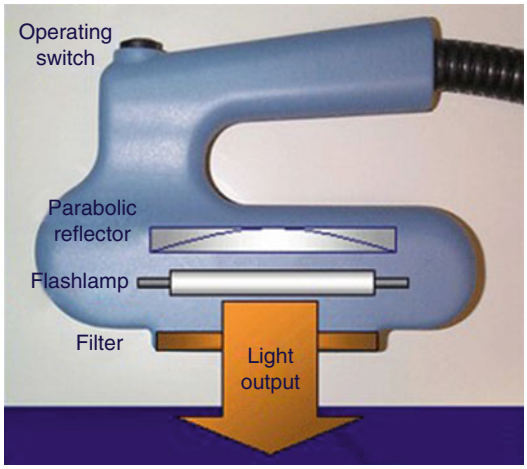

Fig. 31 Schematics of an intense pulsed light – IPL (Lumenis)

Fig. 32 IPL handpiece with different filters

Light-Tissue Interaction

Light can interact with living tissue in the following forms (Anderson and Parrish 1981; Goldman and Fitzpatrick 1994; Arndt et al. 1997; Kulick 1998):

Photothermal: light energy is absorbed by the target tissue (chromophore) and transformed into heat, causing coagulation or vaporization.

Photomechanical: fragmentation by mechanical effect, as in the Q-Switch described above.

Fig. 33 Physical filters that change the spot size of the output or the application area of an IPL in the tissue

Photochemical:

1. Direct breaking of chemical bonds between atoms of a molecule produced by, for example, an ultraviolet excimer laser when sculpting a cornea, thus with great accuracy.
2. Light activates a chemical reaction that produces reactive free radicals, as in photodynamic therapy (PDT), described in a following chapter.

Photobiomodulation: light is used to modulate intra- and intercellular activities. It employs low-power laser and LED panels. It has anti-inflammatory action and the effects of wound healing and tissue regeneration (Lopes 1999).

Selective photothermolysis: it is the art of combining wavelength, pulse duration, and energy to obtain the desired effect on the target tissue preserving adjacent areas, as described below.

When a beam of light hits the tissue, it is (Fig. 35) partially transmitted, reflected, spread (scattering), or absorbed.

Laser light will only produce a therapeutic effect if the target tissue is "in tune" with the energy that is being used, as in a mobile phone. At any given time, there are thousands of mobile phone waves passing where we are, but the phone does not ring. It will only be triggered when the emitted wave is in tune with the device. Similarly, we can place several wavelengths of light in the skin, but the target tissue will absorb only a

specific light. In particular, the energy deposited by the most commonly used lasers in medicine is transformed into heat and thus produces a temperature increase on the chromophore.

We can summarize the effect of the temperature increase in the tissue in the following ranges:

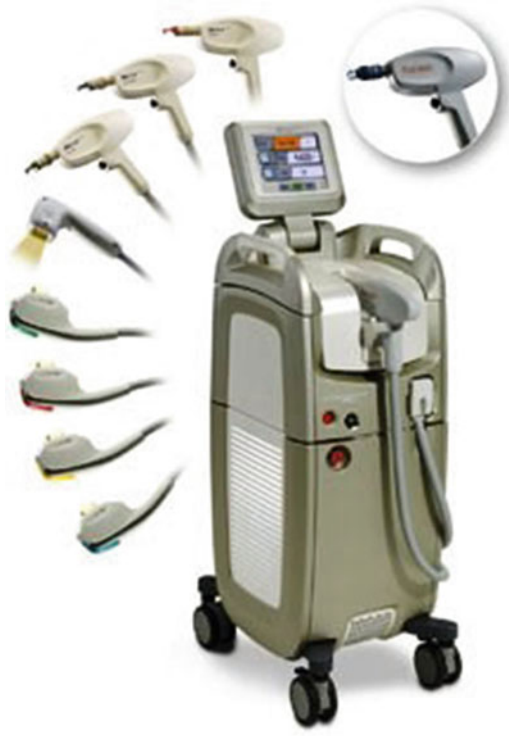

Fig. 34 Treatment Platform Harmony™ with several handpieces (Alma Laser)

1. 37–43 °C: accelerated cell metabolism, stimulation, contraction of elastic fibers, and skin tightening. There is less effect and it is reversible.
2. 44–45 °C: exponential increase in cell metabolism acceleration, changes in protein, collagen stimulation, and cell apoptosis with long application time, because of hyperthermia.
3. 50–70 °C: protein denaturation, coagulation of collagen (which must be replaced – regeneration), cell membranes, and hemoglobin; permanent contraction of collagen fibers.
4. 90–100 °C: formation of extracellular vacuoles, evaporation of liquids.
5. Above 100 °C: vaporization of tissue, charring.

The laser parameter that most influences the absorption factor, also called the "tuning" effect, is the wavelength of the light (its color; its frequency). Each part of our organism or component of our skin responds differently or has affinity to a particular wavelength. Certain tissues are transparent to a particular laser; others absorb it completely. Therefore, we can induce the necessary thermal effect to treat it selectively at a specific point without affecting the surrounding tissue, giving rise to the phenomenon of the "selective photothermolysis" theory developed by Dr. Rox Anderson et al., in Boston, USA (Anderson and Parrish 1983, 1981; Goldman and Fitzpatrick 1994).

The graph of Fig. 36 represents the fundamental result of the publication of Anderson et al. It shows the variation with wavelength of the absorption

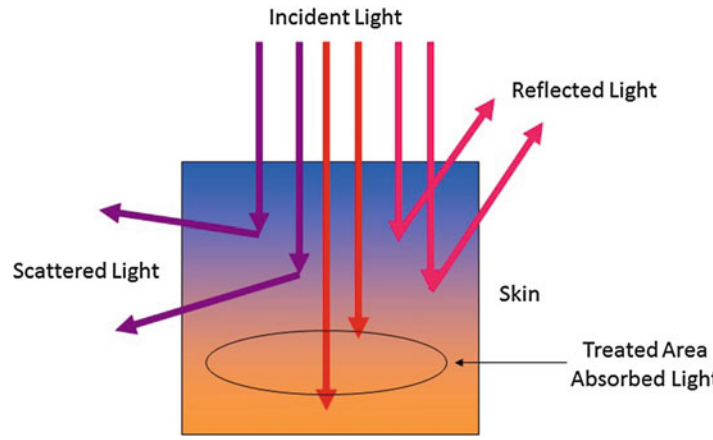

Fig. 35 Light-tissue interaction

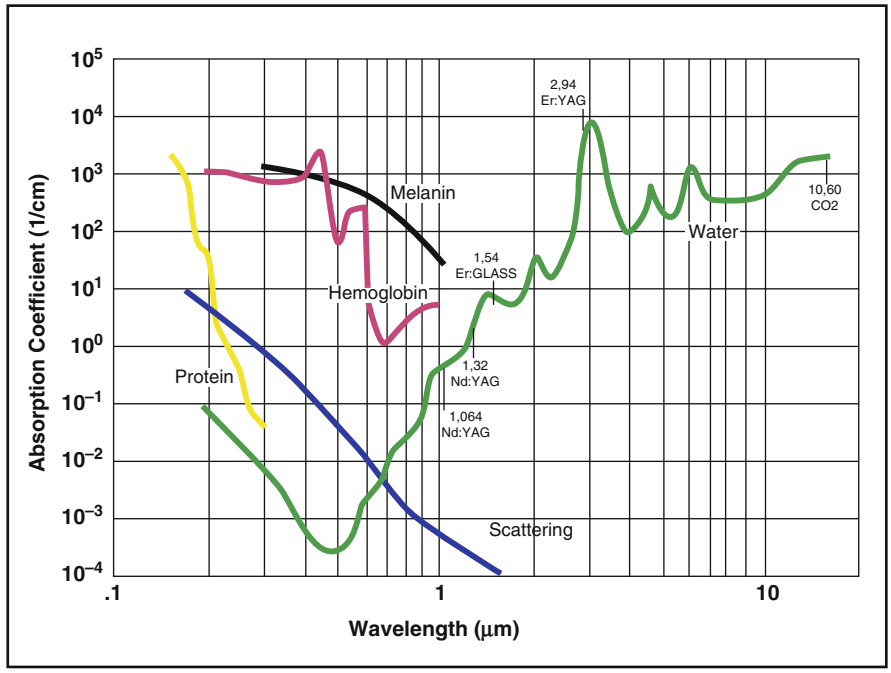

Fig. 36 Curve of the absorption coefficient of some tissue components as a function of wavelength, pointing out the most popular laser systems

coefficient of certain skin components, such as melanin, hemoglobin, and water molecule. We can see that melanin has a high absorption for lasers in the visible range, such as green (KTP), which can be used, for example, in the treatment of pigmented lesions. Hemoglobin has an absorption peak in the range of yellow light (dye laser), making it a good option for treating vascular lesions. The ruby laser, in the range of red light, is well absorbed by the melanin and dark pigment in the skin. On the other hand, it is positioned at a minimum for hemoglobin absorption, which explains in part the difficulty that these systems have to remove red pigments in the treatment of tattoos and vascular lesions (low coagulation effect).

When the light of these lasers enter the skin in fast pulses, or rather ideal pulses, it is able to cross the skin without causing any damage and is absorbed only by the target tissue with which it has affinity. These components are referred to in the literature as "chromophores."

We also note from the graph that the absorption of melanin in the visible and near infrared (invisible) is very wide which allows for a number of different lasers to be used effectively for treating pigmented lesions and hair removal, such as the 810 nm diode laser and 1,064 nm Nd:YAG. Because of the its longer wavelength, the Nd:YAG penetrates deeper in the skin, as described below, and its absorption coefficient for melanin is lower when compared to visible lasers, such as green. These are properties that make these lasers suitable for a variety of treatments, since they present reduced risk of damage of the skin surface, because of the absorption of melanin, and are effective for dermis treatments such as deep vascular lesions and melisma.

The Er:YAG (2,940 nm) and CO_2 (10,600 nm), in the infrared, have high absorption coefficients for water molecule. As water is the major component of the cellular structures, its interaction with these wavelengths is predominant. Therefore, the first layers of cells rapidly absorbs the energy from these lasers increasing their temperature to the vaporization level, making it an excellent tool for cutting or precise and superficial tissue removal, such as in laser skin resurfacing or fractional laser skin resurfacing. The Er:YAG laser

wavelength is at the peak of water absorption, with a coefficient at least ten times higher than the CO_2 laser. Since its light is more rapidly absorbed, the energy penetrates less, what makes it have a more superficial action compared to CO_2. The treatment will also have lees thermal effect being gentler to the skin (Chernoff et al. 1995; Alster et al. 1999; Weinstein 1998).

Another important aspect of light-tissue interaction is the laser pulse duration (pulse length or exposure time). This must be such that the energy produces an increase in temperature that is confined (concentrated) to the target tissue, with minimal dispersion to the surrounding areas. In other words, the laser pulse duration has to be long enough to increase the temperature on the target tissue up to its destruction level, while being short enough not to irradiate heat to the surrounding tissue. A similar situation happens when we want to verify if the iron is hot enough for ironing clothes. Usually, we place the finger on the iron for enough time to check that it is hot, but remove it very fast to guarantee that we do not burn it.

In order to achieve the correct pulse duration, we need to observe the thermal relaxation time (TRT) of the target tissue.

The TRT is the time the tissue takes to cool after being intensely heated. Following the principles of physics, chromophores with large volumes or cross sections take longer to cool and therefore have a higher TRT. For example, a thick hair has an average TRT of 40 ms, whereas a thin hair has a TRT of 1–3 ms.

For a flat object, such as a melanosis, the TRT can be estimated by the ratio (Anderson and Parrish 1981; Goldman and Fitzpatrick 1994; Arndt et al. 1997; Lapidoth et al. 2015):

$$\mathbf{TRT} = \mathbf{d^2/4a}$$

where "d" is the thickness of the material and "a" is the thermal conductivity of the material.

For a cylindrical object, such as hair or vein:

$$\mathbf{TRT} = \mathbf{d^2/16a}$$

where "d" is the diameter of the object.

Thus, to confine the energy or heat in the target tissue, we need pulses that are less than or equal to the chromophore TRT.

We can reach an important conclusion from this: by using the same wavelength (the same laser), we can perform different treatments by simply changing the laser pulse duration. For example, with a long-pulse Nd:YAG laser, in milliseconds, we can treat varicose veins or perform hair removal. Installing a Q-Switch, with nanosecond pulses, allows the removal of tattoos or melanosis, because the melanosome TRT is of the order of 100 ns.

From what is discussed above, the basic principles of selective photothermolysis are (Anderson and Parrish 1983; Goldman and Fitzpatrick 1994):

(a) **Ideal wavelength** that is absorbed only by the target tissue or chromophore
(b) **Ideal pulse duration** that should be sufficient to produce the desired effect on any target tissue, but fast enough to cause minimal effect on the surrounding tissues, i.e., confining the energy in the chromophore
(c) **Energy** enough to reach the treatment effect

In summary, the vast majority of treatments in photomedicine happen as follows:

1. Light is absorbed by the target tissue or chromophore.
2. The absorption of light causes a selective heating of the target while preserving the surrounding tissues.
3. The chromophore selective heating causes its coagulation or vaporization, reaching the goal of the treatment.

The Melanin "Curtain"

The curve of absorption of Fig. 36 (Anderson and Parrish 1983, 1981) shows that skin melanin presents absorption for most lasers on the visible and near-infrared range. Thus, it is important to remember that in applications where the target tissue is below the papillary dermis (hair, vascular lesions, pigmented lesions, etc.), or below the melanin layer

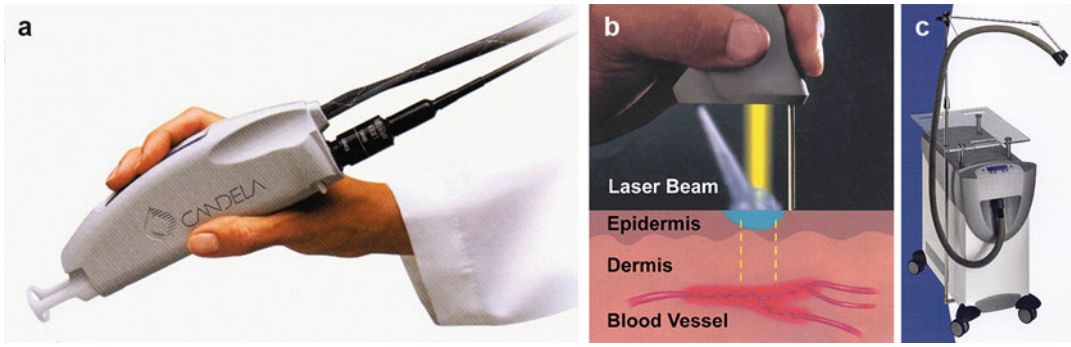

Fig. 37 (**a**) Example of a dynamic cooling device coupled to the laser handpiece, DCD™ (Syneron Candela). (**b**) Working diagram of a dynamic cooling device, DCD™. A spray of cryogenic gas freezes the skin just before the laser pulse (Syneron Candela). (**c**) Cool air jet system, Cryo 6™, a stand-alone unit to cool the skin during treatment (Zimmer MedizinSysteme)

where we need greater light penetration, energy will always be attenuated, reducing the efficiency of the treatment. The melanin present in the top layers of the skin acts as a window curtain. Energy absorption by this melanin "curtain" will increase with darker skin patients or with patients at the higher positions of the skin types on the Fitzpatrick scale. The absorbed energy will generate local heat, which when excessive can generate unpleasant adverse effects such as burns, hypochromic spots, or stimulate melanocytes producing hyperchromic spots.

Thus, lasers and IPLs, which work with higher energies, employ systems for the protection of the epidermis, ranging from simple solutions, such as cooling the area with cold gel or ice packs, to the sophisticated cooling systems coupled to the handpiece. All are extremely necessary to dissipate some of the heat generated by light absorption in the first layer of the skin.

Epidermal cooling systems can be (Waldorf et al.; Alster and Apfelberg 1999; Goldberg 2000a; Ross and Hardway 2000; Klavuhn 2000):

1. **Static**: the handpiece has a sapphire window cooled with water or cryogenic gas, which remains in contact with the skin removing excess heat during the laser pulse.
2. **Dynamic**: also coupled to the handpiece, the system triggers a cryogenic gas jet, which freezes the skin immediately before the laser pulse, which then rapidly brings the skin temperature back to normal. In this system, it is possible to vary the duration of the gas jet (according to phototype and patient discomfort), as well as the interval between the cryogenic spray and the laser pulse.
3. **Continuous/independent**: a separate device that provides a cold air blast cooling the tissue during the procedure and operating independently from the laser or pulsed light.

The advantages of using these devices are:

1. Possibility of using higher energies, increasing the efficacy of the treatment
2. Reduction of patient discomfort and risk of adverse effects
3. Possibility of treating darker skin types (Fig. 37)

Light Penetration Depth

Giving great importance to the effectiveness of the treatment, light penetration depth is primarily governed by the wavelength, observing the following factors (Anderson and Parrish 1981; Raulin and Karsai 2011; Sardana and Garg 2014; Lapidoth et al. 2015):

1. Scattering of light in the visible part of the spectrum.

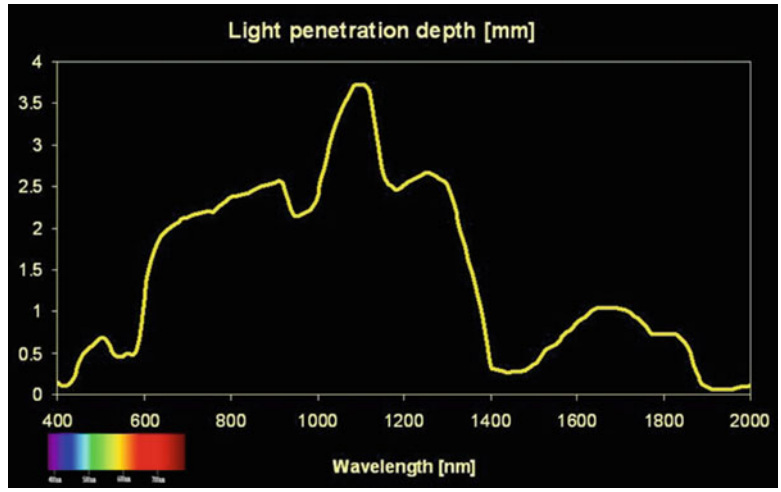

Fig. 38 Light penetration depth as a function of the wavelength

2. Absorption by water in skin cells, particularly the epidermal ones on the near-infrared wavelength range.
3. For a given wavelength, the higher is the energy, the deeper the energy will reach.

Going back to the graph of absorption coefficient of Fig. 36, we see that light scattering (blue curve) becomes stronger for smaller wavelengths on the visible range. Therefore, for this part of the spectrum, regardless of the energy used, penetration is usually very small as shown in the graph of Fig. 38. The scattering effect begins to reduce in red light (700 nm) and practically disappears in the near-infrared range, around 900–1,100 nm, which allows these wavelengths to penetrate deeply into the tissue. After 1,200 nm, the absorption of the water in the chromophore present in abundance in the skin cells starts to become significant, again reducing the light penetration.

As it penetrates the skin, light energy is absorbed and scattered along the way, decreasing the intensity until it disappears. The power distribution along the light path in the tissue will reduce as it penetrates the skin. The energy in the surface is always higher than at any point within the tissue. Therefore, for a given wavelength, light with higher energy at the surface will have a slight increase in tissue penetration.

In summary, visible wavelengths are ideal for the treatment of superficial lesions such as spots or port-wine stains. It is common to observe in the treatment of superficial pigmented lesions that some spots do not clear completely. This can indicate that part of the spot is located on a deeper layer where light does not reach.

Wavelengths on the range of 900–1,100 nm, near infrared, should be used for the treatment of deep lesions such as varicose veins or hemangiomas and dermal melasma.

Another mechanism can control the light penetration depth. For a given wavelength and fluency (energy/application area), it is possible to achieve a greater energy penetration by increasing the spot size. Figure 39 illustrates the effect of the spot size on light penetration. Using a small spot size, it is not possible to achieve the concentration of light deep into the skin because of the scattering. For a larger spot size, the dispersion is the same, but it compensates the scattering effect by achieving a greater energy concentration deeper into the skin. Therefore, the larger the spot size, the greater the energy concentration, or the deeper the penetration. This effect is important, for example, in laser hair removal, treatment of dermal melasma, and tattoo removal (Raulin and Karsai 2011; Kaminsky Jedwab 2010; Sardana and Garg 2014).

"Ablative" and "Non-ablative" Skin Rejuvenation

A wide application of lasers working in the near and mid-infrared, from 900 to 10,000 nm, and intense pulsed light (IPL) has revolutionized the

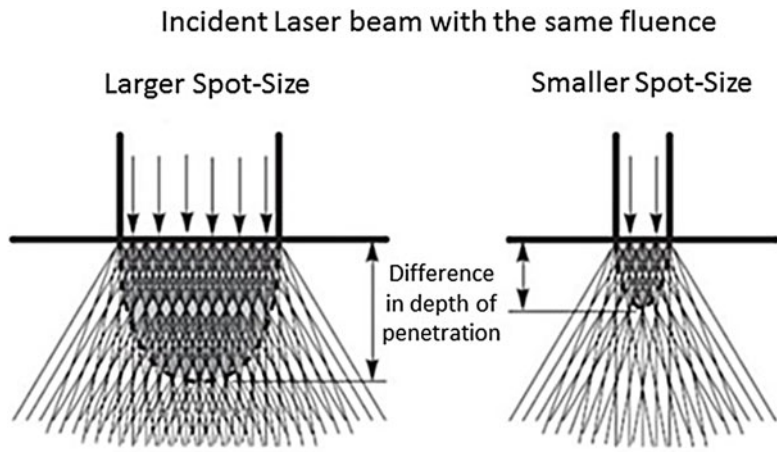

Fig. 39 Spot size effect on the penetration depth of a laser beam with the same fluency

skin rejuvenation technique. By definition, an ablative laser is one that removes the skin surface and produces controlled coagulation of the tissue underneath. Non-ablative systems produce only tissue coagulation, keeping the skin surface intact (Muccini et al. 1998; Goldberg 2000b; Khan et al. 2005; Munavalli et al. 2005).

At the near-infrared range, the absorption of melanin reduces drastically. Moreover, the absorption of water increases exponentially. Thus, through appropriate selection of wavelength and pulse duration, it is possible to vary the intensity of the heat generated in the skin changing from non-ablative to an ablative interaction.

Therefore, the difference from a non-ablative to an ablative laser is simply its wavelength and consequent intensity of interaction with the water in the chromophore. The graph of Fig. 40 shows the curve of absorption of the water in the chromophore for two lasers used in skin rejuvenation, Er:Glass (1,540 nm) and CO_2 (10,600 nm) (Anderson and Parrish 1983, 1981).

The absorption coefficient of water at the Er:Glass wavelength is approximately 10, while at the CO_2 wavelength, it is approximately 3,000, a difference of 300 times. Thus, for two lasers with the same fluency, the Er:Glass will heat the skin to an average temperature of 60 °C, occurring only coagulation (cell death), while the CO_2 laser will increase the temperature of the tissue up to 180 °C, leading to vaporization, since this value is much higher than the boiling temperature of water. The histology of Fig. 41 shows the difference of laser-tissue interaction for two fractional lasers, which will be described below.

The non-ablative treatment promotes the regeneration of deep tissue, with collagen remodeling, promoting a natural filling effect of the skin. It has a fast recovery time with little interference in the patient routine. Treatment takes four to five monthly sessions. It improves fine lines, open pores, skin texture, and overall skin quality.

The ablative treatment promotes a skin surface removal (resurfacing), regeneration of underneath tissue (same as the non-ablative effect), and skin tightening, because of the high temperature reached and the removal of a percentage of the skin by laser vaporization. It promotes a more complete treatment than the non-ablative one, but with a longer recovery time. Treatment takes two to three sessions with 45–60 days apart. It shows good results for deep wrinkles, scars, tightening, texture, and overall skin quality (Pitanguy et al. 1996; Chernoff et al. 1995; Alster et al. 1999; Lask 1995).

As the IPL systems employ a range of wavelengths ranging from the visible to the near infrared, they are able to treat many types of skin lesions simultaneously. While it improves skin quality with wavelengths in the near-infrared range, the visible part of the spectrum removes superficial pigmented lesions and small surface telangiectasia. However, it shows milder and more superficial effects than lasers.

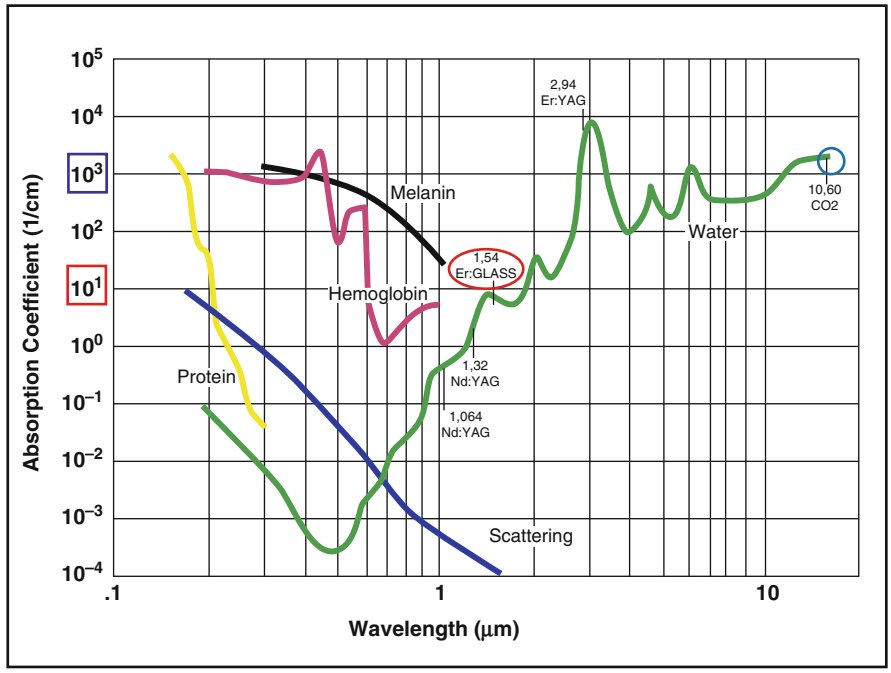

Fig. 40 Curve of absorption as a function of the wavelength of the laser showing the difference in the absorption of water for the Er:Glass laser (non-ablative) and the $C0_2$ laser (ablative)

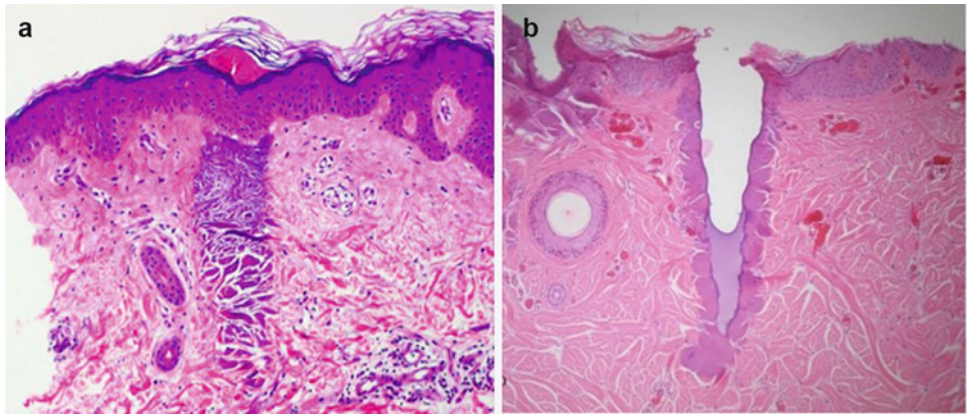

Fig. 41 Skin histology showing the effect on tissue for: (**a**) non-ablative fractional Er:Glass laser (1,540 nm), with only a coagulation column and the intact skin surface, and (**b**) fractional ablative CO_2 laser, with tissue vaporization at the center of the column and coagulation around it

Several manufacturers have produced laser systems and pulsed light for this purpose; some examples are:

CO_2 (10,600 nm) – produces a balanced mix of ablation and coagulation of the tissue leading to a complete rejuvenation result that is still the gold standard of the market.

Er:YAG (2,940 nm) – has ten times greater absorption coefficient for water than the CO_2 laser and thus produces more ablation then coagulation. Ablation is shallower and milder, with less collagen remodeling in the dermis.

Nd:YAG (1,064 nm and 1,320 nm) – a line of the Nd:YAG laser, which typically produces 1,064 nm, has its resonator altered to produce

this new wavelength. It has non-ablative effect only in the coagulation of the dermis (Muccini et al. 1998; Goldberg 1999, 2000b; Goldberg and Whitworth 1997).

Tm:**YAG** – thulium laser working at 1,927 nm; non-ablative effect.

Diode – a compact system with wavelength of 1,450 nm; non-ablative effect (Goldberg 2000a; Ross and Hardway 2000).

Er:**Fiber** or **Er**:**Glass** – using the erbium ion, but on a different material, such as an optical fiber or a glass crystal, has the wavelength of 1,550 nm or 1,540 nm. Both are non-ablative (Mordon et al. 2000).

Intense pulsed light – versatility, milder treatment, and good cost-benefit of these devices have led to the development of various devices in recent years dominating the landscape of non-ablative skin rejuvenation, although the effect is generally superficial.

Fractional Laser Systems

To appreciate the revolution introduced by the fractional laser technology, let us imagine a patient who seeks an aesthetic improvement of the skin as a family photograph that needs some finishing touches. Today, a photograph is digitally altered pixel by pixel, to improve the appearance of objects in the image. Likewise, damaged paintings are restored gently in a small area at a time.

This same concept is employed in systems that use the fractional photothermolysis technology. The laser produces microscopic thermal injury called microthermal zones (MTZs), approximately 100–150 μm in diameter – the thickness of a human hair – and depth from 0.2 to 2.4 mm (IPL devices in general achieve a maximum of 0.3 mm below the surface). These MTZs are surrounded by healthy tissue that is not affected and will help in the recovery of the micro-damaged area. The surrounding tissue will also be mobilized in the overall skin regeneration process. The resulting rejuvenation effect is comparable to deep chemical peels or dermal mechanical abrasion, but with minimal side effects and little downtime (Fig. 42).

An intelligent scanning system (optical scanners) located on the handpiece ensures the even

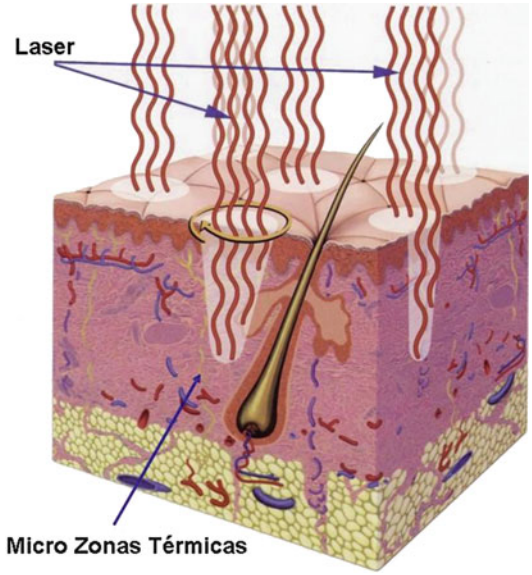

Fig. 42 The science of fractional photothermolysis

distribution of MTZs. The operator can choose directly in the laser panel the amount of MTZs that will be put on the skin or the percentage of the total skin area that will be stimulated, controlling the aggressiveness of the treatment. More MTZs means greater stimulus, being more aggressive the application and consequently showing more results. This leads to an application control that hitherto did not exist in dermatological treatments.

The method was developed by the parents of selective photothermolysis, Doctors Rox Anderson and Dieter Manstein, at the Wellman Laboratories in Boston, USA. The first fractional laser system, the Fraxel SR, was shown by Reliant Technologies Inc. in the Congress of the American Academy of Laser (ASLMS – American Society for Laser in Medicine and Surgery) in April, 2004 (Laubach et al. 2005; Geronemus 2006; Raulin and Karsai 2011).

The system follows the principles of selective photothermolysis with wavelength in the 1,550 nm range, where the water of the chromophore is present in the skin cells. In its original design, the fractional systems perform a non-ablative treatment, preserving the skin surface, and the temperature of the tissue increases only up to the coagulation point, producing microthermal zones. Treatment takes three to five monthly sessions.

Beyond the minimum recovery time, the advantages of this treatment include the possibility to use the laser to treat other regions of the body besides the face with safety and efficacy and to remove deep pigmented lesions, and also there are surprising results on the improvement of unaesthetic and acne scars. The following chapters will discuss in detail applications of fractional treatment.

Some commercial non-ablative fractional systems are:

Fraxel re:Store – 1,550 nm wavelength, Er:Fiber laser. It has a handpiece with an intelligent continuous scanning system that measures the speed of the application of the operator to distribute the MTZs on the skin homogeneously.

Palomar Lux1540 – it has a fractional handpiece of the Palomar StarLux platform, which employs an Er:Glass laser. It uses a fixed filter at the output to split the beam and to generate the fractional effect. Thus, the number of MTZs and application area is fixed.

Lutronic mosaic – it is a fractional system from Lutronic Inc., which is a Korean company that also employs an Er:Fiber laser with wavelength at 1,550 nm. It uses the intelligent scanner at the handpiece; thus, it is possible to choose the number of MTZs (density of the treatment), and the application can be in a static or continuous scan mode, as Fraxel (Fig. 27).

The great success of the fractional technology led to the diversification and improvement of the method originating the ablative fractional treatment. The laser drills micro-holes with controlled depth in the skin, with a thin tissue coagulation zone around them. The surface is damaged producing small crusts and more persistent erythema. The recovery time is longer, and there are restrictions on the skin type and body areas to be treated. The histology of Fig. 41 clearly demonstrates the difference of a non-ablative and an ablative technology.

The ablative fractional treatment brought back the CO_2 laser to the rejuvenation scenery because it gave control, safety, and less restriction to the previous efficient CO_2 laser skin resurfacing that still remains the gold standard of skin rejuvenation. Another advantage is that it can also be used for precise cuts and vaporization in minor surgeries.

Bellow, we show some examples of commercial fractional ablative lasers:

Lutronic eCO$_2$ – it is a CO_2 fractional laser with static and dynamic scanning system (Fig. 7). It is possible to program the diameter and density of MTZs.

Fraxel re:pair – it is a CO_2 laser, which uses the same fractional technology as the non-ablative Fraxel re:Store with an intelligent continuous scanning system.

Lumenis Total Active FX – it also uses a CO_2 laser with intelligent scanners, which allow for static and dynamic scanning modes. The diameter and density of MTZs can be programmed.

DEKA SmartXide (Boechat et al. 1991) **DOT/RF** – it is a CO_2 laser with scanners and radio frequency (RF) technology integrated in the handpiece.

Alma Pixel CO$_2$ – it is a CO_2 laser with an array of micro-lenses on the tip to split the beam and to produce the fractional effect. The number and diameter of MTZs are fixed although it offers handpieces with different sizes.

Alma Pixel Handpiece – it is a fractional handpiece from the multiplatform harmony employing an Er:YAG wavelength of 2,940 nm and a filter effect to split the laser beam and to produce the fractional effect. The MTZs are thicker than in the other devices, of the order of millimeters in diameter, and more superficial, reach only the epidermal layer, because of the wavelength and energy of the system.

Radio Frequency

Radio frequency (RF) consists of a high-frequency electric current, of the order of 1 MHz, and has been used in medicine for several years. Just for comparison, household appliances, such as TVs and refrigerators, work with 50 or 60Hz, which are low frequencies.

Going back to Fig. 1, the chart of the electromagnetic spectrum, we see that RF occupies the kHz to GHz range, used for radio communication, which gave it its name. Medical equipment uses a portion of the narrow band of this range – from 200 kHz to 40 MHz – in different applications. In this frequency range, the effects of stimulation of nerves and muscles decrease, and thus the energy can be applied gently to achieve different levels of tissue heating (Lapidoth et al. 2015).

The basic idea behind the use of RF on the skin is the ability to deliver volumetric heat in depth. The movement (current) of electrons (ions) causes the heating of the tissue, unlike the light, in which the increase in temperature occurs by photon energy absorption. There is no selectivity, i.e., the high-frequency current heats the tissue as a whole regardless of the skin type. There are also no losses by reflection or scattering as with a laser light. It is safe for dark skin types and effective for clear chromophores. Energy diffusion depends only on the tissue conductivity.

As we saw earlier, the concentration of light energy (fluency), or power density, controls the effect on the tissue. The same is true with RF. A high power applied over a large area using large electrodes will cause a mild heating, but when concentrated in small areas, as an electrode in the form of a needle, it will cause the ablation of the tissue.

The penetration of the RF energy into the tissue, or instead the attenuation of the energy as it penetrates the tissue, will depend on the fluency used, the configuration of the electrodes (monopolar, bipolar, or unipolar), the anatomy of the area being treated, and the characteristics of conductivity of the tissue.

The RF systems can be "monopolar," "bipolar," "multipolar," and "unipolar" (Lapidoth et al. 2015).

Monopolar RF

These devices use an active electrode to apply the RF to the area of treatment, in the form of a handpiece, and a return electrode, usually in the form of a grounding pad with a large contact area,

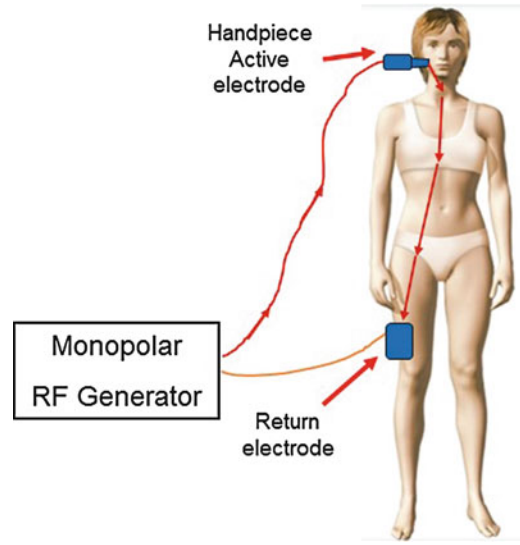

Fig. 43 Basic configuration of a monopolar device

which is placed far from the treatment zone (Fig. 43).

A high RF current density is created at the active electrode, and the current diverges as it penetrates the tissue going toward the large return electrode. Therefore, the heat is generated near the active electrode, and it does not depend on the size, shape, or position of the return electrode.

The RF current diverges rapidly away from the electrode thus the heating effect decreases. At a distance equal to the electrode size, heating becomes insignificant. The heat zone can be estimated as half the size of the electrode. Therefore by controlling the RF power and the geometry and size of the electrode, it is possible to control the penetration depth and the effect on the tissue.

Popular monopolar system uses are in surgery for the cutting and coagulation of blood vessels. In dermatology, there is the application for skin tightening and collagen remodeling, as the geometry of the large electrode targets the deeper tissues of the dermis (Fig. 44).

Bipolar RF

This configuration uses two electrodes which are placed close to each other and in contact with the treatment zone. The RF current flows between the

electrodes and does not spread to other parts of the body as in the monopolar configuration. This geometry creates a more uniform heating at the treatment zone compared to the monopolar devices (Fig. 45).

Both electrodes create an equal thermal effect near them, and the divergence of the RF current is reduced because of the small distance between them. Therefore, most of the heat is concentrated near the electrodes, thus allowing a greater control over the size of the treated volume.

The penetration depth is a function of the size of the electrodes and the distance between them. By increasing the separation of the electrodes, the RF current can go deeper, but the divergence also increases thus reducing the desired heating effect. If the separation is too high compared to the electrode size, the heating profile will be similar to two monopolar electrodes. When the separation of the electrodes is comparable to the size of the electrode, the penetration depth is approximately half of the distance between them (Lapidoth et al. 2015).

The penetration depth can also be controlled by varying the operating frequency of the system, and thus treatment can occur at different depths within the limits imposed by the separation of the electrodes, as shown in the diagram in Fig. 46. In

Fig. 44 Example of monopolar device used for skin tightening, Thermage ThermaCool, Solta Medical

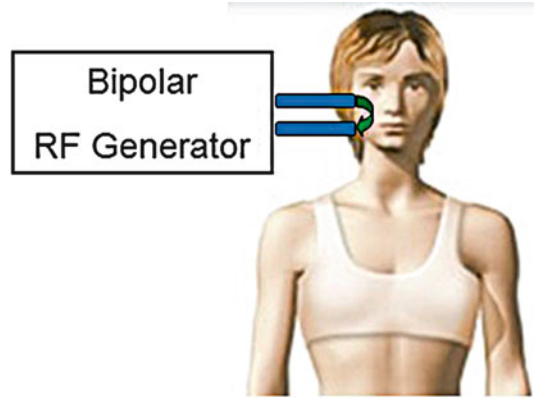

Fig. 45 Schematic of a bipolar RF system

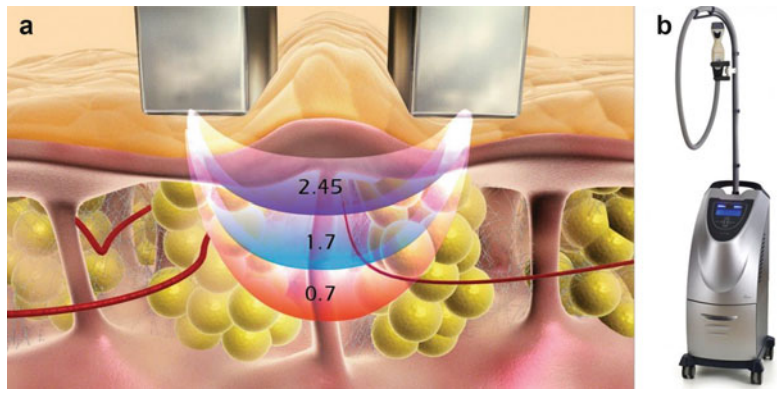

Fig. 46 (**a**) Variation of heating effect with the operating frequency of the system, 2.45 Mhz, 1.7 Mhz, and 0.7 Mhz, Reaction™. (**b**) RF + Suction, Reaction™ (Viora)

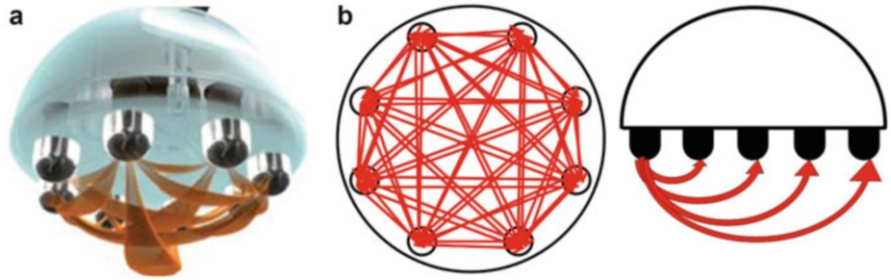

Fig. 47 Schematics of a multipolar RF configuration showing RF current flow between electrodes at different penetration depths

this way, the higher the frequency, the shallower the heating effect.

The folding of the skin between the electrodes, for example, by applying negative pressure (in the form of vacuum), allows a uniform heating of a large tissue volume that can reach up to a few centimeters. This technique is used in devices for body contouring and cellulite such as Reaction™ of Viora (Fig. 46b) and VelaShape™, which uses the Electro-Optical Synergy (ELŌS) technology developed by Syneron Candela, describe below.

Bipolar RF also presents reduced energy loss, because of the proximity of the electrodes, and reduced energy density at the area of treatment, with subsequent reduction in the risk of overheating and burning of the skin below the electrode. The application is better tolerated and cause less pain.

It has also allowed the development of fractional bipolar RF technology as we describe it bellow.

Multipolar RF

It is an interesting approach to the bipolar RF geometry. In this case, a series of bipolar electrodes are used in a circular or linear configuration. The RF current flows between them, producing a more homogeneous heating effect over a larger tissue volume and variable penetration depths, as shown in Fig. 47. It also quickly reaches the desired treatment endpoint temperature, since more electrodes are used simultaneously (Fig. 48).

Unipolar RF

This RF configuration uses a single electrode that works, in some ways, as an antenna for electromagnetic energy coupling in the skin. It is different from monopolar RF, which uses one active electrode and one return electrode, and in this case, the RF current flows into the skin (Fig. 49).

The electromagnetic field coupling in human tissue produces heat. The RF heating effect depends on the operating frequency of the device. There are two mechanisms of heating biological tissue containing water: ionic current, which is produced by moving charged particles (electrons), and rotation of dipoles of water molecules. These two forms of interaction lead to heating and consequent increase in temperature of the biological tissue.

The RF configurations described so far – monopolar, bipolar/multipolar – utilize lower frequencies, 1–3 MHz, and the dominant mechanism in these cases is the ionic current hitting the skin molecules, which in turn vibrate producing heat.

At frequencies around 10 Mhz and above, the rotation of water molecules starts to be noticeable, and at frequencies greater than 30–40 Mhz, this mechanism is the predominant cause of heating of the tissue (Lapidoth et al. 2015).

Unipolar devices use high frequency of RF, from 20 to 40 MHz, so that the electromagnetic field produces the rotation of the molecules to induce the heating of the tissue.

The penetration depth in this case depends on the operating frequency, geometry and configuration of the electrode, input power, and the time

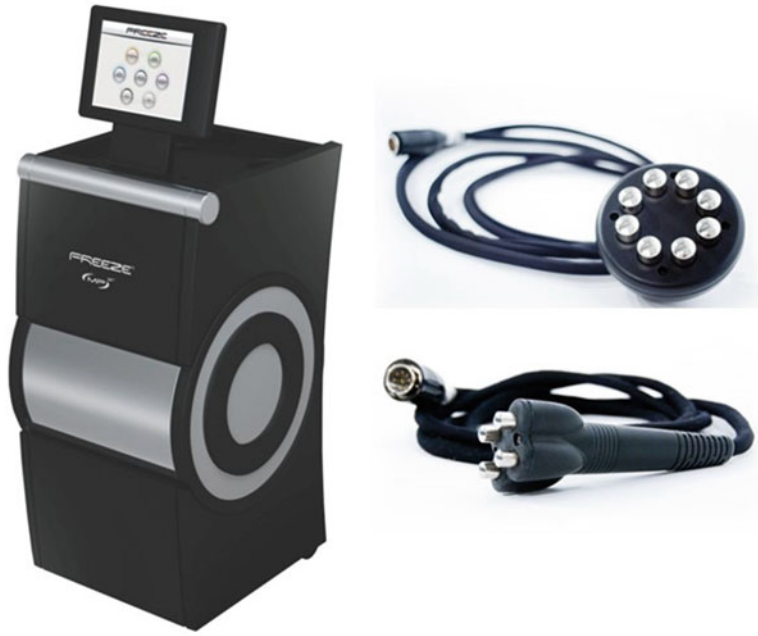

Fig. 48 Freeze™ multipolar RF and its applicators, from Venus Concept

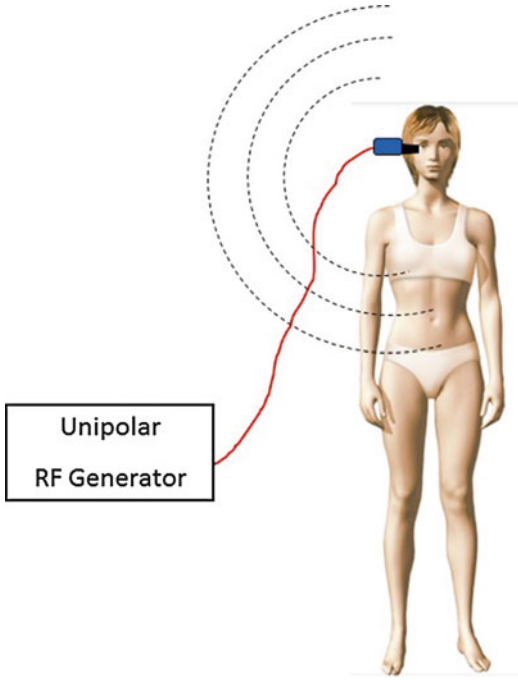

Fig. 49 Schematics of a unipolar RF generator

and mode of treatment (stationary – using a panel with electrodes over the treatment area – or motion, moving the electrode over the skin).

As it happens with the ionic current heating, the penetration depth of the energy in unipolar RF also decreases with higher frequency. Therefore, by operating with different frequencies, it is possible to concentrate a key volume of energy in a specific skin layer. For example, by working with high frequencies such as 40 MHz, the main effect is skin tightening since the energy is mainly concentrated in the dermal area. Lower frequencies, such as 27 MHz, will deposit the energy in a deeper layer, which works for body contouring and fat destruction (Fig. 50).

It is importance to note that the effect of the treatment (skin tightening, collagen remodeling, and fat reduction) is not only a function of the temperature but also of the length of time that this temperature is applied, or the RF pulse duration. Exposure to a temperature of 70–90 °C for a few milliseconds causes tissue coagulation, while the application of a lower temperature such as 42 °C for tens of minutes also causes irreversible damage to sensitive cells. For example, fat cells are especially sensitive to temperature changes. By using the correct electrode geometry, low input power (in order not to overheat the skin surface) and long application time (several minutes), it is

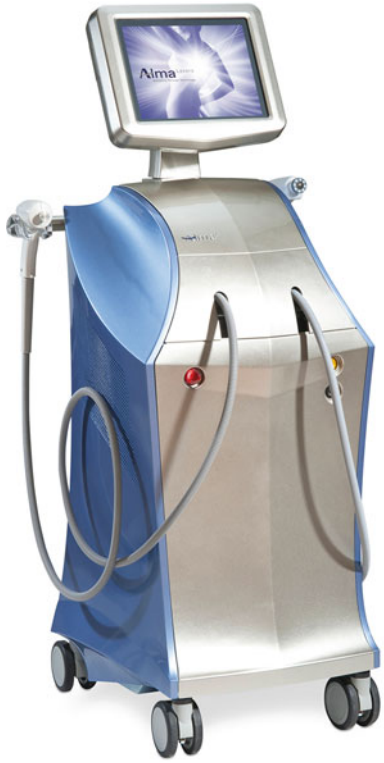

Fig. 50 The platform Accent Ultra™, from Alma Laser, with a unipolar handpiece operating at 40 MHz

Fig. 51 Vanquish™, from BTL Aesthetics, uses a frequency of 27 MHz, low power, and long exposure time for fat reduction and body contouring

possible to cause apoptosis of fat cells in body contouring procedures. The skin damage function can be described by the Arrhenius equation (Lapidoth et al. 2015):

$$D = A\boldsymbol{t}\,exp[-\Delta E/R\boldsymbol{T}]$$

The degree of damage (D) is a linear function of exposure time, or pulse duration (***t***), and an exponential function of the tissue temperature (***T***) (Fig. 51).

Fractional RF

Fractional bipolar RF (FRF) was developed following the same concepts and success of fractional lasers as described previously and is gaining great popularity in dermatology. The procedure is based on the heating or ablation of multiple small points in the skin (MTZ), with a spot size of 100–400 μm, leading to improvements in the quality of the skin, wrinkle reduction, treatment of acne scars, and stretch marks (Lapidoth et al. 2015; Brightman et al. 2009; Rongsaard and Rummaneethorn 2014).

The RF has the potential to provide different patterns of energy and heat distribution from the MTZ shape interaction of fractional lasers. In contrast to lasers where the thermal effect is limited to the periphery of the ablation crater (ablative procedure) or the coagulated column (in non-ablative procedures), the RF energy flows through the entire dermis, adding volumetric heating to the fractional treatment. This produces a more effective effect of skin tightening.

There are mainly two types of RF fractional technologies:

1. A matrix of bipolar microelectrodes applying the RF energy from the surface
2. A grid of microneedles which internally deliver the RF energy within the dermis

The surface electrodes provide a more superficial effect improving texture and lines, treating stretch marks and smoothing acne scars. The bipolar RF is applied with a matrix of active microelectrodes as shown in Fig. 52.

A normal bipolar device, described above, uses a large-area electrode and has low-power density, and the current and subsequent heating effect is limited to the tissue between the electrodes. In FRF, the active electrode is converted into a series of microelectrodes, which increases the energy density, thus producing an ablation effect near the electrode, and as the energy flows to the large return electrode, it spreads, reducing the effect which is limited to skin coagulation and skin tightening (Fig. 53). This action is similar to

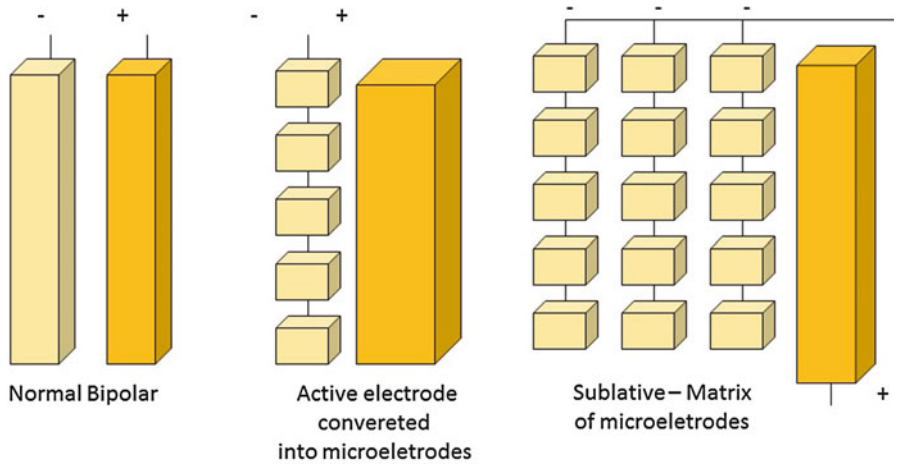

Fig. 52 Schematics of a fractional RF device

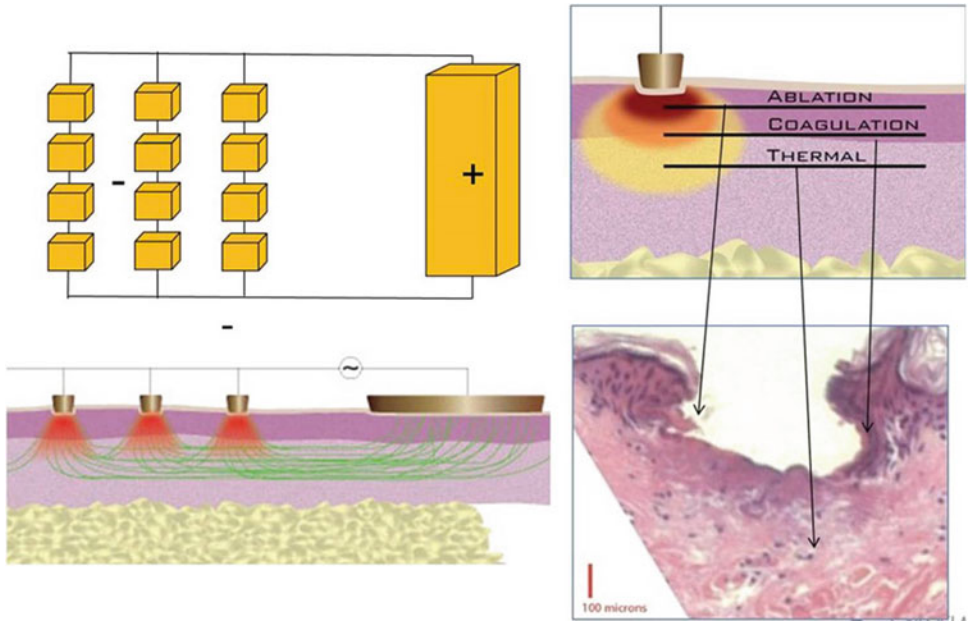

Fig. 53 Impact of the fractional RF in the tissue

Fig. 54 The eMatrix™ and the Sublative™ tip, from Syneron Candela

a water nozzle. If we approach the nozzle, and the water jet is concentrated, we can become excessively wet. As we move away from the nozzle, the water spreads and only a few drops can reach us.

An interesting variation of the fractional bipolar RF was developed by Syneron Candela, the "Sublative RF," used in the Matrix RF and eMatrix devices. The proposal is to deliver heat energy to the dermal layer of the skin with minimal epidermal damage. By controlling the RF current energy and delivery pulse, it is possible to correct epidermal defects and promote aggressive remodeling of the deeper dermis. Since the effect on the epidermis is minimal, the recovery time is shorter and it also reduces the risk of infection and pigmentary changes (Fig. 54).

The RF microneedle approach is based on the introduction of a set of fine dielectric coated needle electrodes deep into the skin, which is then activated to deliver energy producing a strong dermal remodeling. Since the energy is directly deposited into the deep dermis, there is no effect in the epidermis, which is preserved. Side effects and recovery time are minimal. Compared to the surface fractional RF application, microneedles can produce higher temperatures in the deep dermis and therefore stronger collagen contraction, which leads to the improvement of deep wrinkles and skin tightening (Lapidoth et al. 2015).

The RF energy penetration depth is controlled by adjusting the size of the needle, and the effect is confined to the skin between the electrodes (Fig. 55).

The combination of a superficial fractional treatment (Sublative), improving epidermis and collagen remodeling in the upper dermis, with deep dermal remodeling produced by the microneedle device, represents a high potential for a complete skin improvement with minimal adverse effects and recovery time.

It is often said that fractional RF is safe for all skin types because of its "color-blind" characteristic. However, it should be noted that, while the RF interaction with skin does not depend on the presence of melanin or any other chromophore, darker skin types and tanned skin are still susceptible to post-inflammatory hyperpigmentation (PIH). The FRF will heat and induce a wound healing process response in the skin; therefore, it is wise to treat these high-risk skin types with greater caution.

Another important characteristic of the skin that influences the RF current treatment is its conductivity or its resistance (impedance). The RF current works somehow as water; it flows through the path of less resistance. For example, a piece of metal is an excellent electric conductor (low impedance/resistance), as current easily flows even with low energy and there is little

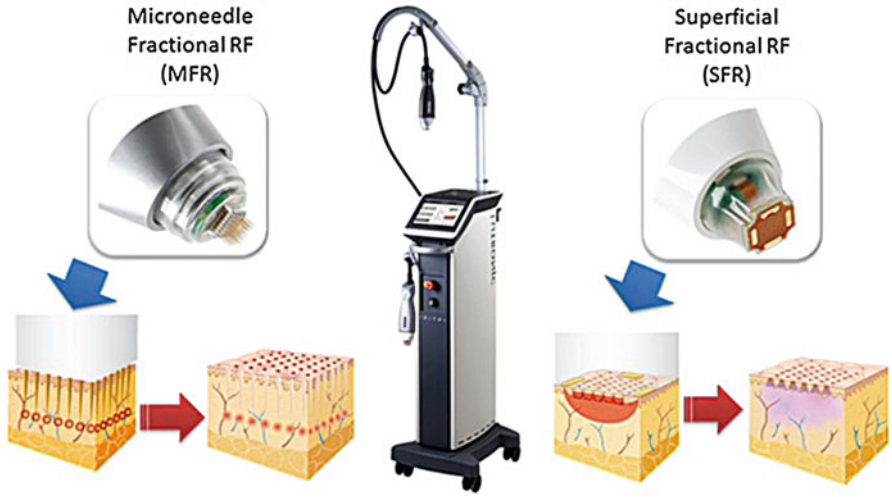

Fig. 55 INFINI™ skin treatment platform, with surface fractional RF and microneedle handpieces, from Lutronics Inc.

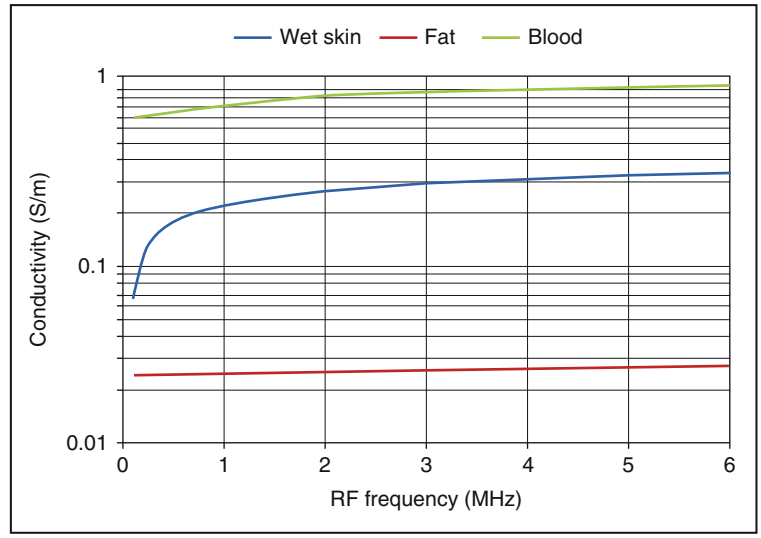

Fig. 56 Variation of conductivity of skin components with RF operating frequency

heat dissipation. On the other extreme, a piece of plastic does not conduct electricity (high impedance). Our skin is located somewhere in the middle between a metal and a plastic, and some characteristics can change skin impedance. A young skin, with good vascularity and well moisturized, is a good electrical conductor (as a metal), while an aged, dry, and poor vascularized skin behaves more as a piece of plastic. In this case, higher energy is needed for the current to flow, and there is heat dissipation.

The graph of Fig. 56 shows how the conductivity changes for some skin components as a function of the RF operating frequency. We can see that blood is a good conductor than wet skin, and finally fat cells are bad conductors (Lapidoth et al. 2015).

Temperature also changes the conductivity of the skin or its impedance. The RF current prefers the heated, warm tissue, as shown in the graph of Fig. 57 (Lapidoth et al. 2015).

Therefore, by changing the temperature of the tissue, we can "direct" the RF current. In other

words, we can force the current to flow or be concentrated in given parts or layers. For example, by using a cooling contact tip on the surface of the skin, the RF current flows deeper into the dermis. It also can generate certain selectivity, as the RF current will be concentrated or flow preferentially on the skin layer or tissue, whichever is hotter. This technique is the basis for the Electro-Optical Synergy (ELŌS) system developed by Syneron Candela, which we will present bellow (Fig. 58).

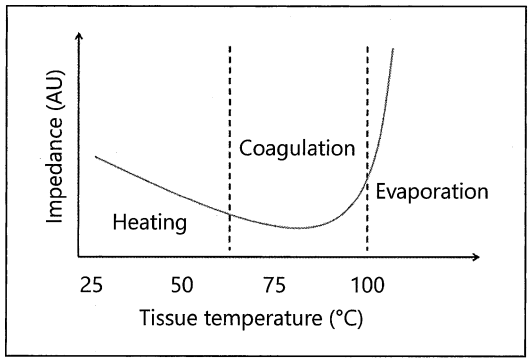

Fig. 57 Variation of tissue impedance with temperature

Hybrid Systems

Looking to overcome limitations and to expand the safety and efficacy of treatments with laser or intense pulsed light (IPL) systems, the industry has diversified technology associating light to other forms of energy creating the so-called hybrid systems.

An example of great success of this diversification is the Electro-Optical Synergy (ELŌS™) technology synergy of light with radio frequency (RF) developed by the inventor of the intense pulsed light, Dr. Shimon Eckhouse, in Syneron Candela, Israel (Doshi and Alster 2005; Sadick et al. 2005; Lapidoth et al. 2005; Sadick and Trelles 2005).

The ELŌS™ technology employs a bipolar RF with a water-cooled tip simultaneously with the laser or IPL pulse, as illustrated in Fig. 59.

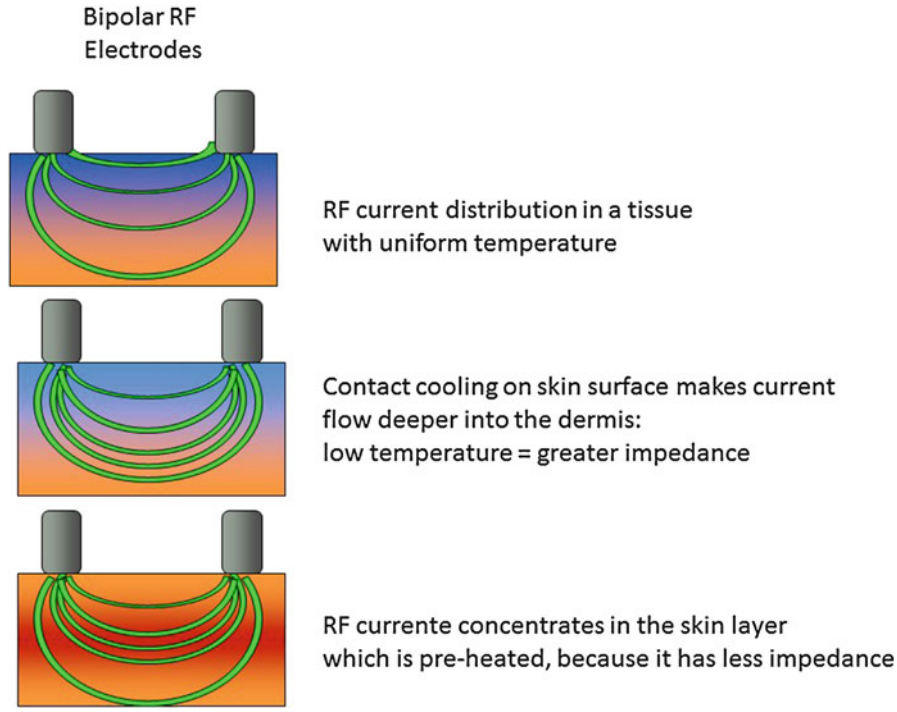

Fig. 58 Effect of a cooling contact tip on a bipolar RF current

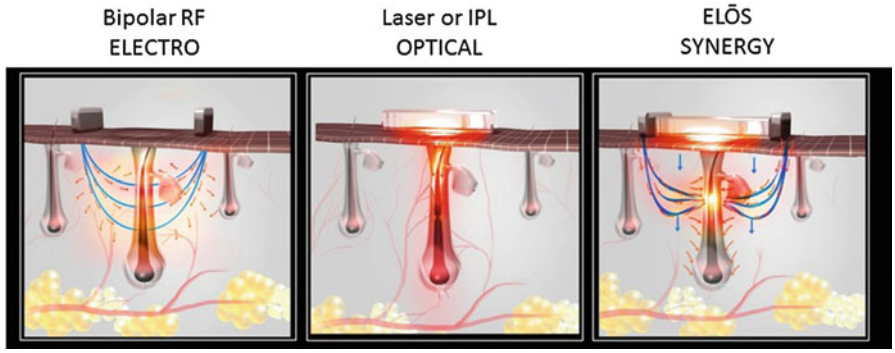

Fig. 59 The ELŌS™ effect, synergy of bipolar RF + light in hair removal

Following the principle of selective photothermolysis, light heats the chromophore preserving the surrounding tissue. A cool tip protects the surface of the skin and "pushes" the RF to deeper layers. The RF will be concentrated in the heated tissue because it has better conductivity, and this will cause the chromophore to overheat leading to the desired therapeutic effect.

Figure 59 illustrates this synergic effect in hair removal treatment, but the same occurs in the treatment of pigmented and vascular lesions, skin rejuvenation, and tightening (in which an infrared light source in the range from 700 to 200 nm is used with bipolar RF) (Fig. 60).

The main advantage of the ELŌS™ is the reduced optical fluency needed for the treatment, thus minimizing patient discomfort during the session and increasing safety for darker skin types. Because of the RF action, simultaneous effects such as skin tightening during a treatment of pigmented lesions can also happen.

Other applications of this technology are circumferential reduction, cellulite treatment, and skin tightening. In this case, bipolar RF is associated with an infrared source, a lamp emitting from 700 to 2,000 nm, or a high-power LED (870 nm), rotating cylinders, which produces massage, drainage, and suction. The cylindrical rollers are the RF electrodes. The suction causes a skin fold, which increases the penetration of the RF and light as explained before (Alster and Tanzi 2005; Wanitphakdeedecha and Manuskiatti 2006; Boechat 2009) (Fig. 61).

The goal is to increase the temperature of (up to 43 °C) deep tissue, which accelerates the metabolism of fat cells and thereby reduces their size leading to circumferential reduction. For a longer exposure time and higher temperature (45 °C), it is possible to produce apoptosis of fat cells since they are more sensitive than skin cells thus reducing localized fat. The effect of skin tightening occurs because of the stretching of elastic fibers and the remodeling of collagen, improving the overall skin quality.

Conclusion

Laser and intense pulsed light systems are pure light sources with important properties, which allow us to treat accurately and selectively different types of tissue damage, preserving the surrounding healthy tissue. Synergy with radio frequency shows how this equipment can still evolve becoming safer and more efficient. With the advent of fractional skin treatment, a new horizon of applications that are at the same time gentle and effective have emerged in dermatology.

In many applications, light appears as the only effective solution, as in the case of flat vascular lesions in the face, or port-wine stains. It has brought a rapid and long-lasting result for unwanted hair removal, the treatment of pigmented lesions, and tattoo removal. It is used in skin tightening, cellulite treatment, circumferential reduction, and localized fat reduction. In a

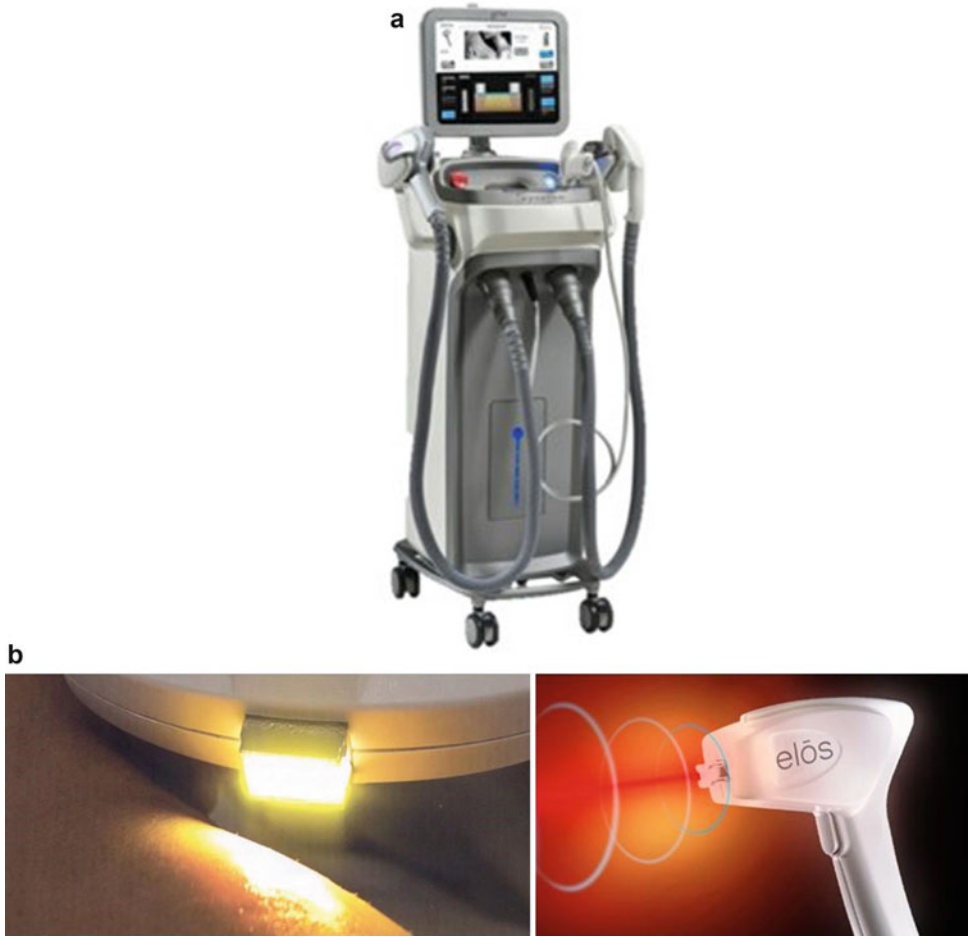

Fig. 60 (**a**) ELŌS Plus system, Syneron Candela – multiplatform with several handpieces including laser, IPL, infrared, all associated with bipolar RF, and a fractional RF. (**b**) ELŌS handpiece showing the bipolar electrodes and the IPL simultaneously

number of applications in dermatology, light emerges as an important complement to the existing techniques, as is the case of rhytidectomy in plastic surgery. It also improves body areas that normally are not treated by surgery, such as neck, chest, hands, and arms using ablative or non-ablative fractional lasers.

The future will certainly bring more efficient and compact devices. We will have a wider range of applications and, among them, the development of lasers that have the ability to act at the cellular level, stimulating the production of enzymes, which have the purpose of preventing skin aging and skin cancer. Systems that have the subdermal fat as chromophore can open a new horizon of applications for circumferential reduction, cellulite treatment, and improved skin quality. The diagnostic medicine will also benefit from this development.

The more we study about the effects of the interaction of light with living tissue, the more we learn on how to appreciate the variety and complexity of these critical interactions. The result will certainly open doors to a large number of remarkable applications in the following years.

We only have to “tune in” with the energy of light!

Fig. 61 ELŌS for circumferential and fat reduction, cellulite treatment, and skin tightening, VelaShape III, Syneron Candela

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Take Home Messages

1. The visible light that we experience in our day to day is only one facet of a much broader physical phenomenon known as "electromagnetic radiation." The difference between each laser or every color of light we see is its wavelength or frequency.
2. All laser devices consist of the resonator/oscillator – with the active medium, which produces the light and thus determines the wavelength; the excitation source (also called pumping) – which delivers power to the active medium producing the photons; laser beam delivery system from the source to the hand of the operator; and the handpiece, with focusing lens or a scanning system.
3. Best way to determine which laser or IPL is best for a given application is to use the principles of selective photothermolysis: the wavelength that will be only absorbed by the target tissue, pulse duration that will confine the heat to the chromophore, and sufficient energy to reach the desired effect.
4. Radio frequency effect on skin does not depend on chromophore absorption, what makes it safe to treat all skin types.
5. The radio frequency effect in the skin is a linear function of time and an exponential function of temperature. A small change in treatment temperature by a few degrees will increase the tissue effect by several times; on the other hand, it is necessary to increase the application time by several minutes or hours to get the same effect.

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Intense Pulsed Light for Photorejuvenation

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Caio Roberto Shwafaty de Siqueira

Abstract

Intense pulsed light (IPL) is a non-laser, versatile light technology that is a key tool in dermatology. It is widely used for the treatment of photoaged skin. Also, it is used for hair removal, acne treatment, and treatment of vascular lesions. IPL works through selective photothermolysis to reduce dark spots, telangiectasia, wrinkles, and skin laxity (photorejuvenation) caused by chronic sun exposure. This chapter will discuss all the aspects about the physics behind the IPL technology, clinical indications, treatment, and possible complications.

Keywords

IPL • Photorejuvenation • Photoage • Dark spots • Telangiectasia • Wrinkles • Skin laxity

Contents

Introduction

The appearance of the skin has been a constant growing reason to visit dermatologist's clinics not only for aesthetics reasons aiming youth but also for medical reasons, such as treat and prevent skin diseases. Therefore, the number of procedures to improve the quality of the skin with laser and non-laser light devices grows each year (El-Domyati et al. 2015).

The *main goal* of this chapter is to discuss all the issues regarding the use of intense pulsed light (IPL) for photorejuvenation of the skin. This modality of treatment is popular because it doesn't cause epidermis disruption, limiting adverse effects and minimizing downtime (El-Domyati et al. 2015).

Basic Concepts

The Biology of Photoaging

The aging process of the skin reflects both extrinsic and intrinsic factors (Table 1) (Balibas et al. 2010; Friedmann et al. 2014).

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Table 1 Biologic factors behind skin aging

Intrinsic factors	Extrinsic factors
Chronological senescence of dermal fibroblasts	Chronic exposure to UV light
Lower production of collagen and hyaluronic acid	Pollution
Poor extracellular dermal matrix	Tobacco smoke
	Production of reactive oxygen species and activator protein-I
	Higher expression of metalloproteinases
	Higher fragmentation of collagen fibers
	Decreased TGF-β1 levels
	Chronic inflammatory response
	Defects on DNA repair system

UV ultraviolet, *TGF* transforming growth factor, *DNA* deoxyribonucleic acid

The *intrinsic factors* are related to chronological senescence of dermal fibroblasts, leading to lower collagen and hyaluronic acid production that leads to poor extracellular dermal matrix (Goldberg 2012; Friedmann et al. 2014).

The *extrinsic factors* are related to long-term, chronic ultraviolet (UV) light exposure (usually by the sun), pollution, and tobacco smoke. All of them enhance the breakdown and fragmentation of collagen fibers through the production of reactive oxygen species and activator protein-I, which upregulates abnormal expression of matrix metalloproteinases, the main reason that destroys collagen fibers (El-Domyati et al. 2015; Friedmann et al. 2014).

In normal skin, the transforming growth factor-β (TGF-β) upregulates the collagen production (Ali et al. 2013). At the photo-damaged skin, TGF-β1 has its levels decreased, causing reduced collagen production. This results in poor levels of collagen I and III at the dermal matrix (Ali et al. 2013; El-Domyati et al. 2015).

Also, it is well-known that the chronic inflammatory response to long-term UV light exposure leads to permanent DNA damage. Locally at the skin, UV light may trigger DNA photoproducts, isomerization of trans- to cis-isoform of urocanic acid in the stratum corneum, and UV-induced alteration of the membrane redox potential. All these events lead to UV-induced immune response that causes immunosuppressive effects, UV mutagenesis, and UV carcinogenesis. The DNA repair pathways no longer are capable of detecting and repairing effectively the DNA defects, leading to replication and transcription of damaged genes. Besides the obvious carcinogenic and mutagenic consequences, these events also change the normal half-life time of epidermal cells, leading to excessive (or even abnormal) proliferation of melanocytes and keratinocytes at the basal and Malpighi's layers, respectively (Bolognia et al. 2008).

Clinically, all these events result in laxity, chronic tanned skin, wrinkles, telangiectasia, rough and sagging skin, and melanocytic lesions (like lentigos and ephelides), all together named photoaging (Gold and Biron 2013; Sasaya et al. 2011).

The Biophysics Behind IPL

IPL devices are non-lasers, non-ablative sources of high-intensity light that use a high-output xenon flash pump light source to produce a polychromatic, noncoherent, non-collimated diffused light with broad wavelength (500 nanometers (nm) – 1,300 nm). There are simultaneous emissions of green, yellow, red, and infrared wavelengths (Mattos et al. 2009; Balibas et al. 2010; Goldberg 2012; Ali et al. 2013; El-Domyati et al. 2011; Friedmann et al. 2014).

IPL was first approved by the Food and Drug Administration (FDA – USA) in 1998 on the treatment of photoaged skin.

Nowadays, there are more than 300 different IPL devices available on the market. The last generation of devices is much safer because all of them have protective features to prevent epidermal damage by excessive heat. Most of them use cooling systems of sapphire or quartz

Fig. 1 Figure showing special smaller tips (on the *left*) and cut-off filters (on the *right*)

interface to promote this safety at the epidermal layer (Goldberg 2012). The light pulse is usually single, but they can be double or triple depending on the device, with smooth delivery of energy, with peak flow occurring at the early shot, squared shaped. It is not possible to deliver energy in nanoseconds as the Q-switched lasers. This system prevents prolonged heating of epidermis, treating the majority of the chromophores at the same time with one single shot. The pulse duration time should be equal or below the thermal relaxation time (TRT) of the target structures to prevent unselected damage to the surrounding tissue, but should be at least 50 % of the TRT's targets to generate their cell death (Mattos et al. 2009; Balibas et al. 2010; Goldberg 2012). The normal skin has an average of 10 milliseconds (ms) of TRT. Vessels with diameter of 0.1 mm have TRT of 10 ms; larger vessels (0.3 mm) have TRT of 100 ms (Goldberg 2012).

The handpiece allows the physician to choose which wavelength will be applied into the patients' skin. These cut-off filters block the lower wavelengths that are not desired to the treatment, but don't filter the higher wavelengths. The usual filters available on the market are 400 nm, 515 nm, 540 nm, 550 nm, 560 nm, 570 nm, 590 nm, 595 nm, 615 nm, 650 nm, 695 nm, and 750 nm (Fig. 1). The energy fluency varies from 8 to 100 joules (J), and the pulse time varies from 5 to 100 ms, depending on each device.

IPL works at skin sites based on the principle of *selective photothermolysis*, first described by Anderson and Parrish with pulsed dye lasers (Railan and Kilmer 2000). The normal skin contains substances that act as chromophores (i.e., substances that absorb energy depending on their intrinsic color, transforming them into heat), such as hemoglobin, carotene, melanin, and water (Fig. 2) (Goldberg 2012). Each substance has their own curve of maximum and minimum absorption of light (medium wavelengths of light absorption for deoxyhemoglobin are 550–560 nm, for oxyhemoglobin are 540 nm and 575–580 nm, and for vascular lesions and melanin are 400–755 nm) (Friedmann et al. 2014). The photodamaged skin contains higher amounts of these chromophores, distributed in different forms (localized spots or diffuse, multiple-layer manner). These substances have the capacity to absorb the photons, transforming it into heat, which destroys the colored target and dissipates the heat into the surrounding area, promoting the activation of collagen production by the fibroblasts (collagen I and III) through cytokine activation and upregulation of TGF-β1 (Balibas et al. 2010; Ali et al. 2013).

IPL light targets all the chromophores at the same time, specially melanin and hemoglobin. The overall immediate end point after the application of IPL into the skin is darkening of melanocytic lesions, blurry telangiectasia, and light redness through all skin surface treated.

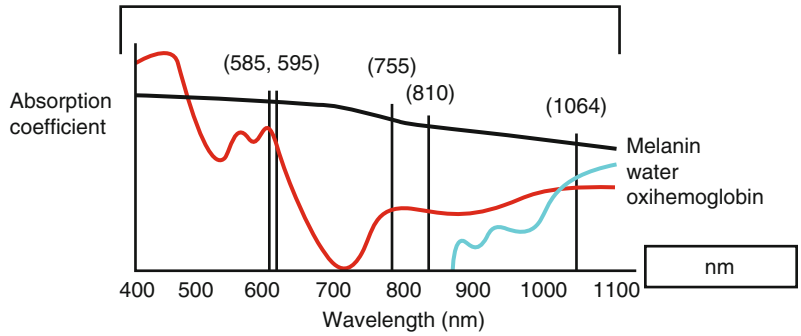

Fig. 2 Figure showing the absorption curves of skin chromophores

The goal of treating *vascular lesions* is to raise the blood vessel temperature high enough to cause its coagulation, leading to its destruction and replacement by fibrous granulation tissue. Oxyhemoglobin (red lesions), deoxygenated hemoglobin (blue lesions), and methemoglobin can be targeted by IPL (peak absorption of 418 nm, 542 nm, and 577 nm, respectively). Therefore, the best IPL filters to treat vascular lesions stay between 400 and 600 nm. Some devices allow the adjustment of a vascular tip into the handpiece, to increase the delivered energy only at the desired target (Fig. 1).

The goal of treating *pigmentary lesions* is to elevate the rapid differentiation of keratinocytes induced by thermal heating, using melanin as target. This results in an upward transfer of destroyed and non-destroyed melanosomes along the necrotic keratinocytes, resulting in their elimination as crusts that can be seen on the days after the treatment session. Lower cut-off filters are the usual best choice for treating melanocytic lesions, usually around 400–540 nm (Goldberg 2012).

The goal of treating *skin laxity and wrinkles* is to heat dermal water to stimulate dermal fibroblasts, which increases the synthesis of extracellular matrix proteins, such as collagen I and III and elastin. The higher cut-off filters are the best choice to achieve these goals, usually around 600–1,200 nm (Goldberg 2012; El-Domyati et al. 2011).

The histopathology findings that confirm all these changes are seen as an increase in the number of fibroblasts associated with an increase in collagen compaction, thickening, and density. This also indicates collagen remodeling. Also, the dermal papillae and the interpapillary crests are more pronounced, showing the higher deposition of collagen after IPL treatments. The melanin pigment has a more homogenous distribution at the basal layer. The number and diameter of blood vessels from the superficial plexus reduced, as well, in one-third of treated patients (Fig. 3) (Scattone et al. 2012; Friedmann et al. 2014).

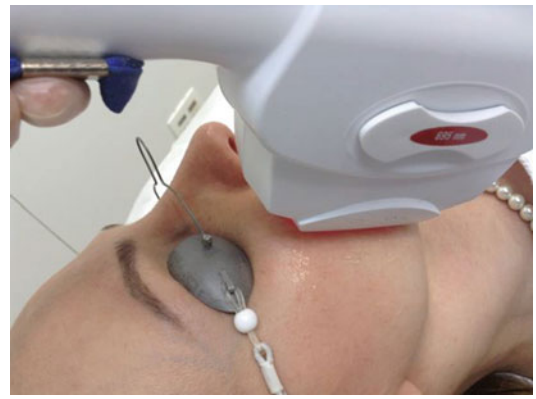

Fig. 3 Patient laid down, with thin layer of transparent gel at the skin face, receiving IPL treatment with IPL 695 nm filter, sapphire cooling system on

The Clinical Aspects of IPL on the Daily Practice

IPL is a key tool in the treatment of photoaged skin.

In the first place, the physician should establish the skin color type of the photoaged skin accordingly to Fitzpatrick's classification for skin types

Table 2 Fitzpatrick's skin color classification

Skin type	Skin color	Characteristics
I	White; very fair, red or blonde hair; blue eyes; freckles	Always burns, never tans
II	White, fair, red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white, fair with any eye or hair color (common)	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; mid-eastern skin types	Very rarely burns, tans easily
VI	Black	Never burns, tans very easily

Table 3 Exclusion criteria's for IPL treatments

Pregnancy
Lactation
Infected skin
Photosensitizing medications/oral retinoid
Photosensitivity
Surreal expectancies
Scars: keloids, hypertrophic
Suntan
Photo-induced skin disorders

(Table 2). The use of IPL on higher skin color types ($\geq$ IV) and on highly photo-damaged skin (too much targets) demands lower fluencies, higher milliseconds, cooling systems on, and multiple treatment sessions.

Pregnancy, lactation, infected skin, use of photosensitizing medications or oral retinoid, photosensitivity by any disease, surreal expectancies, keloids, hypertrophic scars, suntan, and photo-induced skin disorders are *exclusion criteria for treatment* (Table 3) (Balibas et al. 2010).

The number of sessions varies depending on each patient, i.e., it depends on the skin color type and the degree of photoaging. Usually four to six sessions are required to achieve the overall improvement of the skin (Fig. 4).

Before the treatment starts at the office, one should lay down the patient into a comfort office chair; clean the skin area to be treated with lotions without high concentrations of alcohol, removing makeup and sunscreen. Photos should be taken, as a term of consentient should be signed explaining the possible outcomes and results from the treatment, as well as possible complications. The use of topic cream with anesthetics is not necessary. In fact, they can cause vasoconstriction, decreasing the quantity of hemoglobin at the target site, reducing overall results (Mattos et al. 2009).

The patient and the staff must use eye protection at all time during application. The skin should be covered with a thin layer of transparent gel (like those used for ultrasound exams), cooled or not.

Before initiating the treatment, the doctor must tell the patient that the light will be triggered to reduce patient anxiety (Fig. 5). Usually we start the application with the chosen parameters at the border of the area to be treated, specially covered areas, to prevent any complications on exposed sites (Balibas et al. 2010). The handpiece should be applied perpendicularly to the skin surface, gently touching it. After three to four shots, we should stop the treatment and look into the skin. The *immediate end point* should be slight redness of the skin, darkening of brown spots, and blurriness of telangiectasias (Fig. 6). Each spot should overlap the previous one by 10 %. When treating isolated and resilient lesions, the physician may use a perforated plastic shield with varying aperture sizes (Fig. 7) or small special tips applied into the handpiece (Fig. 1), to deliver higher energy only to that target (Balibas et al. 2010). If one sees urticarias, blistering (Fig. 4), or gray-toned skin, then the treatment should stop immediately, the parameters should be reviewed, and ice or cooling substances and topic corticosteroid creams should be immediately applied, because these are signs of excessive heating of the skin, with possible burning.

In the areas that more results are needed, one could apply the shots twice, but the second application should be perpendicular to the first one, avoiding "zebra marking." Usually the patients feel little discomfort, little heat, and little pain

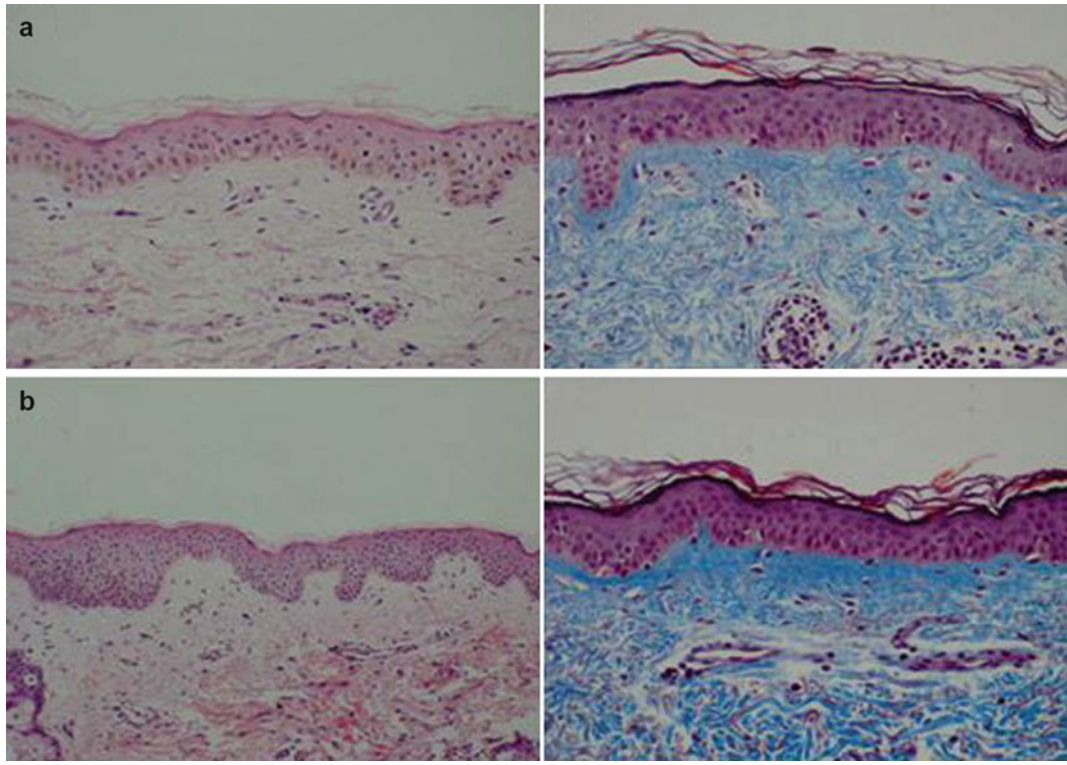

Fig. 4 (Left) Histopathology of photoaged skin (**A**) before and (**B**) after 3 IPL treatments, stained with hematoxylin and eosin (HE), x 200. Note that were increase in interpapillary crests. (Right) The same sample as before, stained with Masson´s trichrome, x 200. (**A**) before treatment and (**B**) after 3 IPL treatments, showing thickening and compaction of collagen fibers. (Adapted from Scattone L, Alchorne MMA, Michalany N, Miot HA, Higashi VS. Histopathologic Changes Induced by Intense Pulsed Light in the Treatment of Poikiloderma of Civatte. Dermatologic Surgery. 2012;38:1010-1016.)

during the session. Anything different from that should alert the doctor to review the parameters that has been used, because it can mean excessive heating of the skin.

At the end of treatment, the staff should apply spray thermal water and soothing creams to reduce skin redness and discomfort and also broadband sunscreen creams.

Overall, the physician should keep in mind that the *targets should be treated in layers*, because this is actually how the excessive pigments are displayed on the skin. First, we should reduce darker brown spots and superficial telangiectasia, and then we can stimulate collagen at the deeper layers. *Most of the complications occur when one tries to destroy all the targets, at all layers, at the same time, with the same high energy.* Another reminder is that one should reduce the parameters (lower energies, higher pulse time duration) when the patient has too much targets at the skin area to be treated, to prevent excessive heating of the skin.

For skin color types $\leq$ *III*, we can start the treatment by choosing the 515–540 nm filters, 10–20 ms, 10–15 J/cm^2. If there is too much targets, one should use 15–20 ms, 8–13 J/cm^2 (Table 4). With the progression of the treatment, targets at the middle layers will reduce, so the physician can elevate the energy delivered and reduce the pulse duration to target the remaining lighter chromophores (localized vessels, lighter dark spots) at the superficial layers, using lower filters, usually applied specifically at the target. Also, the physician can elevate the energy delivered to the deeper layers, using higher filters and higher milliseconds to stimulate the overall skin tightening.

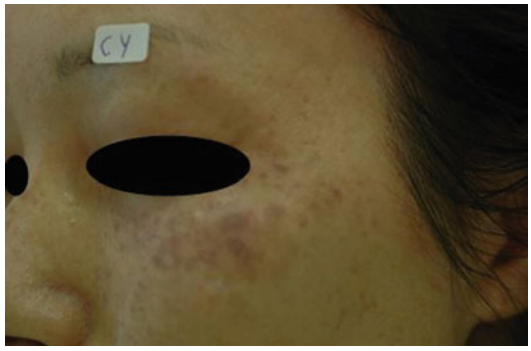

Fig. 5 Immediate end-point after IPL treatment: slightly redness skin, darkening of brown spots, blurriness of telangiectasias

Fig. 6 Perforated plastic shield with varying aperture sizes to isolate specific targets

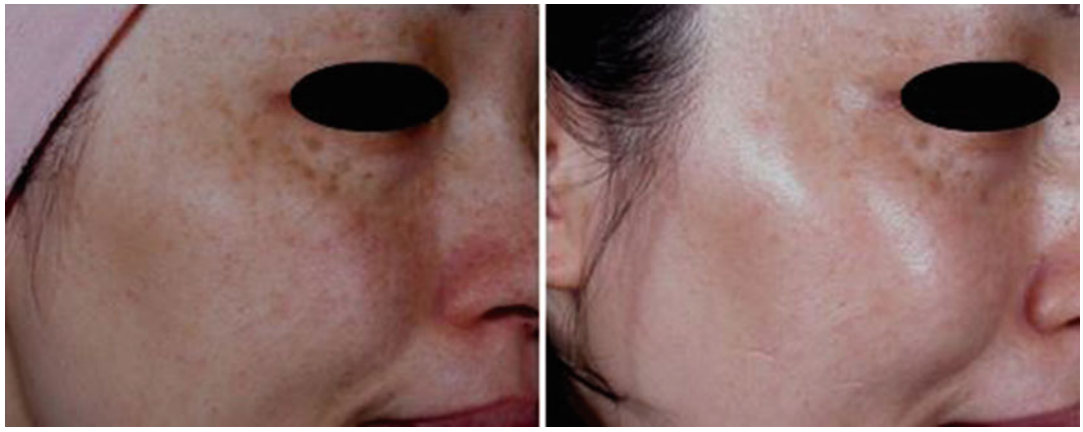

Fig. 7 (*Left*) Pretreatment and (*Right*) after treatment with IPL Harmony (Alma Lasers – Israel) 540 nm, 12 a 14 J/cm^2, 12 ms

For skin color types $\geq$ *IV*, we can start treatment using 570–695 nm filters, trying to avoid the natural higher concentrations of melanin presented at the basal layer of the epidermis on these color skin types, 20–100 ms, 6–10 J/cm^2 (Table 4). With the progression of the treatment, targets will reduce, so the physician can elevate the energy (but maintaining the long milliseconds) and deepen the light penetration using higher filters.

The healing process of facial skin differs from the skin of other areas, because the higher density of sebaceous glands at the facial skin provides quicker healing by prompt cell restoration. So, application of IPL outside the facial skin demands higher caution, lower fluencies, higher pulse time durations, and overlapping the application of the light so it doesn't cause "zebra effect." Usually it takes 7–10 days to complete healing of the facial skin; it may double that time of heal outside the facial area.

The authors use mostly the 540 nm and 695 nm filters at their routine dermatologic practice, because these two filters targets both superficial and deep chromophores in a global manner.

IPL can be associated with other treatments, with or without devices, at the same session. We must advise that the parameters chosen for these multiple simultaneous treatments should be more conservative, since we are combining different ways of treating the whole skin at the same time session.

Table 4 Initial parameters suggested for IPL treatments

Targets	Skin color type ≤ III	Skin color type ≥ IV
Little to moderate quantity	515–540 nm	570–695 nm
	10–20 ms	20–100 ms
	10–15 J/cm^2	6–10 J/cm^2
Moderate to high quantity	515–540 nm	570–695 nm
	15–20 ms	100 ms
	8–13 J/cm^2	6–8 J/cm^2

IPL intense pulsed light, *nm* nanometers, *ms* milliseconds, *J* joule

The authors have experience in combining at the same session IPL with lasers, chemical peelings, and laser hair removal.

Laser Alexandrite 755 nm may be used when dark spots are resilient to IPL or to epilate few facial hairs before any other laser is applied, for angiomas or for larger telangiectasias.

Laser Ruby 694 nm Q-switched (QS) and *Laser KTP* (potassium titanyl phosphate) 532 nm QS may be used to treat lighter brown spots resilient to IPL and Laser Alexandrite.

Laser Nd:YAG (neodymium-doped yttrium aluminum garnet) 1,064 nm long-pulsed may be used for telangiectasias larger than 0.1 mm and for epilation of facial hair in dark-skinned patients.

Laser Nd:YAG QS device may be used for skin tightening, to treat lighter freckles and dark spots and reduction of skin sebaceous pores.

Laser fractionated ablative (CO2 10,600 nm and erbium 2,940 nm) may be used for skin tightening, wrinkle reduction, comedone reduction, and rough-aged skin improvement.

Also, IPL can be associated with all types of *chemical peelings*, such as retinoid acid, glycolic acid, Jessner Solution (combination of resorcinol, salicylic acid, and lactic acid), salicylic acid, trichloroacetic acid (TCA), phenol acid, mandelic acid, and so on. One must point out that the association between IPL and chemical peelings should not occur when the end point has already been achieved by the IPL itself and/or the patient refers that the skin is burning too much after IPL treatment. Therefore, we prevent complications that may arise from overtreatment of the skin.

Applications with botulinum toxin and hyaluronic acid fillers may be associated with IPL sessions, usually right after this ends.

After treatment at home, patient must use products to minimize excessive inflammation. For all situations, patient should use broadband sunscreen, cleansing gel to wash the treated skin, spray thermal water for burning relief, topical low-potency corticosteroid cream if the patient presents with higher burning sensation or itching sensation, and herpes simplex prophylaxis if there is personal history of this disease (Balibas et al. 2010). If the patient was treated only with IPL and/or non-ablative lasers, one should use simple creams or gel creams, usually containing alpha-bisabolol, vitamin C, and essential oils (grape seeds, sunflower seeds). If the patient was treated with IPL associated with ablative lasers, one should use creams or ointments containing healing substances, as well antimicrobials agents (copper, zinc, triclosan, vaseline).

During the 7–15 days after the session, the treated skins will peel off gently. The dark spots will become darker with little crusts, and the vanished telangiectasias may reappear blurred or bluish. After the minimum period of 7 days after initial treatment, the patient can be submitted to other healing/tightening procedures, like radiofrequency and micro-focused ultrasound.

Possible side effects are (Table 5) blistering, purpura, excessive crusting, persistent erythema, dyschromias, irritating contact dermatitis, atrophy, scarring, hypertrophy scarring, keloid formation, and infection (bacterial and/or viral) (Balibas et al. 2010; Friedmann et al. 2014). All of these can be prevented through correct indication and individualization of parameters and respect to the skin color type of the patient. We can divide these complications in two groups: immediate complications and late complications.

Table 5 Possible side effects of IPL treatment

Blister
Purpura
Excessive crusting
Persistent erythema
Dyschromias
Irritating contact dermatitis
Scars: atrophic, hypertrophic, keloid
Infections

Immediate complications are those related to excessive energy delivered into the skin. Possible causes are the following wrong parameters: excessive joules delivered or little time for thermal relaxation, skin tanned or too many targets at the skin location, and misclassification of the true skin color type of the patient.

The patient may present with acute burning pain, urticarias, purpura, gray skin, and blisters right after the treatment (Fig. 4).

When these occur, the physician must immediately stop the procedure, apply cooling substances, and apply high-potency corticosteroid cream into the skin site. Low-intensity laser (LIL) can be applied into the burned areas, in a daily basis, until total healing, because this modality of treatment blocks excessive inflammation. Patient should maintain use of medium- to high-potency corticosteroid creams at home, twice a day, until total healing (usually 7–10 days), and avoid sun by physical blocking and the use of broadband sunscreens.

Late complications are scars (atrophy, keloids, hypertrophic scars), infections, allergy and dyschromias, and both postinflammatory hypercromia (PIHE) and hypochromia (PIHO). These usually are transient complications, resolving spontaneously within 2–3 months after it started.

The *scars* (Fig. 8) usually occur after episodes with burned skin, especially after blistering. Overall, the scars may become white and atrophic. Depending on the personal background of the patient, keloids and hypertrophic scars can develop on specific locations (the jaw line, earlobe, chest, back, neck, upper arms, and abdomen). Just after the healing process has ended after the immediate complications, the skin may

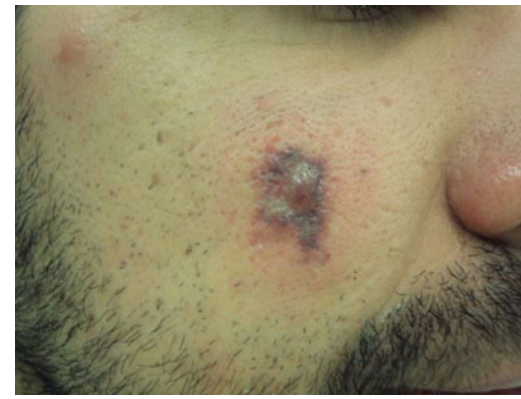

Fig. 8 Acute immediate complication of IPL treatment: blister and urticaria over a hemangioma lesion at the face of a male patient

show persistent erythema. This may sign out that excessive inflammation is taking on, which may trigger the formation of the mentioned scars. To prevent them, besides treating the immediate complications, the physician should apply at the persistent erythematous area IPL as photodynamic therapy every week (very low fluency between 6 and 10 J, filters 540–695 nm, 100 ms of time pulse), LIL on daily basis, and anti-inflammatory creams (medium-potency corticosteroid creams, rose hip oil, silicone oil). If keloid scars or hypertrophic scars occur even after the preventive treatment, the physician may treat the scars with local infiltration with injectable corticosteroids or bleomycin, once a month until total regression. For cases of keloid scars resistant to infiltration therapy, surgical options may be indicated, like shaving of the lesion associated with beta therapy. If atrophic scars occur, the physician may treat them with fractional ablative lasers and chemical peelings (like chemical reconstruction of skin scars [CROSS] chemical peeling), in multiple sessions, once a month (Fig. 9).

Infections are rare complications, but they can be devastating since they may arise suddenly without warnings. The most common one is activation of herpes simplex virus, which may lead to local or widespread infection at the treated area (simulating Kaposi varicelliform eruption seen on atopic skin). Bacterial infections are rare, taking place most often around contaminated skin sites

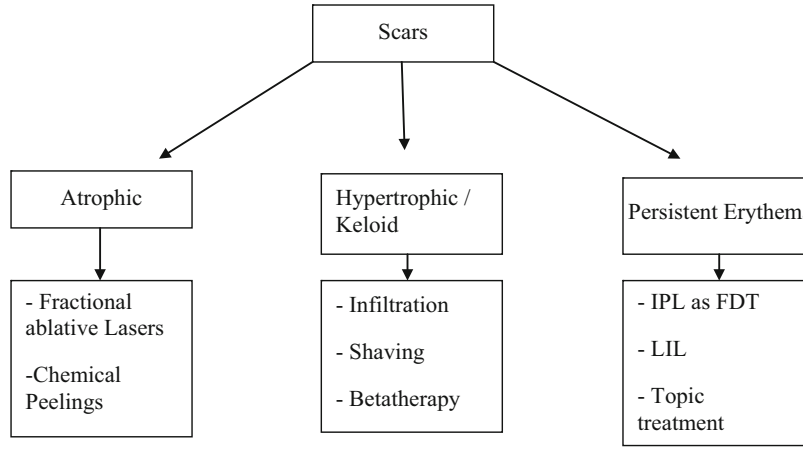

Fig. 9 Flowchart on how to proceed on scars after IPL treatments

(perioral, paranasal, perineum, hands, feet, axillae, skin site with bacterial folliculitis, or any other bacterial skin infection), usually by Gram-positive bacteria (*Streptococcus* sp., *Staphylococcus* sp.). Risk factors for them are high-energy ablative fractionated lasers, high-energy IPL, burning complications, medium-potency chemical peelings (Jessner Solution associated with TCA), and large areas treated at the same time. The most important measure to prevent them is to anticipate them, by prescribing herpes simplex prophylaxis for the patients with this background when they are submitted to the treatments above listed (to be initiated 1 day before the treatment), as well as prescribe topical and/or oral antibiotics or antimicrobial topic creams to use after the procedure, until total healing of the treated skin site. We don't recommend treating any skin site with IPL with evident infection of any kind.

Allergies are rare, it may occur when epidermal disruption is seen, leading to possible higher absorption of allergens and/or of irritating substances. In all cases, the physician should not use known allergenic substances referred by the patient; after the treatment, the use of creams for better healing of the skin minimizes the risks of allergic contact dermatitis and/or irritating contact dermatitis. If it happens, the patient should apply to the skin low- to moderate-potency corticosteroid creams, twice a day, for 7–10 days.

Dyschromias are the most common late complication seen after IPL treatments. *Persistent PIHE* can be treated with superficial chemical peelings (like retinoid acid and Jessner Solution), associated or not with Laser Nd:YAG QS 1,064 nm. At home, patients should use Kligman's formula (retinoid acid 0,05% +hydroquinone 4% + acetonide fluorcinolona 0.05 % cream) or similar formulas. Persistent PIHE will heal within 3–12 months after the complication.

When *persistent PIHO* occurs, the physician must examine the site through Wood's lamp (WL). If the area is highlighted by the WL, it indicates that the hypochromia may be really persistent; so it should be treated with phototherapy narrowband UVB, weekly, until total healing.

If the area is not highlighted by the WL, it indicates that it is transient, so the physician may observe the natural healing or try to make the surrounding skin lighter with IPL and/or chemical peelings.

For all cases of PIHO, patients should also avoid direct sun exposure, use broadband sunscreens, and use Kligman's formula at home. PIHO usually will heal within 3–15 months.

IPL treatment sessions can be repeated at 30–45 days intervals. Normally, patients require three to six sessions to achieve global improvement, but this must be pointed out that it depends on individual characteristics. Overall, treatment results in better clinical appearance in skin texture, reduction in mottled appearance, and clearance of pigmented and vascular lesions (Scattone et al. 2012; Gold and Biron 2013).

Take Home Messages

- IPL is a key treatment for patients with photoaged skin.
- IPL devices are versatile, but one should always keep in mind that the individualization of treatment should be the leading role to success on achieving the goals of youth and healthy skin.
- Defining the true patient's skin color type is the main measure to avoid complications and to achieve the main goals of the treatment.
- As with lasers, IPL works through selective photothermolysis, in which the skin chromophores absorb photons from the IPL light, causing heat damage.
- The treatment support after sessions should be emphasized, because this measure helps the quick healing of the skin, reducing the chances of all complications.

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Intense Pulsed Light for Rosacea and Other Indications

Juliana Merheb Jordão and Luiza Pitassi

Abstract

Intense pulsed light (IPL) treatment is one of the most effective procedures for patients with vascular and pigmented lesions as well as for photoaging. The nonablative nature of IPL makes it an increasingly attractive alternative for patients unwilling to accept the adverse effects associated with other procedures. ILP has been used widely to treat a number of lesions, including benign pigmented lesions, inflammatory acne, hypertrophic scars, hair removal, and a variety of vascular lesions such as port-wine stains, hemangiomas, telangiectasias, poikiloderma of Civatte, and rosacea. In the last years, many studies and case reports have been written with different indications for IPL expanding its use. Those studies showed that IPL represents a valid therapeutic support with excellent outcomes and low side effects. However, it should be underlined that the use and the effectiveness of IPL are strongly related to the operator's experience.

Keywords

Intense pulsed light • IPL technology • Rosacea • Vascular lesions

Contents

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Introduction

Intense pulsed light (IPL) systems have evolved since they were introduced into medical practice 20 years ago. IPL devices use flashlamps and band-pass filters to emit noncoherent, noncollimated, polychromatic light energy at different wavelengths that target specific chromophores (González-Rodríguez and Lorente-Gualb 2015; Babilas et al. 2010). IPL systems mainly target hemoglobin and melanin, with greatest efficacy in the treatment of color rather than texture, according to certain authors. However, despite discussion over whether they can remodel collagen, they have proved to be effective for skin rejuvenation (González-Rodríguez and Lorente-Gualb 2015).

This selective targeting capability makes IPL a versatile therapy with many applications such as the treatment of unwanted hair growth, vascular lesions, pigmented lesions, and acne vulgaris and as a light source for photodynamic therapy (PDT) (González-Rodríguez and Lorente-Gualb 2015; Babilas 2010).

Similar to lasers, the basic principle of IPL devices is the selective thermal damage of the target structure (Babilas 2010). The combination of prescribed wavelengths, fluences, pulse durations, and pulse intervals facilitates the treatment of this wide spectrum of skin conditions. The large spot size is also a great advantage in terms of treatment duration (Babilas et al. 2010).

IPL was first indicated for the treatment of vascular malformations (Babilas et al. 2010). Actually, it has been used widely to treat a number of vascular lesions, including port-wine stains, hemangiomas, telangiectasias, poikiloderma of Civatte, and rosacea (Ichikawa and Furue 2013). The Food and Drug Administration (FDA) has approved intense pulsed light devices for the treatment of this variety of benign pigmentary and vascular lesions, but the range of disease that can be treated with IPL continues to expand (Wat et al. 2014).

History

Muhlbauer et al. first described the use of polychromatic infrared light in 1976 for the treatment of vascular malformations (Babilas et al. 2010). The effects produced by applying a light source to tissue can be explained by the principle of selective photothermolysis, as described by Anderson and Parrish (1983). Thus, the energy supplied to a tissue has a selective action on a target molecule, denoted the chromophore, with no or minimal impact on the adjacent structures. This selective action is the underlying principle by which intense pulsed light works (González-Rodríguez and Lorente-Gualb 2015).

In 1990, Goldman and Eckhouse described a new high-intensity flashlamp as a suitable tool for treating vascular lesions (Goldman and Eckhouse 1996; Babilas et al. 2010). In 1994, the Israeli engineer Shimon Eckhouse managed to produce a broad-spectrum stimulated light emission, thereby creating IPL. The US Food and Drug Administration approved the technique for therapeutic ends in 1997, after the first article on their use in dermatology, when Raulin et al. used them successfully to treat 14 patients with telangiectasias of the face and legs or with poikiloderma of Civatte. Shortly afterward, the same authors published two cases of permanent hair removal and subsequently have conducted several more standardized studies that have demonstrated the efficacy and safety of the technique (Raulin et al. 1997; González-Rodríguez and Lorente-Gualb 2015).

First-generation IPL devices emit light of the infrared part of the spectrum, which prevalently led to epithelial damage and a high incidence of side effects. Second-generation IPL devices use water to filter off the infrared part of the light spectrum, keeping the wavelength spectrum between 515 and 950 nm. This reduces the risk of side effects (Babilas et al. 2010; González-Rodríguez and Lorente-Gualb 2015). Cooling systems are used to protect the epidermis in contact with the crystal (González-Rodríguez and Lorente-Gualb 2015). In IPL devices, similar to lasers, the basic principle is the absorption of photons by endogenous or exogenous chromophores within the skin, generating heat and, subsequently, destructing target structure (Babilas et al. 2010).

In the following years, multiple technical modifications allowed an easier handling, increased

safety, and amplifying the spectrum of potential indications. The emission spectrum of IPLs ranges from 400 to 1,300 nm, and pulse duration ranges from 2 to 200 ms. Convertible cutoff filters of IPL devices can be easily adapted to the desired wavelength, allowing certain versatility (Babilas et al. 2010; González-Rodríguez and Lorente-Gualb 2015).

Most IPLs have a single pulse, and the energy is proportional to the pulse duration. Some IPLs have multiple sequential pulsing, and some have the ability to independently vary the pulse duration, the energy fluence, or both in each pulse. Other variables include the cutoff wavelengths, spectral output, and size of the delivered light (Wat et al. 2014).

Basic Concepts

Intense Pulsed Light Wavelengths

Traditional indications of IPL consist in its ability of targeting pigmented and vascular lesions.

In pigmented lesions, the target is melanosome, whose chromophore is melanin. This absorbs the appropriate wavelength, transforming the light into heat, causing target destruction. The transfer of melanosomes toward the upper layers accompanies these processes, where they are eliminated along with necrotic keratinocytes (González-Rodríguez and Lorente-Gualb 2015).

In vascular lesions, IPL acts on three target chromophores: oxyhemoglobin (predominant lesions of red appearance), deoxyhemoglobin (predominant in blue lesions), and methemoglobin (González-Rodríguez and Lorente-Gualb 2015).

Oxyhemoglobin contained in red blood cells within blood vessels has a maximum peak of absorption around 540 nm (alpha peak) and 580 nm (beta peak). This holds true of small superficial vessels mainly located on the face and the neck. Vessels on the legs are usually located deeper and contain more deoxyhemoglobin. This situation moves the absorption curve to the right, from 800 nm to 1,200 nm. Infrared wavelengths tend to be more effective in treating deeper blue vessels, while shorter wavelengths are more effective for superficial red telangiectasias (Adamic et al. 2007).

The longer the wavelength, the deeper it penetrates into the skin (Adamic et al. 2007). Although the peak of maximum absorption for oxyhemoglobin is around 418–540 nm, less penetration is achieved and a strong competition with melanin from epidermis occurs. At 577 nm, although absorption is low, the degree of penetration is greater, reducing melanin absorption and avoiding side effects, such as hypopigmentation. For this reason, current devices use longer wavelengths (515–600 nm) to ensure deeper penetration while still being absorbed by oxyhemoglobin (Fig. 4) (González-Rodríguez and Lorente-Gualb 2015). The use of longer wavelengths ensures the safety of IPL in higher phototypes.

Among these wavelengths, the patient's skin type, the skin condition, and the target present determine the choice of suitable cutoff filters and therefore the spectrum of wavelengths to be emitted (Babilas et al. 2010).

Pulse Duration

Pulse duration can be set in relatively wide ranges (depending on the particular device) in the millisecond range. Similar to laser devices, pulse duration should be equal to or lower than the thermal relaxation time (TRT) of the target structure to prevent unselective damage to the surrounding tissue (Babilas et al. 2010).

For IPL systems, usually pulse duration is determined in milliseconds (ms).

For deep lesions, higher pulse durations are suggested. For superficial lesions, smaller pulse durations are recommended.

Selectivity

The key chromophores of the human skin (hemoglobin, melanin, water) show broad absorption spectrums. Thus, monochromaticity is not a requirement for photothermolysis. As IPL devices emit a spectrum of wavelengths, the three key

chromophores can be activated with one single light exposure. This versatility implies in a reduced selectivity (Babilas et al. 2010) and can explain the need of long-term treatment for vascular lesions (Ichikawa and Furue 2013).

Treatment Principles

- Smaller vessels need shorter pulses; larger vessels need longer pulses.
- The deeper the blood vessel is located in the dermis, the larger the spot size, the longer the wavelength, and the longer the pulse duration should be combined with cooling to protect the epidermis.
- Darker skin types need longer pulses and longer wavelengths (Adamic et al. 2007).

Mechanisms of Action

Intense pulsed light systems use a flashlamp that emits high-intensity, noncoherent, and polychromatic broad-spectrum light. The emission spectrum of IPLs ranges from 400 to 1,200 nm. The light is emitted in pulses with various pulse durations and intervals in a large rectangular spot of up to 1 by 4 cm (Raulin and Greve 2003; Meesters et al. 2014).

The mechanism of action of IPL system utilizes the theory of selective photothermolysis (Anderson and Parrish 1983). The basic principle is the absorption of photons by skin chromophores, generating heat, which is responsible for target destruction and selective thermal damage of the target. Selective photothermolysis begins with local absorption of light energy in target chromophores such as hemoglobin in vascular lesions or melanin in pigmented lesions (Babilas et al. 2010).

The combination of prescribed wavelengths, fluences, pulse durations, and pulse intervals facilitates the treatment of a wide spectrum of skin conditions. Various different wavelengths of absorption are emitted to treat various targets, using different filters in order to optimize treatment of different conditions. By selecting a cutoff filter specific for the absorption wavelength of the chromophore, energy can be deposited in the blood vessels, preventing damage and subsequent scarring to the surrounding tissues (Kassir et al. 2011).

For vascular lesions, the mechanism of action of IPLs is related to their selective absorption by hemoglobin (oxyhemoglobin, deoxyhemoglobin, and methemoglobin) within the blood vessels with peaks of absorption at 418 nm (blue), 542 nm (green), and 577 nm (yellow). Successful treatment depends on the type and size of the vessels (Babilas et al. 2010; Barikbin et al. 2011; Goldberg 2012).

Shorter wavelengths may be preferred for superficial vascular lesions such as facial telangiectasias. Lower cutoff filters are effective in treating smaller caliber vessel. For standard-sized small vessels in the papillary dermis with a diameter of 0.1 mm, IPL has been shown to be an effective treatment. IPL is able to treat the surface area of telangiectasias and to diminish the intensity of erythema and flushing seen in patients with erythematotelangiectatic rosacea (Mark et al. 2003; Goldberg 2012).

Indications

The conditions treated with IPL include, mainly, vascular lesions and pigmented lesions, as well as skin rejuvenation, inflammatory dermatoses, acne vulgaris, hidradenitis suppurativa, hair removal, hypertrophic scars, and keloids (Babilas et al. 2010; Vrijman et al. 2011; Goldberg 2012; Wat et al. 2014).

The IPL device had been originally developed for the treatment of a wide range of benign vascular lesions, including telangiectasias and reticular varicose leg veins (Goldberg 2012; Meesters et al. 2014). There are multiple well-established IPL treatments for targeting blood vessels in the skin. IPL devices have been used effectively in the treatment of facial telangiectasias, erythematotelangiectatic rosacea, spider nevi, erythrosis, hemangiomas, venous and capillary malformations, and poikiloderma of Civatte (Acarturk and Stofman 2003; Clementoni et al. 2005; Adamic

et al. 2007; McGill et al. 2008; Li et al. 2010a; Nymann et al. 2010; Campolmi et al. 2011; Dan 2011; Barikbin et al. 2011; Meesters et al. 2014).

Successful treatment of vascular lesions depends on the type and size of the vessels. Fodor et al. conducted a comparative study of IPL and Nd:YAG laser and obtained better results with IPL for more superficial and smaller lesions. A study conducted by Murray et al. in 2012 showed an improvement in systemic sclerosis-related telangiectasias; however, these improvements were not sustained during follow-up, suggesting that other treatments should be added. IPL can also be useful in infants with superficial hemangiomas or rapidly growing lesions >1 cm (González-Rodríguez and Lorente-Gualb 2015).

Rosacea

Intense pulsed light therapy is a safe and effective treatment for the signs and symptoms of rosacea. Several studies have demonstrated the successful use of intense pulsed light for the vascular components of erythematotelangiectatic rosacea, including facial telangiectasia and papular lesions (Schroeter et al. 2005; Papageorgiou et al. 2008; Bae et al. 2009; Babilas et al. 2010; Dahan 2011; Kassir et al. 2011; Liu et al. 2014).

Rosacea is a chronic cutaneous disease that manifests as facial flushing, persistent erythema, telangiectasia, papules, and pustules. Erythematotelangiectatic rosacea is the most common and may have the strongest vascular component among the four subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) (Crawford et al. 2004; Lim et al. 2014). Advantages of IPL include short downtime, mild adverse reactions, and short duration of procedure due to the large application area (Kawana et al. 2007; Babilas et al. 2010; Lim et al. 2014).

The ability to choose the duration of pulses makes IPL a versatile tool in the treatment of rosacea. The possibility of different filter settings allows a wider selection of the range color of the vascular system (Schroeter et al. 2005; Piccolo et al. 2014). IPL can improve rosacea treating abnormal vessels and inducing collagen remodeling (Piccolo et al. 2014).

Various studies have demonstrated the effectiveness of IPL in reducing blood flow, telangiectasia, and severity of erythema in individuals with rosacea (Wat et al. 2014) (Fig. 1). Taub noticed a reduction of 83% of erythema, a reduction of 75% of flushing, and an improved skin texture (Taub 2003).

A prospective trial involving 60 patients analyzed the effect of IPL on facial telangiectasias and found that 77.8% of patients achieved greater than 50% reduction of vessels after treatment. These results were maintained during a 3-year post-treatment follow-up period (Schroeter et al. 2005).

Papageorgiou and colleagues confirmed the efficacy of IPL in the treatment of rosacea disease of phase I. It showed a significant improvement of erythema, telangiectasias, and flushing. The severity of rosacea was reduced more than 50%, and the results were sustained at 6 months (Papageorgiou et al. 2011).

IPL appears to be an effective, well-tolerated treatment option for rosacea (level 2a evidence), with efficacy equal to that of pulsed dye laser. Typical reported improvement was in the 50% range (Neuhaus et al. 2009; Wat et al. 2014).

Other Vascular Lesions

Hemangioma

IPL has been shown to be applicable in infants with superficial hemangiomas and appears as one of the effective and safe treatments. Treating the vascular tumor at the earliest stage probably controls the excess in endothelial growth. IPL is limited by the deep and mixed types of the vascular tumors and a size over 5 cm at initiation of treatment, as well as some locations including the eyelids, lips, nostril, and genitalia (Paquet et al. 2014). Angermeier studied patients with different vascular lesions with IPL. It demonstrated 75–100% of clearance after one or two treatments with IPL in 174 of 188 patients with vascular lesions (45 cases of them had facial hemangiomas) (Angermeier 1999).

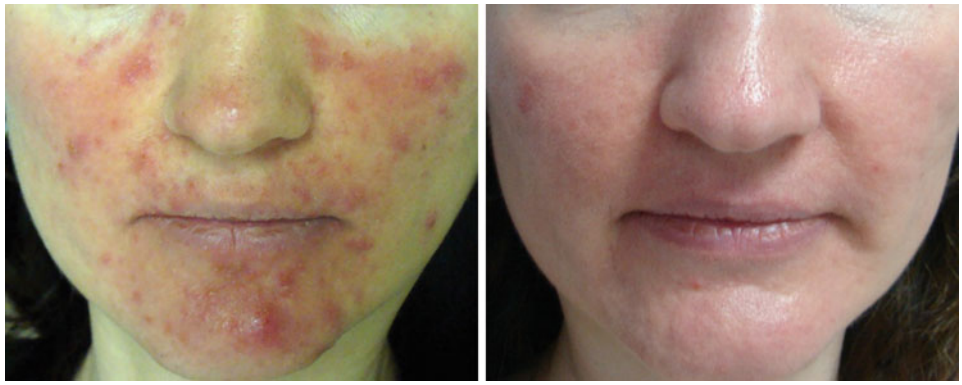

Fig. 1 Successful use of IPL for the vascular components of erythematotelangiectatic rosacea (facial telangiectasia and papular lesions) (Photographs from personal archive of Dr. Luiza Pitassi)

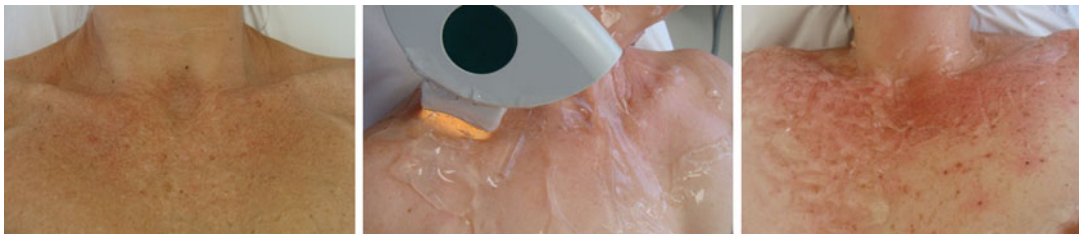

Fig. 2 IPL treatment of poikiloderma of Civatte of the neck and chest showing immediately after treatment their ability to target vascular and pigment simultaneously (Photographs from personal archive of Dr. Luiza Pitassi)

IPL has notably been used in a study of 62 patients with infantile hemangiomas who received four to five IPL treatments at 4-week intervals with a clearance rate of more than 80% (Li et al. 2010a).

Treatment with IPL suggested that lesions larger than 1 cm in diameter at the first visit or those rapidly growing more than 0.5 cm over the first 6–8 months of life must be treated in order to avoid further physical and psychological sequelae. Treatment in an early stage of development with IPL appeared to stop the rapid growth and initiated involution in three treatment sessions, thus preventing any unpredictable disfiguring impairment (Rafiq et al. 2014).

Poikiloderma of Civatte

Because of their ability to target vascular and pigment components simultaneously, IPL sources (IPLs) have been utilized in the treatment of poikiloderma of Civatte (Fig. 2).

Weiss and coworkers have reported their 5-year experience in treating poikiloderma of Civatte of the neck and chest in more than 100 patients. A clearance of more than 75% of telangiectasias and hyperpigmentation was observed, with a 5% incidence of side effects including pigment changes (Weiss et al. 2000; Goldman and Weiss 2001).

In 2008 Rusciani et al. studied 175 patients with poikiloderma of Civatte of the neck and chest treated with various IPL settings. Eighty percent of the vascular and the pigmented components were cleared. Less than 5% of the individuals had side effects, which were minimal and transient (Rusciani et al. 2008). Weiss et al. succeeded in reaching a clearance rate of 75–100% in 82% of 135 patients after three treatments with PhotoDerm VL (Weiss et al. 2000). Goldman et al. achieved a 50–75% improvement

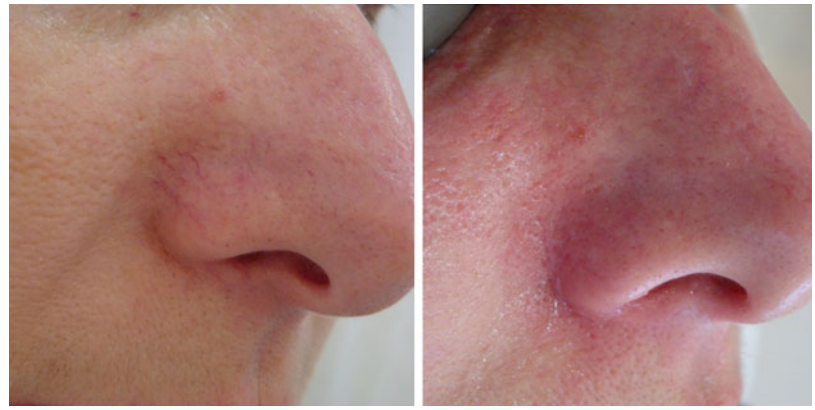

Fig. 3 Nasal telangiectasias immediately disappearing after IPL 540 nm treatment (Photographs from personal archive of Dr. Juliana Jordão)

in the extent of telangiectasias and hyperpigmentation after an average of 2.8 treatments (Goldman and Weiss 2001). Schroeter et al. even had clearance rates of 90% in the vascular part in 15 patients (Schroeter and Neumann 1998).

IPL can be considered a safe and effective therapy for poikiloderma of Civatte due to its wide range of wavelengths, which allows treating both the pigmentation and the telangiectasia at the same time (Barikbin et al. 2011).

Take care in darker skin phototypes treatment, and during cervical area, treatment is necessary to avoid dischomia and scars. When correctly performed, IPL procedure can be considered a safe and effective therapeutic option for poikiloderma of Civatte, allowing a marked improvement of vascular and pigmented lesions with minimal side effects (Rusciani et al. 2008).

Nasal Telangiectasia

Nasal telangiectasia can be treated with IPL. High fluences and stacking pulses should be necessary in resistant telangiectasias. For smaller vessels, short wavelengths and low pulse duration are suggested. For thicker telangiectasias, bigger wavelengths and high pulse durations are more effective.

To be sure, that the telangiectasia was effectively removed is necessary to see the telangiectasia immediately disappearing (Fig. 3) or an edema in the path of the vessel or a purpura in its place. Repeated sessions with 3 week intervals are indicated as some telangiectasias reopen after few days.

Leg Telangiectasia

Studies demonstrated that IPL could be used for multiple forms of telangiectasia treatment. However, clinical evidence for IPL in the treatment of leg veins is scarce. In a multicenter trial of 159 patients, Goldman reported 90% clearance rate with vessels smaller than 0.2 mm and 80% clearance rate with vessels 0.2–1 mm in diameter. Schroeter et al. reported immediate clearing in 73.6% of patients and in 84.3% of patients after 4 weeks (Goldman et al. 1996; Schroeter et al. 2013; Meesters et al. 2014). Doctors have to take into account the skin phototype to avoid side effects.

Striae Distensae (SD)

The exact mechanism of action of IPL in the treatment of SD is unknown, but it is probably related to dermis remodeling, in which the activity of fibroblasts is increased and more collagen fibers are synthesized or rearranged within the stroma (Goldberg 2000; Al-Dhalimi and Abo Nasyria 2013).

Previous studies have demonstrated that IPL induces neo-collagen formation and potentially

improves epidermal atrophy and dermal elastosis. Pérez et al. showed that SD improved clinically and microscopically after IPL with minimal side effects (Pérez et al. 2002).

A comparative study of the effectiveness of intense pulsed light in the treatment of striae distensae showed that both of the wavelengths (650 nm and 590 nm) were effective in the treatment of striae distensae and both of them resulted in statistically significant reduction in the number, the lengths, and the maximum widths of striae. For all of these assessed parameters, the wavelength 590 nm was more effective (Al-Dhalimi and Abo Nasyria 2013).

Port-Wine Stain (PWS)

Raulin and Goldman reported the first successful treatment of an adult port-wine stain (PWS) with IPL (Raulin et al. 1997).

The pulsed dye laser represents the most commonly used laser for treatment of PWS and has the most published literature supporting its use. IPL has also been reported to be an effective alternative to PDL for treatment of PWS. Although IPL has been shown to be effective in the clearance of pink and red PWS, a head-to-head trial comparing the efficacy of IPL against PDL determined that the median clinical improvement was significantly better for PDL (65%) than IPL (30%) (Faurschou et al. 2009). Nevertheless, IPL can be considered for treating PDL-resistant PWS (Ho et al. 2004; Ozdemir et al. 2008; Li et al. 2010b; Adatto et al. 2010; Chen et al. 2012).

Bjerring and colleagues treated 15 patients with PWS that had previously been resistant to PDL and found that IPL was able to achieve 75–100% clearance in 46.7% of cases (Bjerring et al. 2003).

A randomized, controlled, single-blind head-to-head trial comparing PDL with IPL for the treatment of PWS showed that both modalities were effective but that PDL was superior in terms of median clinical improvement and patient preference (Wat et al. 2014).

Recently, Wang and colleagues confirmed the efficacy of IPL in the treatment of facial and extrafacial PWS in Chinese patients (Wang et al. 2013).

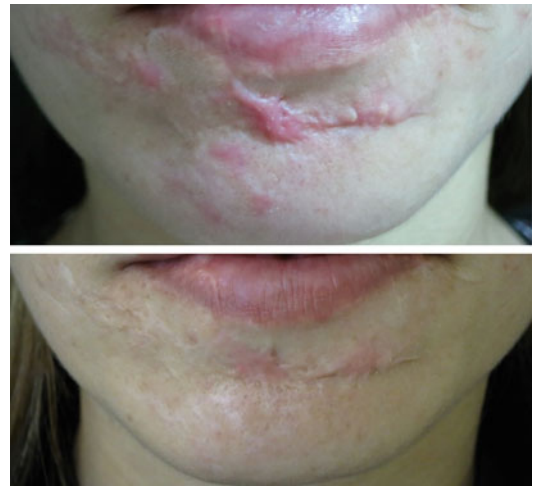

Fig. 4 Traumatic scar treated with eight sessions of IPL 540 nm (Photographs from personal archive of Dr. Juliana Jordão)

There is reasonable evidence to suggest that IPL is an effective, safe modality for the treatment of capillary malformations (level 2a evidence). It may be especially useful for darker lesions that have greater vascularity but minimal nodularity (Wat et al. 2014).

Hypertrophic Scars and Keloids

A recent report of IPL in 109 patients with hypertrophic scars and keloids (due to traumatic wounds, burns, and surgical incisions) demonstrated improvement in 92.5% of subjects, in terms of scar height, erythema, and hardness, with a high level of patient satisfaction (Erol et al. 2008).

In Fig. 4, it is possible to see a good result of a traumatic scar treated with eight sessions of IPL 540 nm.

Hyperpigmented, erythematous, and proliferative scars all demonstrated greater than 50% improvement after a mean of 2.97 sessions, whereas atrophic scars did not respond (Kontoes et al. 2003). A very recent pilot study has demonstrated the effectiveness of IPL in wound healing after suture removal. The basic mechanism is not

yet fully understood, but most probably an action on vascular proliferation, essential for the growth of collagen, and on pigmentation resulting from scar formation is involved (Erol et al. 2008; Piccolo et al. 2014).

Kontoes et al. reported an improvement of more than 75% in the pigmentation of hypertrophic scars, 50% higher than that in the scars from asphalt, and 50% reduction in the size and thickness of hypertrophic scars. This is probably due to the inhibition of the action of the vessel caused by IPL on scar tissue and on the subsequent proliferation of collagen (Kontoes et al. 2003).

Contraindications

Pregnancy, breastfeeding, the intake of retinoids or photosensitizing medications, diseases or genetic conditions causing photosensitivity or tending to aggravate after light exposure (Roelandts 2000), as well as suntan are exclusion criteria for IPL treatment. Patients suffering from long-term diabetes, hemophilia, or other coagulopathies and patients with implants in the treatment area or with a heart pacemaker should be treated with special care. Patients with a history of herpes simplex require an antiviral prophylaxis for holohedral facial treatments (Adamic et al. 2007).

The skin type of the patient has to be documented according to the Fitzpatrick scale because photophysical parameters need to be adjusted depending on the individual patient's skin type. It is recommended to avoid sunlight, in addition to applying a broad-spectrum sunscreen. When treating areas close to tattoos, definitive makeup, ephelides, and nevus, caution should be taken to avoid a possible color change or scar injury after treatment with intense pulsed light at the site.

Recently, a series of home-use intense pulsed light devices has been developed. These devices, in spite of being FDA approved, have scarce controlled studies related to the method's safety and efficacy. All systems tested are attractively packaged with clear educational material for the customer regarding contraindications to treatment such as too dark skin types, active suntan, and medications (Town and Ash 2010).

Side Effects and Their Managements

After the administration of high fluences and short pulse times, there have been reports of transient or permanent pigment changes, edema, erythema, purpura, mild discomfort, blistering, and crusting. These findings typically resolved within 1–48 h but sometimes lasted up to 1 week. These side effects are much more common with older, first-generation flashlamps which emit a higher proportion of infrared light (Wat et al. 2014).

The most common complication after IPL treatment is changed pigmentation, with possible hyper- or hypopigmentation. These are most commonly seen in patients with a darker or recently tanned skin. The skin must be sufficiently cooled during treatment to protect the epidermis from being burned; the cooling can be performed using cooling gels, ice gels, contact spray cooling, or special cooling handpieces (Raulin and Greve 2003).

Blistering and crusting are signs of overfluenced treatment; in case of blisters and crusts, patients must strictly avoid scratching, which may result in infections and scar formation. Antimicrobial ointments help loosening the crusts and prevent bacterial superinfections. Potential side effects that might last longer or may even be irreversible are pigmentary changes, such as hypopigmentation or hyperpigmentation. Adjusting wavelengths and fluences to the patient's skin type and treatment area can mostly prevent these side effects. Unsuitable patients (due to suntan or skin type) are excluded from therapy as well as patients who are unable or unwilling to strictly avoid postoperative UV exposition. Scarring occurs rarely and is almost always evoked by overfluenced treatments or by crusting with subsequent manipulation and infection. In general, the most important measure to prevent side effects is the application of test shots for every chosen set of parameters and even for the same set of parameters applied at different parts of the body (Babilas et al. 2010).

Safety and efficacy with IPL devices rely on the appropriate use of device settings and sufficient operator experience (Wat et al. 2014).

Take Home Messages

- The main skin chromophores present in the skin are melanin and hemoglobin
- Delay the treatment in tanned skins
- Photograph areas before treatment
- The informed consent form should be provided
- Use sunscreens with a high protection factor
- In brunette skins, perform a previous test to increase procedure safety
- Eye protection is mandatory, both for the physician and the patient
- Use the highest amount of safe energy for best results
- Scars are extremely rare, but these may occur when excessive energies are used

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Light-Emitting Diode for Acne, Scars, and Photodamaged Skin

Luiza Pitassi

Abstract

Light-emitting diode therapy was discovered in the late 1960s but only recently has it been widely applied in dermatology to treat a wide range of skin diseases including photoaging, scars, and acne. Since the introduction of photobiostimulation into medicine, the effectiveness and applicability of a variety of light sources have thoroughly been investigated. Light-emitting diode photomodulation is a nonthermal technology used to modulate cellular activity with light, and the photons are absorbed by mitochondrial chromophores in skin cells. Various beneficial effects of light-emitting diode at relatively low intensities have been reported, especially in indications where stimulation of healing, reduction of pain and inflammation, restoration of function, and skin rejuvenation are required. The light-emitting diode therapy is safe, nontoxic, and noninvasive with no side effects reported in the published literature.

Keywords

Light-emitting diodes • Photobiostimulation • Photomodulation • Low-level light therapy • Nonthermal technology • Cellular activity • Mitochondrial chromophores • Inflammation • Restoration of function • Acne • Scars • Skin rejuvenation • Photodamaged skin

Contents

Introduction

Light therapy has been used in many cultures for thousands of years as a therapeutic modality to treat various health conditions (Barolet 2008). Photobiomodulation, also known as low-level light therapy (LLLT), is a medical technique in which exposures to low-level laser light or light-emitting diodes (LEDs) stimulate cellular function leading to beneficial clinical effects (Dincer 2000).

The light-emitting diode (LED) is a semiconductor device available at wavelengths ranging from ultraviolet (UV) to visible to near-infrared

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(NIR) bandwidth that converts electrical current into a non-coherent narrow bandwidth of the electromagnetic spectrum. LED appears to have a wide range of applications of use in dermatology. Because of the combination of high degree of penetration in the skin and absorption by respiratory chain components, light in the spectral range from 600 to 1300 nm is useful for promoting wound healing, reduction of inflammation, relieve pain, and skin rejuvenation (Anderson and Parrish 1981; Barolet et al. 2009).

LED is not an ablative or thermal mechanism but rather a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change. Phototherapy is characterized by its ability to induce photobiological processes in cells. The effective tissue penetration of light and the specific wavelength of light absorbed by photoacceptors are two of the major parameters to be considered in light therapy (Huang et al. 2011).

LED has an additional advantage over lasers as they possess the possibility of combining wavelengths with an array of various sizes, thereby stimulating a broader range of tissue types. LED disperses over a greater surface area than most lasers and can be used where large areas are targeted, resulting in reduced treatment times (Barolet 2008).

The LED was invented in the late 1960s but only recently has it been widely applied in dermatology. Within the past 15 years, a better understanding of photobiology and an increased demand for minimally invasive yet effective dermatologic treatments have led to a growing interest in LED devices (Opel et al. 2015).

LED photomodulation can be used both alone and in combination with a variety of rejuvenation procedures. In dermatology, LED has beneficial effects on wrinkles, acne scars, hypertrophic scars, and healing of burns and can reduce UV damage both as a treatment and as a prophylactic measure (Vecchio et al. 2013).

LED photobiomodulation is the newest category of nonthermal light therapiesand an effective alternative for a variety of medical treatments, with no side effects reported in the published literature when used correctly.

History

Sunlight benefits in treating skin diseases have been used as the earliest form of light therapy in ancient Egypt, India, and China (Barolet 2008). In 1904 Niels Finsen won the Nobel Prize for Physiology and Medicine for his work on using arc lamps to treat cutaneous tuberculosis and red light to prevent scarring from smallpox (Hamblin et al. 2015).

Low-level laser (light) therapy (LLLT) also known as photobiomodulation was discovered in the late 1960s by the surgeon Endre Mester in Budapest, Hungary.

Mester began a series of laser experiments to assess the carcinogenic potential of lasers by using a low-energy ruby red laser (694 nm) on mice. To Mester's surprise, the laser did not cause cancer but instead improved hair growth around the shaved region on the animal's back. This was the first demonstration of photobiostimulation (Mester et al. 1968; Barolet 2008; Avci et al. 2013).

In the 1990s, the National Aeronautics and Space Administration (NASA) developed LEDs that produced a very narrow spectrum of light that in turn allowed for their first clinical applications (Calderhead 2007). The application of light therapy with the use of NASA LEDs will significantly improve the medical care that is available to astronauts on long-term space missions. NASA LEDs stimulate the basic energy processes in the mitochondria (energy compartments) of each cell, particularly when near-infrared light is used to activate the color-sensitive chemicals (chromophores, cytochrome systems) inside. NASA LED arrays have already flown on Space Shuttle missions for studies of plant growth.

The US Food and Drug Administration (FDA) has approved human trials. The use of light therapy with LEDs is an approach to help increase the rate of wound healing in the microgravity environment, reducing the risk of treatable injuries becoming mission catastrophes (Whelan et al. 2000).

Whelan et al. have used the LED originally developed for NASA plant growth experiments in space to access the effects of near-infrared light treatment on wounds in a genetically diabetic

mouse model and have found that certain tissue-regenerating genes are significantly upregulated upon LED treatment. NASA-developed LEDs offer an effective alternative to lasers. These diodes can be configured to produce multiple wavelengths; can be arranged in large, flat arrays (allowing treatment of large wounds); and produce no heat. It is also important to note that LED light therapy has been deemed as a nonsignificant risk treatment by the FDA (Whelan et al. 2003).

In the period of almost 50 years since Mester's discovery, the number of diseases and conditions that can be effectively treated by LLLT has grown exponentially. No longer confined to wound healing, pain, and inflammation, many major organ systems of the body such as the heart, brain, eyes, spinal cord, digestive tract, and respiratory tract can be benefited by light therapy provided the correct light source, parameters, and delivery methods that are used (Hamblin et al. 2015).

Mechanisms of Action

LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light. Phototherapy is based on the direct transfer of incident photon energy between the incoming photons and the cellular energy pool resulting in a viable clinical reaction, but without heat or damage (Calderhead et al. 2015). The basic mechanism for phototherapy involves absorption of the incident photon energy (photoreception), transduction, and amplification of the signal within the target followed by a photoresponse (Karu 1999).

Photobiomodulation is considered to stimulate fibroblast proliferation, collagen synthesis, growth factors, and extracellular matrix production and enhances cutaneous microcirculation through activating the mitochondrial respiratory system of the cells (Lee et al. 2007a).

LED photomodulation has an effect on the human skin that is nonthermal and most likely mediated by mitochondrial cytochrome light absorption, in particular cytochrome c oxidase (CCO), which is contained in the respiratory chain. This complex enzyme has two different heme centers and two different copper centers, each of which can be reduced or oxidized which affects the absorption spectrum. Consequently, a cascade of events occurs in the mitochondria, leading to biostimulation of various processes (Mahmoud et al. 2008; Avci et al. 2013; Weiss et al. 2005).

The mechanism of LLLT is the absorption of red and near-infrared light by chromophores present in the protein components of the respiratory chain located in mitochondria (Mahmoud et al. 2008). The main therapeutic target for the visible light wavelengths is the cytochrome c oxidase enzyme in the mitochondrial respiratory chain in the target cells, resulting in a photochemically induced cascade leading to the production of adenosine triphosphate (ATP) and eventual cellular photoactivation (Karu 2007).

Respiratory chain activation is the central point and can occur by an alteration in redox properties, acceleration of electron transfer, generation of reactive oxygen species, as well as induction of local transient heating of absorbing chromophores. This leads to increased cellular metabolic activity by targeted cells, such as increased ATP, modulation of reactive oxygen species, the induction of transcription factors, alteration of collagen synthesis, and stimulation of angiogenesis (Barolet 2008; Weiss et al. 2005; Opel et al. 2015).

Activation of respiratory chain components stimulates the expression of genes related to cellular migration and proliferation, changes in the cellular homeostasis, alterations in ATP or cAMP levels, modulation of DNA and RNA synthesis, membrane permeability alterations, alkalization of cytoplasm, and cell membrane depolarization. It also alters the production of growth factors and cytokines (Mahmoud et al. 2008).

LEDs appear to affect cellular metabolism by triggering intracellular photobiochemical reactions. Observed effects include increased ATP, modulation of reactive oxygen species, the induction of transcription factors, alteration of collagen synthesis, stimulation of angiogenesis, and increased blood flow (Barolet 2008; Opel et al. 2015). LLLT stimulates the expression of genes

related to cellular migration and proliferation; it also alters the production of growth factors and cytokines (Mahmoud et al. 2008; Evans and Abrahamse 2008).

Important cell types for skin and tissue regeneration are fibroblasts, keratinocytes, and immune cells (mast cells, neutrophils, and macrophages), which can be stimulated using specific wavelengths with significant tissue penetration properties (Huang et al. 2011).

LEDs are small, robust devices that emit a narrow band of electromagnetic radiation ranging from ultraviolet to visible and infrared wavelengths. Emitted light are available at wavelengths ranging from ultraviolet (UV) to visible to near-infrared (NIR) bandwidth (247–1300 nm). LED is different from other types of laser by having a low intensity, which causes low-temperature changes (Weiss et al. 2005). A significant difference between lasers and LEDs is the way the light energy is delivered. The peak power output of LEDs is measured in milliwatts, whereas that of lasers is measured in watts. LEDs provide a much gentler delivery of the same wavelengths of light compared to lasers and at a substantially lower-energy output (Barolet 2008).

While laser procedures require intensive post-treatment care and prolonged downtime and may lead to complications, the LED therapy is an effective, safe, and non-painful treatment (Wunsch and Matuschka 2014).

Other advantages over lasers include the possibility to combine wavelengths with an array of various sizes. LED disperses over a greater surface area than lasers and can be used where large areas are targeted, resulting in a faster treatment time (Barolet 2008).

The absorption of red and near-infrared light by photoacceptor molecules within the respiratory chains can cause alteration in the redox status of the cells and activate the nucleic acid synthesis to accelerate cell proliferation (Karu 1987, 1999)

Different wavelengths have different chromophores and can have various effects on tissue. Wavelengths are often referred to using their associated color and include blue (400–470 nm), green (470–550 nm), red (630–700 nm), and NIR (700–1200) lights. Depth of tissue penetration is primarily dependent upon the wavelength of the light (Barolet 2008). Wavelengths of 630–900 nm can penetrate and be absorbed through the entire papillary dermis.

For best effects, the wavelength used should allow for optimal penetration of light in the targeted cells or tissue. Because cytochrome c oxidase is the most likely chromophore in LLLT, two absorption peaks are considered in the red (~660 nm) and NIR (~850 nm) spectra (Karu et al. 2005; Barolet 2008).

Analysis of the gene expression profiles in human fibroblasts revealed an influence of low-intensity red light with a 628 nm wavelength on 111 different genes that are involved in cellular functions, such as cell proliferation; apoptosis; stress response; protein, lipid, and carbohydrate metabolism; mitochondrial energy metabolism; DNA synthesis and repair; antioxidant-related functions; and cytoskeleton- and cell-cell interaction-related functions (Zhang et al. 2003; Wunsch and Matuschka 2014).

Red light (wavelength range from 620 to 770 nm), which is part of the visible light spectrum, is able to activate fibroblast growth factor, increase type 1 procollagen, increase matrix metalloproteinase-9 (MMP-9), and decrease MMP-1 of the skin dermis due to its capability to deeply penetrate the skin to about 6 mm; thus, it is favored in photodynamic therapy (PDT). An increase in fibroblast number and a mild inflammatory infiltrate following exposure have been demonstrated histologically (Barolet et al. 2009; Issa et al. 2009; Opel et al. 2015).

Red LEDs have the deepest tissue penetration of the visible wavelengths and demonstrate significant reduction of the epidermis thickness, elastotic material, and the dermal inflammatory infiltrate as well as an increase of collagen and procollagen type I and III in the upper dermis. TGF-β is a growth factor responsible for inducing collagen synthesis from fibroblasts and is significantly increased after PDT (Karrer et al. 2013).

Because of the deeper light penetration into the skin, red light is widely preferred in PDT and may also exert anti-inflammatory effects via regulating

the release of inflammatory factors. Important cell types for skin and tissue regeneration are fibroblasts, keratinocytes, and immune cells (mast cells, neutrophils, and macrophages), which can be stimulated using specific wavelengths with significant tissue penetration properties (Calderhead et al. 2015).

PDT typically involves the application of a topical photosensitizer such as 5-aminolevulinic acid (ALA) or its methyl ester (MAL), which is activated by exposure to a visible light source. Following activation of a photosensitizer with light of the appropriate wavelength, ROS, in particular singlet oxygen, are generated. As a consequence of the combination of light, photosensitizer, and tissue oxygen, cytotoxic ROS are formed in diseased tissues, inducing necrosis and apoptosis of the malignant and premalignant cells (Hamblin and Demidova 2006). The oncologic indications, actinic keratoses, nodular or superficial BCCs, and Bowen's disease are approved indications for PDT with ALA/MAL (Morton et al. 2002).

PDT in the treatment of acne is based on the fact that *Propionibacterium acnes* contain endogenous porphyrins, in particular coproporphyrin III (Babilas et al. 2005). The red light module is used to increase blue light phototherapy new tissue growth, enhance healing, and stimulate collagen, thereby reducing lines and wrinkles (Fig. 1).

The beneficial effect of red light on wound healing can be explained by considering several basic biological mechanisms including the induction of expression cytokines and growth factors such as VEGF responsible for the neovascularization necessary for wound healing (Hamblin and Demidova 2006).

Near-infrared light (IR), also known as monochromatic infrared energy is believed to stimulate circulation by inducing the release of guanylate cyclase and nitrous oxide, which, in turn, promotes vasodilation and growth factor production as well as angiogenesis, leading to subsequent wound healing (Karu 1987; Opel et al. 2015) (Fig. 2).

IR LED constitutes the wave band longer than 760 nm and can penetrate the skin between 5 and 10 mm. Near-infrared light 830 nm has been used to treat wound, pain, ulcers, recalcitrant lesions, skin rejuvenation, and acne vulgaris treatment (Opel et al. 2015).

A single treatment of the normal skin with 830 nm LED-LLLT compared with unirradiated controls demonstrated rapid photomediated degranulation of mast cells at 48 h, accompanied by an ultrastructurally demonstrated inflammatory response with the appearance of significantly greater numbers of mast cells, macrophages, and neutrophils (Calderhead et al. 2008).

LED irradiation with a combination of wavelengths, such as 630 or 660 nm combined with 830 or 850 nm, increased cell number and type I collagen expression more than treatment with each wavelength alone and decrease MMP-1expression (Tian et al. 2012).

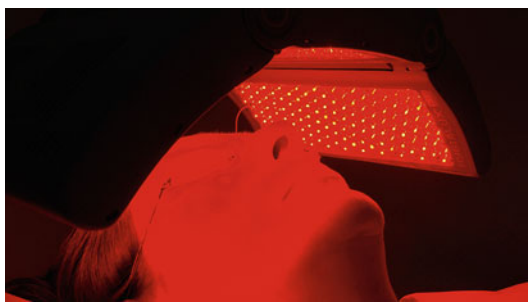

Fig. 1 Red light LED treatment for photodamaged skin (Photograph from personal archive of Dr. Luiza Pitassi)

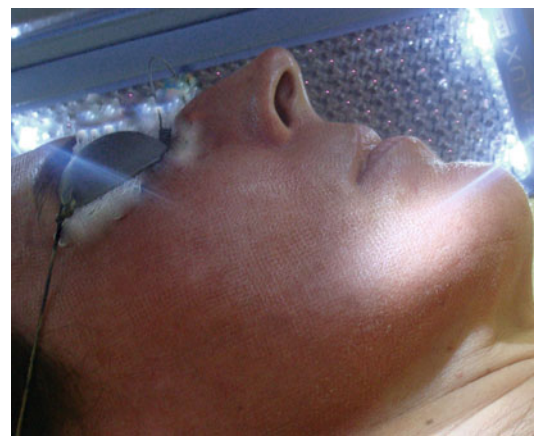

Fig. 2 Near-infrared light (830 nm) treatment after ablative laser resurfacing (Photograph from personal archive of Dr. Luiza Pitassi)

Fig. 3 Blue light LED treatment for acne (Photograph from personal archive of Dr. Luiza Pitassi)

Lee et al. compared the effects among LED treatment with 633 and 830 nm on their own and the combination of 830 and 633 nm with a control group. Although all the LED-treated groups in this study showed statistically significant gross and histological results compared with the controls, the 830 nm group proved superior to the other LED groups in all aspects including collagenesis, skin elasticity, expression of tissue inhibitors of matrix metalloproteinase 1 and subjective patient satisfaction (Lee et al. 2007a).

Blue light (wavelength range from 400 to 480 nm) is UV-free irradiation and appears to exert its effect on acne via its influence on *Propionibacterium acnes* and its anti-inflammatory properties (Fig. 3). *P. acnes* contains naturally occurring porphyrins, mainly coproporphyrin and protoporphyrin IX. Absorption of blue light by these molecules is believed to induce a natural PDT effect with destruction of the bacteria via the formation of oxygen free radicals (Dai et al. 2012; Opel et al. 2015).

One mechanism of action of phototherapy for acne is through the absorption of light (specifically blue light) by porphyrins that have been produced by *P. acnes* as a part of its normal metabolism and that act as endogenous photosensitizers (Lee et al. 2007a; Avci et al. 2013). Because of the effectiveness in reducing cell proliferation, blue light is also propitious to treat hyperplastic diseases and chronic skin inflammation.

The use of a dual-wavelength (red and blue) LED light source enhances PDT results for acne and other sebaceous disorders. Red wavelength (630 nm) can reach the sebaceous glands, and blue (405 nm) light photobleaches any residual protoporphyrin IX (PpIX) in the epidermis, thereby reducing posttreatment photosensitivity (Barolet 2008).

Also topical PDT is a treatment for nonmelanoma skin cancer (NMSC) and the improvement of photoaging. PDT typically involves the application of a topical photosensitizer such as 5-aminolevulinic acid (ALA) or its methyl ester (MAL), which is activated by exposure to a visible light source. As a consequence of the combination of light, photosensitizer, and tissue oxygen, cytotoxic ROS are formed in diseased tissues, inducing necrosis and apoptosis of the malignant and premalignant cells (Gold et al. 2006; Szeimies et al. 2012)

A number of studies have indicated that exposing patients to a combination of LED wavelengths is more effective than monotherapy. This synergistic effect has been investigated on a variety of skin disorders (Russell et al. 2005; Goldberg et al. 2006; Goldberg and Russel 2006; Lee et al. 2007a; Park et al. 2014).

Indications

Review of the literature revealed that differing wavelengths of light-emitting diode devices used in dermatology have many beneficial effects to treat a wide range of skin diseases (Table 1), including acne, scars, and photodamaged skin and side effects were either mild or not reported. It remains prudent to screen individuals with photosensitive dermatoses, or those taking photosensitizing medications, as these are contraindications to treatment. Caution must be emphasized especially for epileptic and photophobic patients especially if LEDs are pulsed (Barolet 2008; Opel et al. 2015).

Wavelengths in the 600–700 nm range are chosen for treating superficial tissue, and wavelengths between 780 and 950 are chosen for

deeper-seated tissues due to longer optical penetration distances through tissue. Because of the possible existence of a biphasic dose-response curve referred to above, choosing the correct dosage of light (in terms of energy density) for any specific medical condition is difficult (Hamblin and Demidova 2006) (Table 2).

LED for Acne, Scars and Photodamaged Skin

Acne

Phototherapy with visible light (mainly blue light, red light, or combination of both) has been proposed as an alternative therapeutic modality to treat acne vulgaris. One mechanism of action of phototherapy for acne is through the absorption of light (specifically blue light) by porphyrins that have been produced by *P. acnes* as a part of its normal metabolism and that act as endogenous photosensitizers (Avci et al. 2013).

Blue light therapy (415 nm) is effective at activating coproporphyrin III and protoporphyrin IX, subsequently destroying the *P. acnes* bacteria (Fig. 4). It has been shown to significantly reduce acne lesions in studies on mild-to-moderate, inflammatory, and pustular acne when irradiating over eight to ten treatments (Goldberg and Russel 2006).

Blue light treatment also appears to have anti-inflammatory effects on keratinocytes by decreasing the cytokine-induced production of IL-1 alpha and ICAM-1 markers (Shnitkind et al. 2006). Blue LED light (400–470 nm) has a maximal penetration of up to 1 mm. It is best suited for the treatment of more superficial conditions, such as to target *P. acnes* in acne vulgaris (Opel et al. 2015). Blue light illuminated to *P. acnes* colonies induces photoexcitation of bacterial porphyrins, stimulates the production of single oxygen, and, finally, results in the endogenous photodynamic destruction of *P. acnes* (Lee et al. 2007b; Joo et al. 2012).

Shalita et al. demonstrated the use of blue light (405–420 nm) for acne treatment, using 10-min light exposures twice weekly. A total of 35 subjects with lesions on the face and back were treated over a 4-week period; 80% demonstrated a significant improvement of noninflammatory, inflammatory, and total facial lesions, with a

Table 1 Most frequent LED indications in dermatology

Wound healing
Photorejuvenation
Hypertrophic scars and keloids
Acne
Post-inflammatory hyperpigmentation
Erythema
Edema
Analgesia
Burn
Alopecia
Photodynamic therapy treatment (actinic keratosis, Bowen's disease, and basal cell carcinoma)
Vitiligo
Psoriasis
Rosacea
Herpes simplex

Table 2 Led wavelengths of light-emitting diode devices used in dermatology

Color	Wavelength (nm)	Skin treatment	Treatment time
Red	610–760	Skin rejuvenation, fine lines, roughness, skin tone, texture, pore size, depigmentation, wound healing, hypertrophic scars, keloids, edema, and erythema	20–30 min session/two per week
Blue	450–500	Acne, hyperpigmentation, keloids, fibrotic skin diseases	20–30 min session/two per week
Infrared	850–940	Skin rejuvenation, hypertrophic scars, keloids	20–30 min session/two per week

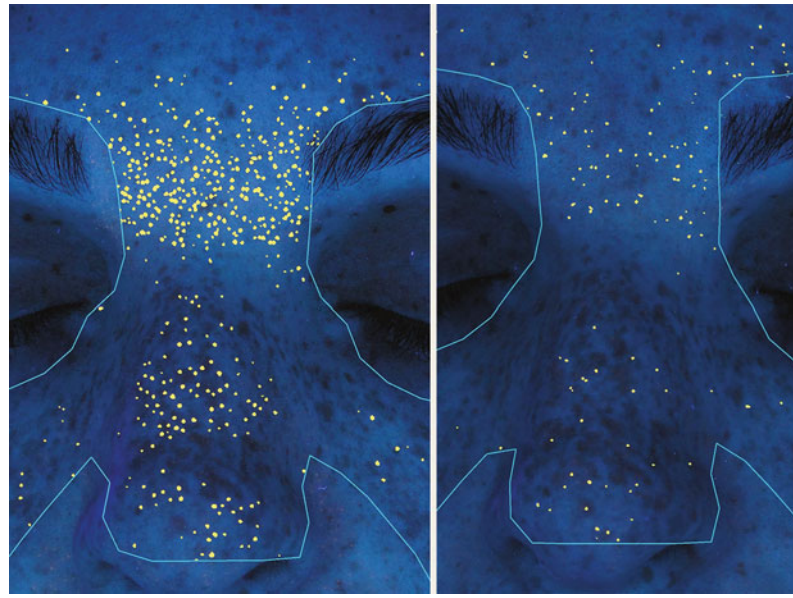

Fig. 4 Photoinactivation of *P. acnes* by its endogenic porphyrins was demonstrated after illumination with blue light at 405 nm for 30 min (Photographs from personal archive of Dr. Luiza Pitassi)

70% mean decrease in inflammatory lesion count 2 weeks after the last treatment (Shalita et al. 2001).

Morton et al. treated 30 patients with mild-to-moderate acne with 8-, 10-, or 20-min blue LED (415 nm) treatments over a period of 4 weeks. The inflammatory lesion counts decreased, with minimal effect on noninflammatory lesions (Morton et al. 2005).

Tremblay et al. gave patients with mild-to-moderate inflammatory acne two 20-min treatments of blue LED (415 nm) per week for 4–8 weeks. Ninety percent of patients were satisfied with the result. Objectively, patients had a 50% reduction in lesion counts (Tremblay et al. 2006).

The blue light treatment is associated with significant reductions in lesion size number, severity, and redness of flare-ups and improvements in the skin's overall appearance, as well as in clarity, radiance, tone, texture, and smoothness (Ash et al. 2015; Opel et al. 2015).

Red light (633 nm) is less effective at activating coproporphyrin III than blue light but is a potent activator of protoporphyrin IX, also found in *P. acnes* bacteria. Since red light penetrates deeper into the tissue than blue, it is possible that red light actively destroys *P. acnes* bacteria residing in the lower regions of the sebaceous gland (Goldberg and Russel 2006).

Red light is believed to stimulate cytokine release from various cells including macrophages and reduce inflammation. The effect of visible red light on the local vasculature is also well recognized. The red light will bring more oxygen and nutrients into the area, further helping to reduce inflammation and enhance the wound repair process (Goldberg and Russel 2006; Sadick 2008; Avci et al. 2013; Sawhney and Hamblin 2014).

The combination of LED for the treatment of acne is also promising. Phototherapy with mixed blue–red light, probably by combining antibacterial and anti-inflammatory action, is a safe, effective, and non-painful treatment for mild-to-moderate acne vulgaris, with no significant short-term adverse effects (Avci et al. 2013; Opel et al. 2015).

Karu demonstrated that when *Propionibacterium acnes* was exposed to blue and red light simultaneously in vivo, there was a marked inhibition of cell activity compared to that seen when red and blue lights were delivered independently (Karu 1999).

Lee et al. treated patients with moderate acne with a combination of blue (415 nm) and red (640 nm) LED devices. A 34% improvement in comedone count and a 78% improvement in the number of inflammatory lesions were observed. Most studies revealed that improvement in inflammatory lesions was higher than the improvement in comedones (Lee et al. 2007b). Kwon et al. demonstrated a decrease of both inflammatory and non-inflammatory acne lesions by 77% and 54%, respectively, following home-use combined blue and red LED (Kwon et al. 2013).

Although blue light has been tried in conjunction with ALA in the treatment of acne in 20 patients, patients experienced greater side effects, and the results were not clinically significant when compared with blue LED alone (Weinstabl et al. 2011; Opel et al. 2015).

Red light can prevent or treat acne post-inflammatory hyperpigmentation (PIH). On the basis of photographic analysis and melanin content measurements, most patients can achieve substantial reduction or absence of PIH lesions in the LED-treated areas (Barolet 2008). Red light therapy is generally performed using wavelengths from the visible spectrum, 670 nm, which is a wavelength absorbed by melanin. The amount of light energy being absorbed by pigments in the skin, such as melanin, should be taken into account when designing a light therapy treatment regimen for a patient. In order to achieve the same energy delivery to structures below the epidermis, patients with skin types in the range of 5 or 6 on the Fitzpatrick scale will require a higher dose of light (fluence) than patients with skin types in the range of 1 or 2 (Brondon et al. 2007).

Various LED wavelengths can affect melanogenesis in normal human melanocytes. LED irradiation at 830, 850, and 940 nm reduced melanogenesis through decreased tyrosinase expression without exerting any cytotoxic effects. The LED wavelength at 830 nm also reduces melanin synthesis and might be helpful therapeutic tools for treating patients with hyperpigmentation (Kim et al. 2012).

Papageorgiou et al. investigated the effects of a combination blue and red light treatment in a randomized study of 107 patients with mild-to-moderate acne. Results displayed a 76% reduction in inflammatory lesions in the combination group. This result was significantly superior to that achieved by blue light alone (Papageorgiou et al. 2000).

Blue and red light combination LED phototherapy is an effective, safe, and non-painful treatment for mild-to-moderately severe acne vulgaris, particularly for papulopustular acne lesions (Lee et al. 2007b).

Scars

Scars, hypertrophic scars, and keloids are cosmetically and psychosocially disfiguring and may result in patients seeking a variety of treatments to address the aesthetic and functional concerns attributed to scarring. Hypertrophic scars and keloids can form after surgery and trauma and are characterized by fibroblastic proliferation and excess collagen deposition (Uitto and Kouba 2000; Lev-Tov et al. 2012).

Light-emitting diode devices have been shown to stimulate fibroblast activity and hasten wound healing. Studies have revealed the possible benefit of red and infrared low-level light therapies to improve scars. It has been reported that collagen synthesis is reduced, and interstitial matrix metalloproteinases (MMP-1), the collagenase involved in normal turnover of skin collagen, are upregulated in aged skin (Brondon et al. 2007).

It has been proposed that interleukin (IL)-6 signaling pathways play a central role in this process and thus that IL-6 pathway inhibition could be a promising therapeutic target for scar prevention. As LED therapy has been shown to decrease IL-6 mRNA levels, it may potentially be preventing aberrant healing (Ghazizadeh et al. 2007; Uitto 2007; Barolet 2008).

LED phototherapy using near-infrared 805 nm light is a method to prevent or attenuate the development of hypertrophic scars or keloids in patients that underwent surgical excision or CO_2 laser ablation of keloids or hypertrophic scars (Mamalis et al. 2014).

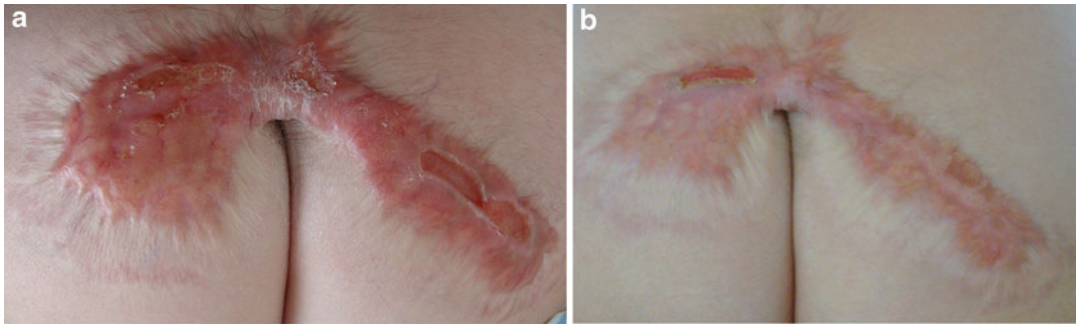

Fig. 5 Keloid treated for 30 min two times a week for 60 days with a combination of red LED device (630 nm) and IR LED device (850 nm) showed significant improvement after 6-month follow-up (Photograph from personal archive of Dr. Luiza Pitassi)

In vitro studies demonstrate that LED phototherapy, at both red and near-infrared wavelengths, can suppress fibroblast proliferation and may provide a mechanistic foundation for future treatment of keloids (Barolet and Boucher 2010) (Fig. 5).

Scars treated for 15 min daily for 30 days with an infrared LED device (805 nm at 30 mW/cm^2) showed significant improvement with no associated side effects as evidenced by improvements in VSS score, measurement of scar height by quantitative skin topography, and blinded clinical assessment of photographs (Mamalis et al. 2014).

A recent study has demonstrated that light-emitting diode blue can inhibit adult human skin dermal fibroblast proliferation and migration speed and is associated with increased reactive oxygen species generation in a dose-dependent manner without altering viability. LED blue has the potential to contribute to the treatment of keloids and other fibrotic skin diseases (Mamalis et al. 2015).

The potential of PDT on scar tissue has been previously investigated. In vitro studies have shown that ALA-PDT induced collagen-degrading matrix metalloproteinase (MMP)-1 and MMP-3 in dermal fibroblasts while reducing collagen type 1 mRNA expression (Karrer et al. 2003). A retrospective blinded study by Sakamoto et al. found aminolevulinic acid (ALA) or methyl ester aminolevulinic acid (MAL) combined with red LED to statistically improve scar appearance after two or more treatments (Sakamoto et al. 2012).

Nie et al. reported a positive effect of PDT in a patient with a persistent keloid which had not responded to a number of routine therapies. Following five MAL-PDT sessions, scar color had improved, and the keloid had reduced in size, become flatter, with reduced erythema in the surrounding margin (Nie et al. 2010).

PDT can reduce scar formation in keloid as evidenced by lack of recurrence and improvement in signs and symptoms as well as by decreased blood flow, increased pliability, and decreased collagen and hemoglobin levels (Ud-Din et al. 2013).

Photodamaged Skin

The use of LEDs for skin rejuvenation is unique in that it does not produce any thermal damage. It is proposed that specific LED light wavelengths are absorbed in the skin and used to modulate cell function, proliferation, and repair in sun-damaged tissue, in a process termed photobiomodulation (Baez and Reilly 2007).

Photobiomodulation is considered to stimulate growth factor production (i.e., fibroblast growth factor, TGF, PDGF), extracellular matrix production, and increased synthesis of collagen and procollagen and enhances cutaneous microcirculation through activating the mitochondrial respiratory system of the cells (Lee et al. 2007a).

A number of clinical studies provide evidence of the effectiveness of LED therapy in photorejuvenation using a variety of LED light sources. LEDs have been shown to improve UV-damaged skin conditions, including photoaging, suggesting that the mechanism of action between LEDs and UV radiation is different (Kim et al. 2012).

Trelles has suggested that LED therapy represents a potential approach in antiaging prevention. The prevention can be achieved via irradiating low-level photoenergy with specific wavelengths that, based on the photobiological findings, can stimulate both epidermal and dermal cells (Trelles 2006).

Recent studies suggest that LLLT (specifically red or NIR radiation) may provide effective protection against UV-induced photodamage. This is believed to be due to the fact that, earlier or during the day (morning time), red/NIR wavelengths of the solar spectrum predominate and prepare the skin for the potentially harmful UV radiation that predominates later on in the day (noon/afternoon) (Barolet 2008; Sawhney and Hamblin 2014).

Irradiation with red light increased fibroblastic growth factor synthesis from photoactivated macrophages and accelerated mast cell degeneration (Lam et al. 1986).

The induction of collagen synthesis by LED in the red spectrum has been shown to occur largely in the papillary dermis. Barolet et al. showed that LED therapy reversed collagen downregulation and MMP-1 upregulation. This could explain the improvements in skin appearance observed in LED-treated individuals. These findings suggest that LED at 660 nm is a safe and effective collagen-enhancement strategy (Barolet et al. 2009).

The red light is used to increase new tissue growth, enhance healing, and stimulate collagen, thereby reducing lines and wrinkles. It also has been used to improve skin roughness, depth of rhytids, skin tone, texture, pore size, dyspigmentation, edema, and erythema (Sauder 2010).

A split-face study of red LED (633 nm) in patients who had undergone blepharoplasty and periocular resurfacing demonstrated a statistically significant improvement of edema, erythema, bruising, and pain on the treated side of the face (Opel et al. 2015).

Light at 830 nm (near-infrared) wavelength is absorbed in the cellular membrane rather than in cellular organelles which remain the target when using light in the visible spectrum. Irradiation at 830 nm has accelerated fibroblast-myofibroblast transformation and mast cell degranulation. In addition, chemotaxis and phagocytic activity of leucocytes and macrophages are enhanced on cellular stimulation by this wavelength (Russell et al. 2005).

Infrared wavelength phototherapy with an LED at 830 nm has anti-inflammatory effects and is useful for the regeneration of damaged skin. The wavelength of 830 nm is well known to dramatically increase the action potentials of wound-healing cells, particularly those in the inflammatory and remodeling stages, and would therefore cause a considerably faster resolution of post-laser adverse effects such as erythema and pain (Russell et al. 2005; Trelles 2006).

Previous work has been published on the combination use of 633 and 830 nm LED therapy in the treatment of photoaged skin. Red (633 nm) light has been shown to increase fibroblast growth factor and collagen synthesis in the skin (Baez and Reilly 2007).

The 830 nm wavelength is well associated with photobiomodulation of the wound-healing cells: the mast cells, neutrophils, and macrophages. The subsequent doses of 633 nm concentrate on the fibroblasts but maintain the reaction level in the other cells. Both wavelengths are well associated with increases in local blood flow rate and volume, and 830 nm also stimulates the transitional remodeling phase (Trelles 2006).

The synergy of 633 and 830 nm wavelength lights will combine these effects to enhance fibroblast proliferation and thus increase collagen synthesis, as well as stimulating inflammatory cell lines such as mast cells and macrophages (Calderhead et al. 2015).

Goldberg et al. investigated the combination of red (633 nm) and IR (830 nm) LED treatment on photodamaged skin and reported softening of

periorbital wrinkles in 80% of subjects. There was subjective improvement of softness, smoothness, and firmness. Histologic examination demonstrated increased number and thickness of collagen fibrils (Goldberg et al. 2006).

An improvement in skin appearance in aged/photoaged individuals has been documented after full-face or split-face serial treatments with red (630, 633 nm) or red in combination with infrared (830 nm) light (Barolet et al. 2009).

Previous findings were able to correlate fibroblast activity and dermal matrix remodeling processes, with an increase in intradermal collagen density and reduced signs of aging (Lee et al. 2007a). The proposed underlying mechanisms include the photostimulation of terminal molecules in the electron transport chain and the subsequent adenosine triphosphate (ATP) concentration increase, along with the selective light-driven activation of water molecules, thereby enhancing metabolic exchange and influencing the ion transporter systems found in cellular membranes (Wunsch and Matuschka 2014).

A prospective, placebo-controlled, double-blind, split-face trial by Lee et al. randomized patients with facial rhytids to receive red LED (640 nm), IR (830 nm), both, or sham treatments. Patients demonstrated a statistically significant reduction in wrinkle severity across all treatment groups: 26%, 33%, and 36%, respectively. Skin elasticity also improved. Tissue assays were notable for an increase in collagen and elastic fibers adjacent to highly active fibroblasts (Lee et al. 2007a).

A study performed with a light device combining narrowband blue light (420 nm) and near infrared (850–890 nm), using 20 min exposure and a total dose of 60 J/cm^2, has demonstrated a dramatic improvement in skin photorejuvenation when associated with glycolic acid peels and topical vitamin C (Fournier et al. 2006). LED treatments work well after any procedure that causes erythema and irritation, including chemical peels or ablative laser systems with extremely high satisfaction levels.

The combination of LED light wavelengths was shown in in vitro results to improve the cell shape homogenization, cell proliferation, and the level of major proteins involved in the healing process (Chabert et al. 2015). LED system is known for its healing and anti-inflammatory properties and also enhancing the results of facial cosmetic procedures.

Conclusion

LED phototherapy is a non-ablative, nonthermal, and nontraumatic treatment, which stimulates cell activities and functions through a photobiomodulative effect.

Light therapy can be a safe and effective alternative for treating acne, scars, and photodamaged skin and a variety of medical treatments with no adverse effects or downtime reported during or after LED treatment.

Take Home Messages

- LED is non-ablative and nonthermal, making it safe for all skin types.
- The treatment is hands-free with no need for operator presence.
- The infrared spectrum is invisible to the eye.
- Eye protection is mandatory, both for the physician and the patient.
- LED can be used as an adjunctive treatment to all laser
- LED therapy helps wound healing after surgery
- The results are better when LED is used in combination
- LED therapy is an effective, non-painful, and no-downtime treatment modality

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Non-ablative Lasers for Photorejuvenation

Maria Angelo-Khattar

Abstract

Photoaging of the skin principally depends upon the amount of melanin in the skin and the degree of exposure to ultraviolet radiation. Solar damage to DNA leads to a reduction in the skin's collagen content and ultimately to a deficit in the structural integrity of the skin. This manifests as clinically visible skin atrophy, lines and wrinkles, and dyschromias such as telangiectasias and pigmented lesions. Photorejuvenation entails an improvement in the tone, texture, and pigmentation of the skin. Various laser technologies are available that rejuvenate skin by resurfacing the uppermost layers and allow for the regeneration of new skin cells. The myriad of laser systems includes ablative and non-ablative lasers in both fractionated and nonfractionated or conventional forms. In varying degrees, all of these lasers treat pigmented lesions, soften wrinkles, and reduce the appearance of scars. Although the ablative technologies yield more effective results in terms of the overall reduction of photoaging, the non-ablative lasers allow for swift healing and are rarely associated with any complications or downtime. Furthermore, non-ablative lasers offer a wider spectrum of clinical indications, since they can be used to treat vascular lesions such as telangiectasia, generalized erythema, and rosacea that are commonly associated with aging skin.

Apart from photorejuvenation, non-ablative lasers have multiple applications including the reduction in sebum secretion in acne and the treatment of a variety of scars. However, this review aims to give an overview and highlight the clinical advantages of both fractionated and nonfractionated non-ablative laser platforms in current use for the treatment of photodamaged skin.

Keywords

Photoaging • Photodamaged skin • Skin atrophy • Aging skin • Wrinkles • Dyschromias • Pigmented lesions • Photorejuvenation • Resurfacing • Non-ablative lasers • Fractionated laser

Contents

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Introduction

The appearance of the skin in humans is integral to the perception of both health and beauty. Hence, in the vast majority of cases, it has a great bearing on the individual's overall well-being and self-esteem.

Skin aging is a complex biological process influenced by a combination of factors and may be broadly categorized as chronological or intrinsic aging and photoaging. Unlike intrinsic aging, which is determined by the individuals' genetic predisposition, photoaging depends mainly on the degree of repeated sun exposure and the amount of melanin in the skin. In fact, skin injury by the sun's ultraviolet (UV) rays account for over 70% of skin aging (Kligman and Kligman 1986).

Chronological and photoaging can be easily distinguished clinically, but they share important molecular features. The clinical characteristics of chronologically aged skin include fine wrinkles, laxity, xerosis, and the development of benign lesions such as solar lentigines, cherry angiomas, and seborrheic keratosis (Krutman and Gilchrest 2006).

The features of photoaging include rough skin, wrinkles, deep furrows, pigmented lesions, telangiectasias, poikiloderma of Civatte, solar elastosis, precancerous lesions, and skin cancers (Yaar et al. 2002; Gilchrest 1990). Sun-exposed areas, such as the face, neck, décolleté, hands, and forearms, are most frequently affected. Furthermore, fair-skinned individuals with a history of intensive sun exposure are more susceptible to severe photodamage.

The Mechanism of Ultraviolet Damage to the Skin

Ultraviolet rays induce numerous changes in the skin including melanogenesis, angiogenesis, immune suppression, and degradation of connective tissue, DNA mutations, and oncogenesis.

Advances in skin biology have increased our understanding of the mechanism whereby UV radiation contributes to photoaging and cutaneous disease.

UVB (280–320 nm) rays are reported to have direct cytotoxic and mutagenic effects on skin cells, while UVA (320–400 nm) rays exert their damaging effects predominantly through the production of reactive oxygen species (ROS). A number of transcription factors and inflammatory cytokines are released in response to ultraviolet rays, which result in an increase in matrix metalloproteinase (MMP) production and ultimately accelerated degradation of the dermal matrix.

The widely accepted pathway is via the upregulation of activator protein-1 (AP-1) and nuclear factor kappa B (NFk B). The latter plays a key role in the signaling pathway leading to the activation of the inflammatory cascade that stimulates the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha. In addition, activation of NFk B upregulates the expression of MMP-1, and consequently dermal collagen is degraded. Furthermore, NFk B downregulates type I collagen synthesis (Rijken and Bruijnzeel 2009) (Fig. 1). Ultraviolet radiation can also upregulate c-Jun, a component of AP-1, and can downregulate retinoic acid (RA) receptors, which decrease RA inhibition of AP-1. This ultimately results in the loss of dermal bulk and skin thinning (Krutmann 2000).

Over the past several years, a plethora of both energy-based and nonenergy-based anti-aging strategies have been developed to retard and reverse skin aging.

Both treatment categories work on the principle of "controlled wounding," whereby the induction of skin trauma initiates a wound healing response and ultimately results in collagen

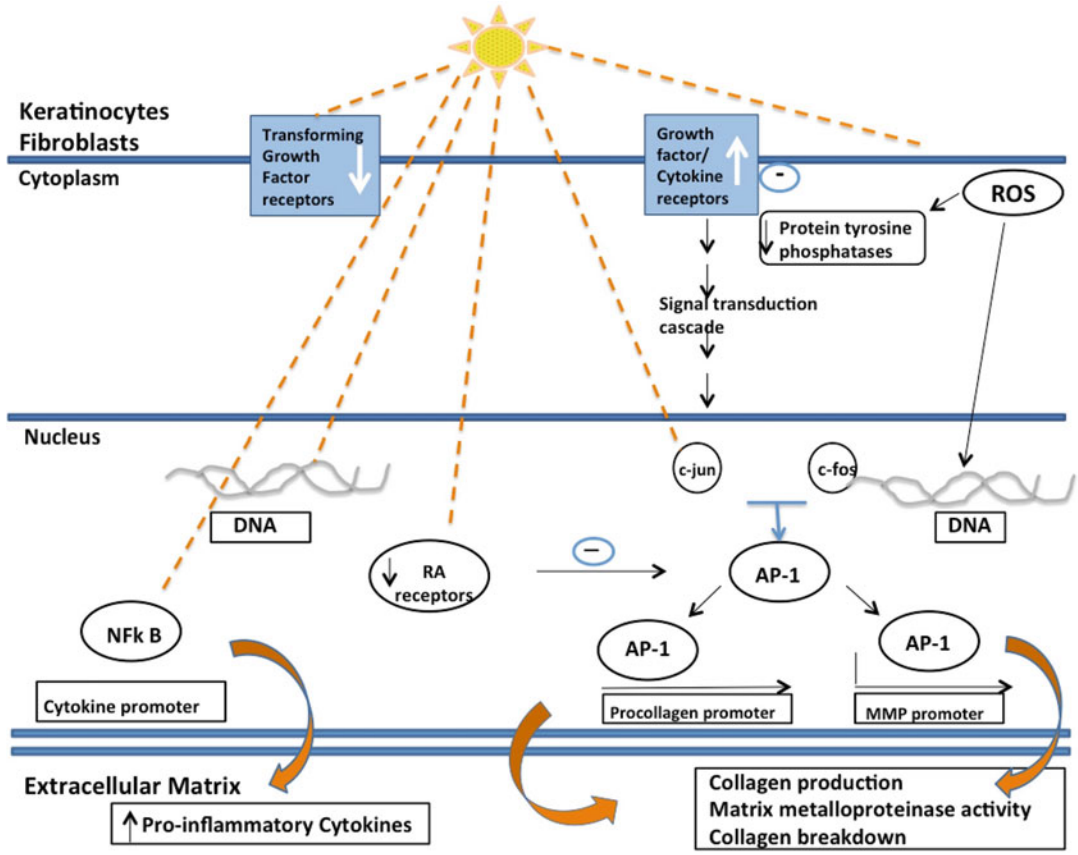

Fig. 1 Molecular cascade in the skin following UVR via AP-1 and NFk B (Adapted from Rabe et al. 2006)

remodeling and dermal repair (Rivera 2008). Nonenergy-based treatments include chemical peels, dermabrasion, intradermal injection of growth factors from autologous platelet-rich plasma, fibroblast, and, more recently, stem cell transfer. However, the energy-based devices, which selectively target skin chromophores, have become the preferred treatment modality for many skin conditions including pigmented lesions, telangiectasias, skin laxity, lines and wrinkles, as well as surgical scars, atrophic acne scars, and stretch marks. The energy-based systems include the full spectrum of ablative and non-ablative lasers, intense pulsed light systems, a variety of radiofrequency devices, and high-intensity focused ultrasound systems.

The focus of this chapter will be the full spectrum of non-ablative lasers that are used for photorejuvenation.

History of Non-ablative Lasers

The myriad applications of lasers in dermatology burgeoned with the milestone publication by Anderson and Parrish on selective photothermolysis in 1983 (Anderson and Parrish 1983).

Since then, over the last 30 years, there has been a tremendous evolution in laser technology and design, allowing better control of laser parameters and a consequent increase in safety and efficacy of laser treatments.

Non-ablative lasers are of two types: non-fractional or conventional lasers that act on the entire surface area of the skin and fractional technologies that produce only small columns of thermal injury interspersed among predominantly intact skin.

Historically, the use of lasers in the management of photoaged skin began with the introduction of fully ablative skin resurfacing procedures. The mid-1990s saw the introduction of the carbon dioxide (CO_2) and erbium-doped:yttrium-aluminum-garnet (Er:YAG) lasers (Alster 1999). These high-energy pulsed devices create full-thickness wounds and yield impressive clinical outcomes (Alster and West 1996). To date, full resurfacing remains the gold standard for photodamaged skin. However, the procedure is associated with prolonged recovery and poor patient tolerability.

In the late 1990s, Hsu and his colleagues first described non-ablative dermal remodeling due to an incidental observation of the reduction of wrinkles in areas treated with the conventional pulsed dye laser (PDL) for telangiectasias (Hsu et al. 2005). Hence, this led to a move toward minimally invasive procedures, giving rise to a generation of non-ablative resurfacing lasers such as the 1450-nm diode, 1064-nm and 1320-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers, and 1440-nm, 1540-nm, and 1550-nm erbium-glass lasers (Tanzi and Alster 2004). However, this first generation of non-ablative systems showed only moderate efficacy. In 2004, the introduction of fractional photothermolysis (FP) by Manstein and his colleagues (2004) revolutionized the field of laser skin resurfacing and has resulted in the development of numerous non-ablative and ablative fractional laser devices. The popularity of these technologies is due to their ease of operation, lower risk of side effects, good patient tolerability, and relatively quick patient recovery. It is widely accepted that the fractional ablative lasers offer superior efficacy in terms of skin rejuvenation; however, the gentler fractional non-ablative lasers have the advantage of quicker healing and reduced downtime. An increased number of treatment sessions with the non-ablative lasers may ultimately result in equivalent efficacy to ablative lasers.

Non-ablative Laser Photorejuvenation Mechanism of Action

Photorejuvenation consists of two essential factors:

1. *The removal of epidermal signs of photodamage by selective photothermolysis*

   Microscopic structures such as blood vessels and pigmented cells are photocoagulated by selectively absorbed photons of light, hence resulting in the attenuation of solar lentigines, ephelides, and telangiectasias.

   Laser energy absorbed by oxyhemoglobin results in erythrocyte coagulation and the destruction of ectatic vessels. This has been demonstrated by the histological examination of port wine stains after pulsed dye laser. Fibrin, thrombin, and agglutinated red blood cells have been found in the superficial dermal blood vessels (Stratigos and Js 2000). As a consequence, neovascularization occurs with replacement of the destroyed abnormal vessels.

   The precise molecular events involved in the destruction of melanosomes by lasers are unknown (Santiagos et al. 2000), but it is believed that both photothermal and photomechanical mechanisms are responsible (Ara et al. 1990). A sudden rise in temperature results in the vaporization and expansion of target tissues with the consequent destruction of pigmentary lesions. Clinically, frosting is observed immediately after pulsed lasers. This serves as a treatment endpoint and is proposed to be due to the formation of gas bubbles following a sudden increase in temperature of the target tissue (Santiagos et al. 2000). Histologically, destroyed melanosomes, vacuolization, and pigment leakage from cells have been shown (Dover et al. 1989a).
2. *Dermal remodeling resulting from patterns of microscopic thermal injury to the dermis*

   The reduction in fine lines and wrinkles and overall improvement in skin texture and tightening are due to new collagen formation and dermal thickening. The mechanism of dermal remodeling by non-ablative lasers centers upon

the fact that the non-ablative resurfacing laser wavelengths are absorbed to varying extents by intradermal water. Hence, this results in thermal injury to the dermis that is dependent upon both the amount of energy delivered and the exposure duration. A critical intradermal temperature of 60–80 degrees is required for effective denaturation of collagen and initiation of the wound healing response (Paul et al. 2011). Temperatures above this range can lead to complete denaturation of collagen and result in scarring.

The non-ablative lasers treat photodamaged skin without physically removing or vaporizing the skin as opposed to ablative procedures that literally vaporize a fraction or all of the epidermis and layers of the dermis. All of these lasers selectively utilize technology to cool and protect the epidermis while creating controlled thermal injury to dermal structures.

Non-ablative Nonfractional Lasers

The first generation of non-ablative conventional laser modalities entered the market in the late 1990s primarily for the use of skin rejuvenation. These included lasers that emit light in the visible, near-infrared, and far-infrared spectrum (Table 1). This diverse group of laser technologies includes the potassium titanyl phosphate (KTP; 532 nm), pulsed dye (PDL; 585 nm, 595 nm,), Q-switched (QS) ruby (694 nm), QS alexandrite (755 nm), long-pulsed and QS Nd:YAG (1064 nm), long-pulsed Nd:YAG (1320 nm), long-pulsed diode (1450 nm), and erbium-glass (1440 nm and 1540 nm) lasers.

Table 1 Non-ablative nonfractional lasers for skin rejuvenation

Visible light lasers	Near-infrared lasers	Mid-infrared lasers
532-nm KTP 585-/595-nm pulsed dye 694-nm Q-switched ruby 755-nm Q-switched nanosecond and picosecond alexandrite	1064-nm long-pulsed and Q-switched nanosecond and picosecond Nd:YAG	1320-nm Nd:YAG 1450-nm diode 1540-nm erbium-glass

Wavelengths within the visible light spectrum and specifically the QS lasers are mainly indicated for skin dyschromias, whereas the longer wavelength near-infrared and mid-infrared lasers are better suited for dermal remodeling.

Although the reversal of epidermal dyschromias with the nonfractionated devices is relatively effective and predictable, the improvement in skin texture is much more subtle. Hence, non-ablative nonfractional skin resurfacing is ideal for the patient with mild to moderate photodamage and early signs of skin aging.

Visible Light Lasers

These include the 532-nm KTP, 585-/595-nm pulsed dye, 694-nm Q-switched ruby, and Q-switched 755-nm alexandrite lasers.

These visible light lasers are commonly used to treat vascular and pigmented lesions since their wavelengths are well absorbed by the various chromophores in the skin, such as oxyhemoglobin and melanin. The lasers improve skin color by reducing dyschromias including solar lentigines, ephelides, telangiectasias, and generalized erythema. The visible light spectrum lasers should be used with great caution in darker skin types due to the risk of thermal damage of these shorter wavelengths.

An improvement in skin texture has also been repeatedly demonstrated with the visible light spectrum lasers. The absorption of the 585-nm wavelength by oxyhemoglobin results in a thermal insult to the microvasculature and hence initiates an inflammatory response that stimulates fibroblast activity and ultimately dermal collagen synthesis. Bjerring et al. showed a 48% increase in type II collagen synthesis only 2 weeks after a single session of pulsed dye laser (Bjerring et al. 2002). Orringer et al. reported an increase in dermal remodeling due to an increase in type I procollagen mRNA, and Zelickson et al. also showed that only one pass with the 595-nm pulsed dye laser was sufficient

to improve dermal collagen (Orringer et al. 2005; Zelickson et al. 1999).

Potassium Titanyl Phosphate Laser 532 nm (Cynosure MedLite C6, RevLite S1, and PicoSure; Syneron-Candela Alex TriVantage; Alma Harmony XL Pro)

Current Q-switched KTP lasers include those in the 5–15 ns range and the novel 350 picosecond lasers. The devices incorporate an Nd:YAG (1064 nm) laser as the main source of light that is converted by a KTP crystal to emit the halved wavelength of 532 nm. This green light is well absorbed by hemoglobin and melanin; hence, the KTP can be used for the treatment of both unwanted vessels and pigment. The short wavelength of the KTP laser is very well absorbed by epidermal melanin; hence, caution should be exercised in darker skin types (Weiss et al. 2005). The KTP laser has only mild effects on the improvement of skin texture (DeHoratius and Dover 2007).

The 532 KTP laser has interestingly been used for lip color lightening, which is a common concern of darker-skinned individuals (Somyas et al. 2001).

Pulsed Dye Laser 580–595 nm (Syneron-Candela VBeam)

In the flashlamp-pumped pulsed dye, a flashlamp is used to excite electrons in an organic dye, rhodamine, to emit light of yellow color. The original pulsed dye lasers had a wavelength of 577 and pulse duration of 0.45 milliseconds, which resulted in intravascular thrombosis of small vessels and purpura. Hence, the current pulsed dye systems have wavelengths between 585 and 595 nm and pulse duration of up to 40 milliseconds. The longer wavelengths penetrate deeper into the skin, and the longer pulse durations allow for avoidance of purpura. Apart from the effect on vascular lesions, pulsed dye lasers do afford moderate skin rejuvenating effect (Bjerring et al. 2002).

Q-Switched Ruby Laser 694 nm (Alma Lasers, Sinon)

The QS ruby laser emits red light and is hence not absorbed by hemoglobin but selectively targets melanin. It was, in fact, the first Q-switched laser developed for epidermal and dermal pigmented lesions. The very short, 20–50 ns, pulse durations of the ruby laser selectively target melanosomes, resulting in the photoacoustic destruction of the melanosome cell membrane. This effect is pulse width dependent with shorter pulse durations being more effective in melanosome destruction (Polla et al. 1987; Dover et al. 1989b). Caution must be exercised as darker phototypes may develop permanent hypopigmentation (Rinaldi 2008; Kishi et al. 2009).

QS Alexandrite 755 nm (Cynosure Accolade, Syneron-Candela Alex TriVantage, and PicoWay)

The QS alexandrite laser, emitting light within the red spectrum and with pulse widths of 50–100 ns, selectively targets pigmented lesions by causing the photoacoustic disruption of melanin.

A new picosecond QS alexandrite laser has recently been introduced on the market, and, thus far, most of the studies with this novel device have been on its use in the treatment of tattoos. However, the device shows promise in the effective treatment of pigmented lesions. A recent publication has demonstrated the 755-nm ultrashort-pulsed 550 picosecond alexandrite laser with diffractive lens array to be an effective option for rejuvenation of the photodamaged décolletage (Wu et al. n.d.).

Near-Infrared Lasers

1064-nm Long-Pulsed and QS Nd:YAG Lasers (Palomar QYAG5, Syneron-Candela Alex TriVantage; Alma Harmony XL Pro)

Both the long-pulsed and QS Nd:YAG (1064-nm) lasers in the mid-infrared spectrum are used for photorejuvenation. The incidental rejuvenating effect of long-pulsed lasers including the Nd:YAG 1064-nm laser commonly used for other indications including hair removal and treatment of larger caliber blood vessels was recognized early on. This near-infrared wavelength is absorbed by water in the skin and hence effectively heats the dermis. The resultant thermal injury to the dermis leads to a

limited degree of neocollagenesis and skin tightening (Weng et al. 2011).

The long-pulsed Nd:YAG laser handpiece may be used in constant motion, delivering multiple passes to the surface of the skin until a surface temperature of 39–42 degrees is attained. This is the optimal temperature range for dermal remodeling. Above this temperature, dermal scarring may occur. Hence, prior to treatment with this laser for rejuvenation, patients should not receive any anesthetic, as excessive pain must be reported to alert the practitioner and avoid epidermal injury. Patients treated with long-pulsed Nd:YAG for rejuvenation exhibited a decrease in rhytids (Hong et al. 2015).

The QS Nd:YAG with pulse durations of 5–15 ns, principally used for the treatment of tattoos and disruption of melanin in pigmented lesions, may also be used in an in-motion manner, continuously treating the skin. Treatments may be performed with or without the application of topical carbon solution, which is believed to improve the penetration of the laser beam. A split-face study by Lee et al. demonstrated significant improvement in rejuvenation effects after QS Nd:YAG with no difference in improvement in skin texture after the application of topical carbon solution (Lee et al. 2009). However, skin rejuvenation treatments with the QS Nd:YAG were associated with a high degree of postinflammatory hyperpigmentation at the 1-month follow-up evaluation (Jun et al. 2014). Recently, picosecond Nd:YAG lasers in the 500–750 ps range have developed for the removal of pigmented lesions. To date, no studies have been published on the use of picosecond Nd:YAG laser system for pigmented lesions or skin rejuvenation.

Mid-Infrared Lasers

1320-nm Nd:YAG (Cooltouch CT3 Plus, Alma Harmony XL)

This wavelength is well absorbed by water and effectively heats the treated dermis. The ensuing thermal injury results, to a limited extent, in the stimulation of fibroblasts and the induction of "neocollagenesis." Studies have shown an elevation in basic fibroblast growth factor (bFGF) and histological evidence for a reduction in skin aging by the stimulation of type I, III, and VII collagen (Zhenxiao et al. 2011; El-Domyati et al. 2011).

1450-nm Diode Laser (Candela Smoothbeam)

The mechanism of action of the 1450-nm diode laser is similar to the 1320-nm Nd:YAG. This mid-infrared wavelength creates wounding of the dermis due to its high water absorption coefficient, but the 1450-nm laser has been shown to be more effective in inducing neocollagenesis than the 1320-nm wavelength (Alster et al. 2007).

1540-nm Erbium-Glass Laser (Quantel Aramis)

The mid-infrared 1540-nm laser, which also targets intracellular water, penetrates into the papillary dermis where collagen tightening and neocollagenesis are achieved. This allows for more effective treatment of solar elastosis.

The 1540-nm wavelength is only minimally absorbed by melanin; hence, it is safe for use by darker phototypes.

This laser has been used for the treatment of fine lines, wrinkles, and acne scars. Evidence for dermal remodeling with the 1540-nm laser has been demonstrated by histologic studies as well as ultrasound and profilometric analysis. A 40% reduction in wrinkles and 17% increase in skin thickness were shown after the fourth week of treatment (Fournier et al. 2002; Lupton et al. 2002).

Non-ablative Fractional Lasers

Concept of Fractional Photothermolysis

Fractional photothermolysis (FP), first introduced by Manstein and colleagues in 2004, is one of the most significant milestones in laser technology and resurfacing (Manstein et al. 2004). It has led to a new era in the application of lasers in dermatology and resulted in a tremendous development in fractional laser technology and numerous commercial fractional systems. Fractional lasers have now become the laser modality of choice in the

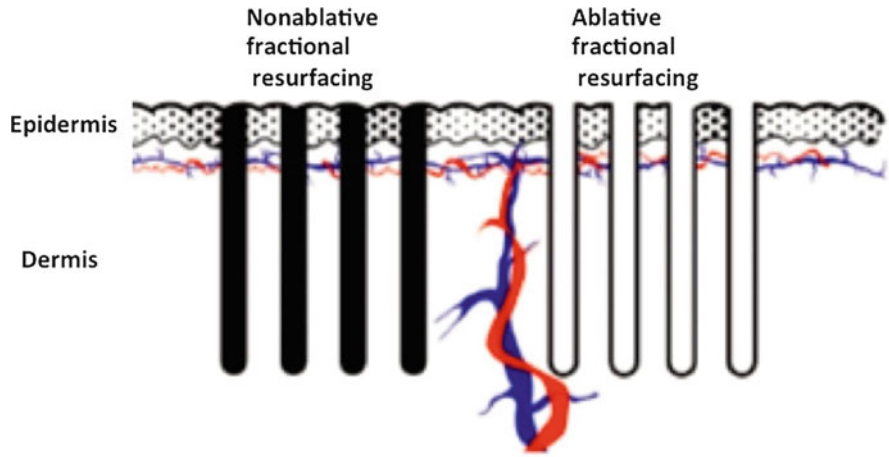

Fig. 2 Schematic representation of mode of action of fractional non-ablative and ablative resurfacing

management of photodamaged skin (Saedi et al. 2012) . These devices bridge the gap in terms of efficacy between the traditional ablative and non-ablative lasers (Alexiades-Armenakas et al. 2012). They are less aggressive than traditional ablative lasers and offer superior clinical outcomes to the non-ablative systems but with the same level of safety. As opposed to the conventional ablative and non-ablative lasers that produce layers of thermal heating, fractional lasers thermally denature only fractions of the skin.

They create micro-columns of thermal injury referred to as microthermal or microscopic treatment zones (MTZs) (Geronemus 2006). MTZs are typically 70–150 μm wide and extend vertically from the epidermis to the dermis at varying depths of approximately 400–700 μm, determined by several laser parameters including laser output energy (Gold 2010). Fractional devices spare skin and stem cells in between the MTZs and hence allow for rapid recovery and increased safety (Fig. 2).

There are basically two types of fractional laser devices: non-ablative and ablative, classified according to the type of MTZs that they produce (Fig. 2). Non-ablative fractional lasers (NAFLs) simply cause thermal injury to the dermis while sparing the epidermis, whereas the ablative fractional lasers (AFLs) vaporize micro-columns of epidermis and dermis (Alexiades-Armenakas et al. 2008). The histologic changes due to non-ablative fractional photothermolysis (NAFP) and ablative fractional photothermolysis (AFP) are shown in Figs. 3 and 4.

The repair of treated skin begins by the extrusion of columns of necrotic skin, known as microscopic epidermal necrotic debris (MENDs), into the stratum corneum (Manstein et al. 2004). Manstein and colleagues (2004) showed that MENDs are button-shaped structures (40–80 μm diameter) that contain melanin and form beneath the stratum corneum above each dermal wound. The production of MENDs indicates the participation of intact keratinocytes, from uninjured skin, in the process of wound repair (Manstein et al. 2004). MENDs seen in histology correspond to the brown spots observed via epiluminescence microscopy, and these are shed from the epidermis within 7 days of FP (Manstein et al. 2004) (Fig. 5). This extrusion process of cellular debris was confirmed by Hantash et al. (2006) who used anti-human elastin antibody to demonstrate the transdermal elimination of MENDs. Manstein and colleagues (2004) showed clear evidence of epidermal repair within the papillary and superficial reticular dermis as demonstrated by increased mucin content as well as an increased undulation in the rete ridge pattern of treated skin at 3 months posttreatment (Fig. 6) (Laubach et al. 2006).

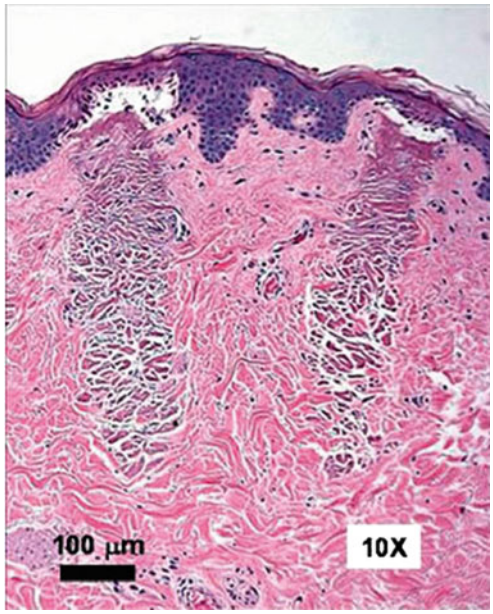

Fig. 3 Histologic slide of human skin after NAFP (1550-nm erbium laser) demonstrating two columnar microlesions extending from the epidermis to the dermis (depth, 560 µm; width, 135 µm) (Adapted from Alexiades-Armenakas et al. 2012)

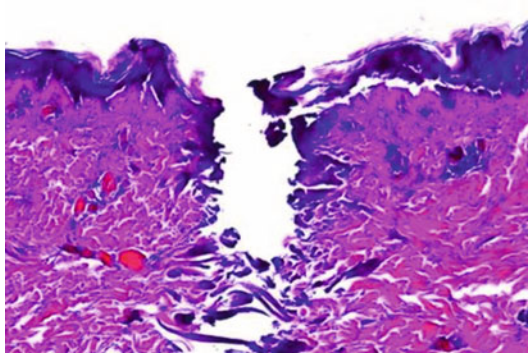

Fig. 4 Histologic slide of human skin after AFL (2940-nm erbium laser) demonstrating a column of ablation extending from the epidermis to the dermis. (Adapted from Geronemus 2006)

Types of Non-ablative Fractional Lasers

All of the non-ablative fractional lasers emit wavelengths in the mid-infrared range that correspond to peaks on the water absorption curve. By virtue of the mechanism of action of the fractional device, whereby only small fractions of the skin are resurfaced in each treatment session, typically 4–6 treatment sessions are required to attain a positive clinical outcome in the treatment of photodamaged skin. The treatment is relatively painful, requiring a combination of topical anesthetic creams and cryoanesthesia. Posttreatment edema and erythema is noticeable for 48 h, followed by skin desquamation over a few days.

1550-nm (Solta Fraxel Re:store, Solta Fraxel Re:store Dual) and 1540-nm (Palomar Starlux, Artisan, Icon) Erbium-Glass Lasers

The first NAFL device to be developed in 2004 was the 1550-nm erbium-glass laser that targets water as a chromophore (Geronemus 2006). The device is tunable such that the density of the MTZs and the energy can be adjusted. Most of the studies on NAFLs were performed with this device (Tierney et al. 2009).

The initial clinical studies by Manstein et al. (2004) demonstrated significant improvement in skin periorbital lines and wrinkles. Many other investigators consistently showed evidence of collagen remodeling as improvements in skin texture and color. The initial results continued to improve over 6–9 months posttreatment (Rahman et al. 2006; Wanner et al. 2007). Non-facial areas are also effectively treated with this NAFL device. A study by Jih et al. (2008) on the hands of ten patients showed 51–75% improvement in pigmentation and 25–50% improvement in skin texture at 3 months. DeAngelis et al. reported good efficacy of the erbium-glass laser in the treatment of striae rubra and alba ranging in maturation age from 1 to 40 years (de Angelis et al. 2011).

Wanner et al. showed fractional photothermolysis for the treatment of facial and non-facial cutaneous photodamage using a 1550-nm Er-glass fiber laser to be a useful NAFL treatment (Wanner et al. 2007).

The upgraded version of this laser, the Fraxel Dual, has a dual wavelength of 1550-nm erbium with a 1927-nm thulium laser on one platform, allowing the operator to target different treatment depths. After a single treatment with the thulium laser, a mean of 69% of subjects at 1 month

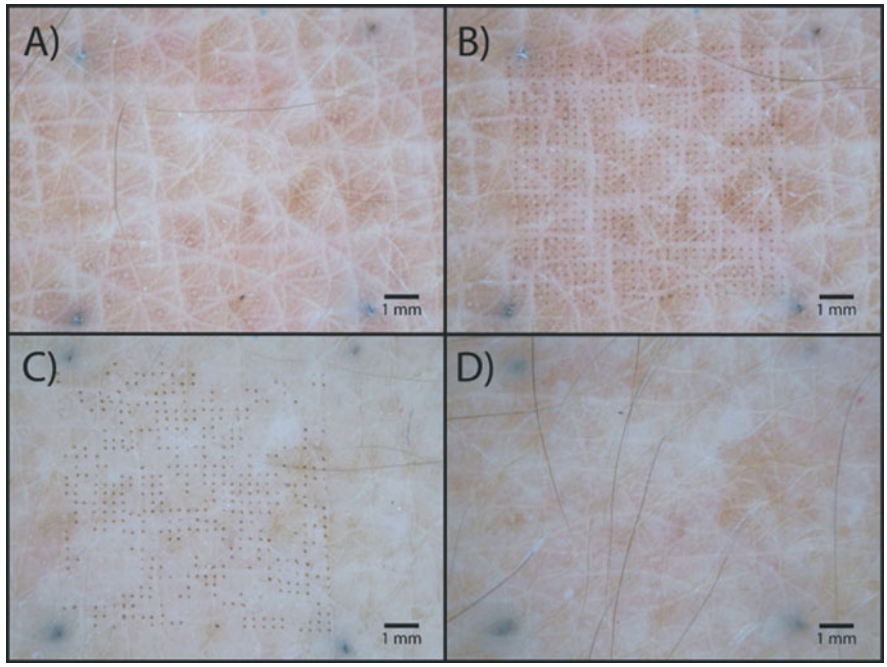

Fig. 5 Cross-polarized photomicrographs showing surface healing of forearm skin following FP: (**a**) pretreatment, (**b**) 1 day posttreatment, (**c**) 1 week posttreatment, (**d**) 3 months posttreatment. Individual brown spots are visible at 1 day and begin to slough by 1 week (Adapted from Manstein et al. 2004)

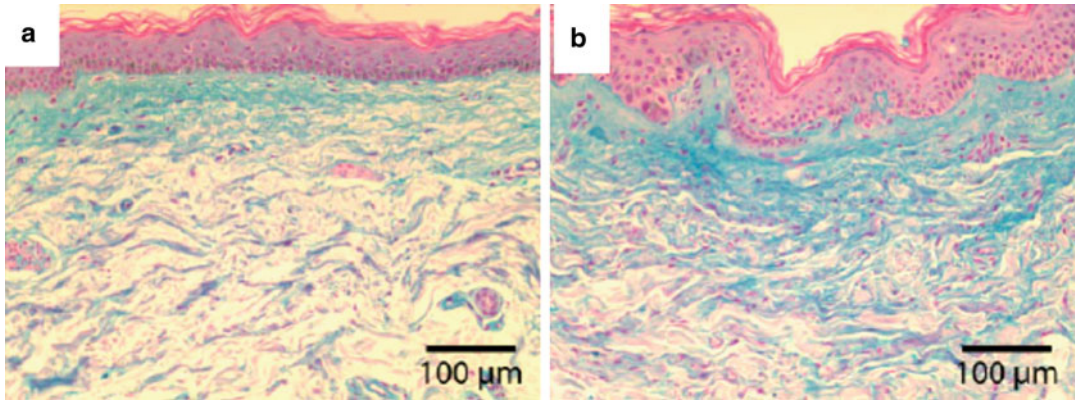

Fig. 6 Histology of forearm skin: (**a**) pretreatment and (**b**) 3 months following FP demonstrating increased mucin content in the superficial dermis and enhanced rete ridge patterning (Adapted from Manstein et al. 2004)

demonstrated a very significant improvement in lentigines and ephelides (Brauer et al. 2014). Hence, superficial treatment of pigmented lesions can be achieved with the 1927-nm wavelength, and collagen remodeling is achieved with the deeper penetrating 1550-nm wavelength.

1440-nm Nd:YAG Laser (Cynosure Affirm) and 1440-nm Diode (Solta Clear + Brilliant)

Fractional devices that deliver 1440-nm wavelengths include the Nd:YAG and diode laser. The cynosure device allows for uniform distribution

of the energy across the skin surface, at depths of 300 um, via combined apex pulse (CAP) technology.

Clinical studies with both devices have shown them to be only moderately effective in the remodeling of scars and treatment of photoaged skin (Marmon et al. 2014; Geraghty and Biesman 2009).

Hence, manufacturers have upgraded the original systems to include dual wavelengths. The cynosure system offers the multiplex technology that combines a 1320-nm wavelength with a 1440-nm laser, allowing for penetration to depths of 1000–3000 um. The 1320-/1440-nm multiplex system resulted in greater skin tightening at 6 months than the 1440-nm laser alone (Geraghty and Biesman 2009).

A new version of the Clear + Brilliant, known as the Clear + Brilliant Permea, includes both diode and thulium media, hence offering both 1440-nm and 1927-nm wavelengths.

1565-nm Erbium-Doped Laser (Lumenis ResurFx)

This wavelength has a slightly lower absorption coefficient for water than that of 1550 nm which results in greater skin penetration. The system uses a sequential scanning system that allows for a variety of shapes, densities, and patterns of distribution of energy. It is also equipped with contact cooling for greater patient comfort. To date, there are no published studies demonstrating the relative advantage of this laser system over the established fractional near-infrared devices (Sadick 2014).

1940-nm Alexandrite Fractional Laser (Syneron-Candela)

This is a relatively novel thulium rod pumped by a pulsed alexandrite laser emitting a wavelength of 1940 nm, which corresponds to one of the water absorption peaks in the mid-infrared range. However, the absorption of this wavelength is much stronger than the other mid-infrared wavelengths (1400–1550) and weaker than the ablative wavelengths (Er: YAG and CO_2). A recent study demonstrated the skin rejuvenating effects of the 1940-nm fractional device. Patient ($n = 11$) received a total of three facial treatments, 4–6 weeks apart, and outcome assessments were made 3 months after the final treatment. Several parameters were evaluated and the results showed a 21% reduction in pigmentation, 14.3% in rhytids, 8.9% in skin laxity, and 22.3% in solar elastosis (Miller et al. 2014).

1064-nm Fractional QS Nd:YAG laser (Alma ClearLift on Harmony XL Pro)

This is a relatively new addition to the arsenal of NAFR lasers that has gained popularity. The 1064-nm laser beam is fractionated by a passive optical element into a 5 × 5 matrix of 25 microscopic perforations, each having a diameter of 200 um. Each pixel receives an energy density in the range of 6–13 J/cm^2. A series of five different focusing tips allow for penetration of the QS nanosecond pulses to tunable depths, selected according to the depth of the pathology being treated. The rapid laser pulses spare the epidermis, and, furthermore, since the 1064-nm wavelength is poorly absorbed by melanin and hemoglobin, the pixels penetrate up to 3 mm into the papillary and reticular dermis. Paasche, at the 2014 American Society of Lasers in Medicine and Surgery meeting, presented histological evidence of microthermal injury deep into the reticular dermis (Paasch 2014). This is advantageous, since we now know that to achieve skin firmness, penetration to deeper levels is required.

Recently, a high-speed roller has been released, known as the iPixel Scan, which allows for efficient and fast treatment of off-the-face areas such as photodamaged hands, arms, décolletage, and legs.

A pilot study by Luebberding and Armenakas (2012) showed an 11% improvement in superficial rhytids on the face and neck following a series of three treatment sessions at 2–4 week intervals. Gold et al. (2014) investigated the effect of the fractional QS 1064-nm laser on several skin parameters. Patients received a total of four treatment sessions at 2–4 week intervals with a follow-up at 3 months post last treatment. They reported an improvement of 70% in hyperpigmentation, 80% in telangiectasias, 80% in skin laxity, and 60% each in tactile roughness and actinic

keratoses. A further advantage of the treatment was found to be the fact that the treatment is relatively pain-free, at a level of 0–2 on a ten-point scale, and has absolutely no downtime.

General Clinical and Treatment Considerations in Non-ablative Resurfacing

Patient Selection

Non-ablative resurfacing is contraindicated during pregnancy, lactation, and in patients who have a history of keloid formation or those that have an active infection. Patients who are on isotretinoin can only be treated 6 months after the completion of a course of treatment.

Ideal patients for non-ablative rejuvenation are those with early signs of photodamage. These are generally younger patients ranging from 35 to 50 years of age. Older patients with severe laxity and deep wrinkles will not benefit from non-ablative laser treatment and are candidates for ablative resurfacing (Fig. 7).

It is important to ensure that patients have realistic expectations and understand that skin rejuvenation with the non-ablative systems requires several treatment sessions.

Non-ablative resurfacing may be performed in patients of all skin types, but particular caution should be exercised when treating darker skin types. In these patients, visible light spectrum lasers that specifically target pigment must be used at conservative setting to avoid side effects such as hyper- or hypopigmentation, blisters, and scars. Although lasers in the near- and mid-infrared wavelengths are safer for darker-skinned individuals, caution must be exercised with respect to the settings. High laser fluences as well as cryogen cooling with some systems can lead to postinflammatory hyperpigmentation. This is usually transient and can be treated with bleaching agents.

Treatment Considerations

Pretreatment, the skin should be cleansed thoroughly to remove oil, makeup, and any debris that may impede the passage of the laser light.

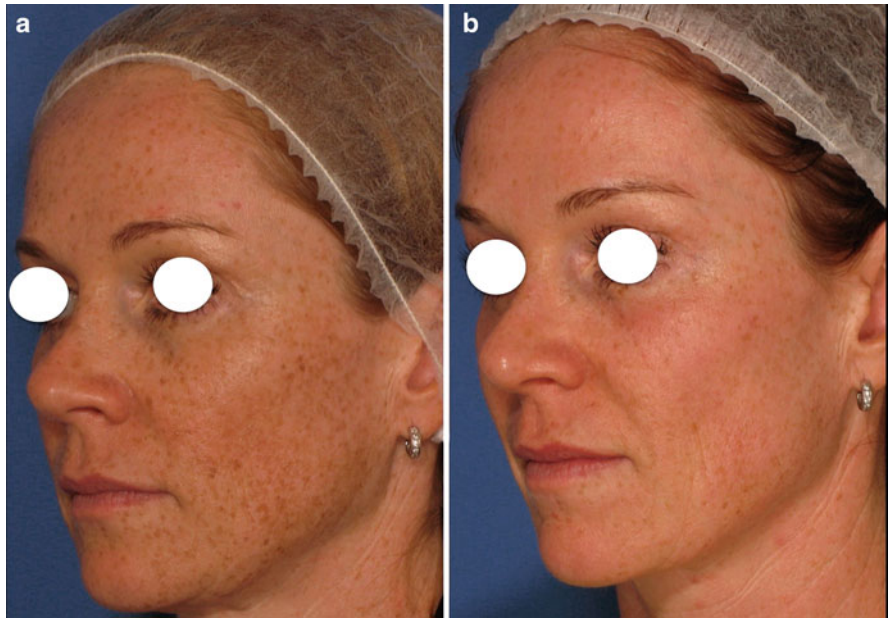

Fig. 7 Photodamaged patient treated with non-ablative system for photorejuvenation: (**a**) pretreatment and (**b**) posttreatment

Topical anesthesia is generally required with most of the non-ablative nonfractional and fractional lasers, the exception being the fractional Q-switched Nd:YAG device. Various formulations and strengths of topical anesthetic creams have been used, from 5% and up to 30% lidocaine. Fractional resurfacing with the mid-infrared laser treatments requires the more potent anesthetic formulations. There is some controversy regarding the application of topical anesthesia as, with some devices, patient feedback in terms of excessive pain is necessary to avoid epidermal injury.

The patient and all present in the laser room should wear protective eyewear as most of the wavelengths in the visible and near-infrared range pose a risk to the retina, whereas the wavelength in the mid-infrared range can damage the cornea.

Prophylactic treatment with oral antiviral medication is advocated to avoid a herpetic breakout, specifically in patients undergoing non-ablative fractional resurfacing.

Skin cooling during and posttreatment with the use of a cool air blower or ice application is required for patient comfort and to minimize posttreatment edema. Typically with the fractional non-ablative systems, edema and erythema resolve within 3 days. Patients are required to avoid the sun and apply sunscreen diligently to avoid the possibility of post-inflammatory hyperpigmentation. Additionally, in darker-skinned patients, bleaching creams are necessary posttreatment to minimize the possibility of complications.

Conclusion

Non-ablative laser treatments are ideal for the improvement of skin color, tone, and texture in relatively younger patients with skin textural imperfections associated with photoaging. These procedures have a unique role in treating skin dyschromias including vascular lesions in patients of all ages. Evidence is mounting that non-ablative lasers may also result in skin tightening; however, further studies are necessary to reinforce this theory (Gold et al. 2014; Kauvar 2014).

Non-ablative systems are often used as maintenance procedures following more aggressive ablative treatments. Furthermore, they play an important role in the prophylaxis of skin aging as they can be performed regularly with little or no downtime. Non-ablative lasers have been mainly used on facial skin; however, interest is rising in the role of these techniques on the neck, hands, arms, and other areas of the body.

Non-ablative skin resurfacing procedures produce excellent clinical outcomes with minimal risk and morbidity; hence, they are of particular importance in the treatment of photodamaged skin.

Take Home Messages

- The visible light spectrum non-ablative lasers, and in particular the Q-switched devices, are the lasers of choice for the treatment of pigmented lesions.
- The pulsed dye laser offers a unique modality for the elimination of vascular lesions such as telangiectasias and generalized erythema associated with photodamage.
- Non-ablative nonfractional skin rejuvenation offers only mild skin remodeling effects and is only suitable for patients with early signs of skin aging.
- Non-ablative fractional lasers produce impressive clinical outcomes in skin rejuvenation with respect to improvement in skin laxity and reduction in wrinkles.
- Non-ablative fractional lasers are associated with swift recovery, minimal complications, and little or no downtime.

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Non-ablative Lasers for Stretch Marks

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Abstract

Striae distensae (SD) or stretch mark (SM), a common skin condition, does not cause any significant medical problem; however, it can cause significant distress to those affected. They are dermatologic lesions, usually asymptomatic, that often arise as a result of mechanical stress, certain endocrine conditions, pregnancy (striae gravidarum), or prolonged exposure to steroids. It can be initially erythematous (striae rubra) but over the time become atrophic with a white color (striae alba). Although there is no "gold standard" treatment for stretch marks, various laser parameters alone or in association with other modalities of treatment have been studied. Over the years, the non-ablative fractional lasers have shown good clinical results and become very popular, especially because it is well tolerated and safe, even in patients with higher phototypes (IV E V). Post-inflammatory hyperpigmentation is the most common complication; however, it is transitory in most cases and its incidence is lower than with ablative lasers. This chapter will approach the use of non-ablative lasers for SD treatment.

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Keywords

Striae distensae • Stretch marks • Striae rubra • Striae alba • Non-ablative fractional laser • Ablative fractional laser • Intense pulsed light • Pulsed dye laser • Photothermolysis

Contents

Introduction

Striae distensae (SD), also known as stretch marks, striae atrophicans, or striae gravidarum, are common skin lesions, which can pose a significant psychological burden for patients. It was first histologically described in 1889 by Troisier and Menetrier, and until now it is a challenge in terms of treatment and prevention. (Troisier and Menetrier 1889). Striae distensae are dermatologic lesions that often arise as a result of mechanical stress (rapid weight change, puberty, pregnancy), certain endocrine conditions (like

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Cushing's syndrome and Marfan syndrome), or prolonged exposure to medications such as steroids, whether topical or systemic. (Hexsel et al. 2012).

It appears that the group at a highest risk of developing severe striae distensae is teenagers (Atwal et al. 2006). The prevalence is diverse between adolescence, pregnancy, and obesity groups and ranges from 43% to 88% and 6% to 86% in pregnant women and adolescent, respectively. Among obese individuals the prevalence reported is 43% (Al-Himdani et al. 2014). Elbuluk et al. observed interracial differences in the severity of SD and concluded that African-American women were more severely affected than white women within the same geographical region (Elbuluk et al. 2009). However, the authors also did note that there was a difference of body mass index and smoking status between the two groups, which may indicate that other factors aside from race could be involved (Al-Himdani et al. 2014).

Anatomical regions can vary depending upon sex and age. In adolescent males, the lower back and knees are usually affected, while in female subjects, the thighs and calves are more often involved. Striae gravidarum occur in more than 70% of pregnant women and are commonly found on the abdomen and breasts, usually developing after the 24th week of gestation (Atwal et al. 2006; Al-Himdani et al. 2014). They tend to appear symmetric and bilateral (Hanauer et al. 2011) and are usually asymptomatic, but in the early stages can cause some itch (Hexsel and Dal'Forno 2013).

Striae distensae are linear atrophic scars, most often initially erythematous (striae rubra) but can also have different colors such as purple and blue and then over the time become atrophic and hypopigmented and attain a white color (striae alba) (Alves et al. 2015; Malekzad et al. 2014). Hermanns and Piérard described two additional types of SD, striae nigrae and striae caerulea, which occur in those with darker skin due to increased melanization (Hermanns and Piérard 2006). The color of the SD is related to the stage of evolution and to melanocyte mechanobiological influences (Al-Himdani et al. 2014).

Pathogenesis

A positive family history is an important risk factor. In adolescents body mass index, childhood obesity, and seborrhea and atopic dermatitis are also reported as influences of developing SD. On the other hand, risk factors in pregnant women may be constitutional or pregnancy related. Constitutional factors include maternal age, smoking, and body mass index. Younger women are more likely to develop SD, implicating a constitutional difference in the stretching ability of the skin. Pregnancy-related factors such as birth weight, gestational age, weight gain, and polyhydramnios support the theory that changes associated with pregnancy can play a role in the developing of SD. Others risk factors include medical conditions such as Marfan syndrome, Cushing syndrome, anorexia nervosa, typhoid fever, rheumatic fever, chronic liver disease, surgery and medications like systemic and topic corticosteroids, HIV therapy, chemotherapy, tuberculosis therapy, contraceptives, and neuroleptics (Al-Himdani et al. 2014).

The pathogenesis of striae is still unknown but probably relates to changes in the components of extracellular matrix, including fibrillin, elastin, and collagen (Singh and Kumar 2005). There are three main theories relating to SD formation that have been described: mechanical stretching of the skin, hormonal changes, and innate structural disturbance of the integument. Mechanical stretching of the skin is postulated due to perpendicularity of SD to the direction of the skin. Hormonal alterations in adrenocorticotrophic hormone and cortisol are thought to promote fibroblast activity, leading to increase protein catabolism and thus decreasing deposition of collagen in the substance of the dermal matrix (Al-Himdani et al. 2014; Khater et al. 2016).

Pregnancy-related hormones are also believed to influence SD formation. Cordeiro et al. described increased estrogen and androgen receptors in the skin exhibiting SD compared with normal skin (Cordeiro et al. 2010). Lower serum relaxin levels were demonstrated in pregnant women with SD compared with those without SD at 36 weeks gestation. SD may also present

altered gene expression, in similar way to keloid disease and scleroderma, which are thought to develop due to disordered gene expression of extracellular matrix (Al-Himdani et al. 2014).

Striae rubra and alba are distinct forms of SD. Their distinction has therapeutic implications (Al-Himdani et al. 2014). Usually the lesion matures from rubra to alba in several steps similar to those of the wound repair mechanism from wounding to scar formation (Ryu et al. 2013; Ud-Din et al. 2016). In early lesion development, there is a deep and superficial perivascular lymphocytic infiltration with edema, vascular ectasia, and possible angiogenesis (Alves et al. 2015; Ryu et al. 2013). On electron microscopy, early histological dermal alteration may be visualized by mast cell degranulation and macrophage activation with release of enzymes such as elastases, which leads to elastolysis of the mid-dermis (Sheu et al. 1991). Inflammation resolves over time, but collagen bundles in the reticular dermis stretch parallel to the skin, resulting in flattening of the epidermis and elongation of rete ridges, absence of hair follicles, and reduction of melanocytes leading to leukoderma, followed by loss of collagen and elastic fibers in the substructures (Al-Himdani et al. 2014; Ryu et al. 2013).

Therapeutic Assessment

Because of the prevalence of SD and its impact on quality of life of patients, there is substantial demand for a reliable treatment option.

Although there is no "gold standard" treatment for stretch marks, various modalities of treatment have been tried. Not only outcome depends on the type of SD but also the patients' Fitzpatrick skin type is important as well, since most of adverse effects, particularly with laser, occur in patients with darker skin type (Al-Himdani et al. 2014).

There are a number of treatment options including topical agents, acid peels, microdermabrasion, radiofrequency, needling, and lasers and light therapies described in literature.

Topical agents such as tretinoin thought to work through its affinity for fibroblasts and induction of collagen synthesis, and it has good efficacy in striae rubra, but poor and unpredictable responses in striae alba. Therefore, it offers only modest benefit in the early stages of the clinical course. Topical creams, lotion, and ointments are used especially in pregnant women at risk of developing SD, but has no statistically significant evidence to support their use for prevention of SD according to a Cochrane review in 2012 (Brennan et al. 2012). Acid peel treatments such as glycolic acid and trichloroacetic acid are thought to act by increasing collagen synthesis. Microdermabrasion, which is a skin resurfacing technique, has been reported to increase type I collagen with a better efficacy on striae alba (Al-Himdani et al. 2014; Aldahan et al. 2016) (see chapter ▶ "Microneedling for Transepidermal Drug Delivery on Stretch Marks"). Treatment with skin needling might be able to induce more collagen and elastin deposition beneath the epidermis as microneedling radiofrequency which can induce growth factor secretion by delivering higher volumetric heating and deeper heat diffusion (Khater et al. 2016; Ryu et al. 2013). However, all of these treatments have inconsistent clinical outcomes (Aldahan et al. 2016).

Lasers and light therapies offer a variety of wavelengths that can target specific chromophores at varying fluences. This poses a theoretical advantage by allowing individualized treatments. Some wavelengths target blood vessels in striae rubra to reduce the appearance, and others induce collagen and elastin production in mature striae. Among the wavelengths that have been studied for striae distensae UVB, UVA, excimer laser (308 nm), intense pulsed light (565, 590, 645, 650 nm), copper bromide (577 nm), pulsed dye laser (585, 595 nm), infrared, Nd:Yag (1064 nm), diode (1450 nm), Er:Glass (1540, 1550, 1565 nm), Er:Yag (2940 nm), and CO2 (10,600 nm) are included (Aldahan et al. 2016).

Ablative fractional lasers and intense pulsed light (IPL) represent emerging therapies that have demonstrated some success (Aldahan et al. 2016). Non-ablative lasers have been studied in the treatment of SD as well.

The 308 nm excimer laser is an ultraviolet laser and has been used to treat SD with improvement

of the pigmentation on mature white striae, but the studies shown that this pigmentation is only temporary requiring many treatment sessions before significant improvement can be seen.

Pulse dye laser (PDL) can also be indicated. It is commonly used for striae rubrae, treatment, as its target is dilated blood vessels (Aldahan et al. 2016, Al-Himdani et al. 2014). Similar to pulsed dye laser, Nd:Yag laser can be used to improve striae rubra, but does not have the same result in striae alba (Aldahan et al. 2016).

The intense pulsed light is characterized by the emission of incoherent light, pulsed, and broad spectrum (515–1200 nm). It is used to treat vascularization of rubra striae, but some studies also show clinical improvement and increased thickness of the collagen in striae alba. Repeated sessions may be required to maintain positive effects (Aldahan et al. 2016, Al-Himdani et al. 2014).

There are two types of fractional lasers used in the treatment of striae distensae: ablative and non-ablative. Fractional treatment is achieved through a pattern of microscopic thermal zones (deliver light energy into the tissue through multiple microscopic columns surrounded by untreated areas) produced by the laser beams at specific depths in the dermis. Fractional photothermolysis stimulates the epidermal turnover and dermal collagen remodeling (Mattos and Jordão 2012).

Ablative lasers use long wavelengths to target water in the epidermis and dermis, thereby vaporizing the cells. Available lasers in this category that have been studied for treating SD include the CO2 and Er:Yag (see chapter ▶ "CO_2 Laser for Stretch Marks"). These techniques provide immediate tissue tightening and induce more collagen stimulation than non-ablative lasers. On the other hand, non-ablative fractional devices are associated with minimal side effects and downtime (Aldahan et al. 2016; Alam et al. 2011; Khater 2016; Tannous 2007).

For the treatment of both striae (rubra and alba), the fractional non-ablative Er:Glass (1540, 1550, 1565 nm) is one of the most used (Table 1) (Stotland et al. 2008; de Angelis et al. 2011; Tretti Clementoni and Lavagno 2015); however, other non-ablative lasers are also used with good results.

Table 1 Parameters commonly used for SD treatment with different wavelengths

Laser – wavelength (nm)	Parameters	Number of passes
Erbium glass – 1540	Energy= 12–55 mJ Density= 100–320	2–3
Erbium glass – 1550	Energy= 12–18 J Density= 125–250	8–12
Erbium glass – 1565	Energy= 40–55 J Density= 150–300	2

Several sessions are necessary (Figs. 1–3) (see chapter ▶ "Erbium Laser for Scars and Striae Distensae").

De Angelis et al. treated SD in 51 patients with skin types II–IV, with two to four sessions of laser therapy, spaced 4–6 weeks apart. All striae were reported to have a least 50% improvement. Histologically increased elastic fibers and neocollagenesis were seen in the reticular dermis. Adverse effects were predominantly erythema and edema; however, eight patients developed transient post-inflammatory hyperpigmentation (de Angelis et al. 2011).

Clementoni and Lavagno evaluated the effectiveness and safety of a novel non-ablative fractional 1565 nm laser on the appearance of SD. Good clinical improvement (between 51% and 75%) was observed in all patients. The average pain during treatment was generally defined as tolerable and the average downtime was 4 days. Transient erythema and severe edema were noted immediately after the procedure, but long-lasting or severe adverse effects were not observed. All patients noted a good improvement and were satisfied with the treatment and the results. Thus they concluded that the treatment with the 1565 nm laser resulted in improved pigmentation, volume, and textural appearance of SD (Tretti Clementoni and Lavagno 2015).

Malekzad et al. studied ten patients with striae alba using fluence of 50–70 J/cm2, and, among the other adverse events, related one patient who developed acne in the treatment area. Unfortunately, this study demonstrated questionable results with nine of ten patients with fair or poor improvement (Malekzad et al. 2014).

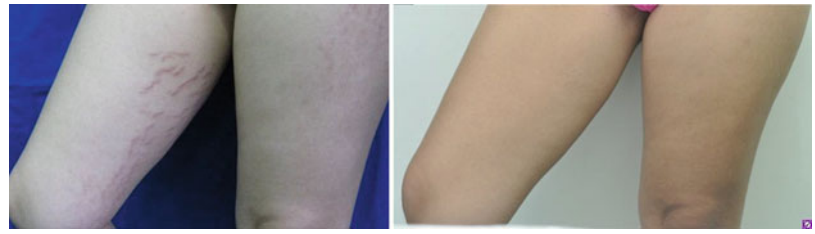

Fig. 1 Non-ablative laser (erbium glass 1540 nm) – fluence, 70 mJ/cm^2; pulse duration, 15 ms for SD rubra on the right thigh before and after three sessions

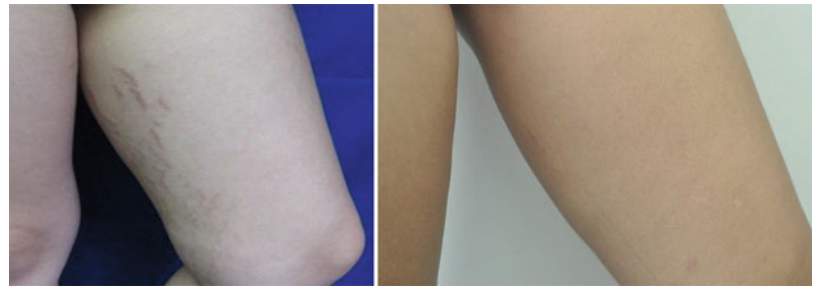

Fig. 2 Non-ablative laser (erbium glass 1540 nm) – fluence, 70 mJ/cm^2; pulse duration, 15 ms for SD rubra on the left thigh before and after three sessions

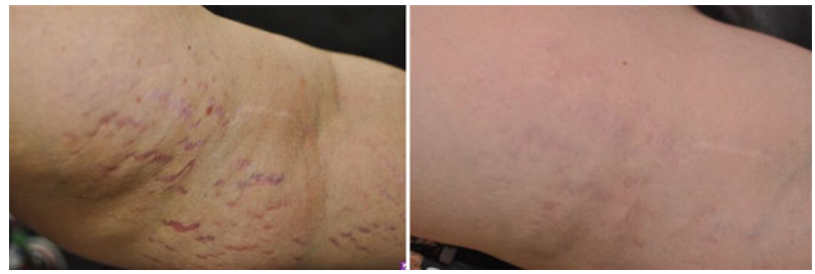

Fig. 3 Non-ablative laser (erbium glass 1540 nm) – fluence, 70 mJ/cm^2; pulse duration, 15 ms for SD rubra on the left arm before and after three sessions

Alves et al. reported four patients with corticosteroid induced striae rubra treated using 1540 nm Er:Glass at 1 month interval. After three sessions, 50% had marked improvement and the other two patients achieved similar improvement for four and six sessions, respectively (Alves et al. 2015).

Bak et al. treated Asian patients with improvement in appearance clinically and histologically. An increase in average epidermal and dermal thickness was seen on posttreatment biopsy, especially in striae alba (Bak et al. 2009).

Stotland treated 14 female patients with 1550 nm erbium-doped fiber laser, only one patient had striae rubra, and all the others had alba striae. He concluded a 26–50% of improvement in pigmentation, with transient edema and erythema in most of them (Stotland et al. 2008).

Guimaraes et al. studied the 1550 nm Er:Glass laser in ten patients with striae rubra of the breast with 4–8 sessions performed at 4-week intervals. Patients who had total improvement received at least six laser sessions (Guimaraes et al. 2009).

Wang et al. compared 1540 nm and 1410 nm non-ablative fractionated laser in nine patients, with abdominal striae. Each one was treated for six sessions – half of the abdomen with each laser. All subjects demonstrated clinical improvement bilaterally after treatment. Skin biopsies showed an increase in epidermal thickness and collagen and elastin density when compared with baseline.

However clinical and histological differences between the two lasers were not statistically significant (Wang et al. 2016).

Based on the number of studies alone, it is clear that the treatment of SD with non-ablative fractional lasers is popular, safe, and well tolerated by patients, with minimal adverse events. Mature striae alba have shown to be the most difficult type to be treated successfully with fractional lasers (Shin et al. 2011). However, this also occurs with other therapeutic modalities (Tannous 2007).

Post-inflammatory hyperpigmentation (PIH) is the most common complication in patients with Fitzpatrick skin types IV–VI; however, its incidence is lower when compared to ablative lasers. Although melanin does not absorb the 1.540–1565 nm wavelength, pigmentary changes can still occur (Sherling et al. 2010). The degree of PIH has been found to be directly proportional to both the energy and density of the treatment, although density appears to be particularly important (Chan et al. 2007). Thus, it is important to start out using conservative settings in these patients, even when using non-ablative lasers (Shah and Alam 2012).

To reduce the incidence of hyperpigmentation, many dermatologists use bleaching creams like hydroquinone, tretinoin, or glycolic acid (before and/or after the procedure). Although studies are inconclusive as to whether these topical agents are capable of preventing hyperpigmentation, they may be effective when instituted postoperatively as a component of the skin care regimen (Manuskiatti et al. 2010; Sriprachya-anunt et al. 2002). In combination with non-ablative devices, it is easier to prescribe these bleaching agents, as the epidermis is maintained after laser (Shah and Alam 2012).

Studies comparing the clinical efficacy of the ablative vs. non-ablative fractional photothermolysis system for the treatment of striae distensae have been conducted.

One of these studies compared the effect of ablative CO2 fractional laser with that of non-ablative 1550 nm erbium (ER)-glass fractional laser on SD in Asian patients. (Yang and Lee 2011). Although CO2 laser resurfacing might promise better clinical improvement because it may induce more dermal extracellular matrix remodeling than the non-ablative laser treatment, this study failed to prove statistical significant difference between the two devices. However, treatment with the ablative CO2 fractional laser was considered more painful than the treatment with the non-ablative fractional laser and resulted in more post-inflammatory hyperpigmentation and longer posttreatment erythema (Yang and Lee 2011).

When the efficacy of these two methods, ablative vs. non-ablative fractional laser, is compared for alba type of striae distensae, a poor clinical improvement is observed for both laser types. On the other hand, both laser treatments have moderate successful for immature striae distensae (rubra type) treatment (Gungor et al. 2014).

Unfortunately, there are some limitations when comparing laser techniques due to variations between study protocols. Parameters such as fluence, pulse, duration, and spot size are different between many devices, making comparison very difficult. Treatment intervals and number of sessions are also an important variable to be considered (Aldahan et al. 2016).

We have good results with erbium-glass 1540 nm for SD treatment, mainly for SD rubra. Parameters commonly used are fluence, 70 mJ/cm^2; pulse duration, 15 ms; and three sessions (Figs. 1, 2 and 3).

Conclusion

A variety of laser parameters have been studied either alone or in combination with other modalities for the treatment of SD, as topics (retinoic acid and glycolic acid), chemical and mechanical peels (microdermabrasion), intradermotherapy, radio frequency, pulsed dye laser, and intense pulsed light. Although there is no "gold standard" treatment for stretch marks, the treatment of SD with non-ablative fractional lasers is becoming increasingly popular, especially because this approach is generally safe, even in higher phototypes. It is also well tolerated by patients with few

side effects (fewer crusts, erythema, and edema) and fast healing time.

Striae rubra are much more amenable to laser and light therapy, probably because of their predominant vascular components. SD rubra can be successfully treated with non-ablative fractional lasers but also with non-ablative and non-fractional lasers as Nd: Yag, pulsed dye laser, and intensed pulsed light. Post-inflammatory hyperpigmentation is the most common complication; however, it is transitory in most cases and its incidence is lower than with ablative lasers.

Combination therapies may be the future for treating SD; however, for further conclusions, it is necessary to standardize study protocols, with a larger number of patients and long-term follow-up evaluation.

Take Home Messages

- Striae distensae can be cause by mechanical stress, endocrine conditions, pregnancy, or prolonged exposure to steroids.
- It can be rubra or alba.
- The pathogenesis is still unknown but probably relates to changes in the components of extracellular matrix, including fibrillin, elastin, and collagen.
- There is no "gold standard" treatment, but treatment with non-ablative fractional lasers is becoming increasingly popular, as it can be safely used by patients with high phototypes.
- Better results are achieved for SD rubra treatment.
- Post-inflammatory hyperpigmentation is the most common complication, but usually transitory and less frequent comparing with ablative lasers.

Cross-References

- ▶ Erbium Laser for Scars and Striae Distensae
- ▶ Microneedling for Transepidermal Drug Delivery on Stretch Marks
- ▶ CO_2 Laser for Stretch Marks

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Non-ablative Fractional Lasers for Scars

Roberto Mattos, Juliana Merheb Jordão, Kelly Cristina Signor, and Luciana Gasques de Souza

Abstract

The knowledge of microenvironment of tissue repair enables better understanding of the healing process and the techniques currently employed for its correction. There are different types of scars and the treatment should be chosen according to lesion. Laser mechanism of action on scars is based on two pillars, to reduce blood flow and to reorganize collagen fibers. Devices available for scar treatment include intense pulsed light (IPL), in the vascular mode, non-ablative lasers, and ablative lasers. In this chapter we are going to discuss non-ablative lasers for scar treatment.

Keywords

Non-ablative laser • Non-ablative scars • Keloids • Tissue repair • Blood flow • Collagen reorganization • Skin remodeling

Contents

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Introduction

In mammals, the wounds that occur in the fetus until the first trimester of pregnancy heal by regeneration, creating tissue with the same characteristics of the original (Ferguson et al. 1996). However, after this period, the inflammatory process, with the aim to control infection, results in scar, which is different from the surrounding skin. It can present as atrophy, hypertrophy, or keloid scars (Ferguson et al. 1996; Mccalion and Ferguson 1996; Ferguson and O'kane 2004). Knowing the microenvironment of tissue repair, we can be able to understand the healing process and the techniques currently employed for its correction (Profyris et al. 2012; Martin and Leibovich 2005).

Stages of the Healing Process

Healing is divided into three stages: inflammatory, proliferative, and remodeling. However, it is a dynamic process, so at any point, a phase may overlap another (Profyris et al. 2012).

Inflammatory Phase

It begins immediately after breaking the epithelial integrity and lasts 1–3 days. When injury occurs, the immediate priority is hemostasis that is achieved through the extrinsic pathway activation. It constitutes a hemostatic plug of fibrin that is solidified by the arrival of platelets. It also acts as a mechanical barrier against microorganisms' invasion and avoids bleeding. It is a temporary matrix for cell migration and a reservoir of cytokines and growth factors (Profyris et al. 2012; Werner and Grose 2003).

Once the bleeding risk is finished, the next priority is to remove dead tissue and to prevent infection. During the first 5 days, neutrophils and macrophages reach the injury zone, and through phagocytosis and production of local proteases, they eliminate microorganisms and remove dead tissue. They also secrete multiple growth factors, chemokines, and cytokines. These molecules are essential to signal the events that will occur in the proliferative phase (Profyris et al. 2012; Werner and Grose 2003).

Proliferative Phase

It has the function of wound healing. It begins around the fourth day and lasts about 3 weeks (Park and Barbul 2004).

Granulation tissue is the hallmark of proliferative phase and has this name due to the granular feature, formed by newly vessels (60% of its composition) (Dvorak 2005). It replaces hemostatic fibrin plug of the inflammatory phase (Park and Barbul 2004).

The proliferative phase can be divided into three steps:

The first step is represented by the increased vascular permeability induced by cytokines, as vascular endothelial growth factors (VEGF). Increased permeability of microvessels allows extravasation of macromolecules, such as fibrinogen and other coagulation proteins, which results in extravascular fibrin deposition (Dvorak 2002).

In the next step, there are angiogenesis and migration of endothelial cells. Many molecules have been implicated in this phase: fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGF), transforming growth factor (TGF) beta, angiogenin, angiotropin, and angiopoietin-1. In addition, platelet-derived growth factor (PDGF) is related to cell migration and fibroblast activation, providing a structural network, over which endothelial cells proliferate and produce new vessels (Dvorak 2002).

Epithelialization is essential for reestablishing tissue integrity. The epithelial coating cells, through the action of specific cytokines, proliferate and migrate from the borders of the wound in an attempt to close it. This process is called reepithelialization. The reepithelialization of a wound by keratinocytes is performed by the combination of the proliferative stage with the migration of cells near the lesion. The migration of keratinocytes occurs in the direction of the remaining skin of the lesion to its extremities (Profyris et al. 2012; Dvorak 2002; Martin and Leibovich 2005). TGF beta is the mainly cytokine involved in this step (Werner and Grose 2003; Santoro and Gaudino 2005).

Remodeling Phase

It begins in the third week, lasts up to 1 year and must be seen as an attempt of recovering the normal tissue (Santoro and Gaudino 2005). The third phase of healing consists in remodeling, which begins 2–3 weeks after the onset of the lesion and can last for 1 year or more. The core aim of the remodeling stage is to achieve the maximum tensile strength through reorganization, degradation, and resynthesize of the extracellular matrix. In this final stage of the lesion's healing, an attempt to recover the normal tissue structure occurs, and the granulation tissue is gradually remodeled, forming the scar tissue that is less cellular and vascular. It exhibits a progressive increase in its concentration of collagen fibers. At this stage, there is a deposition of the matrix and subsequent change in its composition. With the closure of the wound, type III collagen undergoes degradation, and synthesis of type I collagen increases (Profyris et al. 2012; Mattos et al. 2009).

The main reason for failure in the reproduction of morphologically identical tissue during healing process is architectural layout of the new collagen in parallel bands instead of the network of normal skin, and, in addition, the absence of hair follicles, sebaceous glands, and sweat glands is remarkable (Profyris et al. 2012).

Scars

The clinical classification of scar guides the therapeutic choice (Mattos et al. 2009; Mutalik 2005). For treatment purposes, scars can be mainly divided into three types (Osório and Seque 2012):

1. Hypertrophic
2. Keloids
3. Atrophic

Hypertrophic scars are erythematous, raised, firm nodular lesions. The growth of hypertrophic scars is limited to the sites of original tissue injury, unlike keloids that proliferate beyond the boundaries of the initial wounds and often continue to grow without regression (Osório and Seque 2012; Sobanko and Alster 2012):

Keloid scars present as reddish-purple papules and nodules, often on the anterior chest, shoulders, and upper back. They are more common in darker-skinned persons and, like hypertrophic scars, may be pruritic, anesthetic, and cosmetically disfiguring. While the histology of hypertrophic scars is indistinguishable from other scarring processes, the histology of keloids may be recognized by thickened bundles of hyalinized collagen, haphazardly arranged in whorls and nodules (Sobanko and Alster 2012; Osório and Seque 2012; Mattos et al. 2009; Mutalik 2005).

Atrophic scars, on the other hand, are dermal depressions that result from the aforementioned acute inflammatory processes. The inflammation associated with atrophic scars leads to collagen destruction with dermal atrophy. Atrophic scars are initially erythematous and become increasingly hypopigmented and fibrotic over time. The most common causes are acne, postsurgical injury, and burn (Osório and Seque 2012; Sobanko and Alster 2012).

Acne scarring is the result of a deviation in the orderly pattern of healing and can have profound psychosocial implications for patients. For this reason, they should be treated whenever possible. Atrophic acne scars are divided into three types: ice pick, rolling scar, and boxcar. Ice-pick scars are narrow, v-shaped epithelial tracts that extend into the deep dermis or subcutaneous tissue. Rolling scars are wide and undulating, due to their tethering from the dermis below. Finally, boxcar scars are sharply delineated epithelial tracts that extend into the dermis but, unlike icepick scars, do not taper at the base. The use of this classification system allows for treatments to be indicated to the specific type of scarring (Osório and Seque 2012).

Treatment of unsightly scars is a big challenge for the dermatologist. Till the date, there is no treatment considered ideal for scars. Gels or silicone tapes are commonly used and recommended in recent scars. Intralesional corticosteroid infiltration is the most common option for keloids and hypertrophic scars. Application peels, subcision, dermabrasion, and surgical excision are traditional options for atrophic scars (Mattos et al. 2009; Mutalik 2005).

Incomplete scar removal, scar worsening, tissue fibrosis, and permanent pigmentary alteration have limited the clinical utility of these treatments. Advances in laser technology have led researchers to study their potential use as a treatment for this therapeutically difficult condition. Laser scar revision is a well-tolerated procedure with clinically demonstrable efficacy and minimal adverse effects and may be used in combination with the aforementioned scar treatments (Sobanko and Alster 2012).

In addition to its indication for treating established scars, recent studies have brought a new therapeutic possibility: the prevention of hypertrophic scars in predisposed patients (Mattos et al. 2009; Mutalik 2005).

Lasers

Much has been studied about the laser systems of action in treatment and prevention of scars. The mechanism of action of these technologies for scars is still poorly elucidated. It is believed that the therapeutic effect is based on two pillars:

1. Reducing blood flow: once the scars have four times greater blood flow than the normal tissue, maintained by angiogenesis and VEGF production, therefore, the equipment should have at least some ability to produce vascular injury (Mattos et al. 2009; Mutalik 2005).
2. Reduction, reorganization, and remodeling of collagen (Profyris et al. 2012).

Three genres of lasers have been shown to improve scars, creating thousands to millions of microscopic thermal wounds distributed throughout the dermis, with or without some epidermal injury. First, millisecond-domain pulsed-dye lasers (PDLs) and similar devices produce selective photothermolysis of small blood vessels. Second, nanosecond-domain Q-switched Nd:YAG lasers produce selective photothermolysis of microvessels and pigmented cells. Third, ablative and non-ablative fractional lasers (NAFLs) produce arrays of nonselective, microscopic thermal damage zones throughout the epidermis and dermis (Profyris et al. 2012; Anderson et al. 2014; Kauvar 2014).

Equipment Available for Scars Treatment

1. Intense pulsed light (IPL) in the vascular mode
2. Non-ablative lasers:
   - Pulsed-dye laser (PDL) 585 nm or 595 nm
   - Nd:YAG 1064 nm Long pulse
   - Nd:YAG 1064 nm Ultrapulsed (genesis)
   - Nd:YAG 532 nm
   - Diode 800 nm or 1340 nm
   - 755 nm alexandrite
   - Erbium glass: 1550 m and 1540 nm
   - Nd:Yap 1340 nm
   - Thulio 1927 nm
3. Ablative lasers:
   - CO_2
   - Erbium 2940 nm

Within the theme of this chapter, we discuss preferably treatment with non-ablative lasers, extending to vascular lasers given the importance of the vessel approach, as stated earlier.

To determine which laser system is better for scar treatment, it is necessary to know the type and severity of the scar and the patient toleration and expectations. Dyschromia (erythema, hyperpigmentation or hypopigmentation), scar type (hypertrophic, flat, or atrophic), scar body location (face, neck, or leg), and patient characteristics (skin phototype and comorbid conditions) should be considered (Profyris et al. 2012; Sobanko and Alster 2012; Anderson et al. 2014).

Flashlamp-Pumped Pulsed-Dye Laser (585 and 595 nm)

There is no consensus on the precise mechanism whereby the PDL exerts its effect on scars. PDL demonstrates to reduce transforming growth factor-b expression, fibroblast proliferation, and collagen type III deposition. Other plausible

explanations include selective photothermolysis of vasculature, released mast cell constituents (such as histamine and interleukins) that could affect collagen metabolism, and the heating of collagen fibers and breaking of disulfide bonds with subsequent collagen realignment (Mattos et al. 2009; Mutalik 2005; Sobanko and Alster 2012).

In fact, the PDL has been successful in improving the depth of moderately atrophic facial acne scars, likely due to stimulation of collagen remodeling. In case of hypertrophic scars, most evidence was found for the PDL 585 nm indicating that it is the best-investigated device for this treatment. As a consequence of this research, the laser of choice in treating hypertrophic, erythematous acne scars and keloids is the vascular-specific 585 nm PDL (Cynergy®). For the PDL 595 nm (VBean®), a moderate efficacy (34–66% improvement) was found (Gira et al. 2004; Sobanko and Alster 2012; Vrijman et al. 2011).

1. During implementation of PDL, the entire surface of injury should be treated by adjacent shots and not overlapping, single pass, or until it reaches purplish erythema (end point) (Gira et al. 2004).

Minimally purpuric settings have reduced erythema with minimal risks. Non-purpuric settings also improve erythema but appear to be associated with less redness reduction per treatment session (Anderson et al. 2014).

Parameters suggested are (Mattos et al. 2009):

- Fluency 6–7.5 j/cm^2 with spot 5–7 mm.
- 4.5–5.5 J/cm^2 with spot 10 mm.
- The most used pulse durations are 0.45 and 1.5 ms.
- You should reduce fluency into 0.5 in higher phototype patients, in more delicate areas such as the neck, chest, and eyelids if vesicles and crusts are present in the previous session.
- It is suggested to raise the fluency in subsequent sessions if the previous was suboptimal.

To select the best treatment option, the scar size is very important, since for very large scars, laser treatment may become impractical by the higher costs of disposable (Gira et al. 2004; Mattos et al. 2009).

Q-Switched Frequency Doubled Nd: YAG 532 nm

This laser is the only device that specifically targets pigmentation. One clinical trial with a small number of patients and a high risk of bias reported low improvement on the Vancouver General Hospital scale (Vrijman et al. 2011; Osório and Seque 2012).

Diode Laser (Laser-Assisted Skin Healing 810 nm)

Its mechanism of action has not been fully established yet. It generates heat that causes releasing of cytokines and the synthesis of proteins involved into healing process (Osório and Seque 2012).

Parameters suggested are:

- 4 mm spot.
- Fluency: 80–120 j/cm^2 – Burn is reported with higher fluences.

Non-ablative Fractional Lasers

Non-ablative fractional lasers possess superior safety profile than ablative ones (Tziotzios 2012). This type of laser is better tolerated and less invasive compared to non-fractionated, with good results in several indications (Osório and Seque 2012). It is considered safe even at higher skin types, being the first choice for these patients.

Non-ablative fractional laser comprises an array of 30 devices, whose wavelength corresponds to the infrared, and its target is the water. The aim is collagen stimulation, normalization of color, and scar remodeling (Tziotzios 2012).

They causes coagulative, fractional, located, thermal injury and epidermal necrosis on microscopic treating zones (MTZ), separated by areas of normal skin. From this intact tissue, epidermal cells migrate into the damaged area performing healing (Tziotzios et al. 2012).

The permanence of histologically intact stratum corneum characterizes it as a non-ablative laser; allows re-epithelialization in 48 h, preserving the epidermal barrier function; and minimizes side effects (Mattos and Jordão 2012).

In an attempt to elucidate its mechanism of action, Laubach et al. reported in 2006 that non-fractional ablative lasers perform microscopic epidermal necrotic debris (MEND) carrying depth melanin to the surface, what explains the improvement of skin color. Hantash et al. showed elimination of elastic fibers by MEND. Finally, Goldberg et al. showed that new melanocytes and viable skin keratinocytes occupy the region (Mattos and Jordão 2012).

Armann et al. have studied ex vivo NAFL effects on skin morphology and molecular effects on gene regulation. Human three-dimensional (3D) organotypic skin models were irradiated with non-ablative fractional erbium glass laser systems enabling qRT-PCR, microarray, and histological studies at the same and different time points. A decreased mRNA expression of matrix metalloproteinases (MMPs) 3 and 9 was observed 3 days after treatment. MMP3 also remained downregulated on protein level, whereas the expression of other MMPs like MMP9 was recovered or even upregulated 5 days after irradiation. Inflammatory gene regulatory responses measured by the expression of chemokine (C-X-C motif) ligands (CXCL1, 2, 5, 6) and interleukin expression (IL8) were predominantly reduced. Epidermal differentiation markers such as loricrin, filaggrin-1, and filaggrin-2 were upregulated by both tested laser optics, indicating a potential epidermal involvement. These effects were also shown on protein level in the immunofluorescence analysis. This study reveals erbium glass laser-induced regulations of MMP and interleukin expression. The authors speculate that these alterations on gene expression level could play a role for dermal remodeling, anti-inflammatory effects, and increased epidermal differentiation (Amann et al. 2016).

A number of studies have demonstrated mild to moderate improvement in atrophic acne scars using these non-ablative lasers. In this case, only patients with boxcar and rolling acne scars are excellent candidates for laser resurfacing as they are distensible scars. Most ice-pick scars with deep bases respond better to punch excision than to fractional lasers, whereas rolling scars might require subcision followed by fractional laser treatment. Because acne scars are usually a mix of ice-pick, boxcar, and rolling scars, the final effect of fractional lasers would depend more on the predominant scars than on the fractional laser used (Tziotzios 2012; Sobanko and Alster 2012; Sardana et al. 2014).

Recent studies have shown increasing evidence of NAFL role in hypertrophic scars. Those one younger than a year have the best results. Scar pigmentation and elasticity are parameters that have better response; vascularization and elevation are the items with most discrete results. Several authors suggest beginning laser treatment of scars for about 2–3 weeks after surgery (Tziotzios 2012). Some authors suggest the use of fractional ablative or non-ablative laser to prevent the development of hypertrophic scars after surgery. Jang J et al. have compared the use of fractional ablative laser and fractional non-ablative laser in recent thyroidectomy scars. After four laser treatment sessions, both types of fractional laser treatments were successful; however, their results indicated that higher effectiveness may be obtained from the use of ablative and non-ablative lasers for hypertrophic scars and early erythematous scars, respectively (Jang et al. 2016). Keloid scars should avoid being treated with non-fractional ablative lasers by the risk of worsening (Sobanko et al. 2015).

Laser Devices in the Market

- 915 nm diode: This laser was recently introduced in the market and associates fractional non-ablative laser with radiofrequency in the same shot. It is widely used in localized areas (periocular and perilabial) to further warming

and improved outcomes. In bony areas, radiofrequency energy should be decreased because there is an increase in intensity of heat as well as the risk of side effects. Erythema is fleeting (Sobanko and Alster 2012).

- Long pulse 1320 nm Nd:YAG: It is associated with an epidermic temperature sensor and a cryogen spray for skin protection. It has a high diffusion rate of heat in dermis. It is applied on a stamp mode, and spots vary from 3 to 10 mm. Prospective studies with the 1320 nm Nd:YAG laser for atrophic acne scars have shown modest efficacy without notable adverse events (Sobanko and Alster 2012).
- 1340 nm Nd:YAG: It has the lowest water absorption coefficient, which increases penetration in the dermis. Pulse duration ranges from 3 to 10 ms, handpiece's density varies from 100 to 400 MTZ. The laser energy is delivered to the dermis by the stamp mode. It is mandatory the use of epidermal cooler to protect the epidermal layer from burning. The most important advantage of this technology is the absence of consumables (Mattos and Jordão 2012).
- 1440 nm Nd:YAG: This very fast handpiece has increased risk of burns and post-inflammatory hyperpigmentation. Pulse duration ranges from 3 to 10 ms; handpiece options are 10, 12, and 15 mm; energy ranges between 2 and 80 mJ/microbeam. The tip has a cooling system to ensure the epidermal protection. These technology doesn't have consumables (Mattos and Jordão 2012).
- 1450 nm diode: Its fluence ranges from 8 to 25 J/cm2; handpiece options are 4 and 6 mm; it is coupled to a cryogen spray. This diode laser showed greater clinical effect with less adverse effect (Sobanko and Alster 2012).
- 1540 nm Erbium glass laser: It is applied in stamp mode; pulse duration ranges from 10 to 100 ms; energy varies from 20 to 100 mJ/cm^2. It has sapphire cooled tip, slower speed of shots, and no consumables (Mattos and Jordão 2012).
- 1440 and 1540 nm in the same devices: It provides an increase of 20–50% in thermal damage depth. It has cooled sapphire tip, which increases their safety (Mattos and Jordão 2012).
- 1550 nm Erbium glass: It allows automatic control of density width and depth of the coagulation column. Its administration is quick, but painful. This NAFXL can deliver up to 70 mJ energy with 300–1400 mm of depth; selection of MTZ density is allowed, providing adjustment of the percentage of skin treated to 5–48%. It is possible to apply several passes in different directions with some cooling intervals to avoid side effects. Considering that the estimative of facial skin depth (forehead, nose, medial and lateral cheeks, lips, chin) is approximately 2196 lm, which consists of the epidermis (105 lm), papillary dermis (105 lm), and reticular dermis (1986 lm), a recent review examined the correlation between depth and energy for all fractional lasers. This review found that, for the 1550 nm fractional laser, for every mJ, the depth of coagulation increased roughly by a factor of 10 lm (10 mJ/100–150 lm). Thus, with a dose of 70–100 mJ, a depth of 700–1000 lm can be achieved, which would be sufficient to ameliorate most superficial and some deep atrophic scars (Sardana et al. 2014).
- Consensus guidelines on NAFXL (non-ablative fractional laser) treatment parameters for acne scars have been proposed for different skin phototypes. Using 1550 nm Erbium glass, for lighter skin phototypes (I–III), the recommended settings are 30–70 mJ energy, treatment level of 7–11, and 8–12 passes. For darker skin phototypes (IV–VI), energy settings of 30–70 mJ are advocated with fewer passes and lower treatment density in order to decrease postinflammatory hyperpigmentation (Sobanko and Alster 2012).
- 1927 nm thulium laser and 1550 nm + erbium glass associated in the same handpiece: The shots are quick in a scanner way. The integrated cooling system

provides comfort and comes with system where you can select the percentage of coverage and aggression. The number of passes is calculated by the device and requires the use of different spot sizes according to selected energy. The combination of two wavelengths allows effective treatment for skin surface and dermis (Mattos and Jordão 2012).

Treatment of Atrophic Scars

Atrophic scars are dermal depressions that result from a relative paucity of collagen after an injury or that are associated with conditions such as acne. The goal of laser treatment in this setting is to stimulate neocollagenesis and remodeling within the atrophic areas. New collagen synthesis is strongly stimulated by fractional laser therapy, and previous studies have demonstrated consistent efficacy for atrophic scars resulting from acne and trauma. For relatively atrophic, shallow, or flat scars, the NAFXL appears to achieve results similar to those of the AFXL (ablative fractional laser) (Vrijman et al. 2011; Anderson et al. 2014).

For acne scars in phototypes IV, V, and VI, including oriental skin, NAFXL is an effective and safe option compared to placebo (Yang et al. 2016). Although NAFXL is generally better tolerated than AFXL, more than one session may be required (Vrijman et al. 2011).

Another option for atrophic scars is PDL, with satisfactory results on improvement of depth of moderately atrophic facial acne scars, likely due to stimulation of collagen remodeling (Vrijman et al. 2011; Sobanko and Alster 2012).

Treatment of Hypertrophic Scars

On the basis of available data from randomized controlled trials, silicone gel or sheeting is the preferred first-line therapy for the treatment of linear hypertrophic scars. In cases where a 2-month course of silicone gel or sheeting does not prove effective or when the scar is severe, pruritic, or both, adjunctive use of intralesional corticosteroid injection or 5-fluorouracil (5-FU) is indicated. For cases when the initial steps fail, laser therapy should be considered (Gold et al. 2014).

The first lasers used in the treatment of hypertrophic scars were ablative (CO_2 laser) and showed recurrence rates of 90% and higher (Vrijman et al. 2011). The incidence of adverse events was also quite high. Therefore other alternatives were developed (Tziotzios et al. 2012). Fractionated lasers and intense pulsed light (IPL) are relatively new techniques used to treat scars.

Another category that has been used for hypertrophic scars is lasers with wavelength directed against oxyhemoglobin, as the PDL 585 nm or 595 nm, 1064 long pulse, and phosphate-titanium-potassium (KTP) 530 nm. These lasers injures the blood vessels, decreasing the eritema, telangiectasias and inflamatory process. Through the thermal damage, PDL act modifying collagen fibers. These sinergistic effects make PDL the ideal treatment for hypertrophic scars and keloids (Mattos et al. 2009; Gira et al. 2004).

It is known that these technologies have a variable response in scars, depending on (Mattos and Jordão 2012):

1. Thickness: better response in less thick scar
2. Etiology: better response in organized scars, like those by surgical procedure
3. Maturity: superior results in recent scar

To improve the response of resistant hypertrophic scars, a combination of silicone gel and laser therapy is suggested. The use of concomitant intralesional corticosteroids or fluorouracil with PDL has been shown to provide additional benefit in proliferative scars. Intralesional injections of corticosteroids (20 mg/mL triamcinolone) are more easily delivered immediately after (rather than before) PDL irradiation because the laser-irradiated scar becomes edematous (making needle penetration easier). An additional consideration is that when corticosteroid injection is performed before laser irradiation, the skin blanches and becomes less amenable for vascular-specific irradiation (Osório and Seque 2012).

Burn Scar Treatment

1. Burn scar treatment is complex and it often requires combination or alternative therapies including silicone gel sheeting; individualized pressure therapy; massage, physical therapy, or both; corticosteroid application; and surgical procedures. Massage, hydrocolloids, and antihistamines may be added to the therapeutic regimen to relieve pruritus (Michael et al. 2014).

The last clinical consensus for burn scar treatment is that fractional lasers are significantly more effective for burn scar improvement than are PDL or Q-switched Nd:YAG lasers. Few controlled, prospective studies have evaluated the comparative efficacy of various fractional devices, but early reports and our clinical experiences suggest that the AFXL has the capacity to induce a more robust remodeling response than the NAFXL. Current AFXL devices have a significantly greater potential depth of thermal injury compared with NAFXL devices (approximately 4.0 and 1.8 mm, respectively) (Mattos and Jordão 2012).

Most patients report significant improvement in pain, itch, and physical mobility within days to weeks after each treatment. Typically, rapid improvement is seen in depigmentation, followed by gradual improvement in the texture and possibly range of motion. Pulsed-dye and fractional lasers have distinct and possibly synergistic roles in burn scar treatment. Inflammatory, erythematous scars encountered within the first few years of injury are most amenable to treatment with PDL. Ablative fractional lasers typically produce the greatest improvement for hypertrophic and contracted scars, with or without the addition of intralesional or topical medications (e.g., corticosteroids) (Michael et al. 2014).

Non-ablative fractional lasers are effective and approximately equivalent to AFLs for treatment of atrophic or flat, mature scars. Pigmentary abnormalities (hypopigmentation, hyperpigmentation, or depigmentation) seem to improve more rapidly than the textural abnormalities during a course of fractional laser treatments (Mattos and Jordão 2012).

Early intervention (within weeks and months of injury) may be advantageous in mitigating scar contracture formation and trajectory with significant benefits in patient rehabilitation, representing a potential breakthrough in the treatment of traumatic scarring (Mattos and Jordão 2012).

The optimal time to begin fractional laser treatment is undetermined. However, in our opinion, AFXL and NAFXL appear to be well tolerated significantly earlier than 1 year after injury. Treatment of freshly healing wounds with unstable epidermal coverage in the first 1–3 months after injury may lead to unpredictable and potentially harmful outcomes. However, clinical experience suggests that wounds that are epithelialized and relatively mature with focal erosions and ulcerations may experience more rapid healing after AFXL treatment. Younger scars (within the first year of injury) are often less tolerant of aggressive treatment than more mature scars, and laser variables should be selected judiciously in regard to settings and combination therapies. A minimum treatment interval of 1 month between fractional laser treatments is suggested, and the treatments are continued until a therapeutic plateau or treatment goals are achieved (Mattos and Jordão 2012).

Keloid Scar Treatment

First-line therapy for the treatment of minor keloids involves the combination of silicone gel or sheeting with monthly intralesional corticosteroid injections. Contact or intralesional cryotherapy is a potentially useful adjunct for these lesions, but it has yet to reach widespread use for keloid management in clinical practice. Administration of an oral analgesic and intranslesional local anesthesia can be used to reduce pain experienced during cryotherapy. If improvement with conservative therapy is not observed within 8–12 weeks, 5-FU in combination with intralesional corticosteroids and, ultimately, laser therapy or surgical excision may be considered (Michael et al. 2014).

Keloids have unpredictable response to any treatment. It may not have any answer to laser-

reduced response in each session and is prone to relapse, especially when the sessions are not performed at regular intervals (Mattos et al. 2009).

Procedure

Before Treatment

After choosing the laser, it is recommended to take photography before and after treatment to evaluate clinical response. Patient should sign the informed consent term. Past history of medicaments and chronic diseases should also be questioned (Gira et al. 2004).

Everyone in the procedure room must wear protective eyewear.

The skin is cleaned and topical anesthetic solution should be applied about 1 h before the procedure. Reducing laser speed application and using cooler equipment may minimize patient discomfort (Degitz and Hautarz 2015).

Parameters

The energy level depends on the device used and on the color of the lesion (amount of chromophore). The redder the lesion, the more the vessels, resulting in abundant target and higher heat production. In these cases, less energy should be used in the first session. Energy should be gradually increased over the course of sessions (Michael et al. 2014).

It has been shown that the use of high-energy settings and multiple passes promotes better clinical results for rejuvenation and atrophic scars. For hypertrophic scars, it is the opposite: high-energy settings and high density should worsen the scar (Anderson et al. 2014).

High density is more likely to result in increased incidence and severity of erythema, edema, and hyperpigmentation. For any equipment, lower parameters should be used for patients with high skin phototype (Degitz 2015).

Safe treatment is based on the avoidance of excessive thermal injury. General principles applicable to laser selection and treatment technique for fractional laser therapy include minimizing the number of concurrent therapies, applying fractional treatments at low densities, using a narrow beam diameter, applying a short pulse width, and minimizing the number of passes. Higher pulse energies require a concomitant decrease in treatment density to minimize the risk of worsening scarring. Results are frequently optimized with a series of treatments. Although individual treatment courses vary widely, patients most commonly receive a series of three to six treatments (Michael et al. 2014).

Results

After the first session, the improvement is very discrete and the results become more visible after two to five sessions (Figs. 1, 2, and 3). Hypertrophic scars may show considerable improvement in the second session, but the response of keloids is often unpredictable. Improvement can be observed on the thickness, erythema, flexibility, texture, and scar itching (Michael et al. 2014).

As with other treatment modalities, better results are achieved with a combination of technologies, such as combining laser and IPL (Degitz 2015).

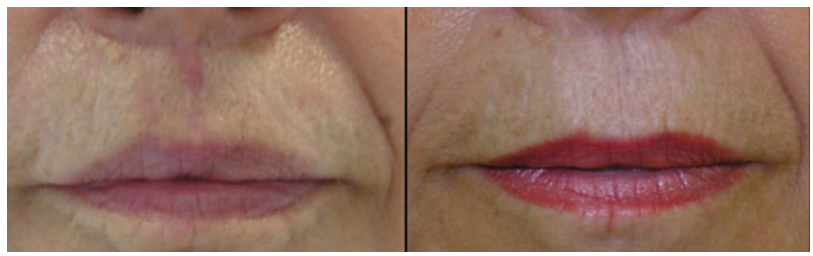

Fig. 1 Pulsed-dye laser 695 nm. Fluence 7 J/cm^2. Three treatments

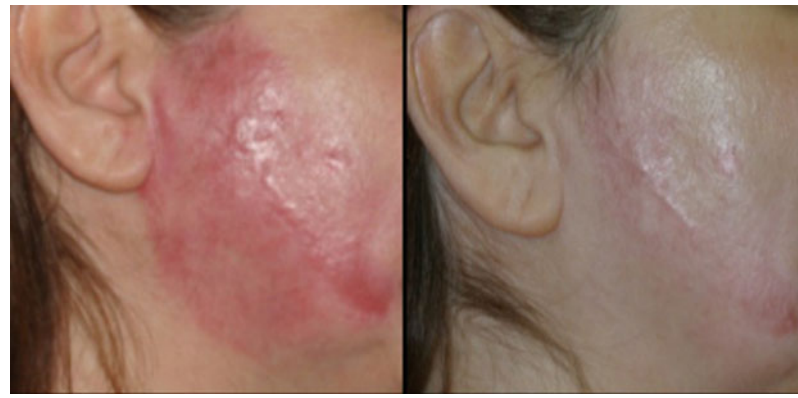

Fig. 2 Ultrapulsed NdYag. Fluence 16 J/cm^2. Four treatments

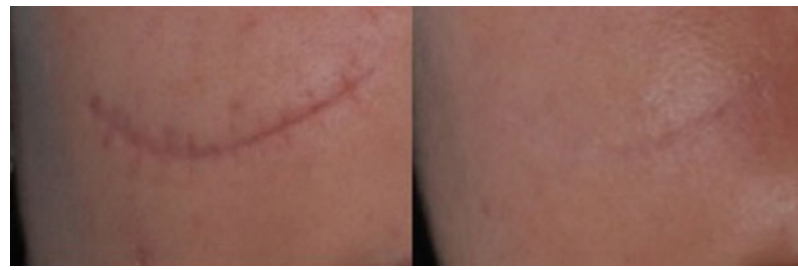

Fig. 3 Non-ablative fractional laser 1550 nm. Fluence 45. Density 4. Four treatments

Some studies have demonstrated better results when associating laser with triamcinolone or 5-FU infiltration comparing to each treatment isolated (Degitz 2015).

Post-Procedure

Edema and erythema are expected. The swelling usually improves within 48 h, and ice packs can be used. Anti-inflammatories and oral steroids are indicated for intense edema (Anderson et al. 2014).

Erythema usually improves within 3–5 days and, in extra facial regions, can extend to 7 days. Recently, the use of LED (light-emitting diode) immediately after the use of NAFXL has decreased the duration of the erythema (Anderson et al. 2014).

The most common adverse effect for treatment with the PDL is postoperative purpura, which often persists for several days (Anderson et al. 2014).

Complications

Complications are inherent of any technique. Focal hemorrhages can occur between 12 and 24 h, with spontaneous resolution without sequel (Ha et al. 2014).

Superficial erosions may occur at an inappropriate contact of the tip with the skin surface and this may course without scars (Sobanko and Alster 2012).

Burns (bullous and indurated erythematous areas) are rare but can occur when a high energy is chosen or a technical error occurs. Hypo- or hyperpigmentation can occur as a burn evolution (Ha et al. 2014).

The post-inflammatory hyperpigmentation usually resolves spontaneously in a few months and can be prevented, preparing the skin using bleaching (combination of hydroquinone with retinoic acid) and appropriate photoprotection. It is more common in high phototypes, in the eyelid area, or in areas that were used with high fluence (Kim and Cho 2009).

The hypochromia is an unusual and late-onset complication, appearing after a few weeks. It is usually related to high fluence, especially in high phototypes. It is commonly preceded by appearance of crusts. It is reversible with the use of steroids, with tacrolimus at the beginning, and with retinoic acid in a later stage. In case of resistant lesions, phototherapy can be a good alternative (Ha et al. 2014).

Infections in the first week have the risk of delayed wound healing. The most common pathogen is herpes simplex that can be avoided from prophylaxis started 1 day before procedure and continued for 5–7 days. There is divergence among authors regarding the herpes prophylaxis in all patients or only in those with past history of herpes or only when using ablative laser (Kim and Cho 2009). In our practice, herpes prophylaxis is formerly recommended for patients with previous herpes history in treatment with ablative laser.

Take Home Messages

1. There is no treatment considered ideal for scars.
2. The mechanism of action of lasers on scars is based on two pillars: reducing blood flow and reorganization and remodeling of collagen.
3. The chosen laser system to be used depends upon the type and severity of scar.
4. Non-ablative fractional lasers possess superior safety profile than ablative ones.
5. Non-ablative lasers are the first choice in higher skin types.
6. Non-ablative fractional lasers appear to achieve results similar to those of the ablative fractional lasers for relatively atrophic, shallow, or flat scars.
7. Lasers have a variable response in hypertrophic scars. Better response is observed in less thickness scar, in organized scars like those by surgical procedure, and also in recent scars.
8. Keloids have unpredictable response to any treatment.

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Q-Switched Lasers for Melasma, Dark Circles Eyes, and Photorejuvenation

Juliana Neiva, Lilian Mathias Delorenze, and Maria Claudia Almeida Issa

Abstract

Melasma is a common and persistent disorder of hyperpigmentation that affects a significant portion of the population, affecting mainly women. It is often a therapeutically challenging disorder. Physical therapies such as chemical peels, dermabrasion, lasers, and intense pulsed light have also been used with varying degrees of success and side effects. Dark circles eyes, also known as periorbital hyperpigmentation, are a common condition that occurs in both sexes with an increasing frequency in females. Aesthetic treatments include microdermabrasion, chemical peels, lasers, radiofrequency, injectable fillers, surgery, fat transfer, and lightening topical products. Clinical signs of photoaging include coarse skin texture, irregular pigmentation, and laxity of skin tone, as well as the appearance of fine lines and wrinkles. Diverse treatment modalities have been used to improve skin wrinkling and laxity, including chemical peeling, soft tissue filler, laser ablation, and facelift surgery. Lasers have revolutionized the treatment of many dermatological conditions. Different types of lasers can be indicated for pigmentary disorders. Recently, Q-switched lasers arose as a successful application in melasma, dark circles eyes, and photorejuvenation due to its low fluence, short pulse, and specific wavelength.

Keywords

Lasers • Q-switched laser • Melasma • Dark circles eyes • Photorejuvenation

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Introduction

Lasers (light amplification by stimulated emission of radiation) are sources of high-intensity monochromatic coherent light that can be used for the treatment of various dermatologic conditions depending on the wavelength, pulse characteristics, and fluence of the laser being used and the nature of the condition being treated (Arora et al. 2012).

Q-switched (QS) lasers deserve special attention due to its recently uprising application in the treatment of melasma, dark circles eyes, and photorejuvenation.

Q-Switched Lasers

Lasers have demonstrated significant efficacy in the treatment of hyperpigmented disorders by selectively destructing pigment cells with a short pulse and low fluence. The effectiveness of laser treatment for pigmented lesions is based on the theory of selective photothermolysis introduced by Anderson and Parrish, which states that when a specific wavelength of energy is delivered over a period of time shorter than thermal relaxation time (TRT) of the target chromophore (Arora et al. 2012; Anderson et al. 1989; Anderson and Parrish 1983; Jang et al. 2011), heat and injury are restricted to the target, with less damage to the surrounding tissue (Anderson and Parrish 1983; Jang et al. 2011). The thermal relaxation time for melanosome with 1-μm diameter ranges from 50 to 100 ns (Polder et al. 2011). Hence, a laser should emit a wavelength that is specific and well absorbed by the particular chromophore being treated.

A selective window for targeting melanin lies between 630 and 1,100 nm, where there is good skin penetration and preferential absorption of melanin over oxyhemoglobin (Stratigos et al. 2000). Absorption for melanin decreases as the wavelength increases, but a longer wavelength allows deeper skin penetration. Shorter wavelengths (<600 nm) damage pigmented cells with lower energy fluencies, while longer wavelengths (>600 nm) penetrate deeper but need more energy to cause melanosome damage (Arora et al. 2012). Besides wavelength, pigment specificity of lasers also depends on pulse width (Chan et al. 2010). These lasers lead to a photoacoustic mechanical disruption of melanin caused by rapid thermal tissue expansion (Arora et al. 2012).

QS Nd:YAG Laser

The 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet (QS 1,064-nm Nd:YAG) laser is widely used in cosmetic laser dermatology (Arora et al. 2012; Chan et al. 2010) for pigmented and vascular lesions, removal of tattoos, and unwanted hair (Chan et al. 2010).

With a wavelength of 1,064 nm, these devices allow for much deeper energy penetration and minimal melanin absorption compared with QS ruby laser or QS alexandrite laser. QS Nd:YAG laser uses a collimated handpiece to deliver a high peak power over very short pulse durations (≤20 ns), maximizing selective photothermolysis of cutaneous melanosomes (Friedmann and Goldman 2015).

The 1,064-nm QS Nd:YAG is well absorbed by melanin, and being a longer wavelength causes minimal damage to epidermis and is not absorbed by hemoglobin. The deeper skin penetration is also helpful to target dermal melanin. Low-dose QS Nd:YAG laser induces sublethal injury to melanosomes causing fragmentation and rupture of melanin granules into the cytoplasm (Arora et al. 2012; Anderson and Parrish 1983; Lee 2003). This effect is highly selective for melanosomes as this wavelength is well absorbed by melanin relative to other structures. There is also subcellular damage to the upper dermal vascular plexus, which is one of the pathogenetic factors in melasma (Kim et al. 2007). The subthreshold injury to the surrounding dermis stimulates the

formation of collagen resulting in brighter and tighter skin (Schmults et al. 2004).

QS Ruby Laser

The Q-switched ruby laser (QSRL) was the first laser reported to be highly efficacious for the treatment of benign epidermal-pigmented lesions (Park et al. 2008; Taylor and Anderson 1993; Nelson and Applebaum 1992).

The 694-nm wavelength of QSRLs is moderately absorbed by melanin, yet poorly absorbed by competing chromophore such as hemoglobin (Friedmann and Goldman 2015; Taylor and Anderson 1993). Rapid delivery of high-intensity energy at this wavelength disrupts melanosomes within keratinocytes, melanocytes, and melanophages, making them ideal for pigmented epidermal and superficial dermal lesions in Fitzpatrick skin types I–II (Friedmann and Goldman 2015; Kopera et al. 1997).

QS Alexandrite Laser

The more deeply penetrating 755-nm wavelength of the Q-switched alexandrite laser (QSAL) has a lower absorption coefficient for melanin and is emitted over a longer pulse duration (50–70 ns) than that of QSRL, which may serve to decrease adverse events (e.g., postinflammatory hyperpigmentation (PIH)) in dark-skinned patients as a result of gentler melanosomal heating. QSAL treatments of Fitzpatrick skin types of IV or lower are typically performed with 3- to 5-mm spot sizes and 4–8 J/cm^2. Lower fluences may lead to equal efficacy with decreased PIH (Friedmann and Goldman 2015; Wang and Chen 2012).

A novel QSAL with energy delivered in picoseconds (as low as 550 ps) may produce greater tensile stress on melanosomes than nanosecond pulse durations, enhancing their photomechanical and photothermal destruction. Collateral tissue heating and associated adverse events are minimized owing to the lower fluences required (Friedmann and Goldman 2015; Dover et al. 2012). As a result, potentially all skin types may be treated with this device. A 3–5-mm spot size and 1.5–2.83 J/cm^2 fixed fluence are favored (Friedmann and Goldman 2015).

Pretreatment Procedure

A history of keloids, conditions that may impair wound healing, recent oral retinoid use, pregnancy, breastfeeding, photosensitivity, and/or abnormalities localized to the treatment area (active infections, malignant lesions, scarring, or burns) should be ruled out before undertaking any procedure. Prophylactic antiviral therapy for herpes simplex virus is not routinely performed before QS lasers (Friedmann and Goldman 2015). Topical depigmentation products can be used pre- and posttreatment (Arora et al. 2012).

All patients should have photographs and written informed consent obtained upon arrival (Arora et al. 2012; Friedmann and Goldman 2015). Before treatment, the area to be treated should be washed with a neutral cleanser to remove any makeup or other impurities. Topical anesthesia is generally unnecessary given the limited treatment area, and it is usually bearable (Friedmann and Goldman 2015).

QS laser treatment of lower eyelid skin within the borders of the bony orbital rim requires intraocular metal eye shields (Arora et al. 2012).

Melasma and Q-Switched Laser

Melasma is a common and persistent disorder of hyperpigmentation that affects a significant portion of the population, affecting mainly women (Werlinger et al. 2007; Park et al. 2011), being more common in Black, Latin, and Asiatic people (Kauvar 2012). Patients report that the condition has a markedly detrimental effect on their quality of life (Park et al. 2011; Balkrishnan et al. 2003; Dominguez et al. 2006).

Melasma presents as symmetric, hyperpigmented macules and patches on the face, usually on the cheeks, bridge of the nose, forehead, chin, and upper lip (Kauvar 2012; Choi et al. 2010;

Grimes 1995; Gupta et al. 2006; Zhou et al. 2011). Typically it affects more women at reproductive age with Fitzpatrick type IV–VI, but can also affect men (Sarkar et al. 2014). The ratio between affected women and men is of 9:1 (Kauvar 2012). Although its photogenesis is not fully understood, pregnancy, sunlight exposure, birth control pills, hormone therapy, genetic factors, mild ovarian dysfunction, and autoimmune thyroid disease may be implicated (Jang et al. 2011; Kauvar 2012; Choi et al. 2010; Gupta et al. 2006; Sarkar et al. 2014; Lee et al. 2010). Sun exposure can trigger melasma because it stimulates melanocytes to produce increased melanin, and even a small amount of sun exposure can worsen the condition. Irritation or inflammation of the skin can also stimulate melanin production and worsen melasma (Kauvar 2012; Grimes 1995). In some cases, it can disappear spontaneously, but in general, the condition remains for the rest of the patient's life (Zhou et al. 2011).

The most widely accepted classification of melasma in recent years is based on the pathological manifestations (Zhou et al. 2011; Rigopoulos et al. 2007), including the epidermal type without melanophages in the dermis, the dermal type with melanophages in the dermis, and the mixed type in which part of the lesion is of the epidermal type and part of the dermal type (Kauvar 2012; Zhou et al. 2011). By Wood's light (340–400 nm), the epidermal melasma can be visualized with brown patches or macules, and the dermal types normally are not visible except when they are present as blue or black (Kauvar 2012; Zhou et al. 2011; Sarkar et al. 2014).

The major clinical feature of melasma is hyperpigmentation in the form of patches or macules, but it also has been observed that some patients have an increased distribution of telangiectatic erythema in the macules (Kim et al. 2007).

In the histologic examination, it is possible to observe that the quantity of melanocytes is not increased; however, their size gets wider with more dendrites. They are also more active. The dermal pigment, when present, will normally show up at the middle dermis within the melanophages. These melanophages are usually near to small and increased vessels, with few or no inflammation (Kauvar 2012; Zhou et al. 2011).

It is known that melanocytes respond to angiogenic factors as they express receptors to vascular endothelial growing factor (VEGF). Kim et al. (2007) demonstrated that the area of melasma has 33,89% more vessels than a near area without macules and 16,28% of these vessels are thicker. It is reported that the keratinocytes have an increase in the VEGF in melasma. The increase of the density and size of the vessels in the melasma area is directly related to the increase of the pigmentation of the macules. Therefore, treatment of the vessels in melasma should be important (Kim et al. 2007).

Melasma is often a therapeutically challenging disorder to the dermatologists. The most important thing to treat melasma is to understand that there are differences in the activity of the melanocytes between people. Despite of the treatment, it is very important not to irritate the skin when using acids. Patients should understand the importance of treating melasma avoiding erythema.

Topical treatment melasma can be divided in two groups: hydroquinone and non-hydroquinone (kojic acid, azelaic acid, ascorbic acid, or alpha arbutin). However, these kinds of treatment provide only temporary results and can also produce long-term complications (Kauvar 2012; Gupta et al. 2006; Katsambas and Antoniou 1995; Jesitus 2014; Polnikorn 2011). Physical therapies such as chemical peels, dermabrasion, lasers, and intense pulsed light (IPL) have also been used with varying degrees of success and side effects (Park et al. 2011; Kauvar 2012; Katsambas and Antoniou 1995).

Physical methods are the only option to remove the melanin and destroy the melanosomes. Hence the treatment with laser is the most recommended since 2005, when the use of fractional laser for the selective photothermolysis in the treatment of melasma began (Se-Yeong et al. 2008).

Various lasers that have been used for melasma include the following (Arora et al. 2012; Goldberg 1997):

- Green light: flashlamp-pumped pulsed dye laser (PDL) (510 nm), frequency doubled QS Nd:YAG (Q-switched neodymium:yttrium aluminum garnet – 532 nm)
- Red light: QS ruby (694 nm), QS alexandrite (755 nm)
- Near infrared: QS Nd:YAG (1,064 nm)

The green light lasers do not penetrate as deeply into the skin as the other two groups owing to their shorter wavelengths. They are therefore effective only in the treatment of epidermal melasma (Arora et al. 2012).

Since the green wavelength is also well absorbed by oxyhemoglobin, bruising and purpura may occur following laser irradiation. The purpura resolves in 1–2 weeks after treatment, and the clinical lesions lighten in 4–8 weeks. Occasionally, the bruising can lead to postinflammatory hyperpigmentation. Green light lasers often have a variable response, and thus test spots may be prudent prior to treating the whole area (Arora et al. 2012; Goldberg 1997).

Red lasers have longer wavelengths and thus may penetrate deeper into the dermis. They can also be used to treat epidermal-pigmented lesions without bruising, as they are not absorbed by hemoglobin (Arora et al. 2012; Stratigos et al. 2000). The pulse duration of the QS ruby laser (QSRL) varies from 20 to 50 ns and that of QS alexandrite laser (QSAL) from 50 to 100 ns (Arora et al. 2012).

Near-infrared lasers include QS Nd:YAG laser (1,064 nm) which has a pulse duration of 10–20 ns. Despite less absorption of this wavelength by melanin compared with the green and red light lasers, its advantage lies in its ability to penetrate more deeply in the skin. In addition, it may prove to be more useful in the treatment of lesions in individuals with darker skin tones (Arora et al. 2012; Goldberg 1997).

QS Nd:YAG Laser x Melasma

There have been several reports of treating melasma with the QS Nd:YAG laser. The mechanism of clinical improvement is proposed to be due to its ability to induce nonspecific dermal wound with healing response and subsequent neocollagenesis (Chan et al. 2010). Mun et al. (2011) found that the treatment of melasma skin with this laser resulted in the decreased number of melanocytic dendrites and altered ultrastructure of melanosome (Mun et al. 2011).

Its proposal is to describe a selective and more stable photothermolysis, minimally invasive, to remove the melanin and melanosomes. It happens due to the use of low energy during the process (Kauvar 2012; Mun et al. 2011; Kang et al. 2011).

For the mechanism of photothermolysis to be efficient, an appropriate wavelength is necessary (1,064 nm is useful because it reaches the dermis and epidermis). The same way, the thermal damage of the emitted pulse must be enough to destroy the melanin. And, at last, the pulse duration must be as minimal as possible to avoid damages in the near tissues. The ideal for melasma treatment is to cause the minimal thermal damage and the highest photoacoustic damage possible (Mun et al. 2011).

QS Nd:YAG is the most widely used laser for the treatment of melasma (Arora et al. 2012; Brown et al. 2011). In general the fluence used is less than 5 J/cm2, spot size 6 mm, and frequency of 10 Hz. The number of treatment sessions varies from 5 to 10 at 1-week intervals (Arora et al. 2012). Zhou et al. (2011) in their studies used QS Nd:YAG laser at low energy levels (fluence of 2.5–3.4 J/cm^2) weekly for 9 sessions in the treatment of melasma in 50 patients (Zhou et al. 2011).

Choi et al. (2011) treated melasma lesions in 20 patients older than 30 years with fluence 2.0–3.5 J/cm2, spot size of 6 mm, and a repetition rate of 10 Hz, in the whole face. The treatment was performed five times at 1-week intervals (Choi et al. 2010).

Over the last few years, QS Nd:YAG laser has increasingly been performed as “laser toning” or “laser facial” for non-ablative skin rejuvenation and melasma in Asian countries. In laser toning, multiple passes of low-fluence laser (e.g., 1.6–3.5 J/cm^2) are delivered through a large spot size (e.g., 6–8 mm) to optimize energy delivery (Arora et al. 2012; Chan et al. 2010). With a clinical endpoint of erythema plus lesional and

hair whitening (Chan et al. 2010; Kauvar 2012), the QS Nd:YAG treatments involve 10, 20, or more weekly treatments with as many 10–20 laser passes per treatment (Arora et al. 2012; Chan et al. 2010; Kauvar 2012). For melasma, laser toning should be considered as a second-line therapy, since this treatment is unlikely to be curative and is not without risk (Chan et al. 2010). Complications from these high cumulative fluence procedures include pain, urtication, hyperpigmentation, long-term hypopigmentation (guttate leukoderma), and rebound of melasma (Arora et al. 2012; Chan et al. 2010; Kauvar 2012; Kim et al. 2009, 2010).

Some publications try to compare the use of different types of laser in melasma treatment. Jalaly et al. (2014) compared low energy fractioned CO_2 laser with QS Nd:YAG 1,064 nm. In each side of the faces of the patients, one of these two lasers was applied. They were treated for 3 weeks with five weekly sessions. Two months after the end of the treatment, the patients were evaluated, and the side of the face treated with fractioned CO_2 had higher reduction of MASI (Melasma Area Severity Index) (Jalaly et al. 2014).

There is no relation between the therapeutic response between the QS Nd:YAG 1,064 nm and the severity of the disease or the Fitzpatrick skin of the patients (Zhou et al. 2011). Some studies suggest that more epidermal melasma respond better with topical treatment and intense pulsed light and that the patients of Fitzpatrick phototype IV respond better to the treatment in comparison with those of phototype III. However, as the QS Nd:YAG 1,064-nm laser reaches the epidermis, even in dermal lesions, this relation is not observed during or after the treatment.

In practice, the treatment of melasma consists of two stages: whitening stage and maintenance stage.

The whitening of the lesions tends to start between the fourth and sixth weeks and increases after each session of the treatment. Xi Zhou et al. (2011) observed, after the nine sessions, 61.3% decrease of the MASI using QS Nd:YAG with low energy. Seventy percent of the patients improved at least 50% of the lesions and 10% had 100% improvement. They concluded that the QS Nd:YAG 1,064-nm laser with low energy and wide spot is the new method of choice for melasma treatment. The response is fast and satisfactory in the whitening of the pigment (Zhou et al. 2011).

Sim et al. (2014) evaluated the outcome of the therapy of 50 patients treated with QS Nd:YAG 1,064-nm laser with 8-mm spot and 2,8 J/cm^2 of fluence. The patients were treated weekly for 15 weeks. Both patients and investigators have reported improvements of 50–74% of the lesions, what was confirmed by image. None of the patients had severe adverse effect during the treatment. So, they judged the treatment to be safe and efficient with this kind of laser (Sim et al. 2014).

Other publications demonstrate that Q-switched Nd:YAG 1,064-nm laser is safe and effective in the treatment of melasma. Sun et al. (2011) evaluated 33 patients and the treatment consisted of 1 session per week, in a total of 10 sessions. The reduction of MASI and the whitening of the lesions were perceptible from the seventh week on. The follow-up in the first, second, and third month after the end of the therapy demonstrated that the whitening process still existed at this period. In this work, no adverse effect was noticed (Suh et al. 2011).

Jeon et al. (2008) published a work evaluating the use of Q-switched ND:YAG 1,064-nm laser with 5-ns pulse in 27 patients. They used a 7-mm spot and 2–2.5 J/cm^2 of fluence in 17 patients and 1.6–2 J/cm^2 in other 10 patients. The number of passes varied from three up to ten until reaching the light erythema. Two months after the end of the treatment, 64.7% of the patients had recurrences of the lesions, but the intensity of the pigment was lower than in the initial macules, and in 29.41% there were no recurrences (Se-Yeong et al. 2008).

This way, the treatment of melasma during the stage of whitening should be gradual with one session per week for 10–12 weeks. It should be applied the larger spot possible (6–8 mm), with pulse frequency of 5–10 Hz. The energy should vary from 0.8 up to 1.8 J/cm2 (400–900 mJ). It should be applied two to four passes per area until the erythema lightens with few overlap (10–15%).

For a better result, the erythema should be as homogenous as can be.

Some studies demonstrate that the use of microdermabrasion before the procedure can help at the response of the laser. The use with one or two passes over the lesions is recommended, followed by the application of QS Nd:YAG 1,064 nm (Kauvar 2012). At the clinical practice, this kind of procedure seems to help cases of more laser-resistant melasma, once the decreasing of the cornea layer would ease the penetration of laser into the skin.

Alsaad et al. (2014) applied a procedure of microdermabrasion before the use of the QS Nd:YAG 1,064-nm laser with 5 ns of pulse, 6-mm spot, and 1.8–2.0 J/cm^2 of fluence in 10 patients, and in other 17 patients, they used the QS Nd:YAG 1,064-nm laser with 50 ns of pulse, 5-mm spot, and 1.6 J/cm^2 of fluence, along with the use of whitening cream at home. The patients were followed up for 3, 6, and 12 months after the end of the treatment. The patients who did three or four treatments had better results than those who did one or two treatments, all of them maintaining any kind of whitening until the completion of the 12 months (Alsaad et al. 2014).

After the procedure, it is recommended to chill the face for 10–15 min with cold mask or with cold air device. After it, a medium power corticoid cream and sunscreen lotion should be applied. The use of corticoids over the lesions can be recommended for up to 2 days after the session of laser, mainly in those lesions that seem to be more instable and reactive to the procedure.

The sessions are usually well tolerated, and the recurrent adverse effects are erythema that can last for 1–3 h and prurience. The less frequent effects are purpura, edema, acne, and decreasing and whitening of the face hair. Postinflammatory hypochromic and hypopigmentation-type guttate leukodermas are described as consequences of the use of the laser with high energy and multiple passes.

The reported cases of hyperchromic in some studies can attack up to 10% of the treated patients and can occur with few laser sessions, but usually due to the use of the QS Nd:YAG laser with the goal of rejuvenation (Chan et al. 2010). In these protocols, more passes or higher energy are applied so the heat can stimulate the production of collagen at the dermis. Many times, the protocols exclude the use of QS; hence, the 1,064-nm laser begins to have a bigger wavelength (e.g., from 5 to 200 ms). In most of the cases, the hypopigmentation persists.

The recurrence of melasma is defined as the increasing of the pigmentation or the increasing of the size of the lesion after the final treatment and still is a problem to the therapy with QS Nd:YAG 1,064-nm laser. The studies demonstrate that the recurrence of the lesions tends to occur from 2 to 3 months after the last session and the characteristics of the lesions are the same of the beginning of the treatment. This return of the pigmentation at the lesions occurs because the thermal effect over the melanocytes is reversible as time goes by. This way, the association of the maintenance therapy is necessary (Zhou et al. 2011; Se-Yeong et al. 2008).

The maintenance phase can cover QS Nd:YAG 1,064-nm laser and/or topical creams and oral medication. The eventual use of hydroquinone during and after the treatment is also described for the extension of the lightener response of the laser, avoiding the association with retinoids.

Wattanakrai et al. (2010) carried a study with patients with dermal or mixed melasma where they had, beyond the use of QS Nd:YAG 1,064 nm, the daily application of hydroquinone 2% versus the control group with patients that use only the hydroquinone. The patients treated with laser had five sessions of treatment using the spot of 6 mm and 3–3.8 Jcm^2 of fluence along with cold air. After 12 weeks, 92% of the patients that had association of hydroquinone with laser obtained a whitening of the macules. On the other hand, in the other control group, only 19,7% of the patients had improvement of the lesions (Wattanakrai et al. 2010).

The topical application of arbutin, hydroquinone, and vitamin C is convenient and preferred (Zhou et al. 2011).

In cases that the use of QS Nd:YAG 1,064-nm laser for maintenance aims to increase the gap between the sessions, initially each 15 days for 2 months and then one session each 30–60 days, according to the maintenance of the whitening.

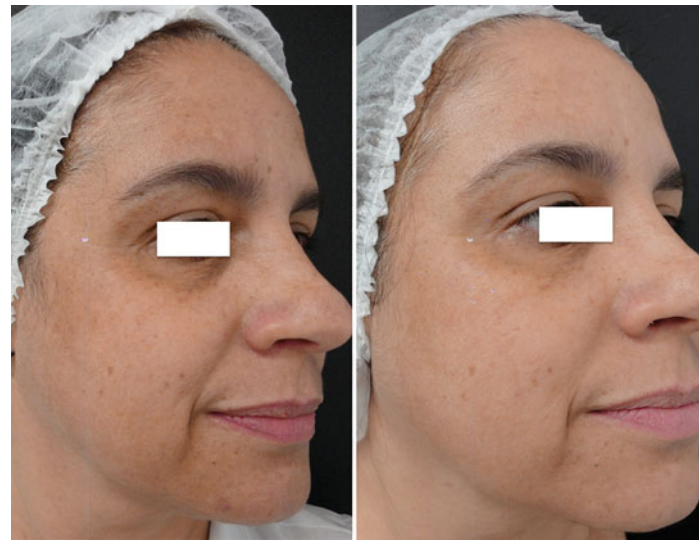

Fig. 1 Melasma: before and after three sessions treatment with fractioned QS Nd:YAG 1,064-nm laser (0.7 J/cm^2 with three passes, alternating sides, each 30 days)

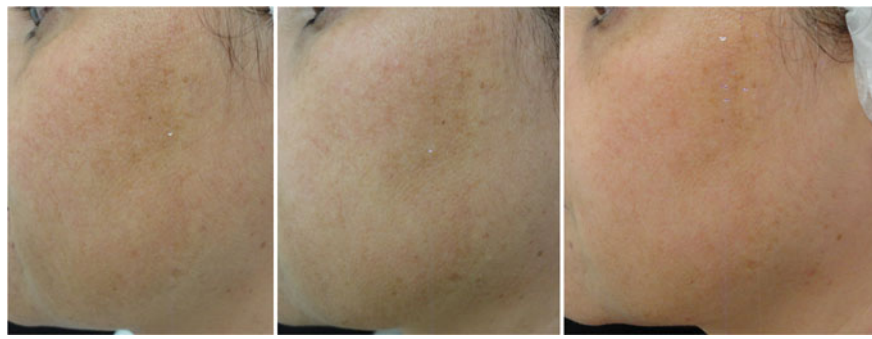

Fig. 2 Melasma: before and after two and three sessions of treatment with fractioned QS Nd:YAG 1,064-nm laser (0.7 J/cm^2 with three passes, alternating sides, each 30 days)

The use of the laser for maintenance demonstrated to be more effective than the use of isolated topical products as the melanocytes tend to stay less active and smaller in the lesions with the laser.

Melasma is a pigmentary disease of the skin with many pathological and aggravating factors involved. This way, a single treatment doesn't get to be completely effective. The best treatment is the combination of therapies, and, among those, the one that presents the best effectiveness and safety in the whitening of the lesions today is the use of low-energy laser Q-switched Nd:YAG 1,064 nm (Figs. 1, 2, 3, and 4). The association with whitening creams, microdermoabrasion, and peelings makes these results even better and lasting.

QS Ruby Laser x Melasma

The efficacy of QSRL for melasma is still controversial (Arora et al. 2012; Jang et al. 2011). The mechanism is the same as that of QS Nd:YAG laser, that is, it causes highly selective destruction of melanosomes. QS ruby laser, having a wavelength of 694 nm, is more selective for melanin than the QS Nd:YAG laser (1,064 nm) (Arora et al. 2012).

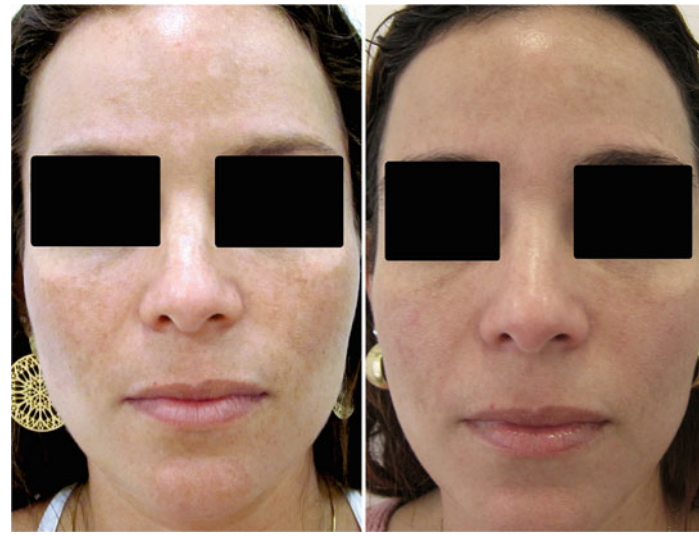

Fig. 3 Melasma: before and after ten sessions with collimated QS Nd:YAG 1,064-nm laser (5-ns pulse, 1.1–1.6 J/cm^2 of fluence and 8 mm of spot) combined with daily topical vitamin C

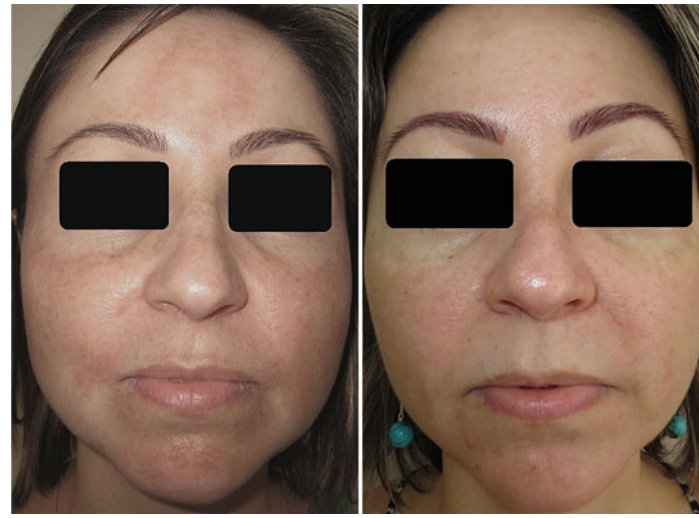

Fig. 4 Melasma: before and after ten sessions with QS Nd:YAG 1,064-nm laser (5-ns pulse, 1.1–1.6 J/cm^2 of fluence). Maintenance stage with vitamin C and daily topical whitening agents

So theoretically QSRL is expected to be more effective than QS Nd:YAG for melasma (Arora et al. 2012), but severe postinflammatory hyperpigmentation and hypopigmentation occurred in some patients within a short period of time (Choi et al. 2010; Hilton et al. 2013), suggesting that the high-energy mode of QS lasers is likely to be ineffective for melasma and therefore not a good choice for therapy for this condition (Zhou et al. 2011; Taylor and Anderson 1994). The role of QSRL is controversial with studies showing conflicting results (Arora et al. 2012).

On the other hand, Jang et al. (2011) showed that the use of multiple treatment sessions of low-dose fractional QSRL may be an effective strategy for the treatment of dermal or mixed-type melasma (Jang et al. 2011).

More studies are needed to establish its efficacy and safety in melasma (Arora et al. 2012).

Dark Circles Eyes and Q-Switched Laser

Dark circles eyes are also known as the periorbital hyperpigmentation. It is a common condition that occurs in both sexes with an increasing frequency in females (Friedmann and Goldman 2015; Roberts 2014). It can impart a fatigued and less youthful appearance to the face (Friedmann and Goldman 2015). Globally, skin-of-color patients are affected more than Caucasians. There is most likely a familial component as it may be seen in family members over generations (Roberts 2014).

The formation of dark circles is often multifactorial, with a number of factors reported to play a role. Among these factors are hollowing/shadowing, dermal melanin deposition, postinflammatory hyperpigmentation secondary to atopic or allergic contact dermatitis, prominent and superficial location of vasculature, and exogenous causes (penicillamine-induced periorbital pigmentation, bimatoprost-induced periorbital hollowing, and hyperpigmentation) (Friedmann and Goldman 2015; Freitag and Cestari 2007; Roh and Chung 2009; Xu et al. 2011). It is important for clinicians, as it may be a sign of an underlying systemic disease, skin disorder, allergic reaction, nutritional deficiency, or sleep disturbance (Friedmann and Goldman 2015; Xu et al. 2011).

Dark circles eyes usually present as bilaterally symmetric hyperpigmented patches around the eyes. One eye may be more involved than the other. It can affect either the upper or lower eyelid or both upper and lower. It may extend to involve the glabella and upper nose (Roberts 2014).

Aesthetic treatments include microdermabrasion, chemical peels, lasers, radiofrequency, injectable fillers, surgery, fat transfer, hydroquinone, and topical retinoids (Friedmann and Goldman 2015; Roberts 2014).

Cutaneous melanin has a broad, polychromatic absorption spectrum that peaks in the UV range and declines steadily as a function of increasing wavelength. Although significantly attenuated past 755 nm, energy absorption is still likely with wavelengths up to 1,064 nm, allowing for treatment of deeper pigment and darker Fitzpatrick skin types. Given that melanosomes have thermal relaxation times of less than 1 μs, ultrashort pulse durations are required to selectively confine photothermal and photoacoustic effects to these structures (Anderson et al. 1989; Friedmann and Goldman 2015). Many Q-switched lasers with nanosecond (and recently picosecond) pulse durations and wavelengths within the absorption range of melanin are currently available. The typical clinical endpoint of these treatments is immediate lesion whitening without pinpoint bleeding. Lower energy settings should be used initially to minimize the occurrence of PIH (Friedmann and Goldman 2015).

QS Nd:YAG Laser x Dark Circle Eyes

As demonstrated in treating melasma, repeated sessions with low-fluence, QS Nd:YAG treatments can decrease stage IV melanosomes, damage melanocytes, and reduce expression of melanogenesis-associated proteins. Higher fluences (4–5 J) can be used with a 3-mm spot size for other types of lower eyelid hyperpigmentation (Friedmann and Goldman 2015) (Fig. 5).

QS RUBY Laser x Dark Circle Eyes

QSRL treatment is performed with 2–4 J/cm^2 using a 5-mm spot size (or varied accordingly) at 1.5 Hz. The clinical endpoint with this device is immediate lesion whitening that resolves over 20 min followed by erythema and edema. Combining QSRL with topical hydroquinone and tretinoin before and after treatment has also led to significant improvement in this location (Friedmann and Goldman 2015).

Photorejuvenation and Q-Switched Laser

Clinical signs of photoaging include coarse skin texture, irregular pigmentation, and laxity of skin tone, as well as the appearance of fine lines and wrinkles (Hong et al. 2014; Yaghmai et al. 2010).

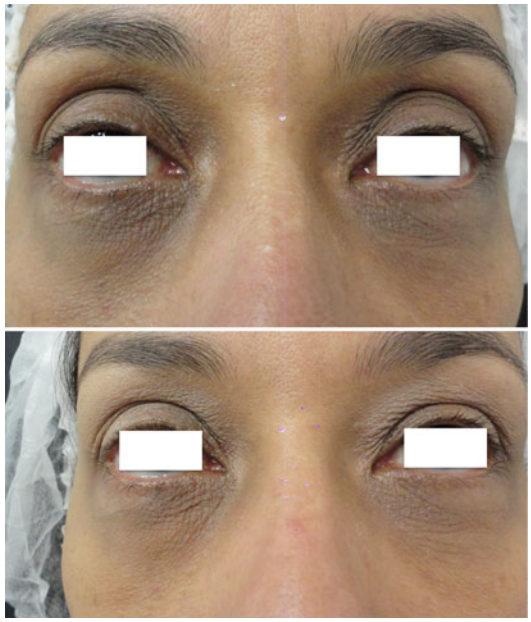

Fig. 5 Dark circle eyes: before and 30 days after four sessions of treatment with fractioned QS Nd:YAG 1,064-nm laser (1.2 J/cm^2 with ten passes each side at a time, each 30 days)

Diverse treatment modalities have been used to improve skin wrinkling and laxity, including chemical peeling, soft tissue filler, laser ablation, and facelift surgery. Recently, among these modalities, laser ablation has been highlighted due to its relatively effectiveness and shorter recovery time compared to other methods. It is classified into ablative laser and non-ablative laser. Generally, ablative lasers are considered more effective than non-ablative ones in treating rhytides, but they have a prolonged recovery time and more chance of complications, such as postinflammatory hyperpigmentation due to excessive thermal energy transferred to adjacent tissue (Hong et al. 2014).

Non-ablative lasers are thought to work through thermal energy transferred to small vessels and tissues in upper dermis, which stimulate dermal fibroblasts to induce collagen and elastin regeneration. Regarding the hypothesis above, long-pulse Nd:YAG lasers (LPND) have the advantage of reaching deeply located blood vessels and transferring energy to collagen adjacent to vessels while bypassing the epidermis. Patients with Fitzpatrick skin type III or more can be treated using with less risk because the wavelengths of the infrared area are weakly attracted to melanin (Hong et al. 2014). Although the typical response to this type of treatment is modest clinical improvement in mild to moderate facial rhytides, non-ablative therapy has gained in popularity over the past few years for photoaging therapy because of its little to no downtime. Laser systems, which have been traditionally used for this approach, rely on thermal induction for tissue change. Introduction of Q-switched laser systems has added a photoacoustic element to the dermal response. The Q-switched Nd:YAG laser has been shown to improve photodamage changes (Yaghmai et al. 2010; Goldberg and Silapunt 2001). With this laser system, relatively lower laser energies are needed resulting in mild immediate side effects (Yaghmai et al. 2010).

Non-ablative laser therapy remains a very advantageous therapeutic approach for skin rejuvenation. The potential of inducing beneficial textural and pigmentary changes to sun-damaged and aged skin without the need of ablation will result in dramatically less postoperative undesired immediate and long-term effects. These approaches have resulted in collagen production and subsequent dermal thickening with a reduction of surface textural changes. In addition, both pigmentary and erythematous changes can be improved. All of this with minor immediate postoperative effects is generally limited to transient erythema and edema. Long-term undesired effects such as fibrosis, scarring, or persistent pigmentary changes have been remarkably diminished relative to ablative procedures (Yaghmai et al. 2010).

The Q-switched Nd:YAG laser has exhibited the ability to achieve clinically desirable improvement in many parameters of skin rejuvenation. Remarkably, this has occurred with a very acceptable adverse effect profile and, as importantly, patient tolerance and acceptability (Yaghmai et al. 2010) (Fig. 6).

The authors have good experience with QS Nd:YAG laser. Dr. Issa has good results using QS (Clearlift – Alma Lasers) for melasma (Figs. 1 and 2) and dark circles eyes (Fig. 5). This device is a fractional (5 × 5 pixel) QS Nd:YAG 1,064-nm

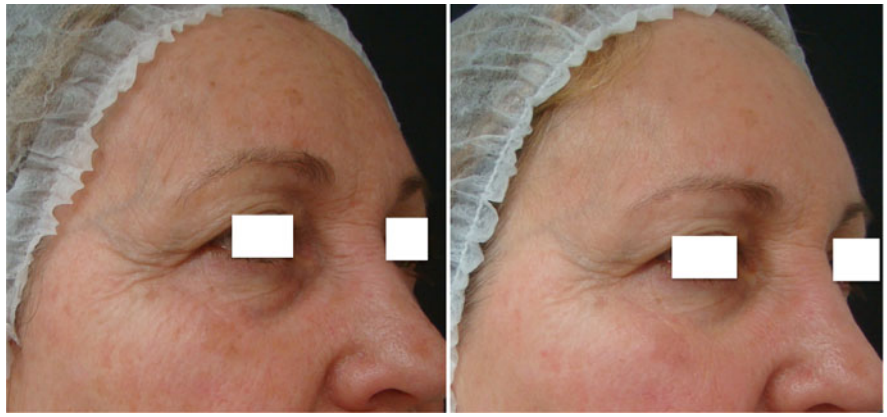

Fig. 6 Photodamaged skin (melanosis solar and wrinkles): before and after three sessions of treatment with fractioned QS 1,064-nm laser

laser with pulse duration of 20 ns, and its fluence ranges from 500 to 1,200 mJ/p. Regarding photodamaged skin, the best results are observed on periocular area (Fig. 6). Dr. Neiva has good experience using QS Nd:YAG (Spectra-Skintech) for melasma (Figs. 3 and 4).

Complications and Post-procedure of Q-Switched Lasers

As low energies are applied, the occurrence of post-procedure complications is very rare. Usually, erythema resolves over minutes to few hours and edema is not observed. The risk of blistering, PIH, and hypopigmentation is minimum due to the low energy used at the treatment.

The authors reinforce the importance of using sunscreen. Lightening creams can be used 24 h after each session during the treatment.

Take Home Messages

1. Melasma is often a therapeutically challenging disorder to the dermatologists. The same way, dark circles treatment and photorejuvenation are not easy to achieve.
2. Lasers have demonstrated significant efficacy in the treatment of hyperpigmented disorders, such as melasma and dark circles by selectively destructing pigment cells with a short pulse and low fluence.
3. Q-switched (QS) lasers, such as QS Nd:YAG, QS ruby, and QS alexandrite lasers, deserve special attention due to its recently uprising application in the treatment of melasma, dark circles eyes, and photorejuvenation.
4. Although QS lasers present the best effectiveness and safety in the whitening of the lesions, combined with other therapies, it can improve the treatment of melasma, dark circles, and photorejuvenation.

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Erbium Laser for Photorejuvenation

Alexandre de Almeida Filippo, Abdo Salomão Júnior, Paulo Santos Torreão, Lilian Mathias Delorenze, and Maria Claudia Almeida Issa

Abstract

The use of ablative lasers for skin resurfacing is considered one of the gold standard treatments for facial rejuvenation. Ablative fractional lasers, mainly erbium and CO2 lasers, were developed to reduce side effects and patient's downtime. The fractional erbium laser produces a thin ablation zone with little thermal injury in the epidermis and superficial dermis. It is well indicated for skin rejuvenation, improving texture, pigmentation, and fine lines. It can also be used for stretch marks and scars. In this chapter, we are going to describe erbium laser concept, mechanisms of action, protocols of treatment, side effects, and management.

Keywords

Erbium:yttrium-aluminum-garnet laser • Er:YAG laser • Facial rejuvenation • Resurfacing with ablative lasers • Fractionated laser technology • Rhytids • Wrinkle • Skin pigmentation • Skin texture

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Introduction

There are many different treatment options for skin rejuvenation, including medium and deep chemical peels photodynamic therapy, radiofrequency (see chapters ▶ "Non-ablative Radiofrequency for Facial Rejuvenation," and ▶ "Ablative Radiofrequency in Cosmetic Dermatology" in this volume), microneedling techniques and non-ablative and ablative lasers (see chapter Lasers, Lights, and Related Technologies in Cosmetic Dermatology, this volume). Fractional ablative lasers are probably the most efficient treatment available when we take into account cost, safety, and results (Campos et al. 2009; Holcomb 2011; Taudorf et al. 2014).

The fractional laser technology was introduced as safer alternative, being less operator dependent and with the aim of reducing the patient's post-operatory restrictions (Sklar et al. 2014; Lee et al. 2012; Kim et al. 2012). The fractional resurfacing method creates microscopic treatment zones (MTZs) with controlled width, depth, and density. These MTZs are surrounded by intact areas of epidermis and dermis allowing for faster tissue repair (Sklar et al. 2014).

Before the development of the pulse variation and the fractional technology, a long recovery time and high frequency of side effects such as bleeding, persistent erythema, edema, and post-inflammatory hyperchromia were common. Those side effects were related to the extent of epidermis ablation and to the almost purely ablative characteristic of the 2940 nm laser (Campos et al. 2009; Holcomb 2011).

Over the years, many operator "modes" have been developed allowing a variety of abilities for the Er:YAG laser that were not present at the beginning. The Er:YAG laser has the highest absorption coefficient for water, which is the chromophore targeted in the resurfacing technique. It is at least ten times higher than the CO2 laser. Biologically, it means that almost all the light energy delivered through the laser will be absorbed by the water present in the skin and will be converted to heat in an exothermic reaction (Holcomb 2011).

Those injuries will be repaired promoting skin rejuvenation (Holcomb 2011). The results with fractional lasers are less evident than those achieved with non-fractionated procedures; however, it is possible to have significant improvement of the photodamaged skin (Kim et al. 2012).

History

The first erbium:yttrium-aluminum-garnet (Er:YAG) laser was approved by the Food and Drug Administration in 1997 for tooth decay. It was later approved for facial rejuvenation. The Er:YAG laser is made of a solid state crystal of yttrium-aluminum-garnet doped with erbium ions (Er3+), and it is pumped by a pulsed broadband flashlamp emitting a wavelength of 2940 nm by the process of laser light amplification (Campos et al. 2009; Diaci and Gaspirc 2012).

The 2940 nm laser was originally conceived as a device to ablate the entire epidermis, completely exposing the dermis. For that reason, several post-operatory side effects were expected and limited the use of the device (Campos et al. 2009; Sklar et al. 2014).

The first generation was almost purely ablative laser, requiring multiples passes for the end point result and inducing dermal bleeding. The second generation was able to avoid unwanted bleeding by adding a long-pulse or a variable-pulse feature designed to promote tissue coagulation (Holcomb 2011).

The variable pulse technology was the ability to extensively control the pulse widths from very

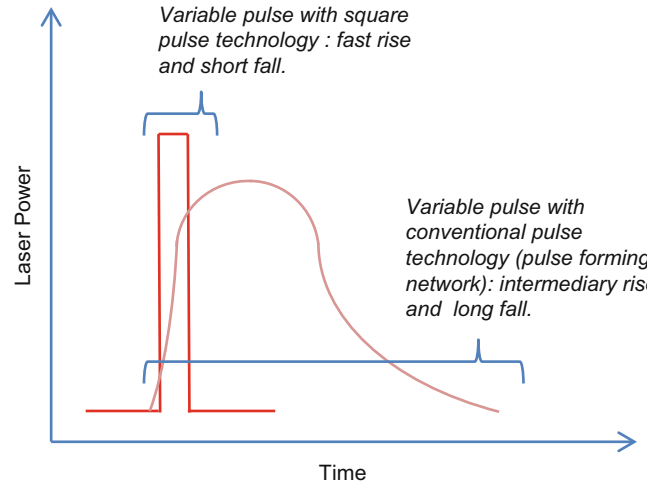

Fig. 1 Diagram comparing the behavior of the power curve over time for the square pulse technology versus conventional pulse technology (Adapted from Matjaz Lukac et al. 2007)

short pulses to very long pulses and the possible combinations of short and long pulses at one single laser shot. An even more developed control over the pulses was called the variable square pulse. It is the ability to deliver strictly the same peak power as the average power during the pulse, which means that there is no rise or fall in the curve that measures the power over time but a square shape (Lukac et al. 2007, 2008) (Fig. 1).

More recently, in the beginning of the 2000s, the development of fractioned version of the 2,940 nm laser was able to reduce skin surface area injured, preserving the efficacy of the non-fractioned version of the laser (Campos et al. 2009; Holcomb 2011).

Laser and Tissue Interaction

How Does Ablation Work?

In order to choose a laser to promote skin rejuvenation through ablation, the first thing that should be taken in account is the wavelength. Water is a major element present in the skin and is the target for all resurfacing laser. There are three major laser lengths that operate within absorption peaks for water: Er:YAG, Er:YSGG (yttrium-scandium-gallium-garnet), and CO2. When irradiated with those wavelengths, the tissue go through three basic phases, as the energy in the photons is transmitted to the water (Lukac et al. 2007, 2008, 2010):

Phase 1: Direct heat within the optical absorption depth. It happens when heat is transmitted directly and almost restrictedly to skin depth that light is capable of penetrating in the tissue, until all the photons are completely absorbed and converted to heat (Lukac et al. 2008).

The Er:YAG laser penetrates approximately 3 μm in the skin as it has the highest coefficient of absorption for water, the Er:YSGG laser penetrates 10 μm and has the intermediary coefficient of absorption for water, and CO2 laser penetrates 30 μm into the skin with the lowest coefficient of absorption for water (Lukac et al. 2008, 2010) (Fig. 2).

So the highest the affinity for water and the highest the absorption coefficients, the shallower the penetration of the laser, as all the energy within the photons is better absorbed by the water (Lukac et al. 2007, 2008, 2010).

Phase 2: Thermal diffusion. It happens when the heat is transmitted to deeper lying tissues, beyond the optical absorption depth. The longer the pulse length, the more evident is the result of thermal diffusion, tissue coagulation. Nevertheless, the shorter the pulse length, the less evident is the result of thermal diffusion as the pulse ends faster than the ability of the tissue to transmit the heat within neighbor structures, like in Q-switch devices (Lukac et al. 2008, 2010).

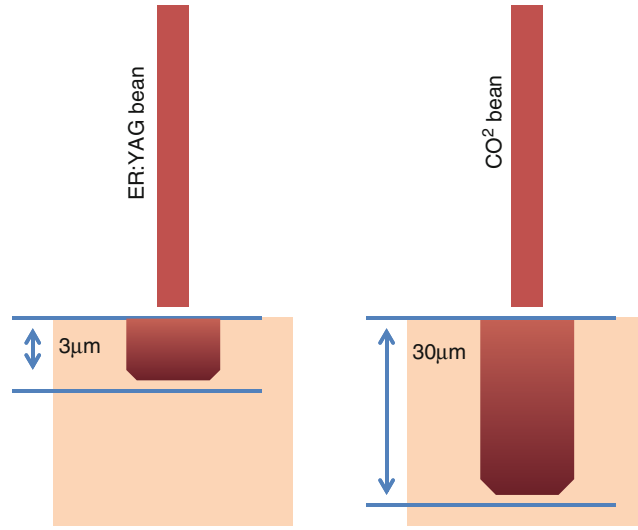

Fig. 2 Diagram comparing the optical penetration depth in the skin for the Er: YAG and CO2 lasers (Adapted from Matjaz Lukac et al. 2008)

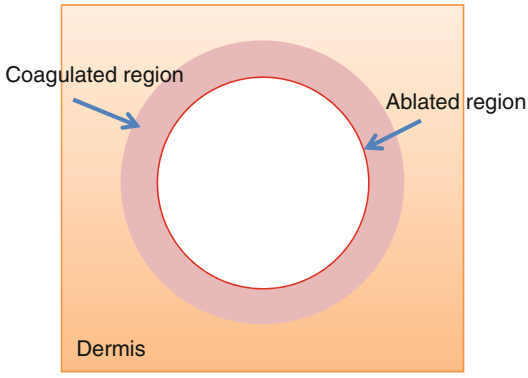

Fig. 3 Diagram showing the effect of the laser treatment on a schematic representation of a cross-sectional transverse view of a skin biopsy (Adapted from Holcomb 2011)

The smallest coagulation zone possible for each laser wavelength is limited by the optical penetration depth, as it is an immutable characteristic of the wavelength determining how much the laser penetrates the skin. But if we manipulate the pulse duration to last longer, heat is accumulated within the tissue, making the coagulation zone thicker through thermal diffusion, beyond the extent of the optical absorption depth. So is not possible to reduce the coagulation zone limited by laser wavelength and the optical penetration depth, but it is possible to increase the coagulation zone through thermal diffusion principle, making the pulse width longer (Lukac et al. 2008, 2010).

This is what is done by Er:YAG lasers to emulate the coagulative effect of the CO2 laser, further explained below in the item Ablative/ Coagulative Mode.

Phase 3: Tissue vaporization. It happens when the top part of the issue close to the surface is heated to a point where ablation occurs, and material is extruded leaving a small hole on the skin surface, followed by tissue injured by the heat in the surround area (Lukac et al. 2008) (Fig. 3).

Fractional vs Non-fractional

The fractional technology was first introduced in 2004 by Dieter Manstein et al., in a pilot study with wavelengths that varied from 1480 to 1550 nm. The ability to reduce the resurfacing side effects maintaining its efficacy allowed this new technology to be develop into several laser wavelengths: initially the non-ablative lasers, then the fractional CO2 laser, followed by the fractional Er:YAG laser (Manstein et al. 2004).

When skin tissue is treated with fractional lasers, vertical channels are created by columns of vaporization, drawing a grid of microscopic treatment zones, also called microthermal treatment zones or even microscopic thermal zones (MTZ). Each MTZ is composed of the ablated channels, also called microscopic ablation zones

(MAZ) and a border of coagulated tissue (Taudorf et al. 2014; Sklar et al. 2014; Skovbolling Haak et al. 2011).

Biologic Effects of the Treatment

Studies evaluating the efficacy of Er:YAG fractioned lasers have shown improvement of collagen arrangement and formation of new collagen types I, III, and VII. Immunohistochemical studies have shown total replacement of the MTZs into new collagen 3 months after treatment. Furthermore, it has been reported that multiple treatments provide continuous new collagen production for more than 6 months allowing skin rejuvenation with shorter downtime and fewer side effects (Taudorf et al. 2014; Sklar et al. 2014; Lee et al. 2012; Hammami Ghorbel et al. 2014; El-Domyati et al. 2014).

Laser Er:YAG Operator Modes

The Er:YAG laser has several modes of operation and can be used in a non-fractioned or fractioned fashion, produce pure ablation, pure coagulation, and blends of ablation/coagulation at several different ablation depths, and even capable of emulating a CO2 laser. Variations in pulse length, energy, fluence as well as pulse stacking and different spots promote versatility to this light source. There are five primary operations modes unevenly presented in different devices and industries (Holcomb 2011; Lukac et al. 2007, 2008).

Ablative Mode or Cold Ablation

It is the Er:YAG native and standard effect. Due to the high affinity for water, the laser produces superficial columns of almost pure ablation, capable of reaching the epidermis to superficial dermis (with pulse stacking) (Holcomb 2011; Lukac et al. 2008), as shown in Fig. 4. During the procedure areas of pinpoint bleeding may be observed, as in this mode there is not coagulation of the blood vessels. It is also used for drug delivery purposes (Jang et al. 2014), mimicking the effect of a superficial microneedling, due to the superficial and purely ablative laser profile, without barriers of coagulated tissue (Holcomb 2011).

Ablative/Coagulative Mode (Warm or Hot Ablation Mode)

It is the most common mode used in many Er:YAG devices commercially available nowadays. It avoids bleeding by inducing greater thermal effect and coagulation of dermis blood vessels. In this mode, the 2940 nm laser emulates the CO_2 laser coagulative effect with the variable pulse or a long pulse operation, generated through a sequence of shots with different energies and pulse durations (Holcomb 2011; Lukac et al. 2007).

There is a train of pulses where the first shot energy is beyond the ablative threshold, and the subsequent energy levels are always below the ablative threshold, cumulating heat in the skin and producing coagulation (Lukac et al. 2007, 2008, 2010) (Fig. 5).

In the warm ablation mode, there is an ablative pulse followed by sub-ablative long pulse, with a medium thick coagulation zone. In the hot ablation mode, there is an ablative pulse followed by longer sub-ablative long pulse, with a thicker coagulation zone (Lukac et al. 2007, 2008, 2010).

This is the best 2940 nm mode addressed to induce skin rejuvenation as there is greater thermal effect and more collagen remodeling, but it may produce hyperchromias or hypochromias due to the coagulation and heat produced during the procedure (Holcomb 2011; Lapidoth et al. 2008).

It is the authors' preference to use this mode when rejuvenating the face with high fluences, 3 to 5 pulse stacks and 2 to 3 passes. For non-facial areas low fluences, 2 stacks, and 1 or 2 passes.

Coagulative Mode or Smooth Mode

In this mode, only sub-ablative fluences and energies are used during the pulses, emulating the

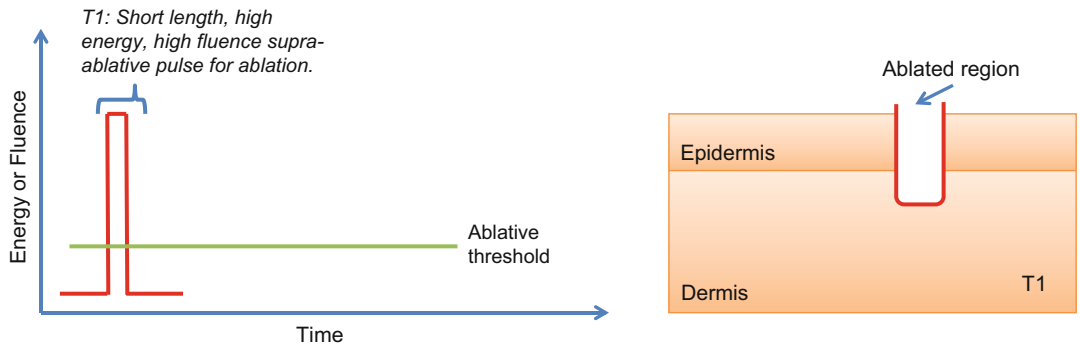

Fig. 4 Diagram showing a high energy, high fluence, and short width pulse above the ablation threshold over time and the effect of the Er:YAG laser on a schematic representation of a cross-sectional vertical view of a skin biopsy (Adapted from Matjaz Lukac et al. 2010)

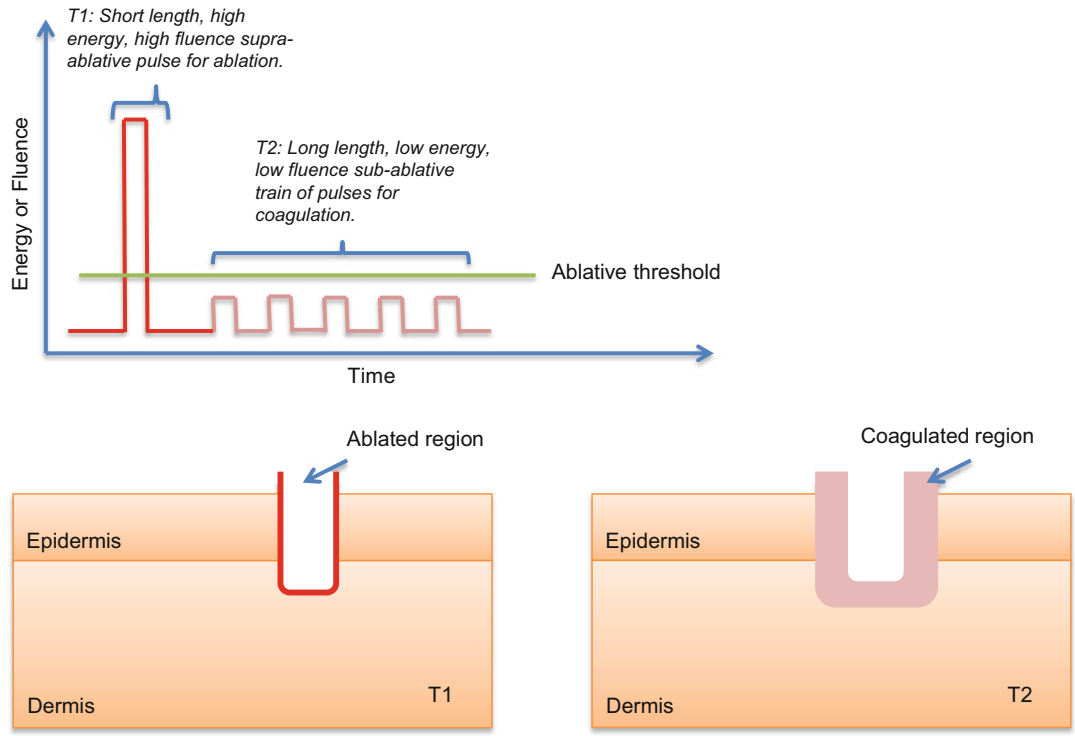

Fig. 5 Diagram showing in T1 a high energy, high fluence, and short width pulse above the ablation threshold over time; followed by in T2 a long pulse composed of few short pulses with low energy and low fluence below the ablation threshold over time; and the effect of the Er:YAG laser on a schematic representation of a cross-sectional vertical view of a skin biopsy (Adapted from Matjaz Lukac et al. 2010)

effect of non-ablative lasers (Holcomb 2011). This is also done through the variable-pulse or long-pulse technology. For the coagulative effect, small amounts of energy are delivered within a long pulse, normally a long train of sub-ablative pulses, building heat up into the tissue, promoting coagulation without ablation or with very little ablation (Lukac et al. 2007, 2008, 2010) (Fig. 6).

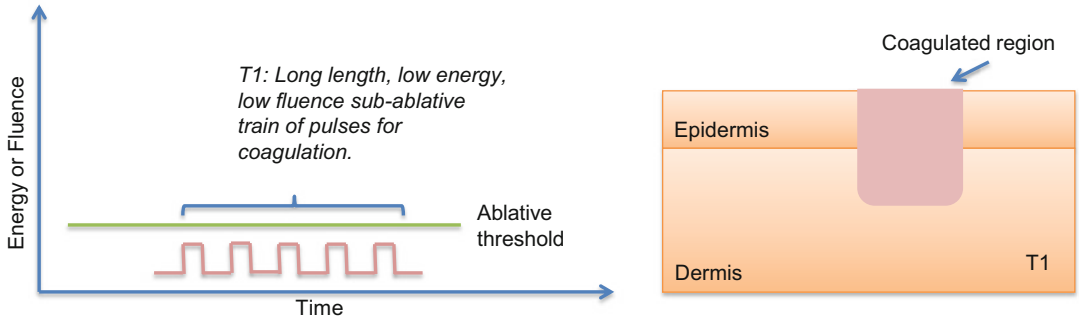

Fig. 6 Diagram showing in T1 a long pulse composed of few short pulses with low energy and low fluence below the ablation threshold over time and the effect of the Er:YAG laser on a schematic representation of a cross-sectional vertical view of a skin biopsy (Adapted from Matjaz Lukac et al. 2010)

Stacking Mode

This is not essentially an operator mode as it can also be present within the previous discussed modes, as in the ablative and ablative/coagulative modes. During the pulse stacking, a train of high-energy, high-fluence, short-length pulses are delivered in sequenced manner, one on the top of the other, without moving the laser handpiece, so the ablation depth of each shot is added to the previous ones, reaching deeper layers in the skin. Again it can appear as an operator mode or it can be hidden within other modes automatically controlling the ablation depth (Holcomb 2011; Lukac et al. 2007; Lapidoth et al. 2008).

Non-fractional Mode

In this mode, the laser beam is not fractioned in smaller lasers beans. Instead, the entire epidermis ablated by the laser, leaving no areas of intact skin, as it was done originally at the Er:YAG full-field resurfacing treatment regimens (Lukac et al. 2008, 2010).

Indications

The Er:YAG lasers can be used in a variety of lesions especially related to sun damage including actinic keratoses, solar lentigines, superficial rhytides, mild dyschromia, and Favre-Racouchot disease. (Janik et al. 2007). Authors have good results for photodamaged skin treatment (Figs. 7 and 8).

It can also be used for colloid milium, angiofibromas, nevi, seborrheic keratosis, xanthelasma, syringomas, sebaceous hyperplasia, rhinophyma, atrophic facial acne scars, trichoepitheliomas, actinic cheilitis, Bowen's disease, erythroplasia of Queyrat. It has also been used associated with antineoplastic drugs as drug delivery purposes in the treatment of actinic keratosis and superficial basal cell carcinomas (Janik et al. 2007).

As the water is the main target, it is well tolerated by higher phototypes patients, up to IV as shown by Lapidoth et al. and Lee et al. (2012).

Pretreatment

Patients should understand the mechanism of action of the proposed treatment, as well as its possible side effects and complications. Dermatologists should explain every step of the process from wound care to normal timelines for healing, diminishing excessive expectations and worries related to the procedure and post-procedure (Holcomb 2011).

Patients must understand that it is normal to feel bearable pain during the intervention and that erythema, edema, and crusts are expected side effects. The erythema can be prolonged according to the used settings. Dyschromias are

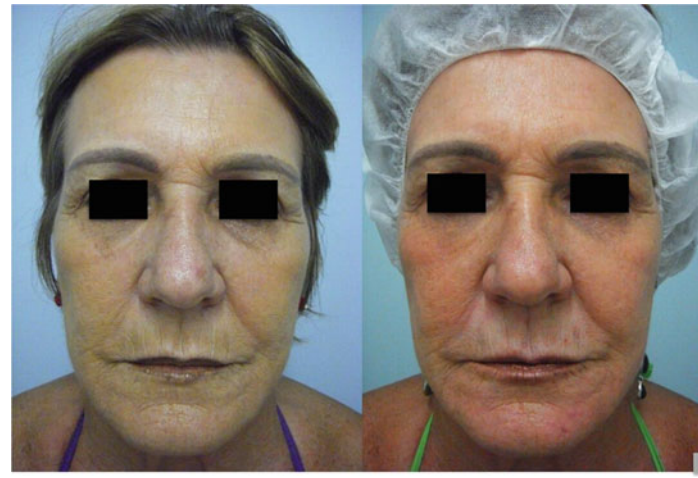

Fig. 7 Before and 90 days after Er:YAG intervention. Treatment regimen: first pass with ablative mode with 15 mJ and 3 ms, and second pass with coagulative mode 27.5 mJ e 5 ms

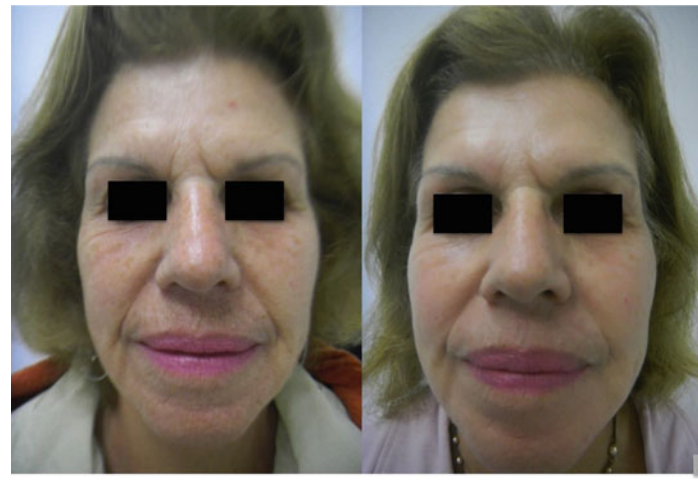

Fig. 8 Before and 90 days after Er:YAG intervention. Treatment regimen: first pass with ablative mode with 15 mJ and 3 ms, and second pass with coagulative mode 27.5 mJ e 5 ms

generally rare and tend to be transitory (Holcomb 2011).

The skin rejuvenation promoted by the erbium laser is significant, although several sessions may be necessary to achieve optimal results and some degree of photodamage may always persist (Holcomb 2011).

It is imperative for patients to start antiviral therapy 2 days prior to the procedure (continued for 5–7 days after or until complete reepithelialization), regardless of the previous history of herpes simplex (Lapidoth et al. 2008).

Patients must also be instructed to use 0.05% tretinoin cream, nightly for 2–4 weeks, prior to laser treatment and should stop few days prior the procedure. (Papadavid and Katsambas 2003)

Techniques

Topical anesthetic cream should be applied 30 min before the treatment and removed just before the procedure.

There are several different techniques that change according to the authors. In 2008, Lapidoth et al. (2008) reported results from a skin rejuvenation study with fractionated 2940 nm Er:YAG laser (Pixel, Alma Lasers Ltd.) in patients with Fitzpatrick skin type II-IV. The authors have used

two to four stacked passes with a 7 × 7 tip (49-dot), which emits 28 mJ/P (per pixel), with the maximum pulse energy output being 1.400 mJ/P. For the first pass, a penetration of 20 μm of evaporative and 30 μm of thermal, for the second pass respectively 35 and 40 μm, for the third pass 50 and 45 μm, for the fourth pass 60 and 50 μm, with a microzone diameter of 150 μm, and a mean number of 3.2 sessions. Sixty days after the final treatment, all patients showed clinical improvement greater than 50%.

Goldberg and Hussain (2011) conducted a study in patients with Fitzpatrick skin type I-III, utilizing Er:YAG laser 2940 nm with a full face and single pass treatment, at low energy settings of 15–30 mJ/microspot at 40 Hz, with 8–21% coverage, for six sessions. All patients presented clinical improvement in the treated skin; half reported over 50% improvement.

Karsai et al. (2010), studied the 2940 nm laser response on patients with Fitzpatrick skin type I-III by applying a total fluence 60 J/cm2, with six stacked pulses in single session. The outcome of this study showed reduction of approximately 10% of wrinkle depth.

A study performed in Korea, by Lee et al. (2012), in patients with Fitzpatrick skin type III-IV with Er:YAG laser (ACTION™, Lutronic, Korea), applied full face treatment, one or two passes with 12–14 mJ per microspot, with 250 μs pulse width and mean number of 2.3 sessions. The results showed an improvement greater than 26% in 62.5% of subjects.

El-Domyati et al. (2013) showed that both multiple sessions of fractional Er:YAG laser or a single session, with multiple passes, of ablative Er:YAG laser have comparable efficacy clinically and on dermal neocollagenesis, and multiple sessions of fractional Er:YAG laser resurfacing are effective with higher safety and shorter downtime (El-Domyati et al. 2013).

Posttreatment

When using the pure ablative mode, pinpoint bleeding is expected; therefore, wet gauze compression for several minutes post-procedure is indicated (Campos et al. 2009; Holcomb 2011; Papadavid and Katsambas 2003).

After the laser session, topical semioccluded dressings ("closed" technique) or topical moisturizers ("open" technique) are applied, as with CO_2 laser postoperative care. It is the authors' preference to apply a d-pantenol or sucralfate healing cream for 8 h and then after that period washing the face with gentle cleanser and reapplying the healing cream four times a day for 7–10 days. It is important to tell the patient not to remove crusts or scratch the skin (Campos et al. 2009; Papadavid and Katsambas 2003).

The use of physical sunscreen is advised and indicated 48 h after the treatment during the day. Antiviral therapy should be carried on for at least 5 days as mentioned earlier. It is important to have let the patient have an emergency number if the post-procedure goes not as planned. Two weeks after laser treatment, association of topical hydroquinone 2–5%, tretinoin 0.05–0.1%, and hydrocortisone 1% cream is recommended for 2–4 weeks (Papadavid and Katsambas 2003).

Complications

Unexpected side effects and complications include persistent erythema, milia, acneiform eruptions, eczema, infections, impaired healing, scars, and permanent hyper- or hypopigmentation (Janik et al. 2007).

Post-inflammatory hyperpigmentation is transient. Late complications, such as hypopigmentation, are seen in very few patients (4%) treated with the Er:YAG laser. Hypopigmentation seems to be related to the ablation depth which is usually more superficial with the Er:YAG laser. The presence of bleeding forces the surgeon to discontinue laser treatment and therefore prevents serious complications, due to the larger absorption coefficient for tissue water and the superficial penetration of this wavelength. The risk of scarring and hypopigmentation could increase if the laser surgeon seeks to achieve considerable ablation depths and more significant clinical improvement.

Conclusion

The Er:YAG laser technology has been continuously developed since its beginning and nowadays has become a powerful versatile tool for the dermatologist. This wavelength is capable of handling from photodamage wrinkles to basal cell carcinomas.

The highest coefficient of absorption for water among ablative lasers assures the smallest penetration depth and the smallest unwanted thermal dissipation effects. Also, variations in pulse widths can obtain deeper thermal effects when such treatment is desired. The Er:YAG laser is therefore the ideal laser for skin resurfacing.

Take Home Messages

- The resurfacing with ablative lasers is considered one of the gold standard methods for facial rejuvenation.
- It can promote improvement of facial rhytids, skin pigmentation, and skin texture.
- The usual treatment delivers short downtime and few side effects.
- It is possible to have significant improvement of the facial photodamaged skin after just one session.
- The Er:YAG highest coefficient of absorption for water, the smallest penetration depth, the smallest thermal dissipation effects.
- Deeper thermal effects can be achieved through pulse widths variations.

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Erbium Laser for Scars and Striae Distensae

Paulo Notaroberto

Abstract

Scars are a very common complication of skin injuries such as burns, surgeries, and trauma (lacerations or abrasions) affecting millions of people every year. The appearance of scars can be very disturbing to patients both physically and psychologically being aesthetically unacceptable and impacting negatively on the quality of life. Treatment of scarring may require many different kinds of treatments, depending on the kind of scarring present; however skin vaporization and residual thermal damage can only be achieved by ablative lasers and explain the superiority of ablative laser treatment over chemical peels and dermabrasion. The present chapter addresses the issue of ablative Erbium (Er:YAG) laser which is highly absorbed by water and together with the possibility of being modulated by variations on pulse durations makes it a precise, safe, and effective tool on managing scars. The aims of ablative Erbium laser on treating atrophic scars are reducing the depths of the scar borders and stimulating neocollagenesis to fill depressions.

Keywords

Laser • Erbium • Ablative • Ablation • Resurfacing • Scar • Striae distensae • Stretch mark

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Contents

Introduction

Scars are a very common complication of skin injuries such as burns, surgeries and trauma (lacerations or abrasions) affecting millions of people every year. The appearance of scars can be very disturbing to patients both physically and psychologically (Harithy and Pon 2012) being aesthetically unacceptable and impacting negatively on the quality of life. Scars can also cause pruritus, tenderness, pain, sleep disturbance, anxiety, and depression in postsurgical patients (Oliaei et al. 2012).

Acne is a common disorder that affects up to 80% of the people with age ranging between

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11 and 30 years (Oliaei et al. 2012; Fife 2011; Al-Saedi et al. 2014) and over 90% among adolescents (Fabbrocini et al. 2010). Several factors are related in the pathogenesis of acne, but the severe inflammatory response involved in the process may result in permanent scars, an unfortunate complication of acne vulgaris: permanent scar (Fife 2011). The incidence of acne scarring is not well studied, but it may occur to some degree in 95% of patients with acne vulgaris. Studies report the incidence of acne scarring in the general population to be 1–11%. Having acne scars can be emotionally and psychologically distressing to patients. Acne scars may be linked to poor self-esteem, social ostracism, withdrawal from society, depression (Al-Saedi et al. 2014), anxiety, altered social interactions, body image alterations, lowered academic performance, and unemployment and is a risk factor for suicide (Fife 2011).

There is no general consensus in the literature as to what is the best treatment (Harithy and Pon 2012). In the last 15 years, laser resurfacing has emerged at the forefront of acne scar treatment. The first lasers to be used for acne scarring were the ablative CO2 and Er:YAG lasers, which emit radiation at wavelengths of 10,600 and 2,940 nm, respectively; having high affinity for water, they ablate the epidermis and stimulate collagen synthesis (Hession and Grabber 2015) (see chapter ▶ "CO_2 Laser for Scars," this volume). Determining which laser system to use depends upon the type and severity of acne scarring, the amount of recovery a patient can tolerate, and the ultimate goals and expectations of each patient (Sobanko and Alster 2012). No treatment is 100% effective on "erasing" scars, and the best result is improvement, not perfection. Treatment of scarring may require many different kinds of treatments, depending on the kind of scarring present (Keyal et al. 2013); however, skin vaporization and residual thermal damage can only be achieved by ablative lasers and explain the superiority of ablative laser treatment over chemical peels and dermabrasion (Alster and Zaulyanov-Scanolon 2007).

The clinician who deals with scar treatment must understand the pathophysiology of scar formation. The process of wound healing is didactically separated in three stages: inflammation, proliferation, and maturation (Harithy and Pon 2012; Fabbrocini et al. 2010). By examining biopsy specimens of acne lesions from the back of patients with severe scars and without scars, Holland et al. found that the inflammatory stage was stronger and had a longer duration in patients with scars versus those without (Fabbrocini et al. 2010).

Erbium 2,940 nm Photothermal Ablation

Erbium (Er:YAG) laser is a flashlamp-excited system that emits light at an invisible infrared wavelength of 2,940 nm. The chromophore for ablative lasers is water. It is not an exaggeration to affirm that the laser target is the skin per se once the skin is made up of approximately 80% of water. Erbium 2,940 nm wavelength light is between 12 and 18 times better absorbed by tissue water when compared to the 10,600 nm wavelength emitted by the CO2 laser. The first generation of Erbium was approved for cutaneous resurfacing by the FDA (Food and Drug Administration) in 1996 (Riggs et al. 2007), and it works emitting a short pulse (SP) of 250–350 μs that is less than the thermal relaxation time of the skin, which is 1 ms (Al-Saedi et al. 2014). The ablation threshold of the first-generation Er:YAG laser for human skin has been calculated at 1.6 J/cm^2 as compared with 5 J/cm^2 calculated for high-energy, short-pulse CO2 laser systems. Because the Er:YAG laser is so exquisitely absorbed by water, the SP Erbium laser causes 10–40 μm of tissue ablation and as little as 5 μm of thermal damage on the surrounding tissue (Al-Saedi et al. 2014). The second generation of Erbium lasers has variable and longer pulses (500 μs–10 ms) and was FDA approved in 1999. Longer-pulsed Er:YAG lasers have shown to increase the

underlying thermal effect zone to approximately 120 μm (Lukac et al. 2010), leading to coagulation and skin tightening but increasing risk of secondary side effects such as erythema and dyschromia (hypo- and hyperchromia) (Alster and Zaulyanov-Scanolon 2007). Side effects and complications after Er:YAG laser resurfacing are similar to those observed after CO_2 laser skin resurfacing, but they use to have less severe in duration, incidence, and intensity (Keyal et al. 2013; Alexiades-Armenakas et al. 2008).

Resurfacing lasers are high-energy pulsed lasers that generate photothermal ablation that occurs with rapid heating when tissue absorbs enough laser energy leading to tissue vaporization. The thermal effect also occurs in the area surrounding the ablated zone due to thermal diffusion and (zone of thermal damage). Modulated Erbium lasers with longer pulse durations result in larger areas of thermal coagulation when compared to the first-generation SP Er:YAG 2,940 nm laser devices (Carrol and Humphreys 2006). Panzer and Golberg conducted a study on the histologic effect of a variable-pulsed Er:YAG laser and concluded that the thermal effect desired from CO_2 can be observed by using longer (50 ms pulse width) Er:YAG laser pulses (Pozner and Goldberg 2000; Khatri 2001). The ablative Erbium laser produces moderate immediate intraoperative contraction, but subsequent wound healing results in dermal shrinkage identical to that seen with CO_2 ablative laser devices (Sapijaszko and Zachary 2002).

Response rates to the first-generation short-pulse Er:YAG lasers ranged from 25% to 90% (Fabbrocini et al. 2010). In order to address these shortcomings, longer-pulsed Er:YAG lasers were developed. In a prospective study of 35 patients with pitted acne scars, results were excellent (>75% improvement) in 36% of patients and good (50–75% improvement) in 57% (Hession and Grabber 2015).

The combination of short pulses (for ablation) with longer pulses (for coagulation) is called dual mode Er:YAG, and the systems working this way range pulse durations from 500 μs to 10 ms. As a group, these lasers have been shown to produce deeper tissue vaporization, greater control of hemostasis, and collagen shrinkage leading to clinical skin tightening. This translates into greater clinical improvement in mild to moderate acne scars than their short-pulsed predecessors and thus represent a good compromise between CO_2 and the Er:YAG laser from the first generation (Keyal et al. 2013).

The aims of ablative laser on treating atrophic scars are reducing the depths of the scar borders and stimulating neocollagenesis to fill depressions. Focused vaporization can be used for treating isolated scars, but performing the treatment over an entire cosmetic unit (field treatment) is highly recommended for increasing the overall collagen tightening effect which promotes improvement of distensible scars. Field treatment also decreases the chance of a sharp demarcation between treated and untreated sites (Alster and Zaulyanov-Scanolon 2007). A feather treatment using gentler energy should be performed on the periphery of the treated area with the goal of smoothing the transition between treated and untreated areas.

The concept of ablative fractional photothermolysis (AFP) was introduced in 2003 as an option for low-risk, short downtime and effective resurfacing techniques. Fractionated lasers work by thermally altering a "fraction" of the skin, leaving up to 95% of skin untouched, leading to a faster healing, shorter downtime, and less adverse effects in comparison to non-fractional ablative laser devices (Loesch et al. 2014; Zgavec and Stopajnik 2014). AFP induces small three-dimensional zones of thermal damage known as microscopic treatment zones (MTZs) (Harithy and Pon 2012). In spite of not ablating a large surface, AFP generates MTZs which are real "columns of heat" capable of generating collagen contraction (skin tightening) and inflammation which stimulates neocollagenesis. For AFP, the depth of penetration is directly proportional to the energy delivered in each MTZ, and the intensity of the treatment increases at the same rate that the density of spots is increased. Densities can be reported as either percentage of laser coverage in a treated area or number of MTZs per square centimeter (Harithy and Pon 2012).

Protocols

Resurfacing

The treatment must be planned, executed, and followed up carefully in order to maximize results and minimize adverse effects.

The skin must be prepared with topical use of glycolic acid or tretinoin associated with vitamin C at least 1 month prior performing the procedure. The topical use of hydroquinone on darker phototypes on the pretreatment period to minimize the risk of residual hyperchromia is not a consensus. All the patients should be advised about the need to use sunscreens with very high UVA and UVB protection and to avoid sun exposure pre- (at least 1 month) and posttreatment (at least 2 months).

Oral prophylactic anti-herpetic therapy regimen should be started 2 days prior the procedure and must be sustained for 5 days, and it is mandatory whenever there is a previous history of herpes simplex or when an aggressive treatment will be performed (especially if the treatment affects the peri-oral area). The prophylactic antibiotic therapy is required when a non-fractional ablative treatment will be performed.

Topical anesthesia used to be enough for pain control, but oral pain reliefs (such as trometamol ketorolac), infiltrative anesthesia, or nerve blocks can be necessary. The use of corticosteroids (topically or orally) can reduce erythema and edema on the posttreatment period, but its use is quite controversial because many doctors believe it may prejudice the final outcome once the neocollagenesis is mainly due to inflammation.

Ointments such as petrolatum must be used during the period of reepithelialization, which takes 2 or 3 days depending on the treatment intensity.

Post-trauma Scars

Kim et al. conducted a prospective trial enrolling of 12 patients of Fitzpatrick skin types III–V with 15 scars resulting from face trauma and repair by suturing on the day of the trauma. Fractionated Er:YAG laser (LOTUSII, Laseroptek, Sungnam, Korea) treatment was initiated at least 4 weeks after the primary repair of the wound, and each patient underwent four sessions with 1 month intervals. Two passes combining short (0.35 ms) and long (1 ms) pulses were performed in each session, and all the patients were submitted to the same parameters of pulse and energy. This Korean study demonstrated that ablative fractional Er:YAG laser treatment improved scars based on objective results and patient satisfaction rates (Kim et al. 2012).

A study carried out in University of Verona (Italy) by Dr. Nocini et al. enrolled ten patients with scarring after unilateral and bilateral cleft lip surgery. All the subjects underwent four passes combining different depths of ablation and coagulation (first pass, 100 μm ablation without coagulation; second pass, 80 μm ablation, 50 μm coagulation; third pass, 60 μm ablation, 25 μm coagulation; and fourth pass, 40 μm ablation to smooth the margins of the surgical area) per session. The authors related a clinical improvement of the non-fractional Er:YAG laser (Contour, Sciton, Palo Alto, California, USA)-treated scars after the first treatment, with continued improvement after the second laser session (Nocini et al. 2003).

Acne Scars

Acne scarring can occur as a result of damage to the skin during the healing of active acne and can be classified into three different types depending on whether there is a net loss or gain of collagen: atrophic, hypertrophic, or keloid. Atrophic acne scars are by far the most common type raging between 80% and 90% of total acne scars and are divided into ice pick, boxcar, and rolling scars. Regarding atrophic scars, the ice pick type represents 60–70% of total scars, the boxcar 20–30%, and rolling scars 15–25%. Ice pick scar is a narrow (less than 2 mm) punctiform and deep scar which does not undergo visible alteration when stretching the skin, and, typically, the opening is typically wider than the deeper infundibulum forming a “V” shape. Rolling scar is a result of dermal tethering of the dermis to the

subcutaneous tissue, and they are usually wider than ice picks ranging 4–5 mm. These scars give a rolling or undulating appearance to the skin and used to improve clinical appearance when being distended. Boxcar scar is round or oval and well-established vertical edges are known. These scars tend to be wider at the surface than an ice pick scar and do not have the tapering V shape. Instead, they can be visualized as a "U" shape with a wide base and can be shallow or deep (Fabbrocini et al. 2010). Often the three different types of atrophic scars can be observed in the same patients, and it can be very difficult to differentiate between them. As the skin ages, the appearance of acne scars often worsens due to a relative weakness in the dermis rather than fading (Fife 2011; Weinstein 1999).

The pathogenesis of atrophic acne scarring is not completely understood but is most likely related to inflammatory mediators and enzymatic degradation of collagen fibers. It is not clear why some acne patients develop scars while others do not, as the degree of acne does not always correlate with the incidence or severity of scarring. Once scarring has occurred, it is usually permanent (Fife 2011). Histologically, post-acne scars are usually limited to the epidermis and upper papillary dermis and, thus, amenable to treatment with a variety of techniques including ablative and non-ablative lasers for skin resurfacing (Keyal et al. 2013).

After physical examination, understanding the patient's concerns and expectations relating to his or her acne scars is the next step in the management of the acne scar and is determinant to the success (Fife 2011).

A study conducted by Woo et al. in the Korea University included 158 Fitzpatrick skin phototypes III–V volunteers with atrophic acne scars who were separated in three groups and treated with short pulse (350 μs – group 1), long pulse (7 ms – group 2), and dual-mode (350 μs followed by 8 ms – group 3) non-fractional ablative Erbium (2,940 nm) laser. The patients treated with short-pulsed Er:YAG showed a better improvement on the ice pick scars when compared with the long-pulsed treatment. On the other hand, longer pulses induced higher improvement on deep and shallow box scars and on rolling scar types when compared to short-pulse results. The group which was submitted to dual mode treatment showed the best overall improvement and for each type of scar (Woo et al. 2004). Jeong and Kye from the University of Korea treated 35 patients presenting atrophic scars with a long pulsed (10 ms) non-fractional Er:YAG (2.940 nm) laser and observed an excellent outcome in 36%, a good in 57%, and fair in 7% (Jeong and Kye 2001).

Deng et al. performed a prospective study in Shanghai Jiao Tong University, Shanghai (China), with 26 patients presenting moderate to severe atrophic acne scarring. Five treatment sessions with a fractional Erbium laser device (Pixel 2,940, Harmony, Alma Lasers, Ltd., Caesarea, Israel) and fluences ranging from 800 to 1,400 mJ/cm^2 at a 49 MTZ/cm^2 and long-pulse duration (2 ms) were applied to the treated area using 8–10 passes, with minimal discomfort and insignificant collateral effects. The authors observed improvement of at least 50% in 100% of all subjects (Deng et al. 2009). Hu et al. from Taiwan (China) conducted a study enrolling 34 volunteers who were submitted to a single session of a fractional ablative Er:YAG laser (Profractional-XC, Sciton Inc., Palo Alto, California, USA) providing 150 μm of thermal damage. This trial revealed a satisfaction rate of 72.7% of patients with minimal side effects (Hu et al. 2011). The fractional ablative Erbium treatment combines the gentleness of the fractional technique with a more intense coagulation mode promoting remarkable skin remodeling and dermal tightening. Nirmal et al. from India performed a clinical trial including 25 patients and noticed that rolling and superficial box scars showed higher significant improvement when compared with ice pick and deep box scars after 2 ms pulse duration fractional ablative Er:YAG treatments (Nirmal et al. 2013).

Figures 1a, b and 2a, b illustrate my clinical experience with Erbium laser for acne scars treatment. These figures show improvement in severe acne scars after 3 treatment sessions with 1-month ineterval between them. A fractional Erbium laser device (Pixel 2,940, Harmony, Alma Lasers, Ltd., Caesarea, Israel) was used with fluences of

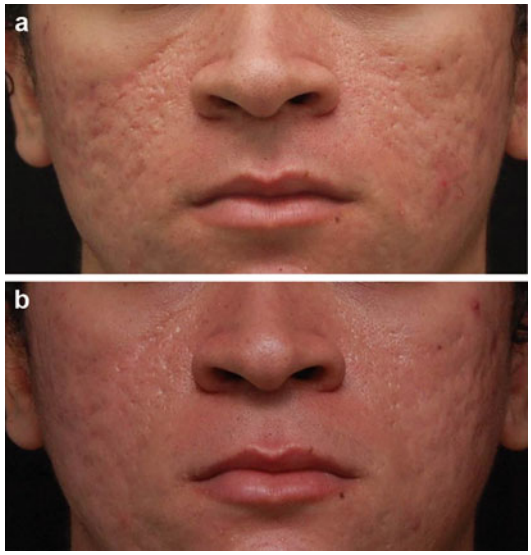

Fig. 1 Acne scars (front view). (**a**) Pretreatement. (**b**) Posttreatment 3 months after the third session with 1 month of interval between each session

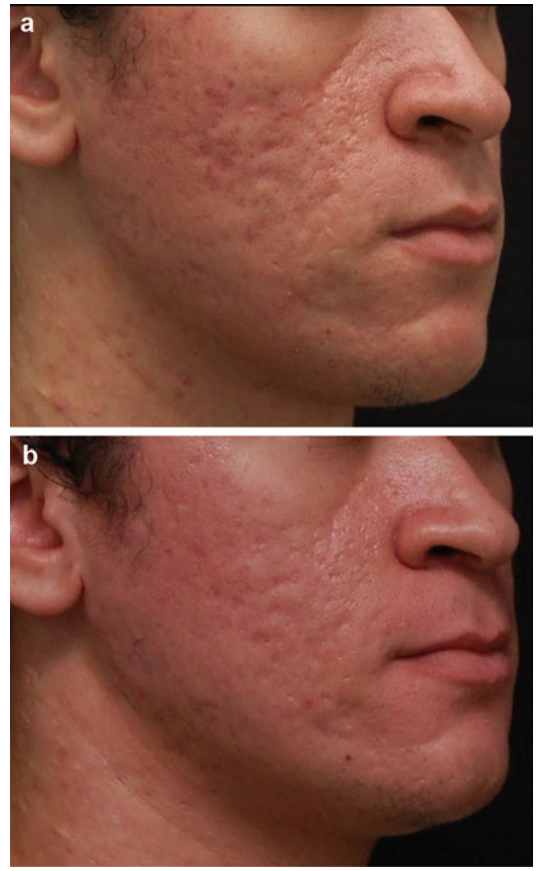

Fig. 2 Acne scars (lateral view). (**a**) Pretreatement. (**b**) Posttreatment 3 months after the third session with 1 month of interval between each session

1,400 mJ/cm^2 at a 49 MTZ/cm^2, long-pulse duration (2 ms), and four overlapping "shots" (stacking).

Often a combination of techniques (e.g., submission or filler injections combined with fractional resurfacing) will ensure a better result compared to one procedure alone (Fife 2011). Yin et al. performed a prospective study enrolling 40 subjects presenting severe acne. Patients were treated with 15% 5-aminolevulinic acid (ALA) photodynamic therapy and subsequently received ablative fractional Er:YAG (2,940 nm) five times at a 4 weeks interval. After 6 months, the lesions showed overall improvement in all of subjects (good to excellent in acne inflammatory lesions), 80% overall improvement in acne scars. After 12 months, most of subjects had improved hypertrophic and atrophic scars (good to excellent in 85%), and no one had recurrent acne inflammatory lesions. Patient self-evaluation also revealed good to excellent improvements (on average) in acne lesions and scarring, with significant improvements in self-esteem after 6 months posttreatment. The authors suggested that the combination ALA-PDT and fractional resurfacing Er:YAG is a promising option for the management of severe acne preventing scar formation (Yin et al. 2014).

Hypertrophic Scars and Keloids

Hypertrophic scars and keloids are not a hallmark on the indications of ablative lasers. The Er:YAG lasers seem to be more suitable on treating hypertrophic scars and keloids because as it is 12–18 times more selective for water than CO2 laser due to its shorter wavelength (2,940 nm), it has less residual thermal injuries and less inflammation (Oliaei et al. 2012; Al-Saedi et al. 2014). Er:YAG at 5 J/cm^2 vaporizes tissue at depth of 20–25 μm with an additional of 5–10 μm zone of thermal necrosis. Er:YAG lasers have showed moderate improvement of hypertrophic

scars and keloids. These ablative lasers target water in the tissue, resulting in tissue vaporization (Harithy and Pon 2012).

Burn Scars

Treatment with ablative full-field CO2 and Er: YAG has been used to treat burn scars but has been associated with prolonged recovery times and contradicting results. Burn scars, especially ones that are new, need to be treated gently. Ablative fractional lasers has the capability to act on a well-controlled skin percentage but can stimulate new collagen formation, remodel the burn scar tissue, and subsequently normalize the texture, elasticity, and color of the scar. Few case reports have shown that ablative fractional resurfacing is safe and effective in treatment of burn scars; however further studies are needed to determine parameters (Harithy and Pon 2012).

Stretch Marks (Striae Distensae)

Strech marks (also called *striae distensae*) are histologically characterized as scars; although there was no break in continuity of the epidermis, it demonstrates microscopic evidence of thinning and flattening of the epidermis, a normal or decreased number of melanocytes, and thinning and retraction of the dermal collagen and elastin (Godberg et al. 2005; Maia et al. 2010). In the early phase, inflammatory changes are remarkable, but later the epidermis is thin and flattened. Recent stretch marks show a deep and superficial perivascular lymphocytic infiltrate. Collagen bands on the upper third of the reticular dermis are stretched and aligned parallel to the surface of the skin. In the latter stages, there is thinning of the epidermis due to flattening of the epidermal ridges and loss of collagen and elastin (Elsaie et al. 2009). Clinically, stretch marks appear as erythematous (striae rubra) on the early phase or hypopigmented (striae alba), linear, dermal scars with epidermal atrophy on the late phase.

There are few researches of good quality focused on the physiopathology of stretch marks (Cordeiro and Moraes 2009). Although the etiology of the stretch marks is not well understood, it is accepted that the combination of mechanical stretching of the skin, genetic, endocrine disorders, and possibly secretion of relaxin during pregnancy, alone or in combination, plays a role in the physiopathology of striae distensae (Maia et al. 2010).

The stretch mark treatment is based on stimulating neocollagenesis and restoring epidermal architecture. The use of ablative technologies such as the Erbium laser induces clinical improvement on body areas, but almost all patients develop a significant post-inflammatory hyperpigmentation, especially in darker skin tones. The sequence of Figs. 3, 4, 5, and 6 illustrates the course of treatment of stretch marks on the thigh area of a type II Fitzpatrick's skin phototype patient. A non-franctional Erbium laser device (Fidelis, Fotona Lasers Ltd., Lujbljana, Slovenia) was used with the LP (long pulse) 600 μs pulse duration. Longer-pulse durations induce low ablation and intense coagulation and inflammation (Fig. 4). The residual post-inflammatory hyperchromya is a hallmark of ablation on body areas (Fig. 5) despite the significant final result (Fig. 6). This is the reason that makes the use of sublative and non-ablative lasers the first options on lasers for managing stretch marks.

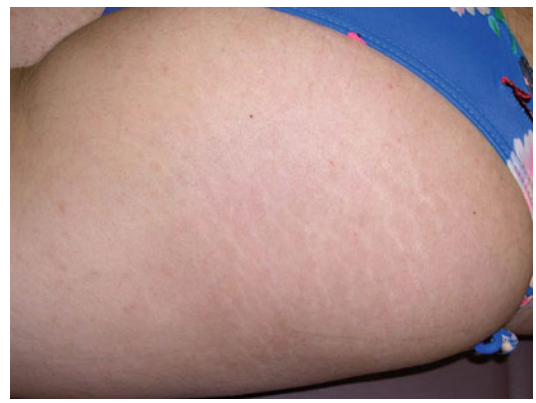

Fig. 3 Stretch marks (striae distensae) on the thigh area, pretreatment

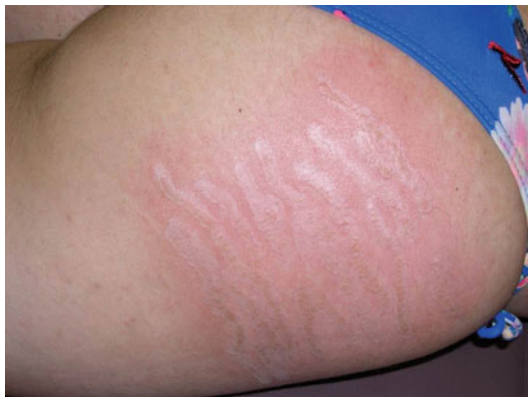

Fig. 4 Stretch marks (striae distensae) on the thigh area, immediately after the first ablative Erbium session with long pulse duration

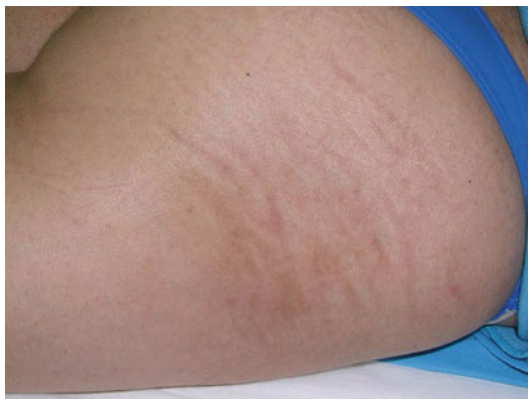

Fig. 5 Important post-inflammatory hyperchromia one after the first session

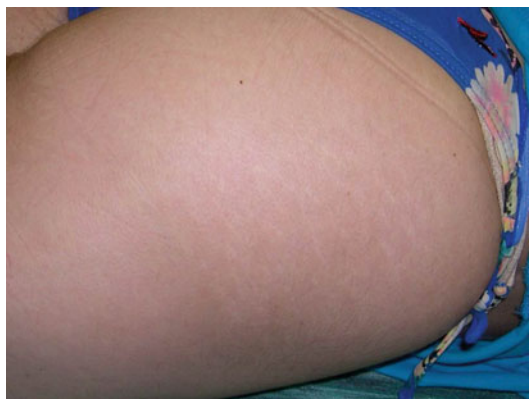

Fig. 6 Significant clinical improvement 3 months after a single session

Post-Procedure Care

The ablative laser procedure does not end when the surgical act is finalized. The post-procedure care is an important subjacent part to guarantee the expected aesthetic result, accelerating the healing process with a smooth recovery, avoiding complications. Open wound care is performed with frequent application of ointments on the surface of the treated area, while the occlusive approach requires the use of occlusive bandages. Open and closed wound care helps to control pain and accelerates the healing process. Unlike open dressings, occlusive bandages increase the risk of infection (Costa et al. 2011) and do not allow visualization of the wound.

Pain can be controlled with cold compresses or cold-water sprays (Costa et al. 2011) most of the times. Effective pain control can be achieved with the use of oral analgesics (paracetamol, codeine) combined or not with an anxiolytic (lorazepan) (Costa et al. 2011). Edema can be managed with the application of ice bags or cold water compresses, but use of an oral (40–60 mg prednisone daily for a variable period of 3–5 days) or intramuscular corticosteroid can be useful in isolated cases (Oliaei et al. 2012; Costa et al. 2011). Ointments and antihistamines can be used to relief intense pruritus.

Complications and Side Effects

Ablative lasers induce thermal destruction of the skin with adjacent coagulation area. Therefore some manifestations are expected and desirable in the post-procedure period. The recovering time depends on the amount of energy targeted to the skin, the pulse duration, and the delivery system (full ablation or fractional). The healing process after fractional treatment is significantly faster compared with full ablative (non-fractional) treatment (Zgavec and Stopajnik 2014).

Erythema and minimal crusting which disappeared in 7 days are the expected side effects after fractional treatment (Zgavec and Stopajnik 2014). The mean erythema duration used to be 2 days, and mean crusting is around

5 days (Nirmal et al. 2013). On the other hand, extensive crusting after the treatment with the non-fractionated handpiece is observed even after a 14-day follow-up (Zgavec and Stopajnik 2014). Pain evaluated by the patients is milder when using fractionated handpieces in comparison with full ablative (Zgavec and Stopajnik 2014) and disappears until the second day after the treatment (Zgavec and Stopajnik 2014; Costa et al. 2011). Pain rarely occurs after the second day of the postoperative period and must be investigated if it occurs (dryness and infection are common causes) (Costa et al. 2011).

Edema usually varies from mild to moderate, with peaks on the second and the third day, and can last for up to 1 week (Costa et al. 2011). Edema is usually more intense on the peri-orbital areas and eyelids. Longer pulse durations with less ablation and more coagulation (deeper heating) usually lead to pronounced edema. Pruritus affects more than 90% of patients undergoing ablative treatments on the first 2 weeks after procedure, and it is due to the healing process (Costa et al. 2011). Once pruritus is intense and persistent, a secondary infection must be investigated. Desquamation and post-fractional, non-ablative laser xerosis occur in 60% and 87% of cases, respectively (Costa et al. 2011). Purpura can occur and recover spontaneously (Costa et al. 2011).

Viral, bacterial, and fungal infections are rare manifestations that occur during the first post-procedure week and require proper identification and treatment to avoid further complications (AlNomair et al. 2012) such as persistent eritema or scar formation. Infection must be considered when intense or persistent pain, eritema, and edema occur. The most common type of infection after fractional laser skin resurfacing is caused by HSV and has been reported in 0.3–2% of cases (Costa et al. 2011; AlNomair et al. 2012). Patients may not present with classic herpetiform vesicopustules but instead may demonstrate only superficial erosions that develop during the first week after treatment (AlNomair et al. 2012). Given that most patients present subclinical levels of HSV, prophylactic use of oral antivirals such as aciclovir, famciclovir, or valaciclovir is always recommended preventively in perioral or full-face ablative resurfacing. Prophylaxis with antivirals taken on regular doses for HSV infection must start 1 or 2 days before the laser procedure and continue until the skin is completely healed. Prophylaxis notwithstanding, herpetic infection sometimes does occur. In such cases, doses of oral antivirals equivalent to those used in treating the herpes zoster virus must be used (Zhang and Obagi 2009). Rates of bacterial infection in traditional resurfacing tend to be low (0.5–4.5% of cases) and even rare when fractional, non-ablative lasers are used, occurring in only 0.1% of cases (Costa et al. 2011; AlNomair et al. 2012). Studies suggest that most bacterial infections related to laser ablation occur with the use of occlusive bandages on the post-procedure period (Costa et al. 2011). When infection is suspected, secretions must be cultured, and an antibiogram test must be carried out and a wide-spectrum systemic antibiotic (penicillin, first-generation cephalosporin or ciprofloxacin) is administered while waiting for the results from the bacterial culture and antibiogram (Costa et al. 2011).

Candida albicans is the most frequent agent related to fungal infections occurring after skin ablation, and the infection starts between the first and the second weeks of the post-procedure period. Patients presenting pruritus, pain, and whitish erosions on a highly erythematous base as well as satellite lesions outside the treated area must be suspected to have fungal infection. A direct mycological examination and culture for fungus must be performed if infection is suspected (Costa et al. 2011).

Acneiform eruptions have been described as a frequent complication of fractional skin resurfacing, and it can be a result of an aberrant follicular epithelialization during healing or secondary to the use of ointments during the recovery time (Costa et al. 2011; AlNomair et al. 2012). The development of milia cysts has been reported in as many as 19% of cases (AlNomair et al. 2012) and appears between 3 and 8 weeks after laser treatment as a consequence of the use of occlusive bandages, oils, or creams during the healing process (Costa et al. 2011).

Post-inflammatory hyperpigmentation (PIH) after skin resurfacing can be transient or long lasting and is one of the most common post-ablative resurfacing complication (Costa et al. 2011). Hyperpigmentation is much less frequent with fractional laser skin resurfacing than with full-ablative resurfacing but is observed in 1–32% of patients, depending on the system used, parameters applied, and skin phototypes treated (AlNomair et al. 2012). Patients with darker skin phototypes (Fitzpatrick III–VI) or melasma have a higher likelihood of developing post-inflammatory hyperpigmentation (Costa et al. 2011; AlNomair et al. 2012). Some studies relate up to 68% of hyperpigmentation after skin ablation (Costa et al. 2011). Patients prone to develop PIH must be prepared during the 3 months prior to the procedure with a combination of hydroquinone and glycolic acid or tretinoin or hydroquinone cream used alone besides the use of sunscreens (Costa et al. 2011). PIH must be treated as soon as possible avoiding aggressive approaches before reepithelialization is complete as they can worsen the condition (Costa et al. 2011). The regular use of wide-spectrum sunscreen and avoiding exposure to the sun for at least 6 or 8 weeks before and after the procedure are important on preventing PIH development (Costa et al. 2011). In addition to sunscreen, blemish agents such as hydroquinone, tretinoin and kojic, azelaic, and glycolic acids are also first-line treatments. Superficial chemical peels and microdermabrasion can be used to accelerate the whitening response (Costa et al. 2011).

Scarring is another known and rare complication of fractional ablative resurfacing (AlNomair et al. 2012) with serious and devastating consequences (Costa et al. 2011) on the aesthetic final result. It is a more frequent complication in the CO2 laser when compared to the Erbium laser skin resurfacing. There are several potential explanations for hypertrophic scarring, including the use of excessively high-energy densities, post-operative infection of the skin, and lack of technical skills. The neck is a well-recognized site that is especially susceptible to the development of scarring and synechia because of the small number of pilosebaceous units and poor vasculature in this region, which are essential for wound healing. In addition, the thin skin of the neck renders it more susceptible to thermal injury. Other scar-prone anatomic locations that require more conservative treatment protocols include the periorbital, mandibular regions, chest, and other areas over bony prominences (Fife 2011).

Conclusion

Ablative Erbium laser is highly absorbed by water and together with the possibility of being modulated by variations on pulse durations makes it a precise, safe, and effective tool on managing scars.

Take Home Messages

- Erbium (Er:YAG) laser is a flashlamp-excited system that emits light at an invisible infrared wavelength of 2,940 nm, and it is highly absorbed by water.
- Erbium (Er:YAG) can be modulated by variations on pulse durations making it a precise, safe, and effective tool on managing scars.
- The aims of ablative Erbium laser on treating atrophic scars are reducing the depths of the scar borders and stimulating neocollagenesis to fill depressions.
- No treatment is 100% effective on “erasing” scars, and the best result is improvement, not perfection.
- Treatment of scarring may require many different kinds of treatments, depending on the kind of scarring present; however skin vaporization and residual thermal damage can only be achieved by ablative lasers and explain the superiority of ablative laser treatment over chemical peels and dermabrasion.

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CO_2 Laser for Photorejuvenation

Jackson Machado-Pinto and Michelle dos Santos Diniz

Abstract

The CO_2 laser is a powerful tool in the fight against aging including extrinsic aging. The operation of this laser is based on the principle of selective photothermolysis. Water is the main target of CO_2 lasers operating at a wavelength of 10.600 nm, in the infrared portion of the electromagnetic spectrum. The rejuvenation observed after CO_2 laser treatment is the result of several phenomena that occur after laser interaction with the skin: collagen contraction and neocollagenesis, photodamaged skin removal, and peripheric thermal damage. The most frequent complications are infections, hypo- and hyperchromia, synechiae, and scarring. Fractionation of lasers greatly diminished the risk of complications that are more frequent in more aggressive treatments and when the laser is applied to non-facial areas. Although several devices and techniques to treat photodamaged skin have been developed, resurfacing with the CO_2 laser remains the gold standard for the treatment of photoaged skin.

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Keywords

Lasers • Carbon dioxide • CO_2 laser • Laser ablation • Photorejuvenation • Adverse effects

Contents

Introduction

The CO_2 (carbon dioxide) laser is a powerful tool against aging, including extrinsic aging that includes the cutaneous signs of aging that are not related to age, but to external factors the most important of which are chronic sun exposure and smoking. Contrary to what occurs with chemical peels, the CO_2 laser allows an abrasion with strictly controlled depth, which makes laser abrasion or resurfacing a safer procedure that, in experienced hands, gives the doctor and his patient a great satisfaction. Although a variety of techniques and devices to treat photodamaged skin has been developed, resurfacing with the CO_2

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laser remains the gold standard for the treatment of photoaged skin (Duplechain 2013; Kilmer et al. 2006; Hafner and Salomon 2006; Hunzeker et al. 2009).

CO_2 Laser for Photorejuvenation

Basic Concepts

The operation of the CO_2 laser is based on the principle of selective photothermolysis, developed by Parish and Anderson in 1983. This principle, which is a direct derivation of quantum theory, says that, in order to obtain tissue ablation, it is important that the tissue receives a very high amount of energy in a very short time period. Water is the main target of CO_2 lasers that operate at a wavelength of 10.600 nm, in the infrared portion of the electromagnetic spectrum. When a CO_2 laser beam focuses on the skin, it vaporizes the affected cells after they experience a temperature rise up to 100 °C in 640 mcs (Omi and Numano 2014). The improvement of the cosmetic appearance observed after resurfacing can be attributed to various factors. The first is tissue ablation by direct removal of the upper portions of wrinkles after each successive laser exposure. This ablation results from the combination of tissue vaporization in the treated area that produces a thermal coagulation necrosis of the cells below and thermal denaturation of proteins of the extracellular matrix (Khatri et al. 1999). CO_2 lasers remove between 25 and 50 um of tissue in each pass (Weinstein 1998). This means that the clinical improvement observed in the wrinkles should also be attributable to other reasons.

During the laser abrasion procedure, immediate contraction of the skin can be observed. Although part of this contraction is due to dehydration by water evaporation, the instantaneous retraction of collagen can also occur, since it is known that collagen shrinks when exposed to temperatures above 60 °C (Fitzpatrick 1996). However, although collagen contraction by dehydration or retraction lasts only 14 days after resurfacing, a continued improvement up to a year can be seen in patients (Seckel et al. 1998). This improvement appears to be a result of the deposition of newly formed collagen and reorganization of the dermis, the extent of which appears to be dependent on the residual thermal damage caused by the laser (Khatri et al. 1999).

The rejuvenation observed after CO_2 laser treatment is therefore a result of several phenomena that occur after laser interaction with the skin: collagen contraction and neocollagenesis, photoaged skin removal, and peripheral thermal injury (Campos and Gontijo 2010; Omi and Numano 2014). It is noteworthy that immediately after the procedure, collagen contraction occurs, and 3–6 months after the laser is applied to the skin, there is a new contraction secondary to the remodeling of collagen (Tierney and Hanke 2011). Electron microscopy studies revealed a decrease in the average diameter of collagen fibrils consistent with deposition of collagen type III after performing fractional laser (Berlin et al. 2009).

History

The CO_2 laser was one of the first lasers to be used. It was initially developed in 1964 by Patel and colleagues at Bell Labs in the USA. It was considered the ideal laser for surgical treatment due to its high affinity for water (Kaplan 2007).

In the early 1990s, the CO_2 laser was the biggest advance among the treatments for epidermal ablation and subsequent induction of a new skin with a more youthful appearance. Later pulsed CO_2 with a computerized scanner were used with excellent results. These first CO_2 lasers were fully ablative and even though they provided extremely satisfactory results, the need for sedation, the great down time period, and the greatest risk of complications such as scarring and dyschromias gave way to fractional resurfacing.

The ablative fractional laser was introduced in 2006 and is responsible for localized disruptions in the epidermis while keeping the skin around intact. Fractionation permits deeper layers of the skin to be reached (up to 1,500 um) depending on the amount of energy delivered to tissue. Despite the indisputable greater security of fractional laser

compared to fully ablative CO_2, the results achieved are not as efficient for rejuvenation and acne scars (Kaplan 2007).

Indications and Contraindications

Skin rejuvenation is the best indication for CO_2 laser treatments. It can be used not only on the face but also on extra-facial areas like the neck, chest, hands, and arms due to fractionation. Besides rejuvenation, CO_2 laser devices have been used to treat several other conditions such as surgical and acne scars, stretch marks, actinic keratoses, seborrheic keratoses, warts, rhinophyma, sebaceous hyperplasia, nevi, and angiofibromas (Hunzeker et al. 2009; Omi and Numano 2014).

CO_2 laser should be used with caution in higher phototypes (IV above) and is contraindicated in black skin. It should not be done in patients with keloids, vitiligo, and photosensitizing diseases and in patients with active infections including herpes virus infections. It should not be done in patients taking anticoagulants, and it is recommended to wait 6 months after completion of oral isotretinoin before undergoing CO_2 laser treatment.

Laser Procedure

Pre-laser

Patients should be carefully oriented about the procedure. The average downtime from the daily activities varies from 3 to 7 days depending on the intensity of treatment. Antiherpetic therapy is particularly necessary in cases of recurrent herpes history and when more aggressive parameters are to be used. Either acyclovir, famciclovir, or valacyclovir can be administered starting 3 days before the procedure and being maintained up to 4 days following the procedure or after complete epithelialization has taken place.

During the Laser

The duration of each application depends on the ability of the laser surgeon. Care should be taken to ensure that the patient is comfortable during the procedure. Naturally, potent topical anesthesia should be applied and fully and carefully removed before lasing. Often it is necessary to use tumescent anesthesia and nerve blockade. Devices that release cold air and application of ice bags on the treated area can be useful to help the patient tolerate the treatment.

Post-laser

Immediately after the procedure, cold compress of saline or thermal water may be used. Healing creams and vaseline may also be used. The use of topical antibiotics is controversial. Sunscreens and makeup can usually be used after the third day. Close monitoring of patients is of the utmost importance for early identification of any complications (Figures 1, 2 and 3).

Side Effects and Their Management

The incidence of complications was greatly reduced with the laser fractionation. However, they may still happen especially in more aggressive treatments and when extra-facial areas are lased (Duplechain 2013; Campos and Gontijo 2010). According to Shamsaldeen et al. (2011) and Campbell and Goldman (2010), complications occurred in 15% of the patients treated.

The most commonly reported complication is transient hyperpigmentation, which takes place between 5% and 83% of patients, especially those with darker skin (types III and IV on the Fitzpatrick classification) (Fitzpatrick et al. 1996). In another series with 749 patients, the most common complication was persistent erythema, which occurred in all patients after the laser. After erythema, hyperchromia occurred in 32% of these patients (Berwald et al. 2004). Hyperpigmentation usually appears between 2 weeks and 2 months after the disappearance of erythema. Depending on the degree of skin irritation, topical tretinoin and hydroquinone should be started between 2 and 6 weeks after the procedure or immediately after completed re-epithelialization, in case of post-inflammatory hyperpigmentation (Ratner et al. 1999).

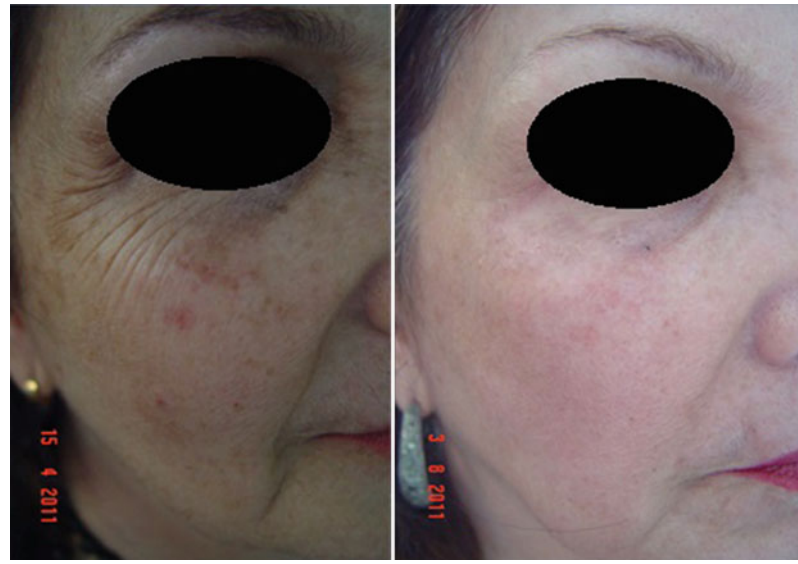

Fig. 1 Before and after CO2 Laser

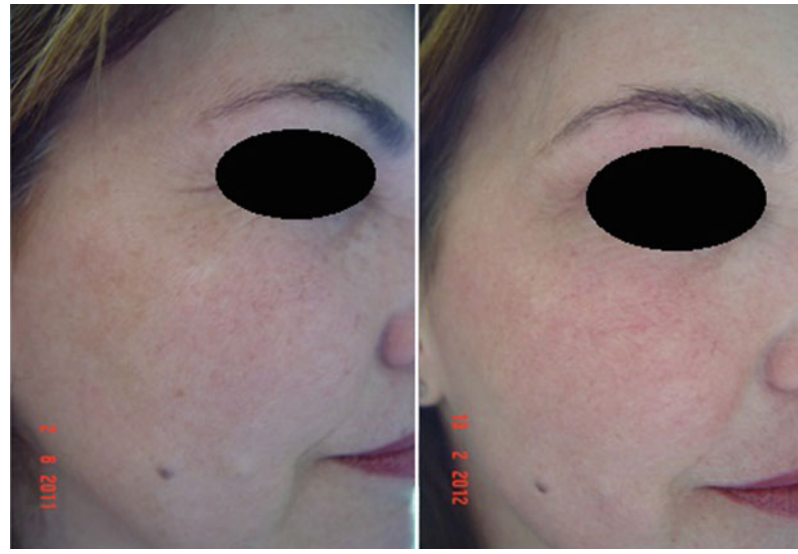

Fig. 2 Before and after CO2 Laser

Infections can also complicate resurfacing between 2 and 10 days after the procedure, increasing the risk of hypertrophic scars. *S. aureus*, *P. aeruginosa*, *S. epidermidis*, and Candida sp. are the most common agents. The presence of pustules in the early postoperative or pain indicates the need of cultures and antibiograms to search for these agents. In mice, CO_2 laser resurfacing reduces the microbial count of microorganisms as compared to the normal skin flora, which can explain the rarity of infectious complications in practice (Manolis et al. 2006). Infection with Candida species can be controlled with oral or topical antimycotics such as itraconazole or fluconazole. Some recommend the systematic use of an imidazole derivative in all patients after the laser. Similarly, herpesvirus infections can be seen, usually in the first week after the procedure Ratner et al. 1999).

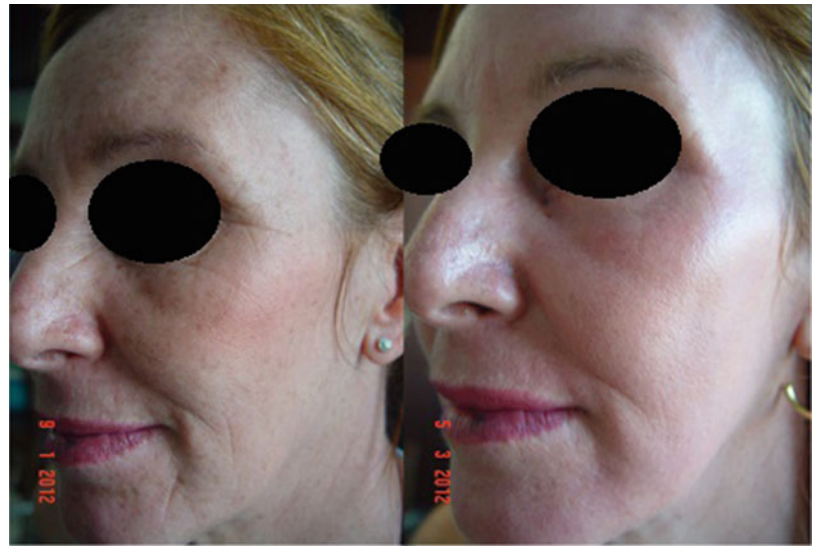

Fig. 3 Before and after CO2 Laser

Hypopigmentation, when it occurs, tends to be a late and permanent phenomenon in extremely photoaged patients after the disappearance of erythema. There is evidence suggesting that the suppression of melanogenesis instead of melanocytes destruction is the most important mechanism (Helm and Shatkin 2006; Hunzeker et al. 2009.).

Synechiae may occur when two adjacent areas have lost their epithelium and remain in constant contact during the re-epithelialization process and are more often observed on the upper eyelids. Acne and milia occur in up to 83.5% of patients, especially those with very oily skin and when very thick sunscreen products are used. The most feared complication is the formation of hypertrophic scars. They occur only rarely and are usually due to improper selection of patients for resurfacing, poor technique, carelessness, or infection in the immediate postoperative period. The more predisposed individuals are those who were on systemic isotretinoin up to a year before resurfacing or who have keloids. Another complication appearing in patients previously subjected to blepharoplasty or rhytidectomy is ectropion. Although ectropion may be transient, it does not always involute spontaneously and sometimes requires surgical correction (Ratner et al. 1999; Rendon-Pellerano et al. 1999) (Figs. 1, 2, and 3).

Take Home Messages

- CO_2 laser is the gold standard treatment of photodamaged skin.
- CO_2 laser has water as a target and operates at a wavelength of 10.600 nm.
- CO_2 laser promotes collagen contraction and neocollagenesis addition to removing the photodamaged skin.
- Fractional CO_2 laser application is a safe procedure and has a low complication rate.
- Treatment of extra-facial areas may be associated with increased risk of complications.

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CO_2 Laser for Stretch Marks

Guilherme Almeida, Elaine Marques, and Rachel Golovaty

Abstract

Stretch marks or striae distensae (SD) are a well-recognized, common dermatologic entity, which affect patients of all ages, genders, and ethnicities and rarely cause any significant medical problems but can have a deep psychological impact on affected patients. Risk factors have been reported, but much remains to be understood about their epidemiology. Although there is no standard treatment for SD, many topical applications, peeling, light, and laser systems, have been tried. Considering the many modalities used to improve SD, lasers have recently become a popular therapeutic alternative. The aim of this chapter is to discuss the causes and possible treatments described in literature, to approach the clinical efficacy and safety of fractional CO_2 laser in the treatment of SD, and to show 5 years of our experience using this device.

Keywords

Stretch marks • Striae distensae • Striae rubra • Striae alba • Striae atrophicans • Striae gravidarum • Laser therapy • Light therapy • Acid peel treatments • Collagen injection • Laser lipolysis • Radiofrequency • Microdermabrasion • Nonablative lasers • Fractional laser resurfacing

Contents

Introduction

Roederer first described striae in 1773, and Troisier and Menetrier made the first histological descriptions in 1889 (Troisier and Ménétrier 1889). Striae distensae (SD), also denominated stretch marks (SM), striae rubra, striae alba, striae atrophicans, striae gravidarum (SG), are a well-recognized common dermatologic entity, which affect patients of all

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ages, genders, and ethnicities. SD is common in adolescence, pregnancy, and obesity. The most commonly affected sites are the breasts, upper arms, abdomen, buttocks, and thighs. Initially, SD present as edematous red or pink linear plaques called striae rubra. Over time, the color fades, and the lesions become hypopigmented, atrophic, and permanent (striae alba). It is rarely caused by systemic diseases but commonly represents a deep psychological impact on affected patients (Al-Himdani et al. 2014; Watson et al. 1998; Ud-Din et al. 2016).

SD is a known feature of several clinical conditions, both chronic and acute, with very distinct pathophysiology (e.g., pregnancy, adolescent growth spurts, obesity, large weight gain, Cushing syndrome, Marfan syndrome, diabetes mellitus, long-term systemic or topical steroid use), making it difficult to determine their true etiology. Most SD research has focused on pregnant women and adolescents. A positive family history is a risk factor in both of these groups alike. Among adolescents, BMI and childhood obesity both influence risk of developing SD (Troisier and Ménétrier 1889).

Epidemiology

The prevalence of SD reported in the literature varies a lot, ranging from 6% to 88% (Cho et al. 2006; Sisson 1954; Kelekci et al. 2011; Thomas and Liston 2014; Chang et al. 2014; Ghasemi et al. 2017; Osman et al. 2017; Davey 1972; Elton and Pinkus 1966; García-Hidalgo et al. 1999; García-Hidalgo 2002). The prevalence ranges from 6% to 86% in adolescents and from 43% to 88% in pregnant women (Cho et al. 2006; Chang et al. 2014; Ghasemi et al. 2017; Osman et al. 2017; Atwal et al. 2006; Canpolat et al. 2010; Maia et al. 2009; Jaramillo-Garcia et al. 2009; Cohen et al. 1997). Among obese individuals with a BMI of 27–51, the prevalence is reported to be 43% (García-Hidalgo et al. 1999). The prevalence among nonpregnant women and adult male varies a lot in literature (Kelekci et al. 2011; Elton and Pinkus 1966; Cohen et al. 1997; Murphy et al. 1992). Risk factors in pregnant women may be constitutional (maternal age and BMI) or pregnancy related (birth weight, gestational age, weight gain during pregnancy, and polyhydramnios) (Ghasemi et al. 2017; Osman et al. 2017; Atwal et al. 2006; Canpolat et al. 2010; Murphy et al. 1992).

Many risk factors have been suggested for the development of SG, such as pregnancy maternal weight (Ersoy et al. 2016; Liu 1974; Thailand J-Orh et al. 2008), weight gain during pregnancy (Osman et al. 2017), maternal age (Atwal et al. 2006), skin structure (Ghasemi et al. 2017), family history (Chang et al. 2014), race, and birth weight (Liu 1974). These have been investigated, but their effect has not been clearly proven (Davey 1972; Liu 1974; Thomas and Liston 2014; Muzaffar et al. 1998; Kartal Durmazlar and Eskioglu 2009). Surgical interventions and medications have also been associated with SD (Osman et al. 2017; Pinkus et al. 1966; Di Lernia et al. 2001; McKusick 1971; Rolleston and Goodall 1931; Shafir and Gur 1999; Tsuji and Sawabe 1993; Gupta 2000).

Ersoy et al. (2016) published a new study to determine individual risk factors related to SD and reported some preventive measures. This prospective observational study included 211 primiparous pregnant women who were hospitalized for birth and did not have systemic diseases or other risk factors (drugs use or polyhydramnios). The use of preventive oil or drugs, smoking status, skin type, water intake, and level of financial income did not significantly predict the appearance of SG.

According to the logistic regression analysis, including all variables found to be significant in one-by-one comparisons, i.e., age, pregnancy BMI, BMI at admission, abdominal circumference, birth weight, family history, sex of the infant, and maternal education level, it was established that each unit of decrease in maternal age increased the risk of SG by 1.15-fold (Ghasemi et al. 2017; Muzaffar et al. 1998; Kartal Durmazlar and Eskioglu 2009; Thomas and Liston 2014).

Histopathogenesis of Striae Distensae

Three main theories relating to SD formation are described: mechanical stretching of the skin, hormonal changes, and an innate structural disturbance of the tegument. Mechanical stretching of the skin is postulated due to the perpendicularity of SD to the direction of the skin. However, contradictory studies dispute this theory (McKusick 1971; Nigam 1989). Adrenocorticotrophic hormone (ACTH) and cortisol are thought to promote fibroblast activity, leading to increased protein catabolism, modifying collagen and elastin fibers (Klehr 1979). Pregnancy-related hormones are also believed to influence SD formation (Osman et al. 2017; Nigam et al. 1990; Cordeiro et al. 2010; Lurie et al. 2011). Disorder of extracellular matrix's gene expression is also postulated as a possible mechanism involved in SD formation (Etoh et al. 2013; Friedman et al. 1993).

The exact pathogenesis of striae is still controversial. Early histological dermal alterations may be visualized on electron microscopy including mast cell degranulation and macrophage activation leading to elastolysis of the mid-dermis. Release of enzymes by mast cell, including elastases, is proposed as a key initiatory process in SD pathogenesis. The inflammatory process induces collagen, elastin, and fibrillin modifications. The reorganization of fibrillin and elastin are thought to play an important role in SD pathogenesis, and those who are predisposed to developing SD may have an underlying deficiency of fibrillin (Watson et al. 1998; Sheu et al. 1991).

A deep and superficial perivascular lymphocytic infiltrate with occasional eosinophils and dilated vessels with edema of the upper dermis are characteristic of newly acquired striae. SD in this stage is referred to as "striae rubra" (SR).

In late stage, elongated collagen bands are concentrated within the upper third of the reticular dermis and arranged parallel to the surface of the skin. In the "terminal" stages of SD, there is a thinning of the epidermis due to blunting of the rate ridges and a paucity of collagen and elastic fibers. SD in this stage are classified as "striae alba" (SA) and are considered permanent (Watson et al. 1998; Ackerman Ab et al. 1997; Arem and Kischer 1980).

Striae distensae can be considered a form of dermal scaring, and their clinical and histological are similar to those of scar remodeling. For whatever reason, dermal collagen ruptures or separates, and the resulting gap is replaced with newly formed collagen that orients itself in the direction of local stress forces (Sisson 1954). Irrespective of the underlying pathology that may incite a cascade of uncertain events, a final common pathway results in the breakdown and tearing of the dermal matrix, which manifests clinically as SD.

A recent study investigates early molecular alterations that may promote laxity of mature striae gravidarum (SG). They investigated the dermal elastic fibers network, which provides elastic properties of the human skin. They obtained skin samples of newly developed, erythematous abdominal SG in healthy pregnant women. Elastic fibers were examined by Verhoeff stain and immunofluorescence. The normal elastic fiber network appeared markedly disrupted in SG, compared with perilesional abdominal skin or control (normal-appearing hip skin). This disruption was accompanied by the emergence of short, disorganized, thin, threadlike "fibrils," which were observed prominently in the mid-to-deep dermis. These fibrils were rich in tropoelastin (the main component of normal elastic fibers) and persisted into the postpartum period without forming normal-appearing elastic fibers. The emergence of these fibrils was accompanied by increased gene expression of tropoelastin and fibrillin-1 but not other elastic fiber components such as fibrillin-2 and fibulin-1, fibulin-2, and fibulin-5. They concluded that in early SG, the elastic fiber network appears markedly disrupted and newly synthesized tropoelastin-rich fibrils emerge as an uncoordinated synthesis of elastic fiber. Because they are thin and disorganized, tropoelastin-rich fibrils do not function as normal elastic fibers. These findings help to elucidate the pathogenic mechanism by which laxity occur in SG (Wang et al. 2015).

Treatment

Striae distensae is a considerable challenge in terms of their treatment. They rarely resolve without intervention. Even with intervention, improvement rather than complete resolution is a more realistic goal. The best results are achieved when treating SD in the early phase. Once SD reaches a mature, static phase, they are significantly more resistant to treatment.

Various treatment modalities are reported to treat or prevent SD. Among them are laser therapy (Cho et al. 2006; Belo and Arceo-Cruz 2009; Alexiades-Armenakas et al. 2011), light therapy (Sadick et al. 2007), chemical peelings (Mazzarello and Farace 2012), percutaneous collagen induction (Aust et al. 2010), laser lipolysis (Freedman 2010), radiofrequency techniques (Suh et al. 2007), and microdermabrasion (Abdel-Latif and Albendary 2008). No single therapy has been advocated to completely eradicate these lesions (see also the following chapters: ▶ "Non-ablative Lasers for Stretch Marks," this volume; ▶ "Transepidermal Drug Delivery with Ablative Methods (Lasers and Radiofrequency)," this volume).

Even when procedures are indicated, topical treatment is considered the most used treatment and can be used before or associated with procedures (Kelekci et al. 2011). A recent article assessed the evidence for the use of topical treatments for SD. They reviewed the published literature in English language, from 1980 onward (Kelekci et al. 2011). The products were categorized by their mechanisms of action, including those which acts in stimulating collagen production, increasing elasticity, and improving cell proliferation and those with anti-inflammatory and rehydration properties. The results showed that there are few studies (n = 11) that investigate the efficacy of topical in management of SD. Trofolastin and Alphastria creams demonstrated level 2 evidence of positive results for their prophylactic use in SD. Additionally, tretinoin used therapeutically showed varied results, while cocoa butter and olive oil did not demonstrate any effect. Overall, there was a distinct lack of evidence for each topical formulation. The majority of topical products failed to mention their effect on early SD vs. later stages of SD (striae rubrae compared to striae albae) and their role in both prevention and treatment. In conclusion, there is no topical formulation that is shown to be most effective in eradicating or improving SD. A structured approach in identification and targeted management of symptoms and signs with the appropriate topical is required. Randomized controlled trials are necessary to assess the efficacy of topical products for treatment and prevention of different stages of SD (Ud-Din et al. 2016).

Lasers and Light Devices

The 585 nm flash lamp-pulsed dye laser (PDL) at low energy densities is commonly used to target the dilated blood vessels of striae rubra. An increase in the amount of collagen has been reported after a series of PDL treatment (McDaniel et al. 1996; Alster 1997). The PDL has a moderate, beneficial effect in reducing the degree of erythema in striae rubra but no apparent benefit in striae alba. Because of the potential for adverse effects, PDL should be performed with extreme caution in patients with Fitzpatrick V-VI skin type. McDaniel et al. undertook a controlled of 39 patients with SD. Treatment sites included the abdomen, thighs, and breasts. Four treatment protocols were used with different spot distances and fluences. Untreated SD was the control. Outcomes were measured by subjective analysis, shadow profilometry, and histological analysis. A significant reduction in skin shadowing was reported in patients with SD in all protocols compared to controls. Additionally, elastin regained its normal appearance in SD treated with low-fluence PDL (McDaniel et al. 1996; Hernández-Pérez et al. 2002).

Intense pulsed light (IPL), characterized by a noncoherent filtered flash lamp with a broadband spectrum (515–1200 nm), has been shown to replace dermal elastosis with neocollagen, thus

improving the appearance of mature SD after a series of treatments (Zelickson et al. 2004).

Radiofrequency (RF) devices produce heat which converts electrical current to thermal energy that is uniformly dispersed to different tissue depths. It increases collagen production by inducing collagen type I mRNA expression (Manuskiatti et al. 2009).

The long-pulse 1064 Nd:YAG is a nonablative treatment for facial wrinkles, and an increase in dermal collagen has been reported after treatment. It also has a strong affinity to vascular targets, making it a useful modality in the treatment of SR. The 1064 Nd:YAG laser can be safely used, even in patients with dark skin types (Goldman et al. 2008).

The 308-nm xenon-chloride excimer laser (XeCl) used in psoriasis, vitiligo, and post-inflammatory hypopigmentation has been used to repigment SD. Posttreatment biopsies showed increased melanin pigment, hypertrophy, and increased number of melanocytes; however, they failed to demonstrate any improvement in skin atrophy (Goldberg et al. 2003, 2005). Alexiades-Armenakas et al. conducted a randomized-controlled trial of 31 patients with SD. Lesions were randomized by alternate allocation to receive treatment or not. Treatments were performed at biweekly intervals until a maximum of ten treatments were undertaken; 75% increase in colorimetric measurements relative to baseline or 100% visual pigment correction was obtained. Outcome measures included visually assessed pigment correction relative to control assessed by three blinded observers and skin pigmentation levels measured on a colorimeter. A statistically significant improvement in pigmentation was identified in treated SD vs. site-matched controls. Improved visual pigmentation levels compared to controls were also reported, but this declined toward baseline after 6 months. Alternate allocations in this study were blinded to treatment. Attrition bias may be another concern as there is no report of how many patients were in the final analysis (Alexiades-Armenakas et al. 2004).

Ablative lasers, as short pulse 10,600 nm CO_2 laser, trigger epidermal vaporization and coagulation of the underlying dermis. They present a risk of hyperpigmentation, particularly in those with dark skin (Alster and Lupton 2002; Lee et al. 2010). Fractional photothermolysis (FP) was developed to overcome adverse effects associated with traditional ablative laser resurfacing and low efficacy of nonablative lasers (Lee et al. 2010; Geronemus 2006).

Fractional laser resurfacing can be delivered in either an ablative or nonablative mode. These laser devices generate focused laser energy that is delivered in a microarray pattern, producing small columns of tissue destruction in the epidermis and dermis, termed microscopic treatment zones (MTZs), with intervening islands of healthy tissue. Within these cones of destruction, the induction of tissue remodeling and synthesis of new collagen and elastic fibers occurs. The surrounding unaffected, healthy tissue serves as structural scaffolding as well as provides nutritional support for the treated zones, offering the advantage of significantly reduced healing times (Fisher and Geronemus 2005). The difference between ablative and nonablative FP lies in the variable degree of vaporization of columns of tissue (ablative) versus thermal injury with residual epidermal necrotic debris (nonablative). The nonablative technique achieves only minimal efficacy and requires multiple treatment sessions over an extended period of time, while the fractional ablative technique boasts superior efficacy, however, with more discomfort, postoperative erythema, and recovery time (Suh et al. 2007).

Fractional laser resurfacing devices demonstrate superior efficacy over other modalities of treatment techniques for photorejuvenation and have proven particularly effectiveness for acne scars, deep facial rhytides and atrophic scarring. Given the clinical and histologic similarity of striae to the dermal scarring characteristic of these conditions, comparable outcomes could theoretically be achieved in SD. The fractional ablative 10,600 nm carbon dioxide CO_2 laser has been shown to be highly efficacious for skin resurfacing as well as for the treatment of atrophic scars due to its ability to stimulate collagen and elastin regeneration and remodeling. Additionally, it has been documented that the fractional CO_2 laser induces neocollagensis to a greater degree than the nonablative lasers (Rahman et al. 2009).

Due to the high risk of pigmentary alteration in ethnic skin, the use of the CO_2 laser in patients with phototypes IV–VI has largely been discouraged; however, when used with appropriate caution, it appears that the fractionated CO_2 systems are safe and efficacious for the treatment of SD with no appreciable increase in risk for PIH.

Combination therapy may be the future for treating SD. Multiple simultaneous approaches may afford the use of lower fluences, ultimately decreasing adverse effects. Strict adherence to laser parameters and standardization of photography will be essential to ensure valid results. While a variety of energy devices could theoretically be used in combination, only a handful of well-powered studies have been performed, so it is hard to say which combination will be at the forefront (Aldahan et al. 2016).

Author Experience

In our daily practice, both striae rubra and striae alba, located in different areas of the body, have been treated with CO_2 fractional laser (Ultrapulse, Deep Fx) in the last 5 years. During this period, we have documented treatment of 500 Brazilian patients (Fitzpatrick skin types III to V) with SD who were followed up for 2 years.

For the treatment, topical lidocaina associated with tetracaina cream was applied on the skin 20–60 min before laser therapy. Treatment consists of applying two passes of laser. The first pass was performed over the SD using a linear pattern, energy of 5–20 mJ, density 5–15%, with single pulses. The second pass was performed using a square pattern, energy of 2.5–10 mJ, densities 5–15%, with single pulses. This second pass was performed not only over the SD but also around the SD. Patients were advised to kindly wash the area, to apply a healing cream twice a day for 2 weeks, and to avoid sun exposure for 3 weeks. After this period, they were oriented to wear chemical and physical topical sunscreen.

Clinical results were evaluated 3 months and 2 years after treatment, through image software, which quantifies SD volume before and after treatment through an overlap of before and after images.

Three months after treatment, 100% of patient had improved. Among them, 15% was considered

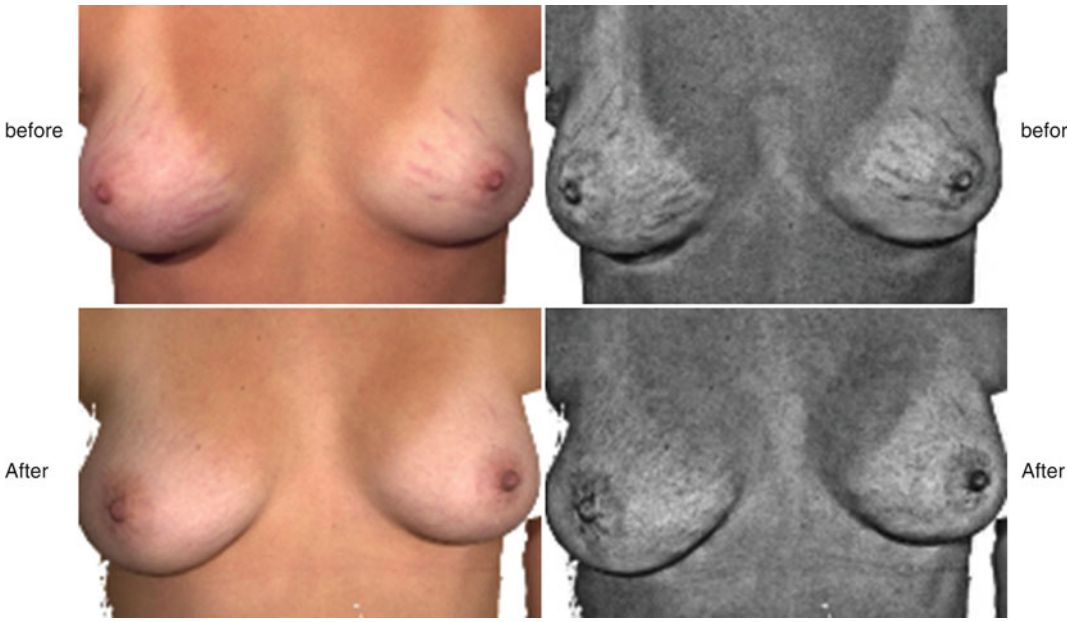

Fig. 1 Before and 24 months after treatment: excellent improvement

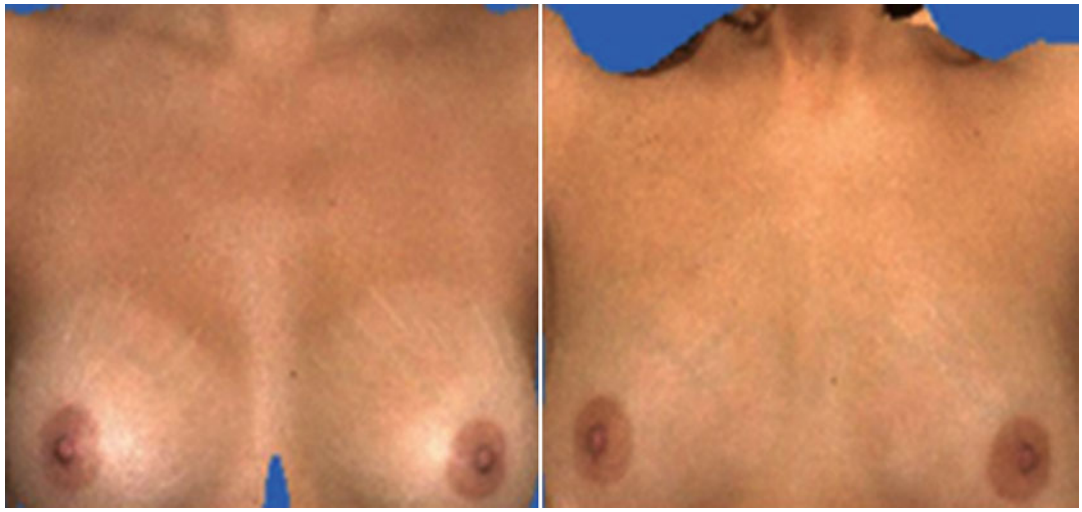

Fig. 2 Before and 24 months after treatment: excellent improvement

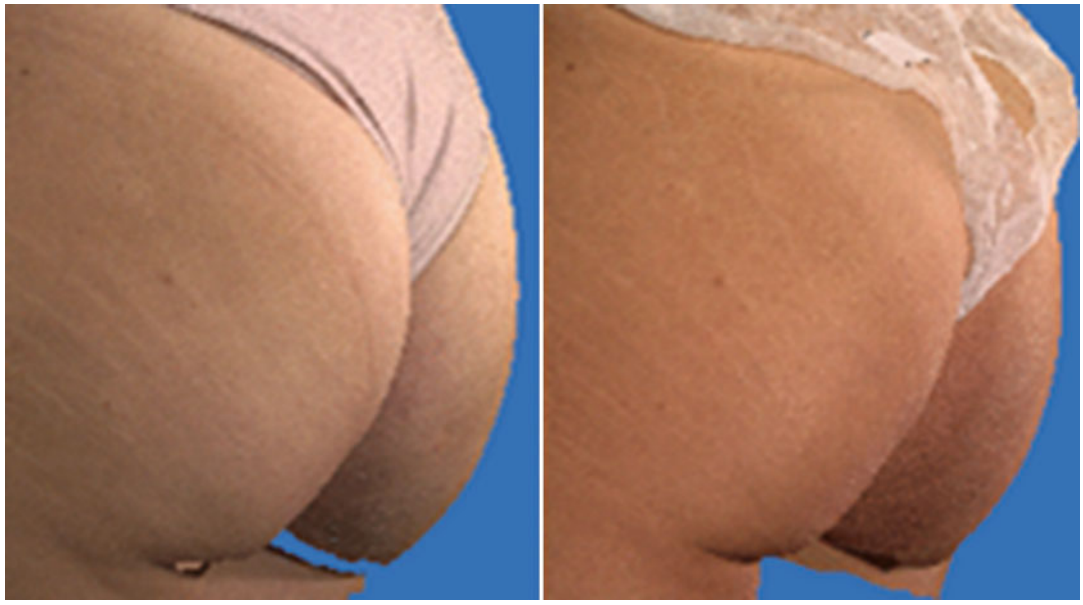

Fig. 3 Before and 24 months after treatment: good improvement

excellent improvement, 65% good improvement, and 20% moderate improvement. These results were sustained during 2 years of follow-up (Figs. 1, 2, 3, 4, and 5).

Best results were achieved for striae rubra, compared with striae alba, and for SD located on the breast. The second best anatomy region to have good results was the abdomen and then the thighs.

Degree of patients satisfaction was considered excellent in 10% and great in 90%.

Post-inflammatory hyperchromia was a transitory side effect. To avoid dyschromia, we advocate the use of low densities.

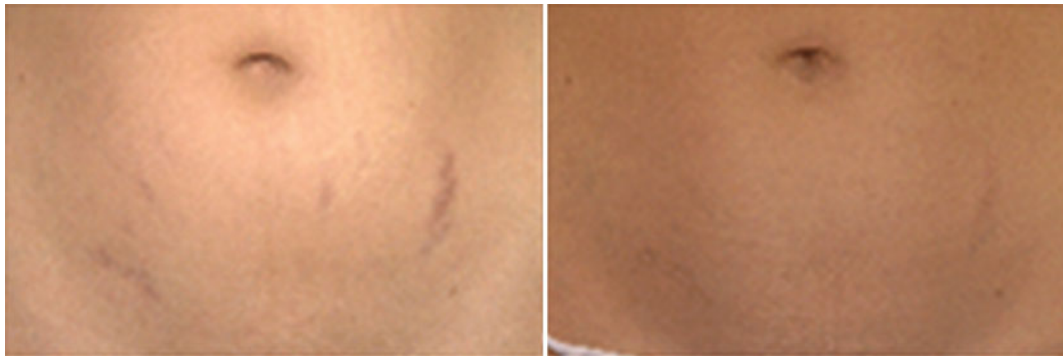

Fig. 4 Before and 24 months after treatment: excellent improvement

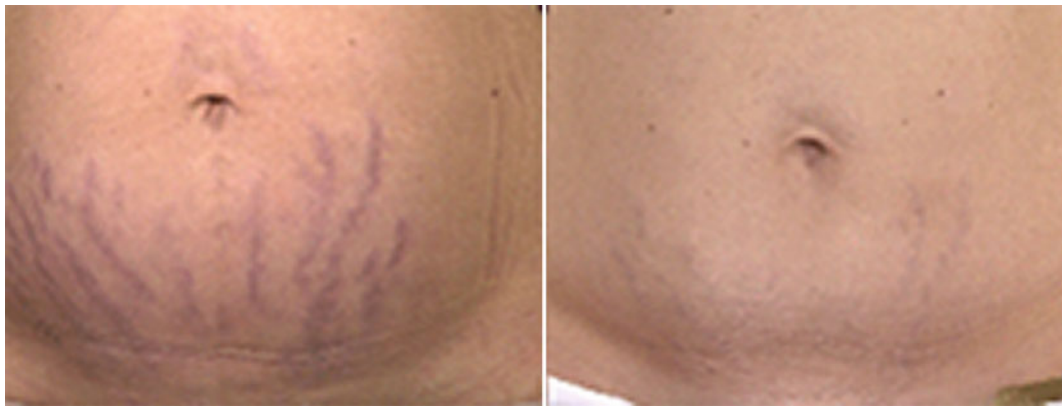

Fig. 5 Before and 24 months after treatment: good improvement

Conclusion

Striae distensae are a well-recognized, common dermatologic entity, which affect patients of all ages, genders, and ethnicities and rarely cause any significant medical problems but can have a deep psychological impact on affected patients. Many treatment modalities are available for treatment and prevention; however, striae distensae is still a challenge for dermatology. Laser treatment can be a good option when performed by experts. Fractional CO_2 laser can bring very good results, but appropriated parameters must be adjusted according to the device. Low density is an important parameter to avoid side effects.

Take Home Messages

- Striae distensae commonly occur in pregnancy, puberty, and obesity.
- Proposed etiological mechanisms are hormones, physical stretch, and structural alterations to the tegument.
- Striae distensae does not have one standard treatment but many different treatment modalities.
- Treatments include topical agents, radiofrequency, percutaneous collagen induction, microneedling, IPL, and nonablative and ablative lasers.
- Expectations must be realistic, but the fractional CO_2 laser has recently shown improvement of these aesthetically distressing lesions.

- Best results were achieved for striae rubra, compared with striae alba, and for SD located on the breast. The second best anatomy region to have better results was the abdomen.
- Parameters should be adjusted according to the device. Low density is advocated. Photoprotection and topical care are recommended to avoid post-inflammatory hyperchromia.

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CO_2 Laser for Scars

Thales Lage Bicalho Bretas, Aline Tanus, Marcia Linhares, and Maria Claudia Almeida Issa

Abstract

Scars result from the substitution of a damaged skin to a new and abnormal tissue following an injury. Ablative devices, including the Erbium and carbon dioxide lasers, have shown to be effective in improving the appearance of scars, including mature burn scars. The CO_2 laser promotes thermal fractionated ablation of the skin, and the resultant selective healing stimuli improve the altered tissue. The scars, then, become more homogeneous with the surrounding skin. The carbon dioxide laser can be combined to other interventions to achieve optimal results. It can also be used to allow drug penetration into the dermis, homogeneously, a technique called drug delivery. It has been reported the use of drugs such as corticoids to reduce the hypertrophic scars and poli-L-latic acid (PLLA) to increase collagenesis in atrophic scars. In post-procedure/post-treatment and burn scars, the early use of the CO_2 laser is important to remodel the tissue before the maturation of the scar, therefore bringing better cosmetic results. In this chapter, we will expatiate on the multiple kinds of scars, the ablative fractional carbon dioxide laser CO_2 peculiarities and the approach of different types of scars through the use of this technology. We will also discuss the precautions to be taken before the procedure (pre-treatment), the procedure itself, the post-procedure/post-treatment care, the most commonly seen side effects and how to deal with them.

Keywords

CO_2 Laser • Scars • Ablative • Fractional • Carbon dioxide

Contents

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Introduction

The healing process involves the release of inflammatory mediators, cytokines, and cell chemotaxis, leading to reepithelialization and deposition of types III and I collagen within the dermis, respectively. Scars are a consequence of abnormal substitution of damaged tissues after trauma, with misbalance of collagen types and their fiber thickness within the dermis, as well as histological disorganization. They represent unaesthetic marks capable of decreasing self-esteem and quality of life, therefore demanding the start of an efficient treatment as quick as possible, in order to offer the patient satisfactory and aesthetic results. Treating scars has never been an easy task for dermatologists, and it usually involves multi- therapeutic approach, with a combination of drugs and technologies. There are unnumbered treatments described, such as ablative and non-ablative lasers, corticosteroid injection, intralesional 5-fluorouracil or bleomycin, silicon patches, cryotherapy, chemical peels, dermabrasion, fillers, punch excisions, punch-elevations, micro needling, subcision, and many others (Ozog et al. 2013; Wolfram et al. 2009; Reish and Eriksson 2008).

In the past decades, the popping up of fractional lasers (ablative or not) took the scar management to another level, offering good results with minimum invasive procedures. The recent use of the carbon dioxide (CO_2) ablative fractional laser (AFL) for the treatment of scars has delivered good results when correctly managed. This laser promotes thermal ablation of multiple small channels between nondamaged skin, called microthermal zones (MTZ), causing healing stimuli that results in neocollagenesis and remodeling of the altered tissue. The expression of some cellular markers of dermal wound healing and neocollagenesis, such as collagen III, heat shock protein 70, alpha-smooth muscle actin, and proliferating cell nuclear antigens have been reported in treated areas. Therefore, scars become shallower and narrower, and their surface tend to look more homogeneous with the surrounding skin (Manstein et al. 2004; Laubach et al. 2006; Walgrave et al. 2008; Alexiades-Armenakas et al. 2011; Rkein et al. 2014).

The CO_2 laser itself, without being combined to other techniques, already offers visibly good improvement in the skin texture, shape and aspect of the scar, as well as its similarity to the surrounding skin. But it has also been used concomitantly with the application of several medications; hence it produces small channels that allow the penetration of drugs into the dermis, homogeneously, a technique called drug delivery. In hypertrophic scars, for example, the CO_2 laser itself does not represent a good option as a monotherapy; it is often used to deliver drugs such as corticoids and bleomycin that will act synergistically with the laser to reduce the hypertrophy and improve even more the aspects of the scar. This method demands special caution and knowledge from the operator, as the laser itself could cause new scars in a person who has some genetic tendency of developing hypertrophic scars, as well as it could over stimulate those scar fibroblasts and worsen the fibrosis already generated by an overreaction of that body to a previous damage stimulus. In atrophic and acne scars, the CO_2 laser can also be used with the delivery of drugs like poli-L-latic acid (PLLA) to increase collagenesis and fulfill the depressions of the scar tissue (Vrijman et al. 2011; Shamsaldeen et al. 2011; Fife et al. 2009; Avram et al. 2009).

Scars

Scars represent abnormal substitution of a damaged tissue after any trauma that reaches the dermis. Functionally, they are less malleable than the normal tissue and they lack cutaneous annexes, such as hair follicles, sebaceous and sweat glands. They can be either hypertrophic or atrophic and

are frequently generated by harms such as burns, surgery, tattoos, accidents, or some inflammatory diseases like acne. There is also a particular kind of hypertrophic scar, known as keloid, which is a result of very exacerbated inflammatory response of the host to skin damages, and demands a different and more cautious approach.

Hypertrophic scars result from uncontrolled proliferation of fibroblasts and extracellular matrix. The reason why this abnormal proliferation occurs is primarily genetic, and afro-descendants are usually more prone to this alteration. The hypertrophic scars are higher than the surrounding skin, and they do not go further than the originating scar borders. Typically, hypertrophic scars can be seen on the shoulders, superior trunk, and ears (Alster and Tanzi 2003; Verhaeghe et al. 2013; Kuo et al. 2004).

A keloid, for definition, goes over the boundaries of the original injury, has a higher recurrence index, and represents a challenging task to dermatologists. Besides its visual impairment, the keloid is usually painful, rigid, with thick fibrosis and low mobility. It does not regress spontaneously, and the patients affected have a high genetic predisposition (Reiken et al. 1997; Alster and Williams 1995; Sherling et al. 2010).

Atrophic scars result from inefficient collagen remodeling and abnormal regeneration of the fibrous tissue. They represent depressions on the skin surface and can be originated by unaware care with a wound or also be influenced by genetic predisposition (Vrijman et al. 2011).

Acne scars originated from moderate to severe acne in teenagers and young adults represent frequent and important complains in a dermatological consultation. Their etiology is related to exaggerated inflammatory reaction that lasts too long, inefficient immune response of the host to the tissue damage, and anomalous healing capacity with low collagen synthesis (Jeremy et al. 2003; Taylor et al. 2011; Fabbrocini et al. 2010; Holland et al. 2004; Sobanko and Alster 2012). Acne scars are classified by the amount of collagen loss or gain by the tissue, by its thickness, its stretching capability, its depth, and its architecture.

Atrophic scars are the most common kind of acne scars and occur because of the destruction of dermic structures by the deep inflammatory infiltrate. They can be divided into ice pick scars, rolling scars, and boxcar scars (Fig. 1). Ice pick scars are narrow, spotted and deep scars, clinically shown as multiple small points of depression on skin surface. They usually have less than 2 mm of width and grow vertically until deep dermis or subcutaneous tissue, assuming a cone figure. Rolling scars are shallower and wider, with a width of 4–5 mm, with sloping edges, and they occur when the dermis gets attached to the subcutaneous tissue, producing a superficial ripple. Boxcar scars are rounded or oval, with a various width, from shallow to deep, and diameter between 1.5 and 4 mm (Levy and Zeichner 2012; Jacob et al. 2001; Lee et al. 2013).

Fractional CO_2 Laser

Basic Principles

The CO_2 laser is an ablative fractional laser (AFL), with a wavelength of 10.600 nm, and its target is the water. The AFL produces

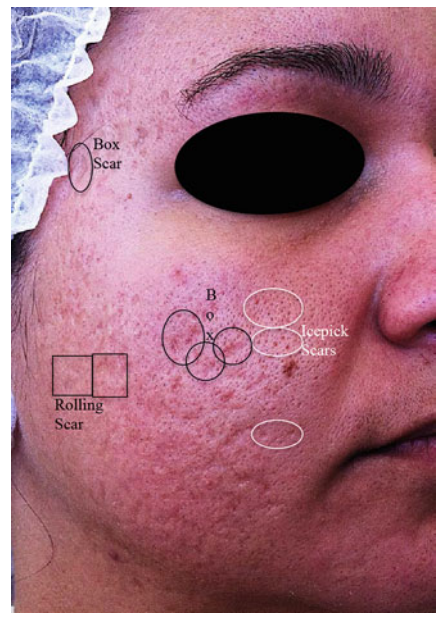

Fig. 1 Different types of atrophic acne scars

microscopic columns of ablated tissue, which extends from the epidermis to the dermis (the so-called microthermal zones – MTZ), saving healthy tissue areas between these columns. Collagen degeneration and focal epidermic necrosis stimulate a process of fast reepithelization promoted by the surrounding healthy skin cells. The AFL technology gave us a new perspective for facial resurfacing treatments, decreasing the side effects and complications of the standard ablative resurfacing so far feared, since it did not use to preserve any healthy skin area. Other kinds of ablative fractional lasers are the Er:YAG (yttrium, aluminium, garnet) 2.940 nm, and the new Er:YSG (yttrium, sapphire, garnet) 2790 nm. They only differ from each other in the wavelength and the water absorption coefficient, as the target is the same: the emanating energy is absorbed by the amount of water in the tissue (Manstein et al. 2004; Laubach et al. 2006; Walgrave et al. 2008; Alexiades-Armenakas et al. 2011; Alster and Nanni 1998).

The Er:YAG has the biggest water absorption coefficient, as it promotes immediate vaporization of cells without thermic damage. It is capable of absorbing 12–18 times more water than the CO_2. The pulse duration of the Er:YAG is much smaller than the CO_2 laser's, resulting in less surrounding thermic diffusion. Nevertheless, the inability of the Er:YAG to cause thermic injury results in less collagen contraction, making it useless to promote per-operatory homeostasis (Alster and Nanni 1998).

The CO_2 laser device has a handpiece that projects small spots on the skin. Depending on the model used, it is possible to adjust the shot format (triangle, square, or round, for example), the spot density and the diameter of each spot, which can range from 125 μm to 1.25 mm. It has the smallest water absorption coefficient, causing large collateral thermic damage and promoting excellent homeostasis when used in the standard mode, nonfractional (Rkein et al. 2014).

There are, basically, four or five parameters to be adjusted in the CO_2 laser, bearing in mind the skin area to be treated, the deepness, the diameter and the ablation degree:

- *Energy*: is the amount of power (in Watts) delivered to the tissue in a given time (the laser pulse duration, in seconds). It is directly proportional to the depth of penetration and the thermic injury promoted, meaning that the higher is the energy, the deeper the laser reaches and the more injury it promotes in the surrounding tissue.
- *Fluency/Density*: is the amount of energy delivered to a certain area – the overall size of the application area or the "spot size" produced by the laser handpiece. Thus, the energy density or fluency is measured in J/cm^2. The higher the fluency, the faster the temperature increases in the tissue and, consequently, the bigger is the intensity of the desired effect. The effect of the treatment is achieved both by varying the laser output energy and the laser pulse duration, at the tissue application area.
- *Pulse duration*: in milliseconds (ms), it is directly proportional to thermal injury of the tissue. The more the pulse lasts, the bigger is the damage made in the target tissue and surroundings.
- *Distance between dots*: determines the balance between the density of energy delivered and the preserved skin in the treated area. It is inversely proportional to density, which means that the smaller is the distance between the dots, the more energy will be delivered into the target area, with denser thermal ablation. Higher densities mean dots overlapping, leaving smaller healthy skin surface preserved and making the post procedure more uncomfortable.

Mechanism of Action of the Fractional CO_2 Laser

Heat shock proteins (HSP) are upregulated and have their role in cutaneous remodeling after thermal injuries. They have anti-inflammatory and cell-protecting actions. Histologic studies have demonstrated enhanced levels of HSP, such as HSP70 and HSP47, that promote the process of collagen generation, leading to dermal thickening

and improvement of scar appearance (Magnani and Schweiger 2014). HSP70 is a procollagen chaperone and plays a crucial role in wound healing, promoting neocollagenesis and the expression of other growth factors, like transforming growth factor β (TGF-β), essential to healing. HSP47 also plays a key role in promoting neocollagenesis. Its peak expression is at 1-month posttreatment, and it remains high at 3 and 6 months. Remodeling and new collagen formation was noted at 3 and 6 months post procedure. The long-term expression of these two heat shock proteins supports the long-term efficacy of fractional CO_2 laser resurfacing (Xu et al. 2011).

The CO_2 laser also enhances the expression of tissue collagenases, such as matrix metalloproteinases (MMP), that act in collagen degradation. As MMPs are not normally expressed in the skin, the balance between collagen formation and degradation results in individual responses for each patient (Vrijman et al. 2011).

As already mentioned before, the CO_2 laser produces small dots in between preserved skin in the treated area, the MTZ, with vaporization of the corneal layer upon these channels. An area of undamaged tissue surrounds each ablative zone. Spared, viable keratinocytes in these areas migrate to the MTZs and promote the healing process, with collagen formation and reepithelization. Immediately after the laser pulse, hypochromic dotted macules may be seen in skin surface, representing this corneal layer's vaporization. These macules evolve to erythema, more visible within 3 days after the treatment. At that time, serosanguinous drainage and swelling occurs in various degrees, according to the parameters used. Bleeding occurs between the stratum corneum and stratum granulosum. Regeneration and desquamation of the epithelium is observed, with preservation of the basal lamina. There is also disappearance of elastin in elastic fibers located in the superficial dermis of scar areas (Magnani and Schweiger 2014).

The healing process finishes with the formation of small brown crusts, corresponding to the extrusion of damaged keratinocytes. Necrotic debris are eliminated within 1–2 weeks (can take even longer in certain patients), leaving skin surface more "tanned" until its complete exfoliation (Rkein et al. 2014). Three weeks after treatment, almost complete regeneration of the epithelium is observed. Microscopically, elastin can be seen in electron-dense deposits, and elastic fibers look fragmented and elaunin-like, which is indicative of the dermal remodeling process (Omi et al. 2011). A visible improvement of scars can be seen within 3 months, but it has already been described up to 12–18 months after treatment, with neocollagenesis and dermal remodeling evidenced by histological analyses.

The Use of Fractional CO_2 Laser in Treating Different Kinds of Scars

Hypertrophic Scars

Although the CO_2 laser has been used to treat hypertrophic scars, the pulsed dye laser (PDL) 585 nm has a higher evidence of efficacy based on the recent findings of the literature. The overexpression and abnormal activity of TGF-β1 and TGF-β2 is enrolled in the pathogenesis of hypertrophic scars and keloids. The mechanism of action of the PDL is not yet a consensus, but it is believed that it reduces the expression of TGF-β, the fibroblast proliferation and the collagen III deposition in the scar. It is also described that, between the mechanisms of action of the PDL, are the selective photothermolysis of blood vessels, the release of histamine and interleukins by mast cells and the collagen degradation with consequent reestablishment of the dermis (Alster and Nanni 1998; Patel and Clement 2002; Reish and Eriksson 2008; Alster and Zaulyanov 2007). Intralesional corticosteroid infiltration aiming to inhibit collagen synthesis immediately after the PDL section is technically easier due to tissue swelling, offering less resistance to the needle penetration into the scar (Mustoe et al. 2002; Jalali and Bayat 2007; Roques and Téot 2008; Manuskiatti and Fitzpatrick 2002; Gupta and Sharma 2011; Chowdri et al. 1999).

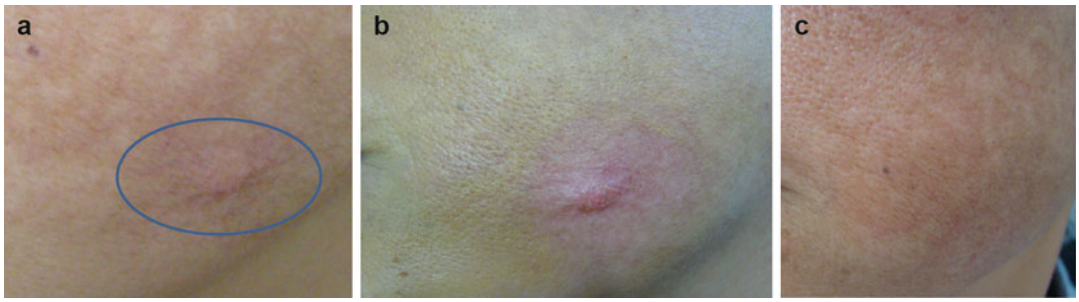

Fig. 2 (**a**) Hypertrophic scar in malar region before laser treatment. (**b**) Hypertrophic scar immediately after CO_2 laser session associated with topical triamcinolone: drug delivery. (**c**) Two years after CO_2 laser treatment associated with triamcinolone: drug delivery

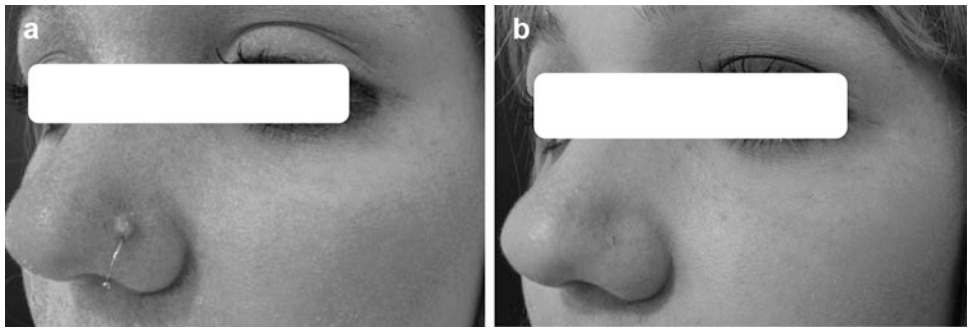

Fig. 3 (**a**) Hypertrophic scar on the *left* nasal wing before the CO_2 laser session. (**b**) Hypertrophic scar on the *left* nasal wing after a single CO_2 session and the use of Triamcinolona 20 mg/gl as a drug delivery

The Fractional CO_2 laser is often used to improve thickness, stiffness, and abnormal texture of more mature scars by ablative destruction and resurfacing (Waibel et al. 2013). The treatment with fCO_2 ablative laser can be started from 12 months after injury or following the conclusion of PDL treatment, in case they are combined. Laser sessions are delivered with 4–6-week intervals until a plateau in improvement is observed. Generally, only one modality is used per session, but more than one platform can be used on different sites in the same session.

The microscopic thermal zones generated by the CO_2 laser have also been used as channels to enhance the penetration of triamcinolone (Fig. 2a–c) and other topical drugs into the skin. This technique, called Drug Delivery, is less painful than the drug injection and allows a more uniform distribution of the medication between the scar's dermis, acting synergistically with the laser. The corneal stratus is normally impermeable to molecules weighting more than 500 Da, nevertheless, the channels created by the laser allows higher penetration and bioavailability of topic medications (Goodman 2006).

Having all that information in mind, the CO_2 laser is usually combined with the Drug Delivery technique to achieve better results in treating keloids and hypertrophic scars (Fig. 3a, b). Knowing that the laser itself can promote a high healing response in people who are already genetically prone to scar formation, it is always extremely advised to start slowly at the first few laser sections, with low potencies/ fluencies and low pulse durations not to worsen scars by feeding their exacerbated inflammatory chain secondary to healing stimuli.

Atrophic Scars in General and Atrophic Acne Scars

Atrophic scars are better treated with AFL, like the CO_2 laser, when compared to nonablative fractional lasers, because the energy reaches deep dermis (1.5–1.6 mm of depth) and the remodeling process can last months. The AFL increases the heat shock proteins (HSP) expression, which in turn regulate the tissue response to thermal injury through activation of epidermic stem cells that will replace the just damaged cells. IL-1, TNF-alfa, TGF, and MMP signalize the removal of the damaged cells and the neocollagenesis.

The CO_2 laser treatment reduces scar's width and depth and stimulates the synthesis and organization of collagen fibers, filling in atrophic areas. It is highly recommended to treat the whole aesthetic unit surface, and neither only the affected areas nor the scar itself, in order to avoid clear demarcation between treated and nontreated areas. As a resurfacing method, the CO_2 laser promotes a higher collagenesis stimuli and a better aesthetic result. It improves the homogeneity of the skin, progressively making the atrophic areas seem more plane, shallower, superficial, and reintegrating them to the surrounding normal skin.

We shall never forget the possibility of the concomitant use of drugs that stimulate collagenesis and reverse the atrophy through the drug delivery system with the homogeneous penetration of medications to improve the skin texture and regain its volume and vitality. In atrophic scars, the poli-L-latic acid (PLLA) is the actual substance used to improve collagenesis through the drug delivery technique, straight after the laser section. PLLA, when introduced, induces local inflammatory response with activation and production of collagen, acting in a synergic way with the laser.

Acne scars are mostly atrophic, subdivided in different types as already mentioned (icepicks, box scar, and rolling scar). The great majority of the affected patients have multiple types simultaneously. With the resurfacing technique, there is a good improvement in the general aspect of the treated aesthetic unit, but multiple laser sessions are usually needed to achieve impressive results. All subtypes of acne scars experiment great amelioration, but box scars are often better responsive. The patients shall be oriented about the need of subsequent sessions, from four to six, to get the best outcome (Fabbrocini et al. 2010; Magnani and Schweiger 2014; Omi et al. 2011) (Fig. 4a, b).

Postsurgical/ Post-Traumatic Scars

Fast and early acting in these scars are essential to improve their thickness and texture. Depigmentation is the hardest alteration to treat. Due to the bigger depth they have in comparison to acne scars, the postsurgical scars usually reach worse results. Fibroblasts and myofibroblasts start migration during the first week, and begin to form a scar tissue after the second week. Therefore, the right approach shall be made readily within the first week after surgery.

Many studies use the Vancouver scar scale (VSS) to promote clinical evaluation of the scar, including the pigmentation (0 = normal, 1 = hypopigmentation, 2 = hyperpigmentation), vascularity (0 = normal, 1 = pink, 2 = pink to red, 3 = red, 4 = red to purple, 5 = purple), pliability (0 = normal, 1 = supple, 2 = yielding, 3 = firm, 4 = banding, 5 = contracture), and height (0 = normal, 1 = <2 mm, 2 = 2–5 mm, 3 = >5 mm) (Chowdri et al. 1999).

Apparently, the CO_2 laser can be used to treat postsurgical and post-traumatic scars (Figs. 5a, b, 6a, b, 7a, b, and 8a, b) as well as they can promote the formation of a new scar. The occurrence of hypertrophic scars secondary to the treatment with the CO_2 laser has been reported. Many suggested protocols for the laser treatment are available, but the energy delivered and the area to be treated must be thoroughly chosen. The suggested densities to approach the face scars range from 30% to 50%, whereas in extrafacial areas they range from 20% to 30%, as the chances of hypertrophic scars are higher at those areas, specially on the neck, as previously mentioned. Moreover, lower energies also offer the best results and lower the risks of erythema and permanent depigmentation after the laser treatment (Roques and Téot 2008; Manuskiatti and Fitzpatrick 2002; Sobanko et al. 2015; Zachariae 1988).

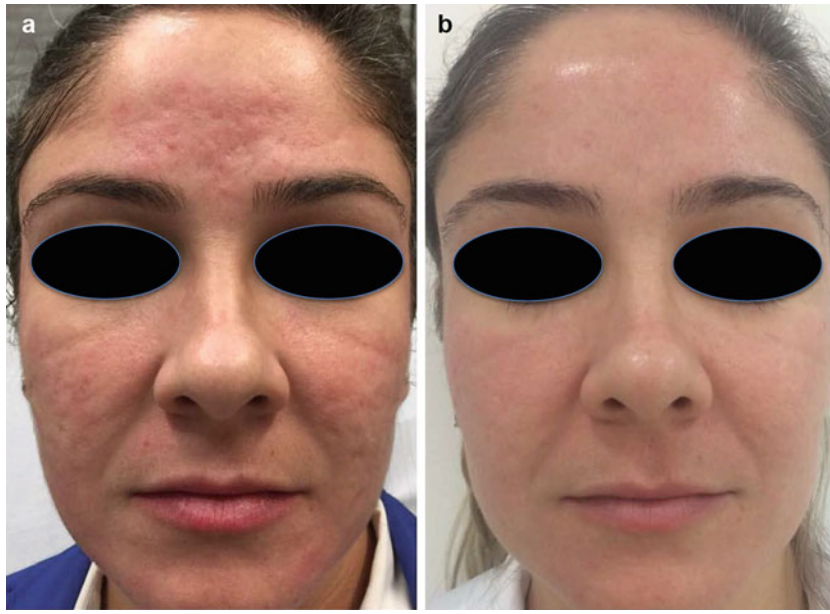

Fig. 4 (**a, b**) Atrophic acne scars before and after two sessions of CO_2 laser with 3 months interval

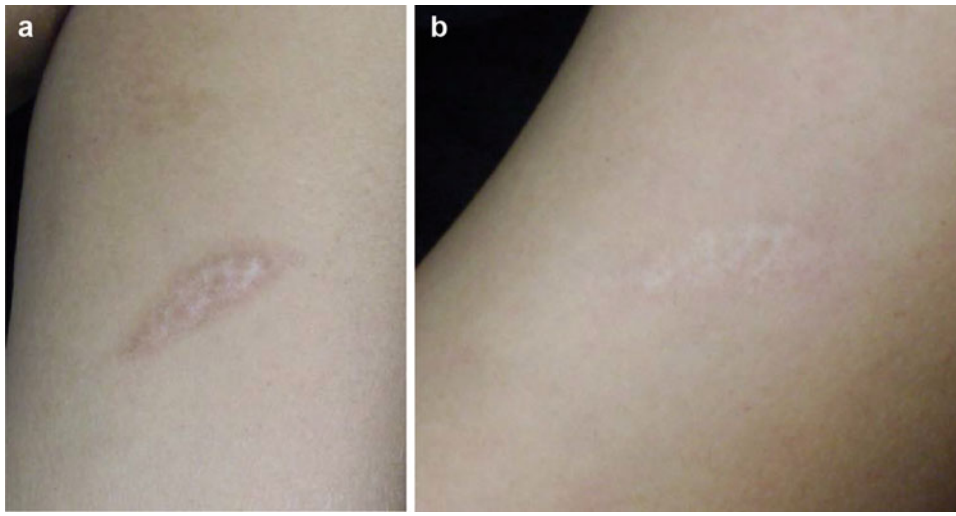

Fig. 5 (**a, b**) Before and 6 months after four sessions: (30 mJ; 100 density)

Burn Scars

Burn scars have a complex formation mechanism that involves trauma responses, and their treatment must focus on aesthetics and functional improvements. Apart of all adequate surgical and curative care, it is common to see the patient complaining about local pain, burning, or itching. In managing burn scars, we shall focus on addressing the aberrant collagen deposition typically shown in mature scars. Mature scars, like adult skin, have a predominance of type I collagen over type III, and this proportion is inverted in fetal skins.

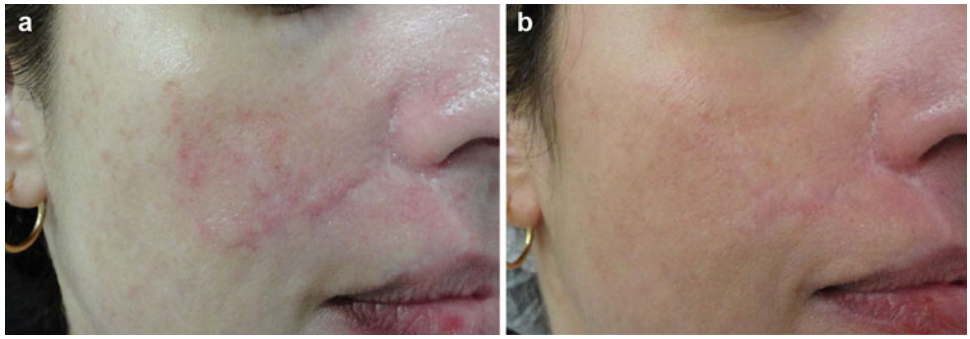

Fig. 6 (**a**) Scar after surgery: before treatment. (**b**) Scar after surgery after one section of CO_2 laser

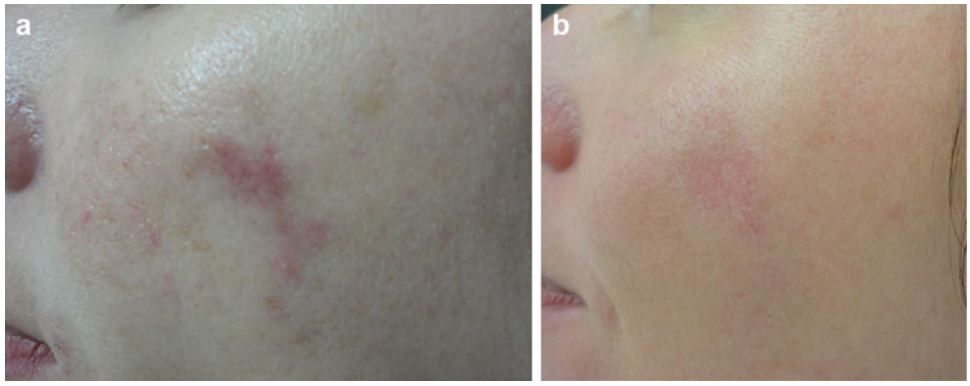

Fig. 7 (**a**) Scar after surgery before treatment. (**b**) Scar after surgery after one section of CO_2 laser

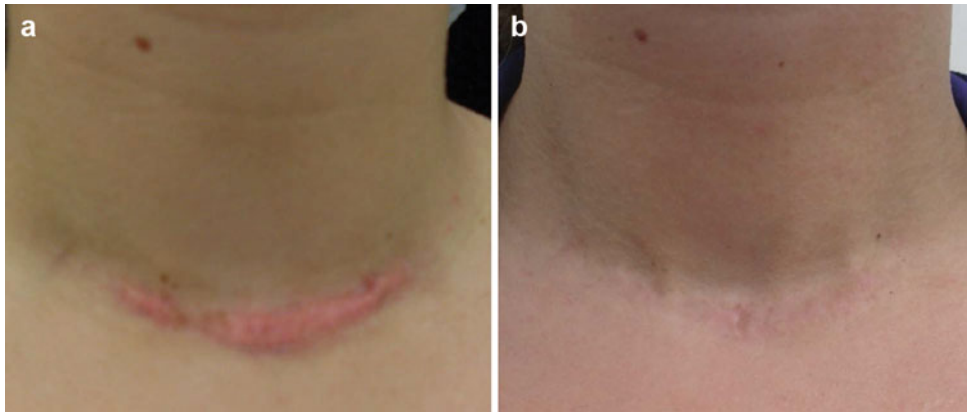

Fig. 8 (**a, b**) Before and 6 months after four sessions: (30 mJ; 100 density)

The use of Fractional CO_2 laser in burn scars has been proved to decrease collagen I and increase collagen III in the treated tissue, rearranging the scar tissue to reestablish the normal collagen deposition seen in young and nondamaged skin. This finding might be the responsible for related gain in mobility of the scar region after the treatment.

Besides the improvement of the skin architecture, there is no way to regain the lost adnexal structures, like hair follicles, sebaceous and sweat glands. Therefore, the aesthetic improvement might be limited in cases of extensive skin areas affected (Ozog et al. 2013).

Preprocedure

The procedure itself depends on each manufacturer's protocols. But there are some general precautions and instructions to be followed, especially before and after the procedure. Starting from a previous well-done anamnesis and after a minimalist physical exam, dermatologists must pay special attentions to the conditions mentioned bellow:

Active infections of any kind (fungal, bacterial, or viral) are relative contraindications to the laser, and should be treated properly ahead of the laser session.

Inflammatory skin disorders on the area to be treated, like eczema or psoriasis, are not to be submitted to the procedure until their complete resolution. Patients with inflammatory skin diseases that have Köebner phenomenon (lichen planus, psoriasis, perforating dermatosis, vitiligo, etc), even outside the area to be treated, shall be well informed of this possibility.

Active acne: Patients with acne scars and active disease should be treated properly with topical or oral treatment prior to proceed to the scar management, in order to control the inflammatory lesions before the laser sessions. There is no point in treating acne scars when new ones are still popping up, since it would prolong the treatment and make it inefficient.

Recent oral Isotretinoin use: Concerning the possibility of healing impairment in patients taking isotretinoin, as well as the risen risk of keloid formation, it is recommended to wait at least 6 months after the end of the treatment to start the laser sessions. There is still a lack of studies evaluating this wound healing impairment, but a consensual interval of 6 months has been established (Zachary and Rofagha 2012).

Herpes simplex personal history: Patients with previous history of herpes simplex infection must undergo a prophylaxis with antiviral agents. The duration is not yet a consensus, but oral Aciclovir (400 mg 8/8 h), Valacyclovir (1 g qd), or Famciclovir (250 mg 12/12 h) should be started at least 48 h prior to the procedure, and be kept until reepithelization, usually 5 days following the laser session (Zachary and Rofagha 2012).

Higher skin phototypes (Fitzpatrick IV to VI): darker skin tones have higher risk of post-inflammatory hyperpigmentation related to the procedure. Therefore, the procedure shall be discouraged, since the risks would exceed the benefits. If extremely necessary, lower fluencies and densities can be used with caution.

Procedure

Proceeding to the laser session, a topical anesthetic should be applied in order to gently cover the area to be treated. After its action time, the skin must be well cleaned and a small area might receive the first laser shot to test the skin ablation and the patient's tolerance to the procedure.

The laser session is to be based on the manufacturer's orientations concerning the specific laser device and its personal parameters to the patient's situation. Both the patient and the applicant must wear safety goggles. The skin, thus, receives the laser shots, and the operator must avoid overlapping, since this practice can increase the laser potency and cause harm to the skin. When a certain area is treated with multiple overlapping, there is higher thermal damage, less healthy skin is left behind, hence elevating the risk of scar formation.

Immediately after the laser application, the doctor has a chance to do drug delivery spreading some active ingredients over the ablated area, depending on the patient's indications, like triamcinolone or bleomycin for hypertrophic scars and PLLA for atrophic ones.

Post Procedure

Immediately after the laser section, the skin presents with erythema and swelling due to the tissue vaporization and an exuberant serous discharge. A refreshing and calming mask can be placed over the patient's face, since one can be experiencing a burning sensation. Meanwhile, orientations to the post procedure are to be given to the patient, like hygiene routines and the application of topical healing creams on the treated area, twice a day, until complete reepithelization. The doctor must be sure that the patients know about the procedure's downtime, recovery, precautions need to be taken at home and how to manage expectations.

It is very important to tell the patients that, during the first few days, the skin is going to seem worse than before the treatment, followed by the appearance of crusts that get better in 7–10 days, when the healing and reepithelization process is going to be completed.

The results are really promising and tend to improve after subsequent sessions, with 2–6 weeks of interval between them. Higher potencies can be progressively used depending on the patient's tolerance and response to the treatment.

Side Effects

Aside the fact that the fractional CO_2 laser offers much less side effects than the ablative standard CO_2 laser, they can still occur. Some precautions are to be taken in order to avoid them, such as using lower energies and not overlapping more than twice at the same place. Side effects occur more often in patients submitted to either higher energies or densities (Vrijman et al. 2011; Shamsaldeen et al. 2011; Fife et al. 2009; Avram et al. 2009; Alster and Tanzi 2003).

Secondary infection is the most related side effect, and the herpes simplex prophylaxis is usually needed to avoid it. Erythema, swelling, and pain can be infection signs and the patient has to be well oriented to readily contact one's doctor in case of any of these changes.

Acneiform eruptions can either be a response to thermal injury or a reaction to the greasy healing creams prescribed after the procedure, and the latter must be replaced by more fluid options. The introduction of some soft topical medicines for acne also optimizes the resolution of acneiform eruptions.

Occlusive band-aids and antibiotics can cause contact dermatitis, better treated with topical corticosteroids. Late complications occur weeks after the procedure and include hyperpigmentation, persistent erythema, spotted appearance of the skin, ectropion, hypertrophic scars, and hypopigmentation. Hyperpigmentation and hypertrophic scars are rare, becoming more usual in extrafacial areas (particularly the neck) and when there have been multiple overlapping or excessively aggressive parameters have been used. Hypopigmentation is even rarer. In cases of dyschromia, topical agents like hydroquinone, retinoic acid, thioglycolic acid and others can be used. Lasers and light devices can also play an important role in cases of persistent erythema (Intense Pulsed Light, Ruby, Alexandrite) and hyperchromia (Intense Pulsed Light, Q-switched Nd-YAG).

Conclusions

The CO_2 laser offers a new and safe treatment to unaesthetic scars, with low incidence of side effects, good tolerance and high efficacy, making it a promising technique to this common complaint in dermatology offices. When well indicated, the results are really satisfying. Nevertheless, there are some precautions to be taken before the application of the laser: evaluate skin type and patient's expectations, antiviral prophylaxis when needed, and good orientation of the patients. They need to know about the downtime of this ablative laser, the possible side effects, how to deal with the recovery, and how to make it easier and faster, keeping the good results.

Concerning the laser device, each one carries their manufacturer's manual, as well as their right parameters taking the patients indication and skin

characteristics into account. However, concepts of fluency, potency, energy, spot size, and pulse duration are values that allow us to understand it as a patterned device: the higher the parameters are, the stronger and deeper the laser will reach the skin.

Take Home Messages

1. Scars are a consequence of abnormal substitution of damaged tissues after trauma.
2. The recent use of the carbon dioxide (CO_2) ablative fractional laser (AFXL) has delivered good results when correctly managed.
3. Treating scars is never an easy task for dermatologists, and involves multi therapeutic approach, with a combination of drugs and technologies.
4. The CO_2 laser creates microthermal zones (MTZ) that stimulate healing process involving heat shock proteins, metalloproteinases, cytokines and chemotaxis, with neocollagenesis and reorganization of the scar tissue and its surroundings.
5. The CO_2 laser can be used to treat scars as a monotherapy or combined to other techniques, such as pulsed dye laser, corticosteroid/bleomycin injections, topical drugs and others to achieve better results, especially in hypertrophic scars.
6. The CO_2 laser can also be used with the concomitant application of topical drugs that will penetrate into the MTZ and reach the dermis, acting synergistically in a technique called drug delivery.
7. In hypertrophic scars and keloids, the use of the CO_2 laser must be even more careful, since it may stimulate the overreacting healing inflammatory reaction found in genetically predisposed people.
8. In acne scars, there is usually concomitant presence of multiple kinds of atrophic scars, with general improvement after the CO_2 laser session. The patients often need more than one session, usually three to six, with 1–3 months of interval. Ice picks scars are the worst responders.
9. In postsurgical and burn scars, the early use is the key for the success.
10. The patients must be very well oriented about the procedure, its downtime, its pre and post precautions, as well as the possible side effects and signs of infection/complications.
11. If the patient has personal history of herpes simplex infection, he/she must undergo prophylaxis schemes before the laser application.
12. The presence of infections or active inflammatory diseases in the skin area to be treated must be completely solved before the laser session, as well as inflammatory skin diseases with Köebner phenomenon shall be discouraged of the procedure.
13. Before the laser application, topic anesthesia with lidocain, tetracain and others must be applied onto the skin area to be treated, and then removed with correct asepsis of the skin.
14. The laser section should be based on the manufacturer's protocol, considering the patient's Fitzpatrick's skin type, the indication and the parameters that match all these informations.
15. The post procedure evolves the use of restorative creams and general precautions like sun protection. If the patient is currently under herpes simplex prophylaxis, it must be continued until the complete skin reepithelization, around 5–10 days after the laser session.
16. The most common side effects are infections, dyschromia, persistent erythema, hypertrophic scarring, and hypopigmentation, the latter being rare. The doctor must feel capable of readily handle these intercurrences.

Cross-References

- ▶ CO_2 Laser for Photorejuvenation
- ▶ Erbium Laser for Scars and Striae Distensae
- ▶ Light-Emitting Diode for Acne, Scars, and Photodamaged Skin
- ▶ Non-ablative Fractional Lasers for Scars

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CO_2 Laser for Other Indications

Emmanuel Rodrigues de França, Alzinira S. Herênio Neta, and Gustavo S. M. de Carvalho

Abstract

The CO_2 laser is an ablative laser and has a strong affinity for water. It has been widely used with the objective to promote the rejuvenation or improve the appearance of scars by stimulating new collagen. As well, its increasingly widespread use has allowed the safe and effective treatment of various dermatoses, from benign epithelial tumors to melanocytic lesions to premalignant lesions (actinic cheilitis). Patient education on pre- and post-laser care is essential to maintaining good result. We discuss below some CO_2 laser indications in routine dermatologist.

Keywords

CO_2 lasers • Laser therapy • Lasers • Gas • Ablative laser

Contents

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Introduction

Dermatologists and plastics surgeons often encounter in their clinical practice injuries initially considered as small, which frequently have a difficult resolution. Pathologies as syringoma, sebaceous hyperplasia, verrucous epidermal nevus, acrochordon, and viral warts can be solved by different methods, but the laser, particularly the CO_2, can be very useful, with surprising results. We will cover the most common dermatologic conditions that can be benefited by this method.

Dermatosis Papulosa Nigra

Dermatosis papulosa nigra (DPN) is a common condition in the black population, particularly in women, with prevalence of 35% in the African-American population (Kundu and Patterson 2013). It begins in adolescence being the most affected women. The number and size of the lesions increase with age. Clinically, it is represented by multiple papules hyperchromic, asymptomatic, typically affecting the head and neck. It histologically resembles the seborrheic keratosis showing hyperkeratosis, irregular acanthosis, horn cysts, and marked hyperpigmentation of the basal layer. This is a benign lesion of genetically determined character – positive family history in around 40–54% of cases (Hairston et al. 1964).

No treatment is usually indicated for DPN. The condition, though indolent, can sometimes be symptomatic or aesthetically undesirable. In such cases, treatment options include *shaving*, curettage, cryotherapy, electrodessication, microdermabrasion, and laser. More aggressive approaches can be complicated by postoperative hyperpigmentation, hypopigmentation, or scars. The keloid formation is a potential complication (Fig. 1).

The lasers have been cited in the literature as useful therapeutic modalities for PDN, including CO_2 (Bruscino et al. 2014), Nd:YAG, diode, pulsed dye, and erbium lasers. Among them, the CO_2 laser has been shown to be safe, with low rates of recurrence or complications (scarring, hypo-/hyperpigmentation) and also a high degree of satisfaction by patients, even at the highest phototypes (Ali et al. 2016). The topical anesthesia is sufficient in most cases and is indicated white petrolatum ointment once a day until reepithelialization of lesions.

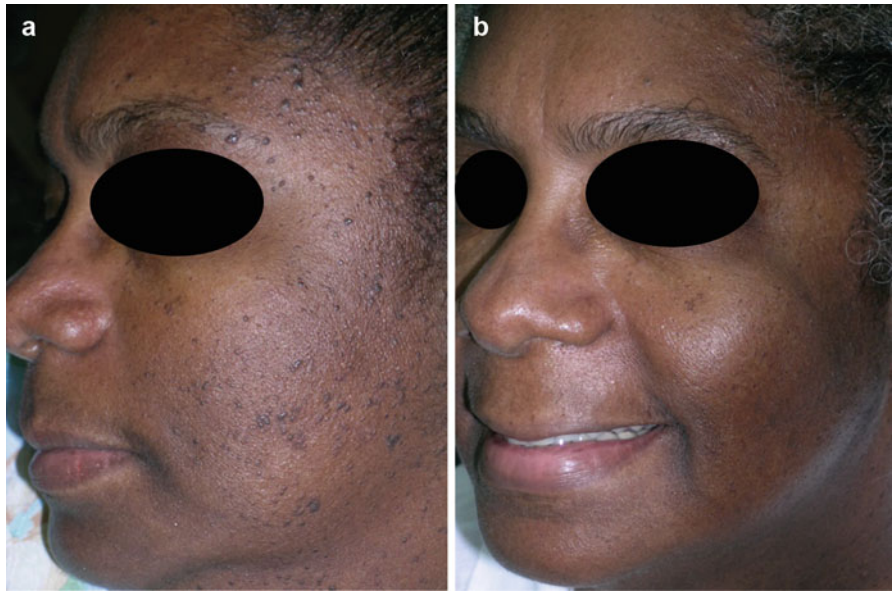

Fig. 1 (**a**, **b**) Dermatosis papulosa nigra treated with CO_2 laser (low fluence)

There must be an interval of 3–4 months between the sessions.

Xanthelasma

This is a benign disorder characterized by yellowish plaques typically located in the periorbital region, especially in the inner corner of the eyes and upper eyelids; it is also the most common form of skin xanthoma. The lesions have a tendency to progress and coalesce with permanent character.

They are due to accumulation of fat within the histiocytes, known as foamy histiocytes, located mainly in the upper reticular dermis. The main component is accumulated cholesterol, which for the most part are esterified. In 50% of patients, normal serum levels of cholesterol are found. The main association is with hypertriglyceridemia, found in 50% of cases. Reduced HDL level can be found in some patients. In such cases, it may be considered a predictor of cardiovascular risk, severe ischemic heart disease, and atherosclerosis, especially if combined with hypertension, diabetes, obesity, and smoking. It is a rare disease in the general population and has a slight predominance in females. They have peak incidence between the fourth and fifth decade of life.

The diagnosis is clinical, but it should be remembered that about half of patients have abnormal lipid levels; therefore, they should have their values measured frequently. Some drugs such as nilotinib, used to treat chronic myelogenous leukemia, may develop xanthelasma (Sayin et al. 2016).

The treatment is based primarily on dietary restriction and lipid-lowering drug if necessary. The aesthetics of xanthelasma is limited to isolated treatment of dyslipidemia. Numerous therapeutic options for the aesthetic xanthelasma treatment are available, such as surgical removal, electrosurgery, chemical cauterization with trichloroacetic acid, and cryosurgery. The pingyangmycin, family antibiotic bleomycin, can be injected into the lesions with good results (Wang et al. 2016). Electrocautery and cryosurgery can destroy superficial lesions, but require repeated treatments. Cryosurgery may cause scarring and hypopigmentation and should be discouraged. The use of ablative lasers as ultrapulsed CO_2, Erb:YAG (Güngör et al. 2014), Q-switched Nd:YAG, diode, pulsed dye laser, and KTP laser has become popular in the treatment of these lesions. The CO_2 ablative lasers are excellent options for localized xanthelasmas and without involvement of muscles (Mourad et al. 2015; Pathania et al. 2015) (Fig. 2).

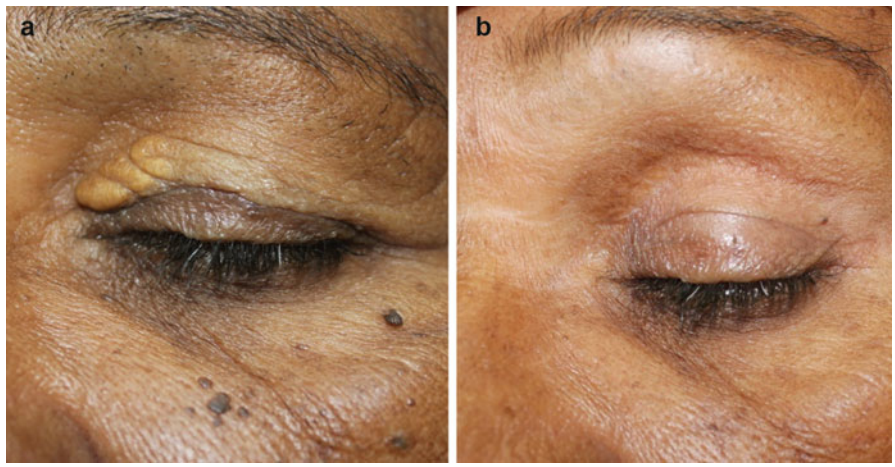

Fig. 2 (**a**, **b**) Xanthelasma treated with ultrapulsed CO_2 laser

Surgical removal is best indicated for cases of diffuse xanthelasma, deep involvement of the dermis and/or muscle. Recurrence is common, with rate of about 40%.

Sebaceous Hyperplasia

It is a common benign condition of the sebaceous glands of middle-aged adults or older. Lesions may be single or multiple and manifest themselves as small yellowish or skin color papules of 2–9 mm, normally with a central umbilication, located on the face (particularly the nose, cheek, and forehead). Occasionally they are seen in the breast, areola, mouth, scrotum, prepuce, and vulva. Rarely reported variants included a giant form, a linear arrangement or zosteriform, a diffuse form, and a familial form. Some consider the rhinophyma a special form of sebaceous hyperplasia. Its frequency is about 1% in healthy elderly adults, but comes to be as high as 10–16% in patients receiving long-term immunosuppression with cyclosporin A. The neonates may present around 43.7% of sebaceous hyperplasia. It has been reported in association with internal malignancy in Muir-Torre syndrome. It must be distinguished from basal cell carcinoma (BCC) – some papules have telangiectasia and molluscum contagiosum.

The histopathology represents a multilobulated sebaceous gland increased in size. The lobes have one or more layers of basal cells at its periphery with undifferentiated sebocytes containing large nuclei and scant cytoplasmic lipid, in contrast to normal sebocytes, which are filled with lipids. The decrease in levels of circulating androgens, associated with aging, appears to be the cause of sebaceous hyperplasia. Ultraviolet radiation and immunosuppression have been postulated as cofactors (Fig. 3).

Treatment

Therapeutic options include photodynamic therapy, cryotherapy, cauterization or electrocoagulation, chemical topical treatment with trichloroacetic acid (TCA), and treatment with argon laser, carbon dioxide, and 1,450 nm and 1,720 nm diodes (No et al. 2004; Aghassi et al. 2000; Winstanley et al. 2012; Simmons et al. 2015a). The complications of these destructive nonspecific therapies include depigmentation and atrophic scarring. Oral isotretinoin has been shown to be effective in removing some lesions after 2–6 weeks of treatment, but the recurrence of the lesions is common after cessation of therapy.

Viral Wart

It is a frequent viral skin infection, with limited course, caused by the human papillomavirus (HPV), being able to produce epidermal proliferation characterized by acanthosis, accompanied by papillomatosis, and it can be found in up to 10% of young adults and children.

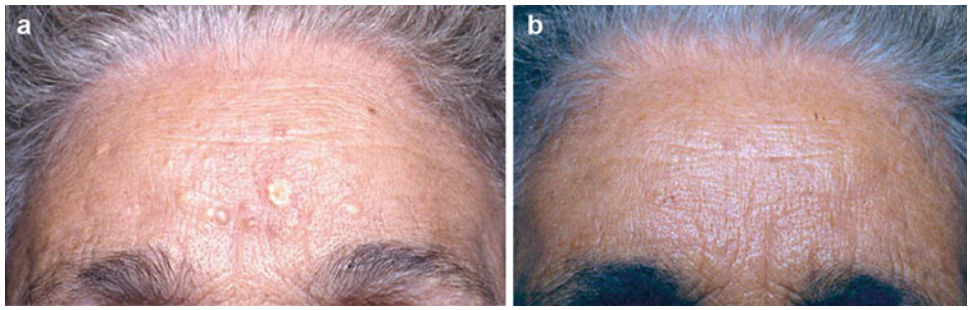

Fig. 3 (**a**, **b**) Sebaceous hyperplasia treated with CO_2 laser (low fluence)

It is caused by papillomavirus of the papovavirus group of double-stranded DNA capable of eliciting cytolytic effect on the infected cells, causing their death.

Clinically, it is characterized by papules or nodules exophytic with roughened surface, sometimes with small darkened spots, which represent thrombosed capillaries. They are commonly located on the back of hands and fingers in the nail bed or periungual and knees folds. About 65% of common warts disappear spontaneously within 2 years. New warts may develop at sites of trauma, constituting the isomorphic Koebner phenomenon which is usually less pronounced than the flat warts.

Infection is acquired by direct contact with patients with clinical and subclinical lesions through objects or contaminated surfaces (pools, gyms). It is believed that each new injury is a result of autoinoculation. Minor traumas predisposes to infection. Nail biting is associated with periungual warts. The trauma while shaving can spread the filiform warts of the beard area. Hyperhidrosis and flatfoot predispose to plantar warts. The average incubation period is 3 months, but can range between 1 and 20 months. The papillomas caused by HPV are initially benign.

The incidence of warts, its malignant potential and regression, appear to be directly related to immune disorders mediated by host cells. Warts occur more frequently, last longer, and appear in large numbers in patients with AIDS and lymphomas and those who take immunosuppressant drugs.

Treatment

The lesions in patients with cell-mediated immunity deficit are generally resistant to treatment. Moreover, treatment of a lesion can lead to regression of many or all warts in immunocompetent individuals (Fig. 4).

The objective is to destroy the infected cells using substances such as fuming nitric acid, salicylic acid, lactic acid, TCA, cantharidin, podophyllin, 5-fluorouracil, or intralesional bleomycin. We may use cryosurgery, photodynamic therapy, and even surgical procedures such as curettage and electrodessication. The surgery with suture and radiotherapy are contraindicated. Among the lasers is the described CO_2 laser or hyperthermia by Nd:YAG laser (Oni and Mahaffey 2011). HPV is

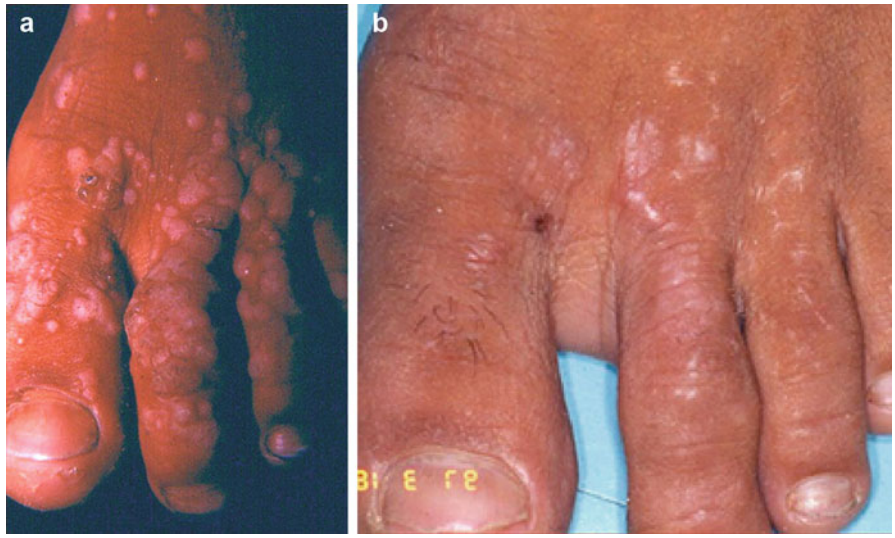

Fig. 4 (**a**, **b**) Verruca vulgaris treated with CO_2 laser

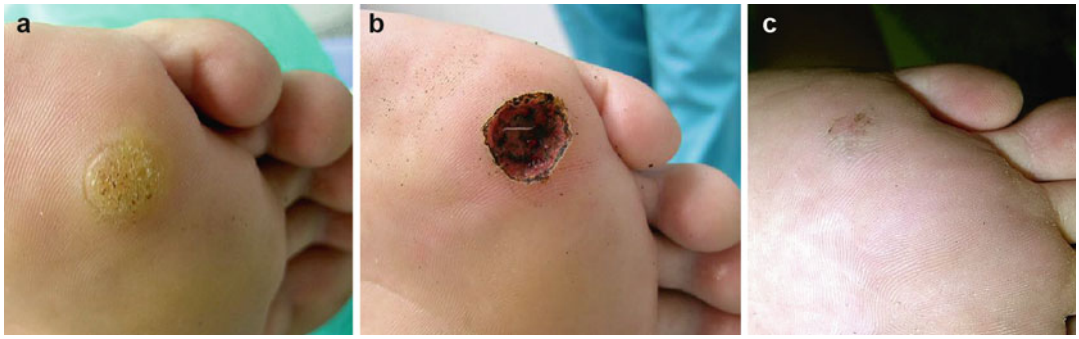

Fig. 5 (**a**–**c**) Plantar wart treated with CO_2 laser

more vulnerable to hyperthermia than the cryotherapy. In the warts resistant flashlamp pulsed dye laser (585 nm) has been used with 80% efficiency.

The reoccurrence of the viral lesions (condylomas and warts) after treatment with CO_2 laser have not been more frequent than isolated techniques. One study showed no recurrence of lesions in 12 months of follow-up after removal of warts with CO_2 laser and imiquimod cream 5% after epithelialization, once a day, five times a week for 2 weeks (Zeng et al. 2014).

Plantar Wart

Plantar warts are notoriously more difficult to treat and eradicate. The use of artificial dermis (curative) after the CO_2 laser ablation, and use of salicylic acid in residual lesions, appears to be effective in these situations. Mitsuishi proved the absence of HPV DNA in the upper epidermis of the treated sites after this technique and the absence of significant scarring or severe pain (Mitsuishi et al. 2010) (Fig. 5).

Genital Warts

The use of CO laser in genital warts is safe and effective (Padilla-Ailhaud 2006). The cure rate in a single session reaches 70%. Relapses are associated with multiple partners and involvement of the cervix in women. Combination therapy with CO_2 laser and photodynamic therapy with ALA (5-aminolevulinic acid) exhibits a lower rate of recurrence of lesions that isolate CO_2 laser therapy for refractory lesions (Huang et al. 2014). The treatment can be done during pregnancy (Savoca et al. 2001). In a study of 18 pregnant women treated between 15 and 38 weeks of gestation, there were no abortions, premature birth, or complications (infection, bleeding) by the procedure (Gay et al. 2003). The Bowenoid papulosis corresponds to intraepithelial neoplasia grade III of the penis or vulva and is strongly associated with HPV 16 (Fig. 6).

Considerations

During the use of the CO_2 laser, emitted smoke consists of gases and/or toxic vapors such as benzene, formaldehyde and hydrogen cyanide, bioaerosols, steam, and live or dead cell remnants (including blood debris and viruses). The use of smoke filter vacuum cleaners, outdoor exhaust smoke, gloves, and laser mask is advisable. The hose can be handled by a helper 2 cm from the operative field or be coupled to the handpiece. Several studies have shown that the smoke resulting from the vaporization of viral lesions by CO_2 laser is an aerosol containing viral particles which are dispersed by a diameter greater than 2 m, even under vacuum,

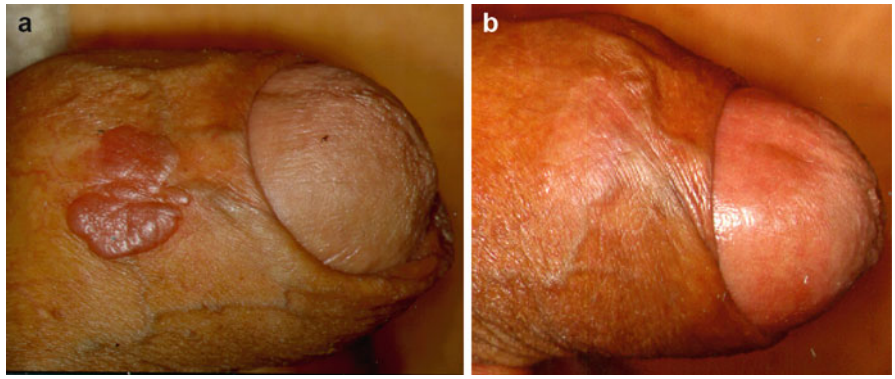

Fig. 6 (**a**, **b**) Bowenoid papulosis treated with CO_2 laser

contaminating the equipment and the people involved (skin and breast nasal) during surgery. For this reason, the CO_2 laser is not a first-choice treatment for viral lesions such as common warts and genital warts. Studies analyzing the resulting smoke from the vaporization of human viral warts with Er:YAG laser did not detect the presence of viral DNA; this laser is apparently safer than the CO_2 laser. However, the case of a doctor who used the Nd:YAG laser to treat perianal warts was described and developed a laryngeal papillomatosis. Viral particles of HIV and hepatitis C virus were also found, in addition to the HPV, in the smoke caused by CO_2 laser vaporization; therefore, it is not recommended for treatment of patients suffering from these infections by this process (Hallmo and Naess 1991).

Melanocytic Nevus

Melanocytic nevus (MN) is a benign lesion of nevus cells that arises as a result of the proliferation of melanocytes. There are two fundamental types: congenital melanocytic nevus and acquired melanocytic nevus.

Congenital melanocytic nevi are present since birth. They usually present as small blemishes or brown papules with smooth or warty, sometimes hairy, even larger lesions that can occupy entire members. When they are larger than 20 cm, they are called giant melanocytic nevi (0.002% of newborns). The average nevus lesions and giant MN often have a hairy surface (95%) and roughened with color ranging from brown to black. Neurological disorders may be associated with giant MN according to the area most affected, such as spina bifida and meningocele, due to infiltration of melanocytes in the nerve structures, constituting the neurocutaneous melanosis. Surgical excision is recommended due to the high risk of malignant transformation, but it is often a difficult treatment to be carried out due to the extent of the injury, being necessary to resort to the use of expanders, patchwork rotation, and placement of grafts.

Other therapeutic options currently available for congenital MN include dermabrasion, chemical peels, and laser ablation. These methods allow to improve the aesthetic appearance, but they are not effective to completely remove the deep nevus cells, since they are surface treatments. Only complete excision of the nevus with clear deep surgical margins can effectively reduce or eliminate the potential for malignant transformation in the future.

The MN acquired are common and usually occur between 12 and 30 years, although they can appear in childhood. They tend to decline slowly from the age of 35 and may increase in size during puberty, pregnancy, corticosteroids, and sun exposure.

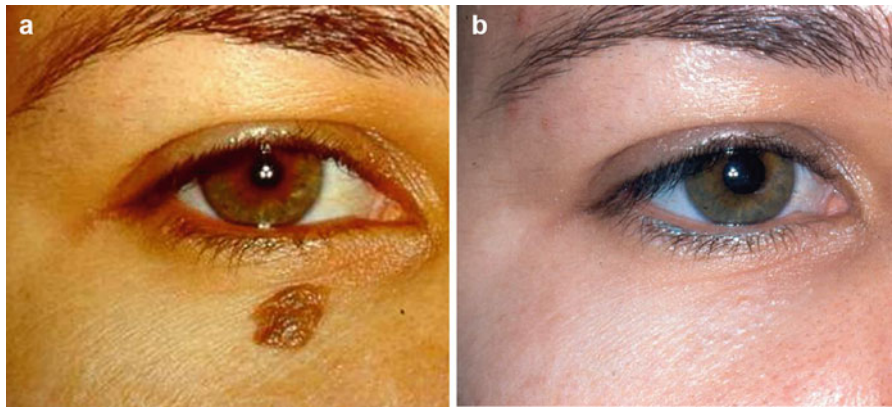

Fig. 7 (**a**, **b**) Acquired melanocytic nevus treated with ultrapulsed CO_2 laser

Clinically they may present as flat lesions, warty, domed, or pedunculated. Histologically they can be junctional, compounds, or intradermal.

Usually no treatment is necessary. In cases by removal of various cosmetic reasons, methods have been used such as surgical excision, cryosurgery, electrodissection, and more recently laser. The nevus lesion should be excised with a margin of 1–2 mm and subjected to histopathological study on suspicion of malignancy.

There are few data in the literature that support the use of laser in melanocytic lesions. Nonablative methods produce selective photothermolysis of melanin pigment, with secondary destruction of the nevus cell, as performed by the Q-switched ruby, Nd:YAG, and alexandrite. These produce a surface whitening effect; although with the cosmetic improvement, there are recurrences in many cases, they may mimic a melanoma (*pseudomelanoma*) and change the potential for malignant transformation, which requires long-term follow-up studies. When removing the possibility of malignancy, for clinical evaluation and dermoscopy, intradermal nevi and compounds may be removed by ablative lasers such as CO_2 or Er:YAG laser with satisfactory cosmetic results (Hague and Lanigan 2008; Bukvić et al. 2010; Baba and Bal 2006). The CO_2 laser is currently preferred to cause less scarring, less bleeding, and simplicity of the procedure. For more than 5 mm nevi, some authors suggest serial ablation of the lesion at intervals of 2–4 weeks between sessions, varying the number of sessions according to the size of the lesion (Ozaki et al. 2014) (Fig. 7).

Verrucous Epidermal Nevus

They are hamartomatous circumscribed lesions formed almost exclusively by keratinocytes. They may arise at birth and during childhood or only become apparent in adulthood. Lesions are typically seen on the trunk, tend not to cross the midline, and follow the Blaschko's lines. The lesions on the limbs tend to be linear and verticalized. Initially, they show up as streaks or pigmented plates, which darken with time and show more and more keratotic surface. When they reach one-half of the body, they are called nevus unius lateris, and if widespread, ichthyosis hystrix.

A variant of verrucous nevus is ILVEN (inflammatory linear verrucous epidermal nevus) having constant itching and has aspect of a chronic eczematous dermatitis or psoriasis; women are more affected. Clinically it is characterized by the appearance since the birth of recurrent chronic inflammatory phenomena, usually unilateral, with intense itching and refractory to treatment (Lee et al. 2001). Another variant is the nevus comedonicus corresponding to a set of papules with central stoppers corneas.

There is no ideal treatment, and this may be often disappointing because of relapses and unaesthetic scars. The therapy includes topical

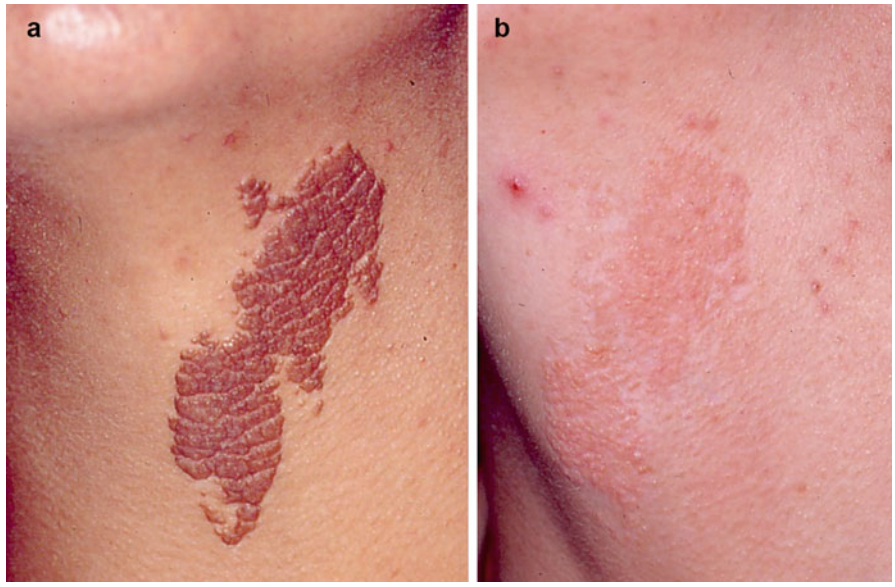

Fig. 8 (**a**, **b**) Verrucous epidermal nevus after treatment with CO_2 laser

agents, dermabrasion, cryosurgery, photodynamic therapy, and laser cutting. The most commonly used are the ablative lasers, such as CO_2 or Er:YAG laser (Thual et al. 2006). The use of lasers allows satisfactory aesthetic results (Boyce and Alster 2002). The Er:YAG laser should be used in less warty lesions (Pearson and Harland 2004) (Fig. 8).

Syringoma

It is a benign tumor fairly common, usually multiple, represented by small rosy-yellowish papules smaller than 3 mm, symmetrical, located in the lower eyelids and periorbital region, mainly in adult women. Sometimes it can be translucent or cystic. They are largely of cosmetic significance.

The syringoma usually appears first in puberty; additional lesions may develop later. There is a form of sudden onset in adolescence that affects the neck, chest, abdomen, and penis that is the *eruptive hidradenoma*. It can also be found on the vulva, armpit, and back of hands. It is characterized histologically by cystic ducts and comma-shaped and solid epithelial cords surrounded by fibrous stroma. The histogenesis of syringomas is probably related to eccrine elements or pluripotent stem cells.

Friedman and Butler classify syringoma in four variants: (1) localized form, (2) form associated with Down's syndrome (3), generalized form that encompasses multiple eruptive syringomas, and (4) a familial form.

Rarely, syringomas may be associated with the Brooke-Spiegler syndrome, an autosomal dominant disease characterized by the development of multiple cylindromas, trichoepitheliomas, and occasional spiradenomas. Syringomas occur with increased frequency in patients with Down's syndrome (6–36% of cases), usually in women over 10 years old (Fig. 9).

Surgical Care

The main reason for the treatment is cosmetic. Complete removal is often unsuccessful and recurrence is common, as syringomas are generally in the dermis. Possible treatments include surgical excision with primary suture, electrocautery, cryosurgery, dermabrasion, TCA, carbon dioxide laser, or Er:YAG laser (Cho et al.

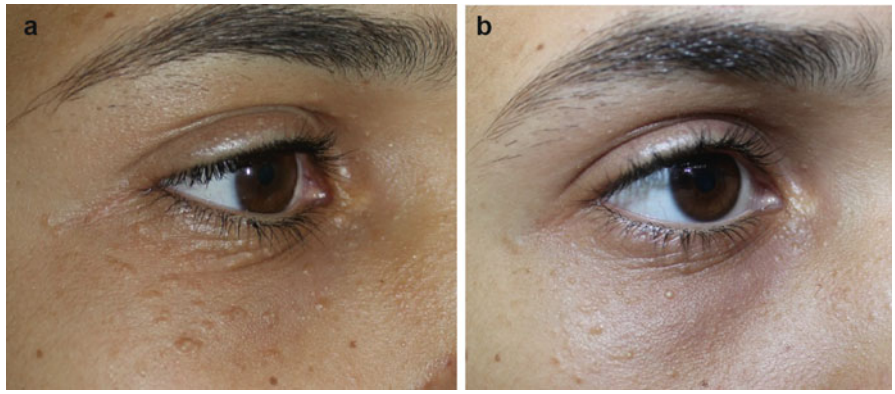

Fig. 9 (**a**, **b**) Syringomas treated with CO_2 laser

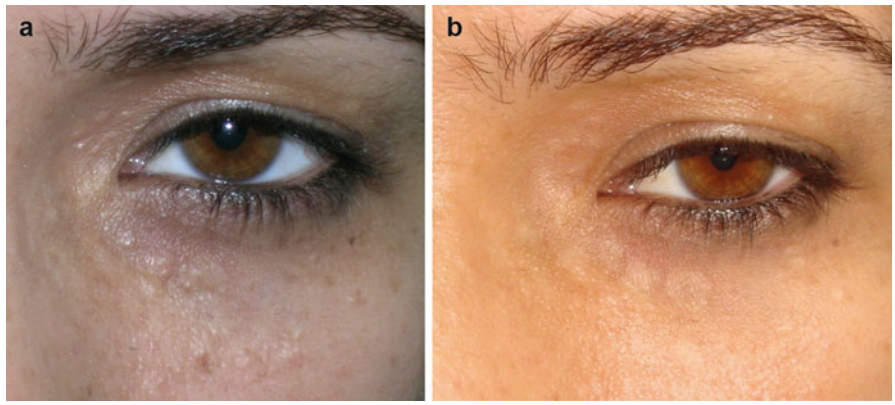

Fig. 10 (**a**, **b**) Syringomas treated with CO_2 laser. Observe post-laser relative hypochromia, contrasting with the hyperpigmentation of the *dark circle*

2011; Sajben and Ross 1999; Kitano 2016; Seo et al. 2016; Lee et al. 2015). Regarding the use of the CO_2 laser, recurrence of the tumor is associated with a surface ablation, and complications such as hypopigmentation and atrophy are associated with deeper ablation (Fig. 10).

Fordyce Spots

The Fordyce granules are asymptomatic sebaceous glands commonly found in the oral mucosa, upper lip, and retromolar region. They are characterized by multiple whitish or yellowish papules with diameter from 0.1 to 1 mm which occasionally may coalesce and form plaques. Only visible sebaceous glands through the epithelium should be considered as Fordyce granules. In children they usually are not noticed until puberty, but are histologically present. Its incidence increases with age, especially after the hormonal stimulation of puberty. The prevalence in adults ranges from 70% to 85% with a slight predominance in males. Histopathologically, the lesions are indistinguishable from the sebaceous glands, but are not associated with hair follicle and its duct opens directly onto the surface.

It is an entity of easy clinical diagnosis and additional tests are not needed. The framework must be distinguished from other lesions of the oral cavity: small colonies of *Candida albicans*, miniature lipomas, Koplik's spots, warts, papular mucosal lesions of Cowden syndrome, lichen planus, and leukoplakia. Despite its asymptomatic

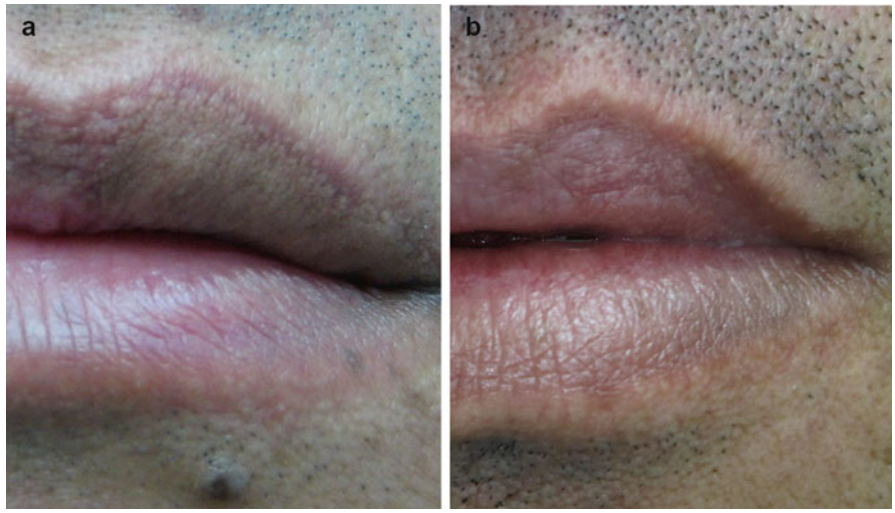

Fig. 11 (**a**, **b**) Multiple yellowish papules on the *upper* lip before and after use of the CO_2 laser

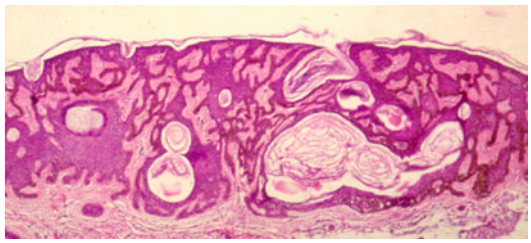

Fig. 12 The histology of seborrheic keratosis showing hyperkeratotic surface and numerous corneal cysts

nature and considered normal variants, some patients seek treatment for cosmetic reasons. There are reports of cases where we used the dichloroacetic acid, CO_2 laser (Ocampo-Candiani et al. 2003), photodynamic therapy using 5-aminolevulinic acid, oral isotretinoin, and curettage with electrocoagulation (Chuang et al. 2004; Baeder et al. 2010) (Fig. 11).

Seborrheic Keratoses

Seborrheic keratoses are keratotic papules or plaques for limited arising from keratinocytes epidermal proliferation. The lesions usually appear after age 40 and are more common in Caucasians. Its surface is rough and greasy, does not reflect light, and can show corneal cysts or have a cerebriform appearance. It has a very variable pigmentation that goes from light brown to black and may be confused with actinic keratosis, melanocytic nevus, or lentigo maligna (Fig. 12).

They are located more on the trunk and face. They may be single or be tens and can be removed by curettage, cryosurgery, electrocoagulation, or CO_2 laser (Fig. 13).

Rhinophyma

Rhinophyma is a dermatologic benign disease of the nose that primarily affects Caucasian men of the fifth to seventh decades of life. There is hyperplasia of the sebaceous glands leading to the appearance of *peau d'orange*. It is characterized by a slowly progressive enlargement of the nose with irregular thickening of the nasal skin and nodular deformation. It is one clinical type of rosacea.

The rhinophyma shows prominence of the sebaceous glands with the development of thickened and disfigured noses in extreme cases. The condition usually does not produce scars. The rhinophyma can occur as an isolated entity, without other symptoms or signs of rosacea. It can be disfiguring and distressing to patients.

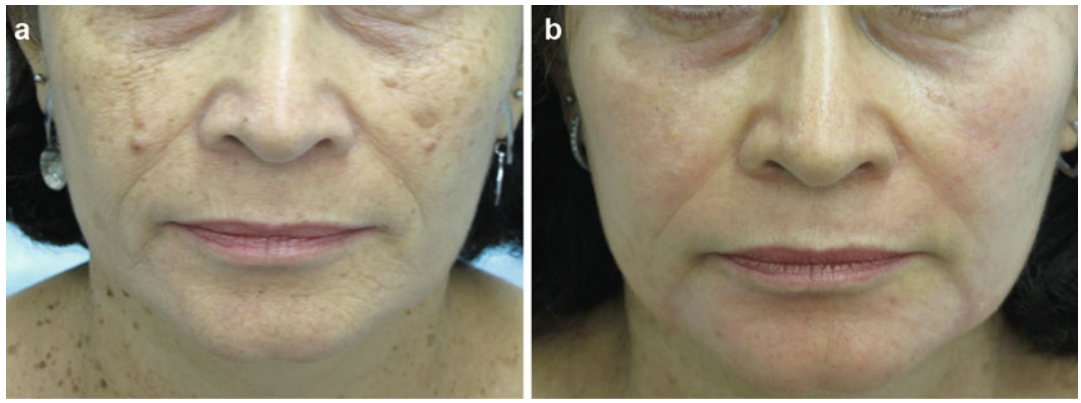

Fig. 13 (**a**, **b**) Seborrheic keratoses treated with CO_2 laser

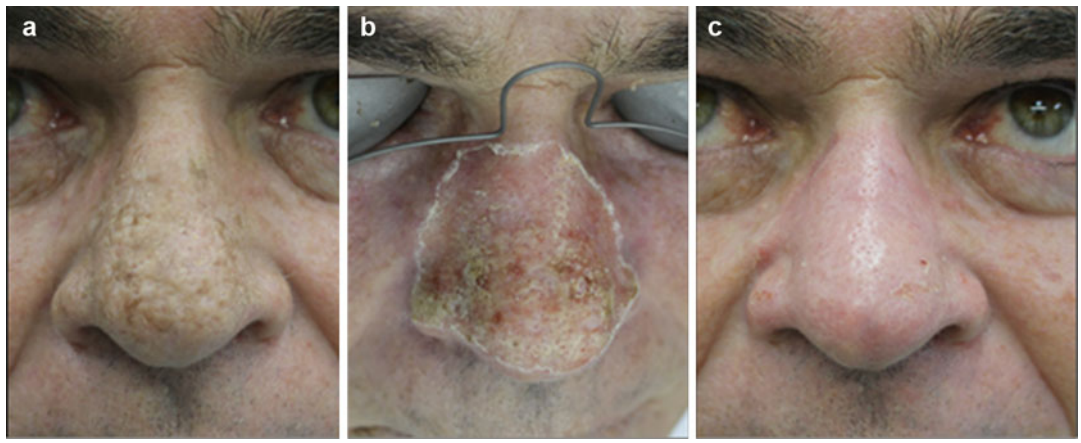

Fig. 14 (**a**–**c**) Rhinophyma treated with ultrapulsed CO_2 laser

Some authors consider the rhinophyma a different disease. The main reasons that lead patients to seek help are aesthetic and functional impairments, such as nasal obstruction and sleep apnea. However, 46 cases of malignancies such as BCC and SCC have been found associated with rhinophyma, which leads us to examine all excised tissue (Fig. 14).

Various methods have been used to correct the malformations produced by this disease in the nose as dermabrasion, electrocautery, and laser therapy. The treatment of choice for rhinophyma is removal surgery of the hyperplastic tumor. The use of CO_2 laser for the treatment of rhinophyma is an appropriate therapy with excellent aesthetic results, minimal surgical morbidity, and little risk. The pulsed dye laser can be used after the CO_2 laser to improve vascular rhinophyma component (Moreira et al. 2010). We may also use the Er:YAG as ablative (Orenstein et al. 2001). The electrocoagulation and cold cut by scalpel provide similar long-term results, but hemostasis is less efficient and the operating time is extended. The period of postoperative healing is faster and scars occur less in the case of CO_2 laser (Meesters et al. 2015; Baró et al. 2015; Serowka et al. 2014).

Actinic Cheilitis

Actinic cheilitis (AC) is considered a premalignant lesion or an incipient and superficial form of squamous cell carcinoma (SCC) of the lip. Genetically predisposed keratinocytes

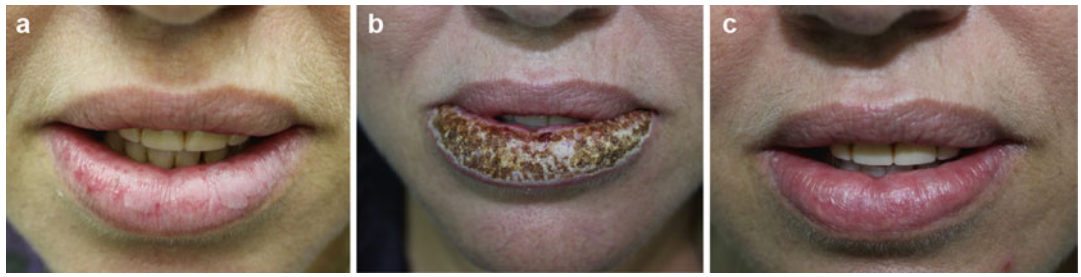

Fig. 15 (**a**–**c**) Actinic cheilitis treated with ultrapulsed CO_2 laser

probably undergo molecular change induced by ultraviolet light B yielding neoplastic keratinocytes. Therefore, AC is in fact the result of clonal expansion of transformed keratinocytes, considered from the beginning of a SCC in situ. It is commonly found in individuals whose professional activities are related to chronic sun exposure, particularly redheads with light skin and lower lip eversion. The lower lip is more vulnerable to sunlight by having a thin epithelium, a thin layer of keratin, and a lower content of melanin. Smoke and lip infections human papillomavirus can cause cytogenetic changes and increase the risk of actinic cheilitis progress to SCC (Wood et al. 2011).

Clinical signs include atrophic diffuse and poorly demarcated plaques or erosive keratotic that may affect all or some parts of vermilion. The definitive diagnosis is obtained by biopsy. Histopathological changes consist from atrophy to hyperplasia of the squamous epithelium on the border of vermilion, with varying degrees of keratinization, disorderly maturation, increased mitotic activity, and cytological atypia. Apoptotic cells are often present, but the basement membrane is intact. The underlying connective tissue shows basophilic degeneration (solar elastosis). Actinic cheilitis should be considered as a SCC intraepithelial or in situ, based on the abovementioned microscopic changes (Fig. 15).

The risk of occurrence of AC progress to SCC varies from less than 1% to 20%. Clinically, pain, induration, large size, marked hyperkeratosis, ulceration, bleeding, rapid growth, and recurrence or persistence may be markers of progression of AC for SCC. The risk of metastasis to the SCC varies between 0.5% and 3%. However, lip SCC resulting from actinic cheilitis is more likely to metastasize than skin SCC, with rates ranging from 3% to 20% (Kwon et al. 2011). The treatment is of crucial importance due to the potential for malignant transformation. Surgical excision of the entire vermilion (vermilionectomy) as histological examination of serial sections is the preferred treatment. Other possible treatments include electrodissection, cryosurgery, photodynamic therapy, topical treatment with the antineoplastic agent 5-fluorouracil or immunomodulator imiquimod, and lasers such as CO_2 and Er:YAG (Cohen 2013; Laws et al. 2000). However, with these arrangements, the tissue is not available for histological examination (Dinani et al. 2015). The prevention of AC can be achieved through the reduction of cumulative exposure to UVB radiation. The use of protective clothing, reducing outdoor activities, and the use of sunscreens should be introduced very early in childhood and continuing throughout life.

Exogenous Ochronosis

Ochronosis is a grayish-brown pigmentation of connective tissues that can be classified as endogenous or exogenous. The endogenous variety, also known as alkaptonuria, is a rare, congenital disorder and autosomal recessive, which results from the absence of the enzyme that converts homogentisic acid to acetoacetic acid and fumaric acids. Affected individuals develop accumulation of homogentisic acid, an insoluble pigment that is deposited in various

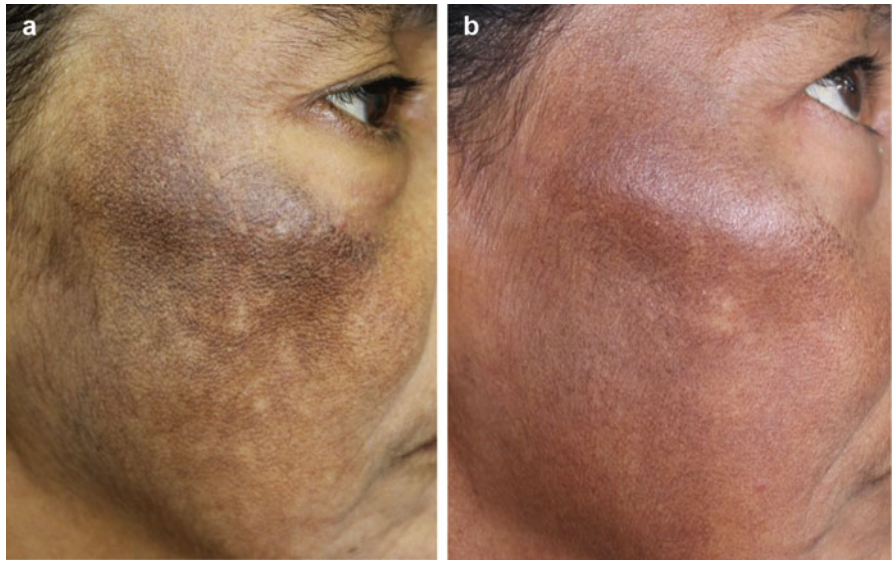

Fig. 16 (**a**, **b**) Exogenous ochronosis treated exclusively with fractionated CO_2 laser

tissues such as the cartilage, skin, and heart valves (Albers et al. 1992).

Exogenous ochronosis is clinically and histologically similar to endogenous, but does not have systemic involvement. It is characterized by blue-black or grayish asymptomatic hyperpigmentation typically located on the face, neck, back, and extensor surfaces of the extremities. It most commonly follows the use of hydroquinone, but resorcinol, phenol, mercury, picric acid, and oral antimalarials may also be involved. It was initially considered to be caused only by the use of high concentrations of hydroquinone for an extended period, but there are reports of recent cases demonstrating the development of this pathology with use of hydroquinone 2% for a period not longer than 3 months. The hyperpigmentation mechanism induced by hydroquinone remains uncertain (Charlín et al. 2008). It is reported the possibility of activation of tyrosinase by high concentrations of hydroquinone, leading to stimulation of melanin synthesis. Other authors suggest that the hydroquinone oxidase inhibits the activity of homogentisic acid in the skin, which leads to accumulation of homogentisic acid, which then polymerizes and forms ochronotic pigment. Melanocytes could be involved; many cases are related to sun exposure, and there is a reported case of ochronosis that spared vitiligo area (Simmons et al. 2015b).

Clinical presentation: It can be identified into three stages in the exogenous ochronosis. In stage I it occurs only as erythema and mild pigmentation of the face and neck. Increasingly, there are hyperpigmentation, "caviar-like" papules, and atrophy, which correspond to stage II. The last stage includes papulonodular, surrounded or not by inflammation injury.

Histopathological examination of exogenous ochronosis lesions reveals yellow-brown filaments or green with banana-shaped in the papillary dermis. These filaments undergo degeneration forming colloid milium with progression to papulonodular stage. In stage III there are inflammatory mediators, including giant cells, epithelioid cells, and histiocytes. Some biopsies exhibit sarcoid-simile granuloma formation surrounded by filaments. In severe cases it may also be described as transepidermal elimination of pigment and pseudoepitheliomatous hyperplasia (Figs. 16, 17, and 18).

Therapy of exogenous ochronosis is difficult. Various treatments have been used, often with disappointing results. Avoiding the use of disease-causing substances is beneficial, but it can take several years for some result. The retinoic acid

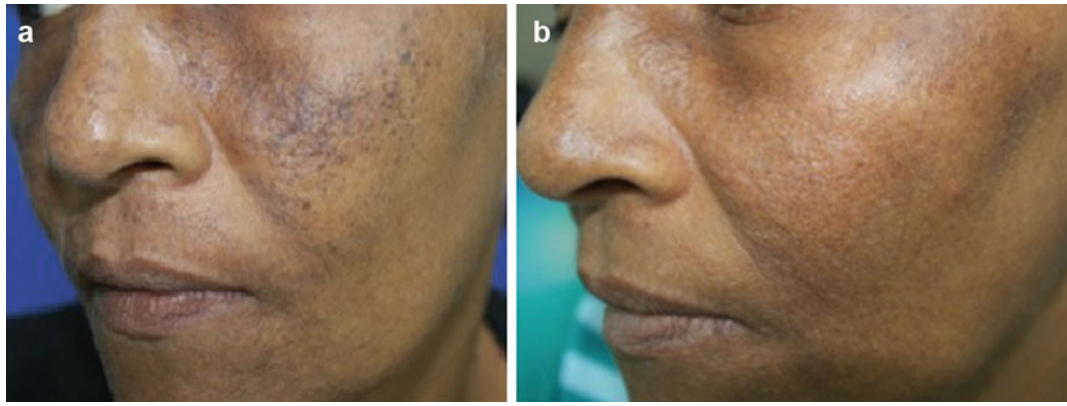

Fig. 17 (**a**, **b**) Exogenous ochronosis also treated exclusively with fractionated CO_2 laser

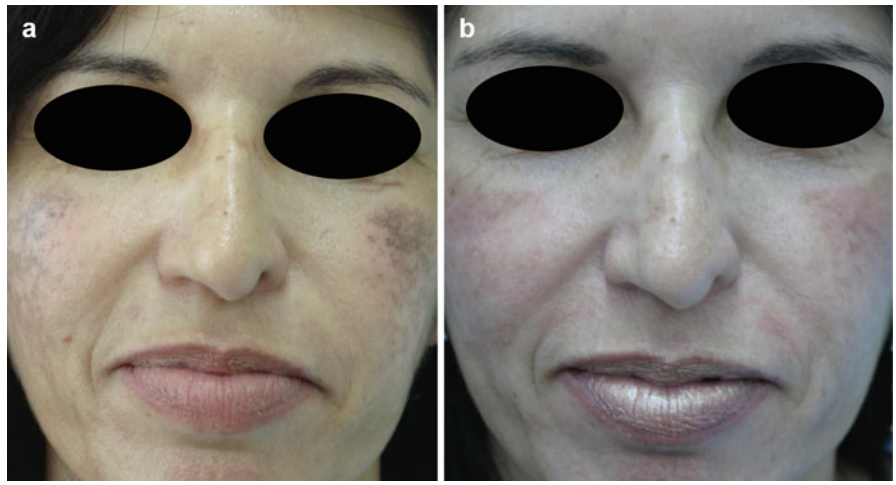

Fig. 18 (**a**, **b**) Ochronosis exogenous treated with fractionated CO_2 laser, combined with IPL and Nd:YAG

was effective in some patients, but in others caused transient hyperpigmentation. The results of the treatments with sunscreens and low power corticosteroids have been variable. There are reports of clinical improvement after use of oral tetracycline, dermabrasion, and CO_2 laser; however, the results are not uniform. Regarding dermabrasion, there is a case report in which there was removal of hyperpigmentation in a white patient. A combination of dermabrasion and CO_2 laser with satisfactory results in the periorbital and nasal regions in a black woman was reported (Diven et al. 1990). The use of Q-switched (Q-S) laser for the treatment of pigmentary lesions and tattoos are well documented in the literature. The Q-S ruby laser 694 nm and 755 nm Q-S alexandrite were used to treat exogenous ochronosis with good results, based on the fact that the pigment of exogenous ochronosis is deposited in the dermis in a manner similar to the tattoo pigment recently (Bellew and Alster 2004; Kanechorn-Na-Ayuthaya et al. 2013; Tan 2013).

There are reports on the effectiveness of intense pulsed light (IPL), as the laser, for the treatment of pigmented lesions. The mechanism of action of both is based on selective photothermolysis of pigmented cells. IPL has the advantage pulse width adjustment and

wavelength according to the skin type and the depth of pigment deposition in the skin. TCA peeling in different concentrations has been used for many years for the treatment of photoaging, acne scars, and pigmentation disorders. The use of ATA in hyperpigmentation is related to coagulative necrosis of the epidermal cell proteins, followed by cell death. The depth of the process depends on the concentration used. The ATA solution between 15% and 25% only determines coagulative necrosis of the epidermis, resulting in surface peeling. In our recently published work, the peeling ATA was used as adjuvant therapy applied immediately after the intense pulsed light sessions; it was observed that this combination was effective for regression of the lesions.

Exogenous ochronosis is a disease difficult to treat, requiring a combination of several methods for obtaining a satisfactory result (França et al. 2010).

Conclusion

The CO_2 laser has great versatility as to its use. It is indicated in various scenarios involving skin excision, vaporization, and coagulation; there are several forms of action for this laser such as collagen stimulating and rejuvenation or removal of tumors and removal of warts, xanthelasmas, and keratoses among others. The CO_2 laser is safe since it is used by trained dermatologist, allowing a dry surgical field, with limited blood loss and induction of collagen and cicatrization. In the case of viral lesions (warts and condyloma), laser can be used with the use of the smoke evacuator filter.

Take Home Messages

1. The CO_2 laser is ablative with high affinity for water, considered safe when used by properly trained physicians.
2. The CO_2 laser may be used in many scenarios as for removal of benign epithelial tumors, keratoses, nevi, warts, and xanthelasma among others.
3. The CO_2 laser has been shown to be safe in removing DPN, with low rates of recurrence or complications, and also has a high degree of satisfaction by patients even at the highest phototypes.
4. The use of topical anesthetic to benign epithelial lesions is sufficient in most cases and is indicated with petrolatum ointment once a day until reepithelialization of lesions.
5. In cases of viral lesions, treatment of a lesion can lead to regression of many or all warts in immunocompetent individuals.
6. The CO_2 laser is not the first choice in the ablation of viral lesions, and the use of the smoke filter vacuum cleaners, as well as gloves and goggles, is mandatory.
7. The surface ablation is associated with recurrence in the treatment of syringomas or nevi with the CO_2 laser, while complications such as hypopigmentation and atrophy are associated with deeper ablation.
8. The period of postoperative cicatrization is faster in cases of rhinophyma treated with CO_2 laser compared to electrocoagulation.
9. The CO_2 laser permits removal of actinic keratoses, but there are no evaluation of the lesion margins.
10. Exogenous ochronosis is difficult to treat and the results with the CO_2 laser are not uniform.

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Fractional Ablative and Non-Ablative Lasers for Ethnic Skin

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Abstract

Ethnic skin is a term used to define the darker skin corresponding to Fitzpatrick's IV, V, and VI skin types. Patients with ethnic skin have an increased risk of problems related to pigmentation, such as post-inflammatory hyperpigmentation or hypopigmentation. For a long time, ethnic skin treatment with lasers was a big challenge, especially when referring to ablative technologies, a technique so widely used and widespread in dermatological procedures. Over time, laser devices have evolved, and recent techniques make its use safer, with less downtime and, consequently, with less damage and risk of post-inflammatory pigmentation. When performed by skilled and well-trained dermatologists, the use of fractional ablative and non-ablative lasers can be considered safe and viable for many different treatments. This chapter is going to discuss ethnic skin and the peculiarities of laser treatment.

Keywords

Ethnic skin • Laser • Ablative technologies • CO_2 laser • Erbium lasers • Fractional and non-fractional ablative lasers

Contents

Introduction

The color or race of the Brazilian population is diverse. Patients with dark color skin are more frequent in the North and Northeast of our country, due to our colonization, and most of them are concentrated at the north and northeast of the country. They have an ethnic skin, a term used to define darker skin and non-Caucasian, corresponding to

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skin types IV, V, and VI of the Fitzpatrick classification (IBGE 2000).

For a long time, treating ethnic skin with laser was a challenge, especially when referring to ablative technologies. Although the main chromophore of this technique is the water and not melanin, the heat generated by them can have serious postoperative complications if not used by trained professionals, making it necessary to have thorough knowledge of the physical basics of lasers (Battle and Hobbs 2003).

The number of melanocytes and the thickness of the skin are approximately the same in all races, but ethnic skin has its own characteristics. We can find in ethnic skin more and higher fibroblasts and bi- or multinucleated and hyperactive fibroblasts. This hyperactivity may explain the predisposition to keloid formation. It is also richer in sebaceous glands and has more collagen (Mateus and Palermo 2012).

The ranging is melanin production speed, number, morphology, size, density, and distribution of melanosomes. Ethnic skin patients have a higher risk to pigmentation problems because the skin melanin competes with main chromophore, increasing the risk of hyperpigmentation and hypopigmentation post. Moreover the risk of pigmentary changes can also be correlated with the depth of the laser injury as well as their effects on dermal heating. Post-inflammatory hyperpigmentation is the most common complication of facial resurfacing in patients with skin-type IV (4) (Sriprachya-anunt et al. 2002; Wat et al. 2017).

Fractional Ablative Lasers

Carbon dioxide (CO_2) lasers are the main representative of ablative lasers and, although devised in 1968, are still regarded as the gold standard treatment for photoaging. Novel technologies are now able to produce a column of ablation and coagulation with rigorously controlled depth, providing increased safety and reduced recovery time. The method is based on the principle of selective photothermolysis, developed by Parish and Anderson in 1983. The principle is the selective and specific destruction of a target in the skin with minimal thermal damage to the components in neighboring tissues. To achieve selective photothermolysis, the appropriate wavelength primarily absorbed by the target tissue or chromophore should be carefully chosen. For ablative lasers, the main chromophore is water (Riggs et al. 2007; Tierney et al. 2011).

However, CO_2 lasers show intense residual thermic effect, leading to a final result much broader than the tissue ablation observed at the end of the procedure. Conversely, water is absorbed 13 times less efficiently with CO_2 than with Erbium lasers, which are more superficial and cause less thermal damage (Kalil and Campos 2012).

A novel treatment concept was described by Manstein et al. in 2004: fractional photothermolysis. In this procedure, the laser produces microscopic lesions, ranging from 100 to 150 μm in thickness and 0.2–2.4 mm in depth, termed thermal microzones (TMZ), which are merely highly controlled microperforations in the epidermis and dermis that are, then, replaced by new organized tissue rich in collagen. Fractional photothermolysis revolutionized laser treatments, allowing for a more efficacious dermal coagulation without major damage to the epidermal layer, thus decreasing the risk of nonaesthetic scarification and reduced recovery time when compared to traditional ablative procedures. Several ablative fractional photothermolysis devices are available, in three different wavelengths: 2790, 2940, and 10,600 nm (Kalil and Campos 2012; Xu et al. 2011; Macrene et al. 2012; Manstein et al. 2004; Wat et al. 2017).

In 2007, Hantash et al. described the use of a new CO_2 ablative fractional laser that generates, by their TZM, ablation and coagulation columns extending through the stratum corneum, epidermis, and dermis. A CO_2 laser beam is able to remove from 25 to 50 μm of tissue in each application, raising the temperature up to 100 °C in 640 ms. The heat leads to an immediate contraction in the skin, although partly caused by water evaporation-driven dehydration and by collagen contraction, which retracts in temperatures higher than 60 °C (Ciocon et al. 2011).

Despite long-lasting clinical improvement, the best results can be seen after 3 months

posttreatment, mostly because of persistent inflammatory responses (demonstrated by the presence of heat-shock protein 47) and by the continuous collagen remodeling observed in histological and immunohistochemical studies. Ortiz et al. reported that patients maintain 74% of improvement in the first 1–2 years of following-up (Ortiz et al. 2010).

Cellular markers for neocollagenesis, such as procollagen III and collagen III, are found in treated areas, and the increase of both collagen density and elastic fibers can be observed up to 1 year posttreatment (Xu et al. 2011; Kim et al. 2013; Orringer et al. 2004).

Currently there are various CO_2 fractional devices in the market, which are characterized by adjustable fluency and pulse length, allowing for precise control of the level and depth of heat in the dermis. These parameters – fluency, pulse length, potency, energy, and density – will determine the effectiveness and safety of the treatment (Kadunc et al. 2012).

The erbium: yttrium–aluminum–garnet (Er:YAG) laser was approved by the FDA in 1996 for skin resurfacing. Because its wavelength (2940 nm) is the closest to water absorption peak (3000 nm), all its energy is practically absorbed by the epidermis and the papillary dermis, causing superficial ablation and less thermal damage than CO_2 lasers. Each Er:YAG short-pulse application (250–350 ms) ablates approximately 20–25 μm, utilizing 5 J/cm^2 of energy. Thermal damage reaches 30–50 μm in depth with a fluency of 5–8 J/cm^2, which is smaller when compared to those cause by CO_2 lasers (50–200 μm in depth with a fluency of 3.5–6.5 J/cm^2). Even with multiple applications, thermal damages caused by Er:YAG lasers are limited to 50 μm (Riggs et al. 2007).

This technology, which acts within the infrared spectrum, proved its higher ablation effect causing negligible thermal damage (5 μm per application). Because of its wavelength with maximum water absorption, short pulse length, and adequate energy, Er:YAG lasers are the preferred technology for fine wrinkles, photoaging, and treatments that demand higher phototypes. Injuries to neighboring tissues are minimum (maximum temperature reaches 30 °C), and bleeding spots started manifesting only after several applications (4–5, depending of the size treated), indicating that the dermis–epidermis junction was reached and therefore the laser application should be discontinued. Time for re-epithelization is around 2–4 days (Riggs et al. 2007).

Another new type of laser, the Er:YSGG (erbium: yttrium, scandium, gallium, garnet) was launched in 2007. It emits energy in the 2790 nm wavelength and presents a coefficient of water absorption of 5000/cm^2, an intermediate value between those for CO_2 and Er:YAG (1000 and 12,500/cm^2, respectively). Thus, the ablation capacity of Er:YSGG lasers is higher than those of CO_2 and lower than those of Er:YAG, with intermediate potential for thermal damage among the ablative lasers. It treats the whole epidermis and causes homeostatic thermal stimuli, which cannot be obtained by Er:YAG lasers. In addition, it does not cause the common side effects observed during CO_2 laser applications, such as thermal damage and long recovery time (Macrene et al. 2012).

The 2790 nm laser allows for two types of ablation (continuous and fractional) in the same session. This combination causes both vaporization of the epidermal surface and coagulation zones in the dermis–epidermis (Munavalli et al. 2011).

The fractional technique is able to produce ablation columns of 300 μm diameter, with a depth of 300–1500 μm, and 40–60 μm of residual thermal damage (Munavalli et al. 2011).

Fractional Non-Ablative Lasers

After the establishment of the principle of fractional photothermolysis in 2004, there were the first lasers not ablative fractionated approved by the FDA (Food and Drug Administration). The primary chromophore is water and includes wavelengths ranging from 1064 to 1550 nm. These devices differ from the ablative technology, which promotes epidermal vaporization. The laser works with irreversible thermal damage,

inducing a healing response in the papillary dermis and upper reticular (coagulation zones), reaching temperatures between 50 and 70 degrees. The coagulation generated by denaturing collagen induces a located necrosis, with consequently formation of a new collagen. Once this kind of lasers generate heat into the deeper layers of tissue without affecting the integrity of the epidermal barrier, this technique can be considered more secure when used in higher phototype patients, reducing risks of unwanted complications when compared to ablative techniques. Coagulation columns can reach great depths in the skin, depending on the amount of energy used (fluence), the density of thermal microzones per application, and the number of passes (Macrene et al. 2012).

Indications for Laser Treatment in Ethnic Skin

Pigmentary Disorders

Pigmentary disorders in ethnic skin are one of the most common complaints in dermatological offices (Ortiz et al. 2010). Among them, melasma and post-inflammatory hyperchromia are very frequent.

The treatment of melasma (chapter ▶ "Q-Switched Lasers for Melasma, Dark Circles Eyes, and Photorejuvenation" in volume "Daily Routine in Cosmetic Dermatology") is still a challenge for dermatology despite of the skin phototypes, but it is still worse in ethnic skin. It is not uncommon not to have any improvement after treatment, as well as darkening of the area treated. Post-inflammatory hyperchromia is a relative common side effect after laser treatment (Jackson 2003). Even though, the use of non-ablative fractionated lasers, Q-switched Nd-YAG laser, with low thermal damage, can be an option for melasma.

Microneedling technique with or without drug delivery (TED) (chapters ▶ "Microneedling for Transepidermal Drug Delivery on Stretch Marks," this volume) is an excellent option for pigmentary disorders, melasma, or post-inflammatory hyperchromia. When associated with drug delivery, hydroquinone, kojic acid, azelaic acid, and tranexamic acid are applied just before the microneedling. These substances can be used isolated or combined. Light erythema is observed after treatment. It lasts less than 24 h, with very rapid recovery. Microneedling treatment or TED with microneedling can be associated with QS laser treatment alternating the sessions every 2–4 weeks.

Some superficial chemical peels, combining retinoic acid or alpha hydroxy acid with lightening medications (hydroquinone, kojic acid, and tranexamic acid) can also be used as a complementary treatment alternating with lasers. It is also possible to apply this peel above the skin, just after QS laser treatment.

Acne

Acne commonly causes post-inflammatory pigmentation and atrophic scars (Taylor et al. 2002). Fractionated non-ablative laser is very well indicated to induce skin remodeling, sparing the epidermis (Jackson 2003). This procedure has a shorter downtime and a fewer risk of dyschromias; however it requires a greater number of sessions when compared to ablative lasers. We also use ablative lasers, although conservative parameters (low energy and low density) should be applied. Controlled radio-frequency microneedles and fractional ablative radio frequency are also excellent options to treat darker skin.

Benign Cutaneous Tumors

Ablative lasers can be used to remove facial angiofibromas, syringomas keratosis seborrheic, as well as dermatosis papulosa nigra, keloidal folliculitis of the neck, and dermatosis with higher prevalence in ethnic skin (Jackson 2003).

In these cases, we use CO_2 or erbium YAG laser in surgical mode of operation, choosing the proper spot diameter according to the lesion dimension, avoiding perilesional thermal damage (Cole et al. 2009).

Stretch Marks

The literature reports numerous treatment options for stretch marks, such as intense pulsed light, pulsed dye laser, ablative radio frequency, Er:Glass, Er:YAG, and CO_2. However, very few discuss those treatments on ethnic skin (Aldahan et al. 2016).

Some studies in Asians (phototype VI) suggest that ablative and non-ablative fractionated lasers are promising technologies in the treatment of this condition (Kim et al. 2008; Lee et al. 2010). In 2011, Yang and Lee (2011) compared the 1550 nm (Er:YAG) laser to fractionated CO_2 in a study involving 24 Asian patients with white abdominal stretch marks. Treatments were randomized to each side of the body with three sessions every 4 weeks. Clinical improvement was somewhat higher on the side whose treatment was performed with fractionated CO_2, despite of more adverse events in this group. Clinically, there was a reduction in the width of the striae, and an increase in the number of collagen and elastic fibers was observed in the histology study (Yang and Lee 2011).

We have experience with fractionated ablative lasers (CO_2 and Erbium 2940) in treatment of stretch marks in phototypes V. Our protocol includes testing two different parameters in a small area 30 days before the first session; using cold air cooling before, during, and after procedure; and applying low energy and low density (Kono et al. 2007). Post-inflammatory hypochromia is a common and mostly transient adverse event.

Rejuvenation

Although relatively more risks of pigmentary disorders and scars are described, effective treatment with lasers can be achieved in patients with higher phototypes (Bhatt and Alster 2008; Shah and Alster 2010). As an alternative to reduce these risks, non-ablative fractionated lasers are an excellent option. The correct parameters are essential to reduce side effects. Both technologies can be used in different sessions, respecting the interval of 4 weeks between the applications.

My Experience with Lasers for Ethnic Skin

Treating ethnic skin with lasers is always challenging. The first step is to evaluate the patient and the dermatosis to be treated and choose the best technology to be applied. We often perform a test treatment in a small area of the skin using two different parameters to check the effectiveness and to avoid side effects. This test is usually done 30 days before treatment.

The use of lightening cream, as hydroquinone isolated or associated with retinoic acid, to prepare the skin before laser application is controversial, but it is part of our routine. We also use these medications 3–4 weeks after treatment.

All patients are photographed before the procedure my experience with lasers for ethnic skin. Topical anesthetics are indicated to reduce the pain. During the procedure we use skin cooling equipment, as we believe that it can minimize inflammation, burning, and pain.

We routinely use conservative parameters at the first session, making adjustments in the subsequent sessions. Low fluence and low density and are indicated to reduce thermal effects, avoiding dyschromia.

Just after procedure we apply steroid cream for the first 3 days associated with a restorative cream, which is maintained until complete healing. After treatment, patients are advised to wear sunscreens with broad spectrum, and it is fundamental to avoid sun exposure (Figs. 1, 2, 3, 4, 5, 6, and 7).

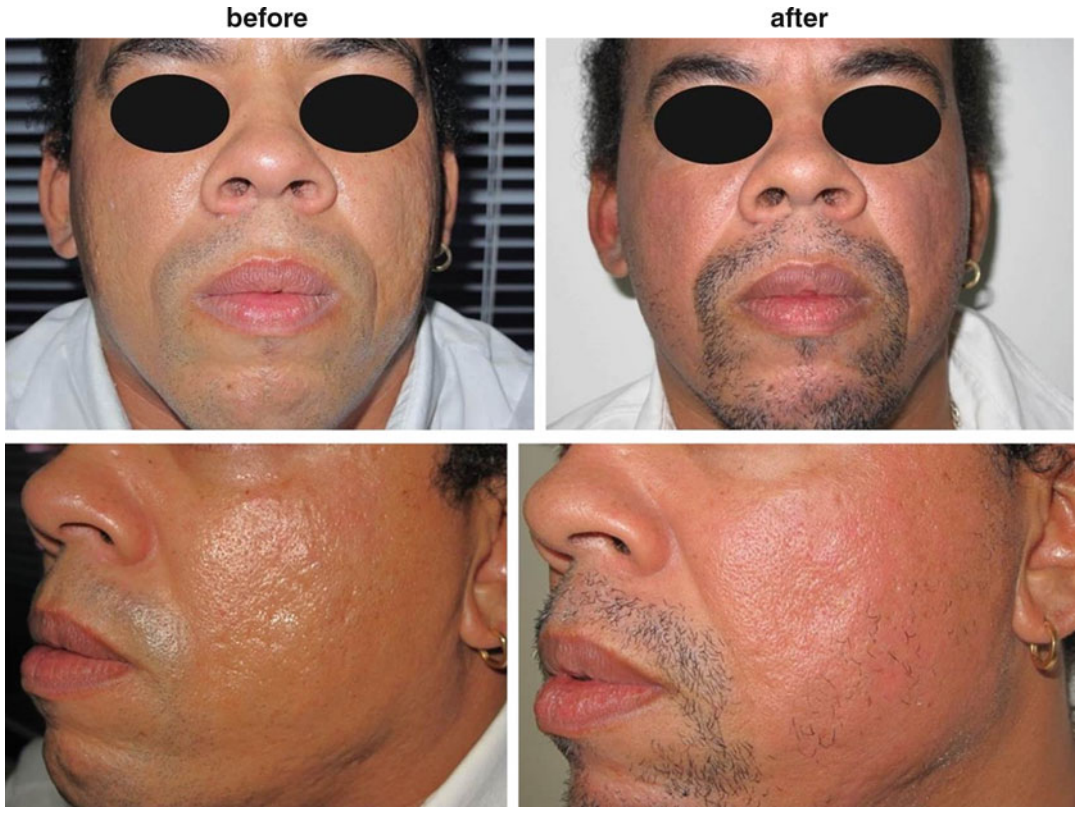

Fig. 1 Acne scars: CO_2 Exelo 2; E: 45 mJ; P: 2 ms; D: 250pt; 2 sessions (front view and lateral view)

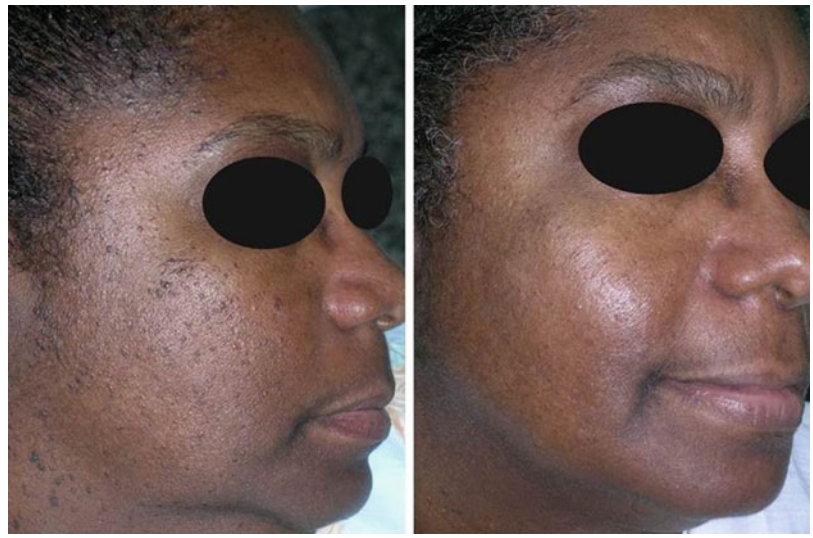

Fig. 2 Dermatosis papulosa nigra: CO_2 Luxar; F: 5W Mode: Dynamic (Cortesy by Emmanuel França)

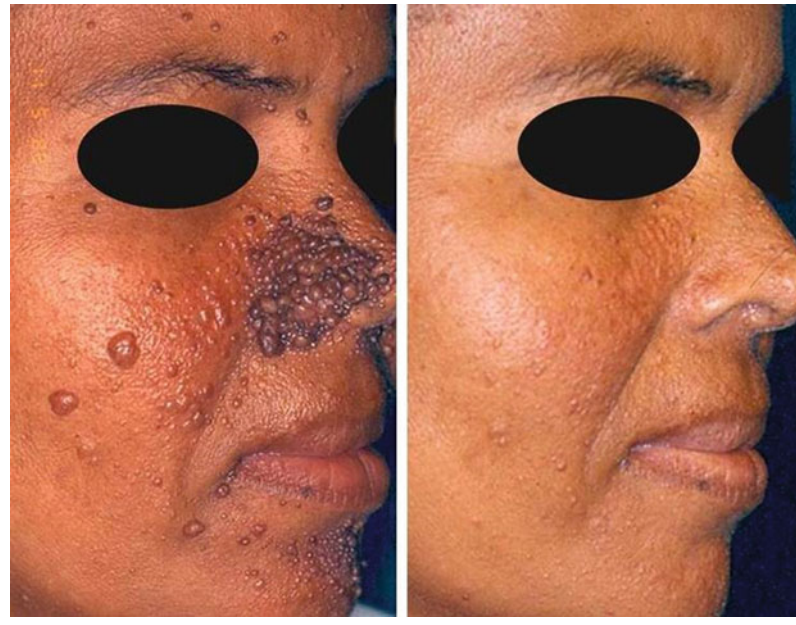

Fig. 3 Tuberous sclerosis – Angiofibromas: CO_2 Luxar; F: 5W Mode: Dynamic (Cortesy by Emmanuel França)

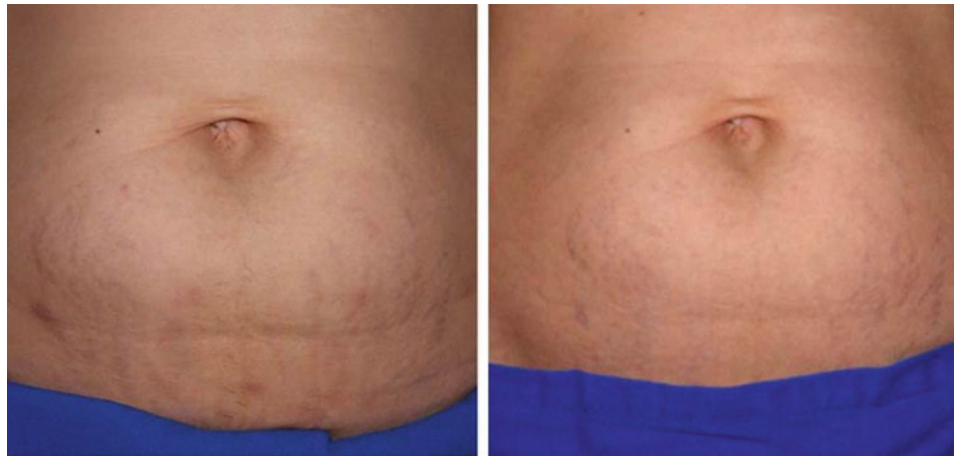

Fig. 4 Striae: CO_2 Exelo 2; E: 30 mJ; P: 2 ms; D: 250pt; 4 sessions

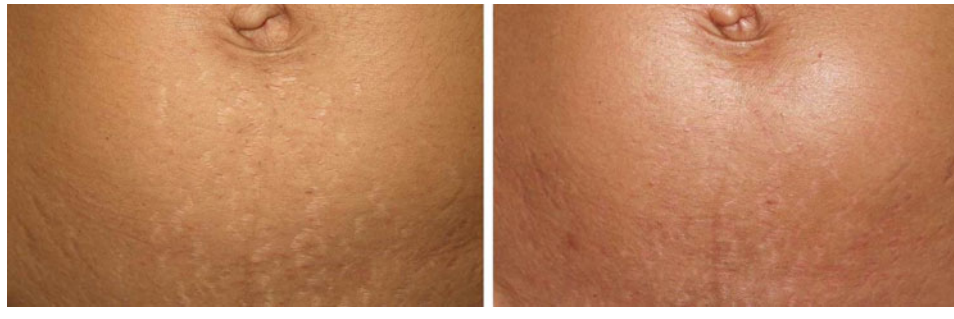

Fig. 5 Striae: CO_2 Exelo 2; E: 20 mJ; P: 2 ms; D: 200pt; 1 session. Starlux 1540 nm 15 mm; 55 mJ; 10 ms; 1 session. Starlux 1440 nm 70 mJ; 10 ms; 1 session

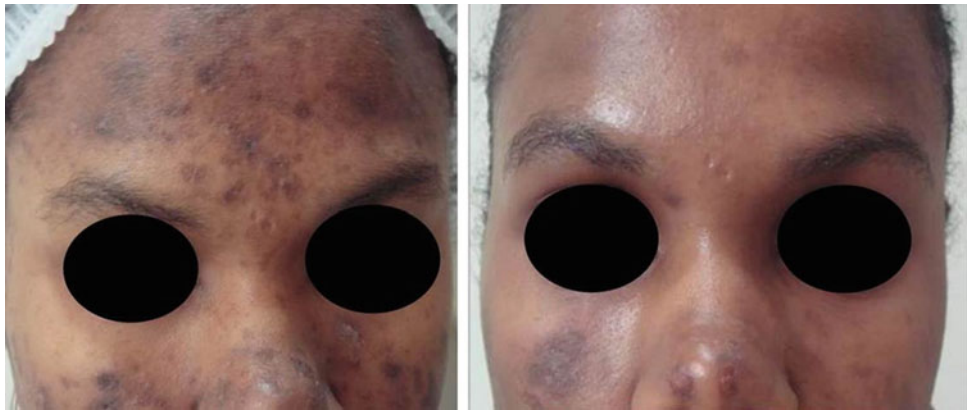

Fig. 6 Post-inflammatory hyperpigmentation and varicella scars. Starlux G 28 J/cm – 20 ms (3 sessions). Starlux 1540 nm 15 mm 15 mJ – 15 ms (3 sessions)

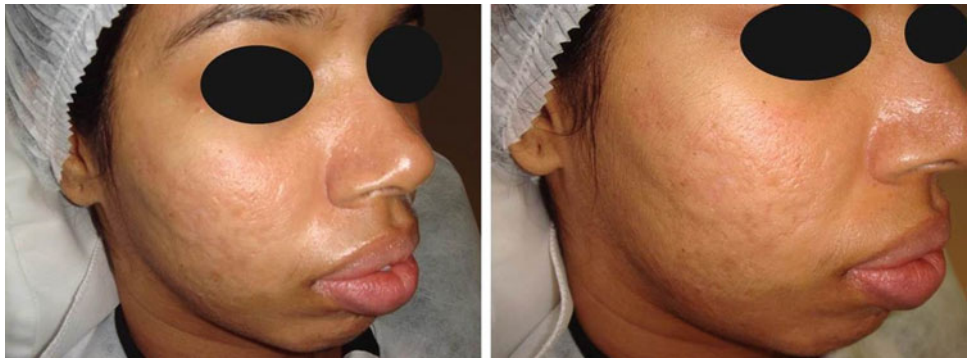

Fig. 7 Acne Scars: Starlux 1540 nm. 55 mJ; 15 ms (1 session) + 60 mJ; 15 ms (2 sessions)

Conclusion

Nowadays, ethnic skin patients are looking for dermatologic treatments, and according to advances in lasers' technology, the best results can be achieved. It is fundamental to photograph the patients before and after each procedure, to use the appropriate parameters according to the indications and to follow the patients during the post-procedure period until complete skin recovery.

Take Home Messages

- Ethnic skin is a term used to define the darker skin corresponding to Fitzpatrick's IV, V, and VI skin types.
- Patients with ethnic skin have an increased risk of problems related to pigmentation, such as and post-inflammatory hyperpigmentation or hypopigmentation.
- The risk of pigmentary changes is correlated with laser injury and thermal damage. It

depends on laser wavelength, fluency, and density.
- Over time, lasers devices have evolved, and recent techniques make its use safer, with less downtime and, consequently, with less damage and risk of post-inflammatory pigmentation.
- When performed by skilled, well-trained dermatologists, fractional ablative and non-ablative lasers become safe and viable for many treatments.

Cross-References

► Microneedling for Transepidermal Drug Delivery on Stretch Marks

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Laser for Hair Removal

Patricia Ormiga and Felipe Aguinaga

Abstract

Lasers for the removal of unwanted hair, using selective destruction of the hair follicle without damage to adjacent tissues, are a common procedure in the dermatologist's practice.

The diode laser, neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser, ruby laser, alexandrite laser, and intense pulsed light are some of the technologies available today for long-term hair removal. Proper selection of the wavelength, pulse duration, and fluence is crucial to the success and safety of the procedure.

Treatment performed with laser and other light sources usually produces a complete temporary hair loss, followed by partial permanent hair removal.

The patient's phototype and hair color must be carefully evaluated as well as the presence of tanning, since the presence of epidermal melanin increases the risks and decreases the effectiveness of the procedure. The ideal patient for laser or IPL hair removal is the one with low skin phototype and dark hair.

There is currently no consensus regarding the number of treatment sessions and the interval between them. Its determination must take into consideration the individual characteristics of hair growth, the body area, and the type of light source used.

The most common complications are hyper- or hypopigmentation, which is temporary in most cases, but there are reports of permanent changes. In general, laser treatment for hair removal is considered to be both safe and effective.

Keywords

Epilation • Intense pulsed light • Laser • Photothermolysis • Hair removal

Contents

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Introduction

The desire to permanently remove unwanted hair is becoming more prevalent everyday. Devices using laser technologies and other light sources, such as intense pulsed light (IPL), are widely used for this purpose.

The term "hair removal" encompasses two different concepts: "temporary hair loss" and "permanent hair reduction." "Temporary hair loss" defines a delay in hair growth, which can last for up to 3 months, according to the induction of telogen phase. "Permanent hair reduction" refers to a significant decrease in the number of terminal hair after treatment administration that remains stable for a longer period than the full cycle of hair follicles, which is now defined as 4–12 months (Dierickx and Grossman 2006; Klein et al. 2013).

Treatment performed with laser and other light sources usually produces a complete temporary hair loss (for up to 3 months), followed by partial permanent hair removal. Therefore, the expected result is an absolute reduction in hair count, while remaining hair becomes thinner, lighter, and grows more slowly.

The efficacy in achieving long-term hair removal, as well as an excellent safety profile, has been demonstrated in the medical literature for all treatment systems available for medical use (Gan and Graber 2013).

History

The earliest reports of skin treatments using lasers were made about 50 years ago (Goldman et al. 1963). But it was with the advent of the selective photothermolysis theory that the concept of achieving selected targets in the tegument was established (Anderson and Parrish 1983).

The neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser was the first device developed for laser hair removal. It was approved by the Food and Drug Administration (FDA) in 1996 (Grossman et al. 1996). The ruby (694 nm), alexandrite (755 nm), diode (800–810 nm), and Nd:YAG (1,064 nm) lasers and IPL (590–1,200 nm), are some of the technologies available today for long-term hair removal (Ibrahimi et al. 2011).

After the development of lasers with longer wavelength and pulse duration, all skin phototypes can now be handled safely (Vachiramon et al. 2012).

The Hair Follicle

The hair follicle is divided into three main areas: infundibulum, isthmus, and bulb. The germinal matrix of the hair follicle is located at the base of the bulb of the hair, about 2–7 mm below the skin surface, and it has a high concentration of melanin in comparison with the epidermis. The matrix is situated around the dermal papilla (or follicular papilla), which plays an important role in determining the thickness, length, and cycle of the hair (Krause and Foitzik 2006 Mar; Campos and Pitassi 2012).

Stem cells or totipotent cells are located in the "bulge," a structure with a great capacity for regeneration located near the insertion of the arrector pili muscles. The bulge is supposed to be the real target of laser hair removal, according to the latest studies.

The hair follicle cycle can be divided into three distinct phases: anagen, when there is active growth; catagen, a regression phase; and telogen when the follicle interrupts its growth (Philpott et al. 1990).

During the anagen phase, the majority of matrix cells are replicating, and the amount of pigment present in the bulb is increased. Anagen duration depends on the activity of those cells.

The proportion of hair follicles in each phase varies in different body areas. Axillary and inguinal regions have more follicles in the anagen phase than the limbs (Kolinco 2000). The telogen phase can last a few weeks in the face and a few

months in the limbs. The complete body hair cycle duration is approximately of 4–10 months. There are differences in hair growth between men and women, due to hormonal variations (Casey and Goldberg 2008).

There are three main types of hair: lanugo (very thin, identified in the neonatal period); vellus (slightly pigmented, approximately 30 μm diameter); and terminal hair (150–300 μm diameter). The hair type produced by each follicle can be changed according to different stimuli (Rosenfield 2005; Ibrahimi et al. 2011).

Mechanism of Hair Follicle Destruction

Light can destroy the hair follicles through three different mechanisms: thermal (local heating), mechanical (wave shocks or violent cavitations), and photochemical (generation of toxic mediators) (Dierickx 2000). Lasers and IPL promote photothermal tissue destruction, which is based on the selective photothermolysis principle, except for Nd:YAG devices equipped with the Q-switched mechanism, which promote photomechanical destruction.

Described by Anderson and Parrish in 1983, the selective photothermolysis principle postulates that there will be selective thermal damage of pigmented structures as long as light's wavelength is selectively absorbed by a target with sufficient energy and for a duration shorter than, or equal to, its thermal relaxation time (TRT) (Anderson and Parrish 1983; Dierickx and Grossman 2006).

When light is applied to the skin, part of it is reflected, another part spreads, and only a portion is absorbed. Only the amount absorbed is converted into heat, causing thermal effects on the treated area.

Light's wavelength is the factor that most influences its absorption. Each structure of the human body has affinity for certain wavelengths. This allows selective absorption of light energy and the treatment of specific targets without any damage to adjacent structures. Targets capable of absorbing specific wavelengths are called chromophores (Boechat 2002).

It is hypothesized that, in order to obtain permanent hair removal, the target of destruction is the stem cells of the follicle, located in the "bulge" area. However, the actual chromophore in hair follicles is the melanin in the matrix, its most pigmented area.

Because of the distance between the chromophore and the real target area, the extended photothermolysis theory has been proposed, which postulates that the heat generated on the chromophore is diffused to the target during the laser pulse (Altshuler et al. 2001).

The electromagnetic spectrum absorbed by melanin ranges from 350 to 1,200 nm. Thus, ruby, alexandrite, diode, and Nd:Yag lasers and IPL devices, which operate in this range, are able to produce epilation (Casey and Goldberg 2008; Ibrahimi et al. 2011; Campos and Pitassi 2012).

We know that, within the range of the electromagnetic spectrum with higher affinity to melanin, this affinity decreases as the wavelengths become larger. Thus, lasers with longer wavelengths have a greater penetration power in the tissue and a low affinity for melanin, with reduced risk of damage to the skin surface, being able to achieve dermal chromophores as the hair follicle bulb (Boechat 2002; Gan and Graber 2013).

Hair has melanocytes in greater number, size, and having more melanosomes compared to the epidermal melanocytes. Therefore, wavelengths near 700 nm are two to six times more absorbed by hair melanin than by the epidermal melanin, which allows the use of laser epilation even if there is little contrast between the color of the skin and the hair of the patient (Macedo 2012).

Thermal damage is more selective when pulse duration is close to the thermal relaxation time (TRT) of the target. TRT corresponds to the time required for the tissue to be cooled to half the temperature it has reached after a laser pulse.

If the pulse duration is longer than the TRT, the heat can dissipate beyond the target, before the thermal damage required occurs. If it is shorter, it can lead to excessive damage. Thus, the pulse duration should be immediately shorter than the TRT, so that the chromophore does not have its heat dissipated and thermal damage remains

restricted to the target (Stratigos and Dover 2000; Gan and Graber 2013).

The TRT is directly related to the target dimensions. Long pulse lasers (measured in milliseconds) are closer to the TRT of the hair follicle (10–100 ms) (Anderson and Parrish 1983; Van Germet and Welch 1989; Ross et al. 1999).

There are two basic principles that should be observed when we evoke the selective photothermolysis concept. The first is to use an optimal wavelength to be selectively absorbed by the target tissue. The second is that the pulse should be long enough to produce an effect on the chromophore, but fast enough to cause minimal effect on adjacent tissues.

However, all technology that targets dermal structures hits the epidermis first, which has a melanin "barrier" in their basal layer. Therefore, there is always some attenuation of the energy used, with less tissue penetration and some risk of reaching the surrounding skin. The higher the phototype of the patient, the bigger is the risk, and, therefore, ideal patients for laser and LIP epilation are those of lower phototypes, with thick and pigmented hair (Boechat 2002).

It is important to note that LIP, that uses lower wavelength and show higher affinity for melanin, needs greater contrast between the skin and hair colors, being less suitable for higher phototypes.

To solve the problem of presence of melanin in the epidermis, the most modern devices use high energy with cooling protection systems. Thus, the treatment effectiveness remains high, with low risk and less pain for the patients, also allowing treatment of higher phototype patients (Dierickx 2000; Zenzie et al. 2000; Mandt et al. 2005).

Parameters

The amount of energy delivered to the tissue is the factor that determines its temperature increases.

The energy is the amount of power dispensed by lasers in a given time interval, measured in Joules (J). The device power is measured in watts (W).

Another parameter required to determine the amount of energy delivered to the target is the spot size, which is measured in millimeters (Nouri et al. 2004).

Fluence is the energy density obtained in each shot, and this is measured in J/cm^2.

$$\text{Fluence}\left(\text{J}/\text{cm}^2\right) = \text{energy}(\text{J})/\text{area}\left(\text{cm}^2\right)$$

The pulse duration is the time, in seconds, during which the tissue is exposed to light (Boechat 2002).

Thus, fluence and pulse duration are important parameters to determine the amount of heat absorbed. Fluence determines the peak temperature obtained on the target structures, and pulse duration determines the time during which the structure is exposed to a given temperature (Gan and Graber 2013).

Proper selection of the wavelength, pulse duration, and fluence is crucial to the success and safety of the procedure (Dawber 2005). To treat thin and light hair, higher fluence should be used. To treat high concentration of thick hair or higher phototypes, lower fluence is required (Macedo 2012). A good method to determine the appropriate fluence is to observe the immediate clinical response, which shows perifollicular erythema and edema on the treated area. Higher fluence is associated with increased effectiveness in hair removal; however, it may increase adverse effects (Ibrahimi et al. 2011).

Hair diameter can influence the structure's TRT and, therefore, the pulse duration selection (Dierickx 2000). For thin hair, shorter pulses are used, around 7–10 ms, while for thick hair, pulses around 30–40 ms are preferable (Macedo 2012).

The matrix depth influences the wavelength, spot size, and energy choice, while the hair color is also decisive for appropriate parameters choice (Randall et al. 2006, Table 1).

Lasers and IPL Characteristics

Light emitted by laser has characteristics that differentiate it from other light sources. It is monochromatic, emitting photons with the same wavelength, and coherent, with all photons going in the same direction. It is also collimated, with photons moving in parallel between them and with minimal angular divergence (Boechat

Table 1 Parameters used in treatments

Power (W or J/s)	Quantity of energy given per time unit
"*Spot size*" (mm)	Tip area
Pulse duration (s)	Time during which the tissue is exposed to light
Fluence (J/cm^2)	Energy dispensed through the tip area

2002). Diode and alexandrite lasers are considered, in general, the most effective for hair removal, followed by IPL and Nd:YAG devices (Campos and Pitassi 2012). Recent studies point that diode laser is more effective than IPL (Ormiga et al. 2014).

The diode laser (800 nm) can be safely used on I–V skin phototypes (Campos et al. 2000). The devices pulse duration varies between 5 and 400 ms and their fluences, in general, between 10 and 60 J (Dierickx and Grossman 2006).

Latest devices have larger tips, about 22 × 35 mm, and a vacuum system that sucks the skin prior to light emission. The objective is to decrease the discomfort and to optimize the treatment of large areas. There are also devices with 10 × 50 mm tips, with which the treatment may be done continuously and scanned. Another recent technology is the combination of radio frequency energy to the laser optics energy, in order to achieve higher target temperatures, even with the use of lower fluence, providing safety and effectiveness to the treatment.

Alexandrite laser (755 nm) has shorter pulse durations than diode laser, showing better results on thin hair. But most studies show similar results on hair removal produced by both technologies when used on skin phototypes I to IV. This technology should be used preferably in patients of lower phototypes, due to increased possibility of complications in higher phototypes.

The Nd:YAG (1,064 nm) has lower affinity for melanin. For this reason, the laser is considered the safer technology for patients of V and VI skin phototypes (Gan and Graber 2013) and also shows good results.

IPL has different characteristics because it is generated differently. The devices use a flash lamp controlled by a computer. The light is polychromatic, emitting various wavelengths. Filters placed in front of the lamps provide the wavelength selection. Another LIP characteristic is to be incoherent, emitted in several directions, being focused with reflective surfaces (Boechat 2002; Gan and Graber 2013).

IPL devices work on a range of 650–1,200 nm wavelength, emitting shorter wavelengths that do not penetrate so deeply into the skin, and are more safer to use in lower phototypes patients, because of its increased risk of reaching the epidermal melanin (Ismail 2012). The IPL pulse duration is given in milliseconds. Because of its broad spectrum, emitting shorter wavelengths, IPL can be used on thin light hair, although with not so interesting results as those seen for dark hair (Campos and Pitassi 2012).

Patient Selection and Preparation

Patient selection should include a thorough clinical examination, hormonal evaluation, and medication use investigation.

The patient's phototype must be carefully evaluated as well as the presence of tanning, since the presence of epidermal melanin increases the risks and decreases the effectiveness of the procedure (Gan and Graber 2013). Hair color evaluation is also important, because light hair hardly responds to therapy. Thus, the ideal patient for laser or IPL hair removal is the one with low skin phototype and dark hair (Dierickx and Grossman 2006).

Around 80% of women with polycystic ovary syndrome develop hirsutism, which may have good response to light treatment, if properly administered (McGill et al. 2007).

The presence of herpes virus infections should be investigated, and chemoprophylaxis is required for patients with recurrent episodes. The propensity to hypertrophic scars or keloids should also be investigated.

Although there is no evidence of risk, patients should not be treated during pregnancy. There is no consensus on the treatment during breastfeeding.

The presence of autoimmune disorders should be investigated, due to the predisposition to

photosensitivity. Diseases that can trigger Koebner phenomenon, such as vitiligo or psoriasis, are also contraindications to the procedure.

Patients using medications with gold or photosensitizing drugs should not be treated, because of the risk of hyperpigmentation (Ibrahimi et al. 2011; Gan and Graber 2013).

There is no consensus on the use of oral isotretinoin and epilation, and although some studies suggest their safety, there is a risk of phototoxicity, skin fragility, scarring, and delayed re-epithelialization. It is proposed the interval of 6 months to 1 year after discontinuing the medication for treatment initiation (Khatri 2004; Cassano et al. 2005; Khatri and Garcia 2006). Topical retinoids may be suspended 1 or 2 days before the sessions.

Drugs such as cyclosporine, cortisone, phenytoin, and penicillamine, as well as hormonal imbalances such as polycystic ovary syndrome or menopause, can stimulate the growth of new hair, and patients may require maintenance treatment regime after completion of conventional treatment sessions (Fields and Pitassi 2012).

Patients should avoid sun exposure, in order to ensure the security of the procedure.

Any traction method for hair removal must be avoided in the 4 weeks prior to treatment, to ensure that the chromophore of follicles is present. The hair should be shaved or removed by depilatory creams, so that its shafts do not become targets in the surface of the skin, increasing the risk of burns.

Conducting Treatment

The parameters choice has already been explained above. However, it is important to discuss other issues to be considered during treatment.

More intense pigmented and thicker hair is more susceptible to treatments. Thus, the cycle hair phases should be considered in determining the frequency of treatment sessions, since the aim is to submit the follicle to thermal aggression in its anagen phase, when it is more pigmented. Furthermore, it is important that the hair is not completely removed from the follicle through traction methods, such as waxing, in order to preserve sufficient melanin for the light source action.

There is currently no consensus regarding the number of treatment sessions and the interval between them. What is known is that the cycle varies according to the anatomical location and gender of patients. Likewise, the time required for hair resurgence after treatment sessions also varies, with an average of 8 weeks. Thus, the ideal interval between sessions remains unclear, and the main authors estimate it to be between 4 and 8 weeks.

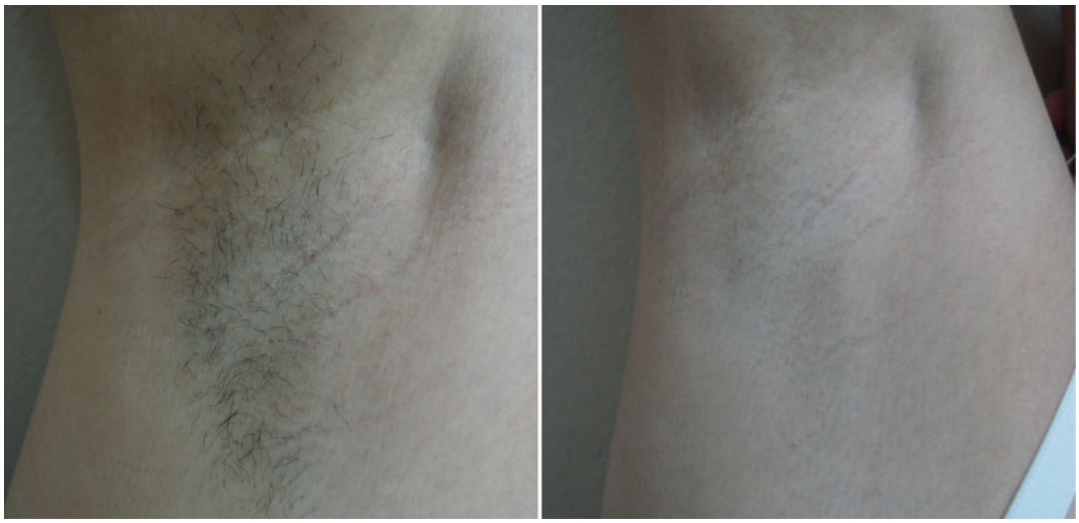
The ideal number of treatment sessions is also not well established. Its determination must take into consideration the individual characteristics of hair growth, the body area, and the type of light source to be used. Most authors agree that repeated treatments increase the effectiveness of the method, recommending three to eight sessions of treatment to achieve satisfactory results (Casey and Goldberg 2008). It is estimated that there is an average reduction of 20–30% in each treatment and that patients with lower phototypes and dark hair, the chance of long-term epilation is 80–89% depending on the apparatus used (Dierickx and Grossman 2006).

The use of proper eye protection is critical to the treatment safety. Each wavelength requires different types of lens, so different machines require the use of different glasses. Patients, applicators, and remaining people in the room must use protection. Treatment of the periocular area is not advised.

At the beginning of the procedure, a test with a few shots in a small area must be performed. Pigmented lesions and tattoos must be avoided during treatment.

After the session, ice packs may be used to decrease the occurrence of pain and edema. If there is evidence of excessive inflammation, with burning risk, high-potency topical corticosteroids may be used to minimize potential side effects (Gan and Graber 2013). Perifollicular erythema and edema are expected reactions, particularly with the laser use. This reaction will be less intense with the use of LIP, which works with longer pulse duration (Fields and Pitassi 2012).

It is extremely important to avoid sun exposure for 6 weeks before and after each treatment session (Pictures 1, 2, 3, and 4).



Picture 1 Axilla before and after 6 monthly sessions of IPL

Complications

The most common complications are hyper- or hypopigmentation, which is temporary in most cases, but there are reports of permanent changes (Ibrahimi et al. 2011). There may also be erythema, edema, pain, burns, blistering, and scarring (Lim and Lanigan 2006). The skin phototype and prior sun exposure of the treated area are crucial in the development of such complications. Protected areas, such as the armpits and groin, tend to have fewer side effects (Gan and Graber 2013).

Paradoxical hypertrichosis occurs in 0.6–10% of patients treated with LIP or lasers. The exact mechanism by which it occurs is unknown, and it is most common after treatment with IPL and alexandrite lasers. Factors associated with its development include the use of insufficient fluence, higher phototypes, hormonal changes, and the use of medications (such as finasteride or corticosteroids) or hormone supplements. Women seem to be most affected and areas such as the face and neck are more prone to this complication (Desai et al. 2010).

Severe and persistent urticaria can occur, even in patients without a history of physical urticaria, possibly caused by the use of cryogens or sensitivity to specific wavelength (Bernstein 2010).

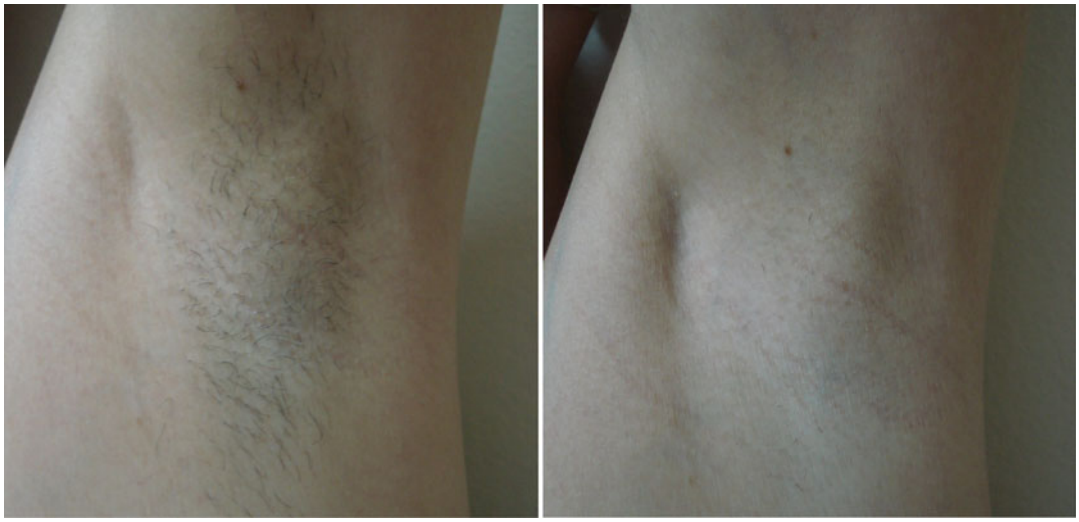
Ocular complications such as cataract, atrophy and iris adhesions, iritis, uveitis, photophobia, pupil changes, and visual field alterations have been described, even in patients who used appropriate glasses. Wavelengths 400–1,400 nm, falling directly on the eyes, can cause burns on the retina and permanent visual disturbances, making mandatory the use of eye protection for patients and applicators (Shullman and Bichler 2009; Gan and Graber 2013).

Acne aggravation, development of lesions similar to those of rosacea, early follicles depigmentation, diffuse erythema, and inflammatory or pigmentary changes of pre-existing nevi were also reported as rare side effects (Rasheed 2009).

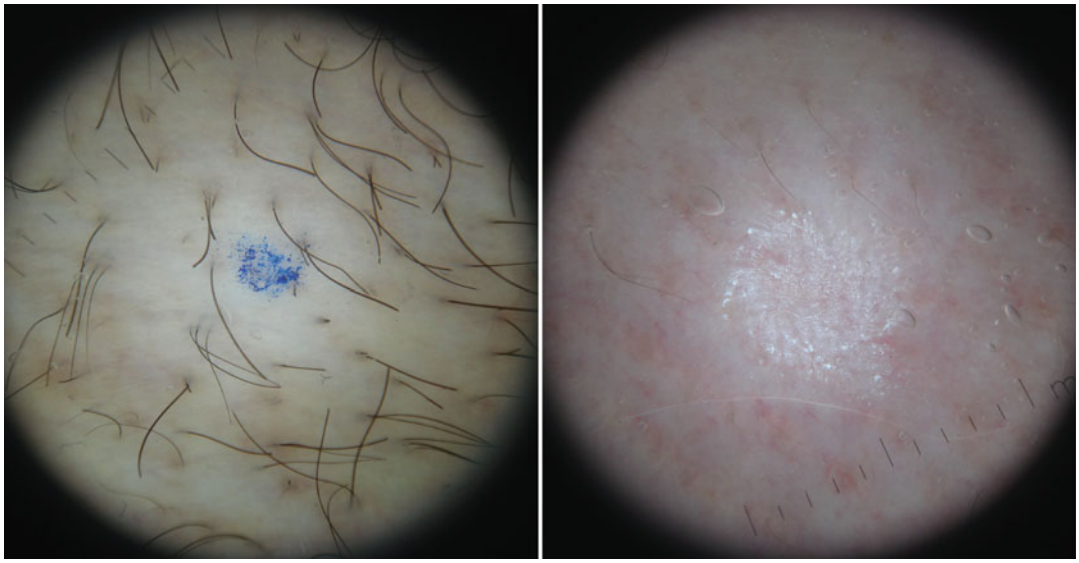
Devices for Home Use

Portable devices for domestic use (home devices) have been developed on a large scale and are gaining popularity because of its low cost and ease of use. They use laser and IPL technologies, with very low fluences when compared to the medical devices.

Although approved by the FDA, there are few controlled studies showing its effectiveness and safety (Thaysen-Petersen et al. 2012).



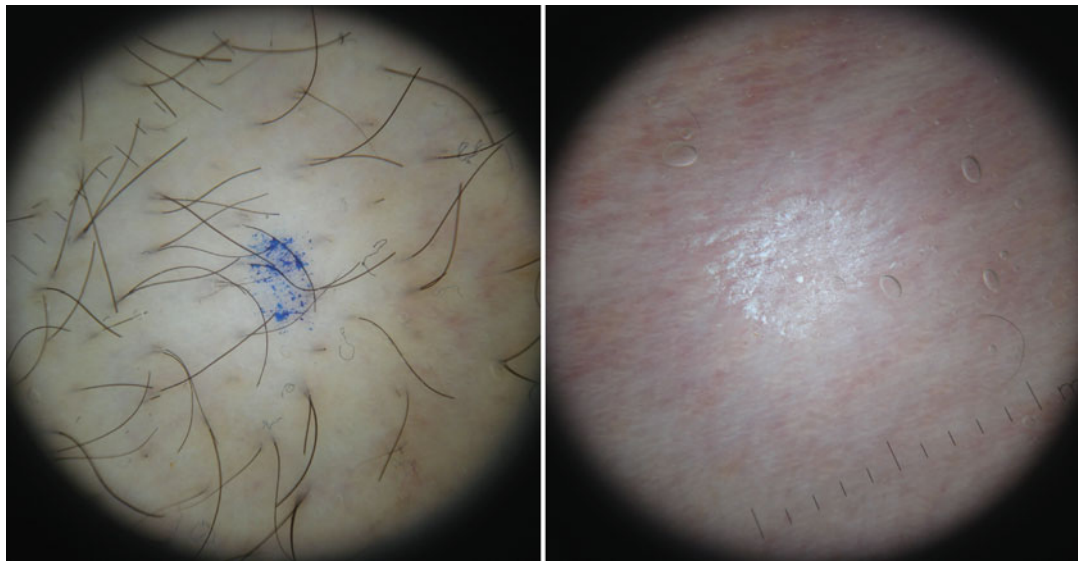
Picture 2 Axilla before and after 6 monthly sessions of diode laser



Picture 3 Dermoscopic images showing axilla before and after 6 monthly sessions of IPL

Take Home Messages

- Laser hair removal has emerged as a leading treatment option for long-term hair reduction. Devices such as diode laser, Nd:YAG laser, and intense pulsed light (IPL) are in constant development, but there are few comparative studies between these technologies. Recent studies point that diode laser might be more effective than IPL.
- Proper selection of the wavelength, pulse duration, and fluence is crucial for the success and safety of the procedure. To treat thin and light hair, higher fluences are required. To treat high concentration of thick hair or higher phototypes, lower fluences might be used.
- The ideal patient for laser or IPL hair removal is the one with low skin phototype and dark hair.



Picture 4 Dermoscopic images showing axilla before and after 6 monthly sessions of diode laser

- There is currently no consensus regarding the number of treatment sessions and the interval between them.
- Hyper- or hypopigmentation, burns, scarring, and paradoxical hypertrichosis are some of the adverse effects reported.

Cross-References

► Biophotonics

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Laser on Hair Regrowth

João Roberto Antonio, Carlos Roberto Antonio, and Ana Lúcia Ferreira Coutinho

Abstract

Alopecia is a common disorder affecting more than half of the population worldwide. There is an urgent need to investigate alternative treatment options, while there are still a few therapeutics options for different types of alopecia in the market. The photobiomodulation phenomenon followed by hair growth was first described in 1967 by Professor Endre Mester, an Hungarian physician, the pioneer of laser medicine. For decades, clinical studies have been conducted to evaluate the efficacy, mechanism of action, and risks of using Low-level laser therapy - LLLT (collimated or non-collimated) in different forms of hair loss as a further treatment option. This chapter will present the clinical studies conducted with LLLT on female pattern hair loss (FPHL), male pattern hair loss (MPHL), alopecia areata (AA), and chemotherapy-induced alopecia (CIA) investigated in several databases including PubMed, Google Scholar, Medline, Embase, and Cochrane. At the end of this chapter, the authors concluded that LLLT may be a promising treatment option for patients who do not respond to conventional treatments and who do not want to undergo hair transplantation. This technology appears to work better for some people than others. Factors predicting who will get the most benefit need to be determined. Larger, longer-term placebo-controlled studies are needed to confirm these findings and reinforce the efficacy of the LLLT in those patients, generating, therefore, more consistent protocols.

Keywords

Laser • Low-level laser therapy • Low-level light therapy • Photobiomodulation • Hair loss • Alopecia • Androgenetic alopecia • Female pattern hair loss • Male pattern hair loss • Alopecia areata • Chemotherapy

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Introduction

The use of laser in dermatology was firstly assessed in the treatment of benign vascular tumors. However, it gained ground while proving clinical effectiveness and safety in the treatment of other dermatological conditions such as removal of pigmented lesions, tattoos, scars, and undesirable hairs and in photoaging treatment.

Laser therapy has become popular over the last years. The first report of the use of the laser for hair growth was carried out by Professor Endre Mester et al. in 1967, during an experimental observation. Investigators reported the hair regrowth in the epilated area exposed to low-potency ruby laser, evaluated to demonstrate the potential carcinogenic effect on the shaved backs of guinea pigs (Mester et al. 1968). This finding triggered the interest not only in identifying which laser apparatus could give efficient clinical responses without risk but also in verifying which therapeutic mechanisms would be involved in those responses.

To understand the mechanism of action of laser in hair regrowth process, mainly in the scalp, laser medicine experts have developed different lines of research in low-level laser therapy (LLLT) and hair loss disorders with available data to date demonstrating efficacy.

The LLLT could be distinguished from other forms of laser therapy using low power and low density. Most low-level laser therapy devices operate at wavelength intervals between 600 and 1000 nm and use much less power than the amount requested to warm tissue (10 mW/cm, 2–5 W/cm2) (Bouzari and Firooz 2006).

Recently, the use of low-level laser therapy (LLLT) has been proposed as an alternative therapy (mono or in combination) for hair loss to stimulate hair regrowth in alopecia: FPHL, MPHL, and AA. In the next paragraphs, experimental and clinical studies conducted with the use of LLLT in these conditions will be discussed.

Historical Data

In 1996, a team of researchers from Kuopio University, Finland, conducted a single-blind placebo-controlled study to assess and compare the effects produced by three different types of laser/light (He-Ne, As-Ga-Al diode, noncoherent LED light) on hair blood flow. The study involved ten healthy male individuals. Two sessions were held, and the placebo (noncoherent LED light) was compared to other two laser sources (He-Ne and As-Ga-Al diode). Measurements were carried out by laser Doppler flowmetry. Results demonstrated that coherent laser sources were the only light sources able to produce vasodilation (Pöntinen et al. 1996).

In 2000, a study carried out by researchers from Harvard Medical University showed that volunteers exposed to ruby laser (694 nm) for hair removal and diode (800 nm), responders or nonresponders, presented some level of hair growth, thinner and without pigment, sometime after the procedure. The authors concluded that changes observed depend on the type of laser and individual response (Lin et al. 2000).

Gerardo Moreno-Arias et al. (2002) reported a phenomenon called paradoxical hypertrichosis or terminalization or induction of terminal hair growth. The clinical finding was described as a rare but significant secondary effect present in patients with hirsutism who undertook intense pulsed light (IPL) treatment during a period from 3 to 6 months. As the authors argue, intense pulsed light would have the property of inducing latent hair follicle in non-treated areas located around treated areas (Moreno-Arias et al. 2002; Desai et al. 2010).

In recent literature's review made by Sophia Rangwala, paradoxical hypertrichosis rates range from 0.6% to 10% after low-energy laser therapies with almost all types of laser: XeCL excimer 308 nm, helium-neon (He-Ne), and fractional

Erbium glass fiber 1550 nm. The event is more frequent over the face and the neck of volunteers with darker skin color (prototypes III–IV), dark hair, and/or with coexisting hormone imbalance (Rangwala 2012).

The appearance of pilli bigeminy in four cases after alexandrite or ruby laser treatments due to suboptimal fluencies insufficiently low to induce thermolysis, but high enough to stimulate follicular growth. Although the face and neck seem to be the areas which are most sensitive to hair growth induction effect, sensitivity and response of scalp under these conditions are not recognized (Ye et al. 1999).

Under some researchers' perspective, laser phototherapy prolongs the duration of anagen phase, stimulates the anagen reentry in telogen hair follicles, increases the proliferation rates of the anagen hair follicles, and prevents the premature catagen development (Chung et al. 2004). There are many theories to explain the LLLT's mechanism of action in hair loss, but it has not yet been fully elucidated (Karu 1989; Karu and Kolyakov 2005; Hawkins-Evans and Abrahamse 2008a, b; Lubart et al. 1992; Oliveira et al. 2008; Mognato et al. 2004; Karu 1987).

Although medical guidelines make special reference to LLLT clinical benefits in alopecia, it is important to reinforce the need for clinical studies of a better quality, randomized with an adequate number of volunteers (Kreisler et al. 2003; Kim et al. 2015; Avram and Rogers 2010; Stillman 2010).

Proposed Mechanisms: LLLT on Hair Growth

The LLLT has biomodulating effects on cells and tissues. These effects activate or inhibit physiological, biochemical, metabolic processes through photophysical or photochemical effects and promote morpho-differentiation, cellular proliferation, tissue neoformation, revascularization, reduction of edema, increased cellular regeneration, microcirculation, and vascular permeability (Karu 1989; Karu and Kolyakov 2005; Hawkins-Evans and Abrahamse 2008a, b).

When laser therapy is used in the visible electromagnetic spectrum, there is an initial photobiostimulation in mitochondria, which activates a chain of biological events. When the irradiation is in the infrared spectrum, there is stimulation of the plasmatic membrane channels, resulting in changes in membrane permeability, temperature, and pressure gradient (Lubart et al. 1992; Oliveira et al. 2008; Mognato et al. 2004; Karu 1987).

Both visible and infrared light can be absorbed by different components of the cellular respiratory chain such as chromophores in cytochrome C oxidase or porphyrins, which results in the production of reactive oxygen species or superoxide radicals. It has been commented that reactive oxygen species have a fundamental role in increasing the proliferation of keratinocytes (Lubart et al. 1992; Oliveira et al. 2008; Mognato et al. 2004; Karu 1987).

According to Mognato et al., the oxidation reaction seems to be associated with stimulation and proliferation, whereas the reduction reaction seems to be associated with inhibition of cell growth (Mognato et al. 2004).

Kreisler et al. (2003) emphasized that there is a stimulation of photoreceptors in the mitochondrial respiratory chain. After the laser light has been absorbed, photophysical and photochemical effects, isolated or combined, stimulate the mitochondrial membrane, increasing the membrane potential and, consequently, changing the mitochondria's properties. LLLT acts on the mitochondria and may alter cell metabolism through photodissociation of inhibitory nitric oxide (NO) from cytochrome C oxidase (CCO), resulting in an increased production of molecular oxygen and ATP, which stimulates the activity of DNA and RNA to synthesize regulatory proteins of the cell cycle, and thus the speed of mitosis can be increased (Kim et al. 2015; Avram and Rogers 2010; Stillman 2010). Moreover, NO is known to be a potent vasodilator via its effect on cyclic guanine monophosphate production, and it can be speculated that LLLT may cause photodissociation of NO not only from CCO but also

from intracellular stores such as nitrosylated forms of both hemoglobin and myoglobin leading to vasodilation and increased blood flow which was reported in several studies (McElwee 2012; Chung et al. 2012).

According to Stein et al. (2005), laser therapy induces the phosphorylation of MAPK/ERK protein kinases in cells, which are known to be associated with the mechanism of cell proliferation. It is worth noting that the interaction of laser light with tissues can lead to different results (stimulation or inhibition) depending on several factors, such as wavelength, dose, power, time, number of irradiations, optical properties of tissues, and type of irradiated cell, besides the physiological characteristics of the cells at the time of irradiation.

In fact, the magnitude of the cellular response to irradiation depends on the physiological state of the cell (the amount of nutrients available and the age of the cell culture). Generally, cells in the exponential phase of growth are more photosensitive than those in the stationary phase of growth (Avram and Rogers 2010; Stillman 2010; McElwee 2012; Chung et al. 2012; Stein et al. 2005; Karu 1988) (See Fig. 1.)

LLLT in Chemotherapy-Induced Alopecia (CIA)

In 2003, a nonclinical study was conducted focusing on assessing the use of low-level laser therapy in guinea pigs (rodents) which presented chemotherapy-induced alopecia (CIA), considering that there was no efficient approach to this type of alopecia.

HairMax LaserComb©, a low-level laser device, was used, whose application had already been authorized by FDA for androgenetic alopecia treatment.

Throughout the study, traditional chemotherapeutical agents were used, cyclophosphamide, etoposide, or a combination of cyclophosphamide and doxorubicin, to induce alopecia in young rats with or without low-level laser therapy (LLLT). As expected, after 7–10 days of chemotherapy, all rats developed complete corporeal alopecia. However, the rats, which had been submitted to low-level laser therapy, recovered their natural state, with hair growth around 5 days earlier than those submitted only to chemotherapy without LLLT exposure. Hair growth in rats treated with laser was confirmed by histological study.

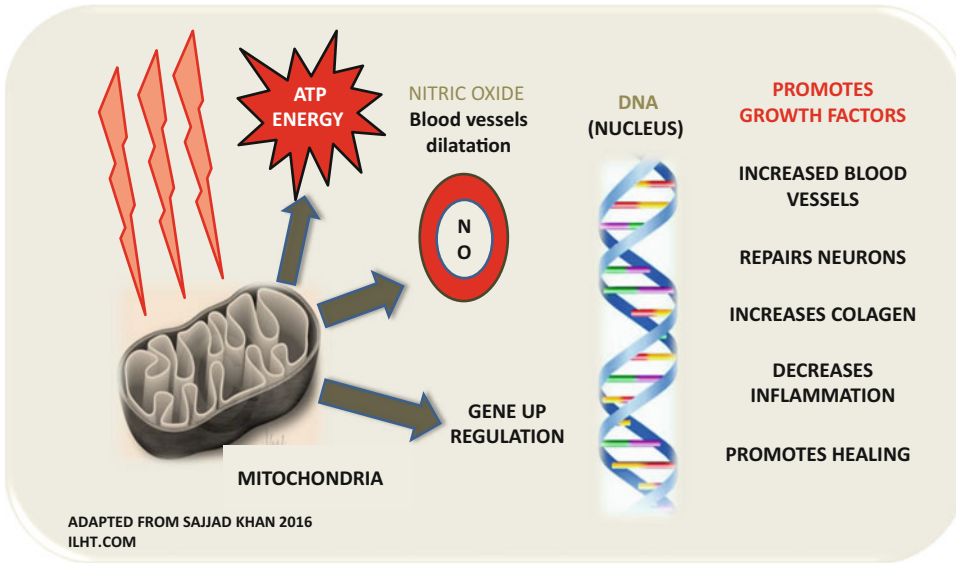


Fig. 1 Schematic drawing of possible mechanisms of LLLT on hair growth

Results showed that low-level laser treatment accelerated significantly hair growth after CIA, without affecting chemotherapy efficiency, concerning the guinea pig model used for that study (Wikramanayake et al. 2013).

LLLT in Androgenetic Alopecia (AGA)

Androgenetic alopecia (AGA) is one of the most common chronic problems seen by dermatologists worldwide, characterized by progressive hair loss, especially of scalp hair. It has distinctive patterns of loss in women versus men, but in both genders the central scalp is most severely affected.

It often begins around puberty and is known to effect self-esteem and the individual's quality of life. In contrast to the high prevalence of AGA, approved therapeutic options are limited. In addition to the scarce pharmacologic treatments, there are numerous nonprescription products claimed to be effective in restoring hair in androgenetic alopecia.

Low-intensity laser therapy or photobiomodulation or photobiostimulation was approved by US Food and Drug Administration (FDA) in 2007 with a safe approach to the treatment of male and female androgenetic alopecia. From then on, a series of devices designed for domestic use (daily or many times a week) became available on the market, relatively cheap if compared to medical treatment and hair transplant surgery.

Although the mechanism of action of this device is still not clear about androgenetic alopecia treatments, some controlled clinical studies show visible hair growth.

Different types of laser have been studied during the assessment of hair growth in androgenetic alopecia, including XeCL excimer 308 nm, helium-neon (He-Ne), and fractional Erbium glass fiber 1550 nm (Blumeyer et al. 2011; Tsuboi et al. 2012; van Zuuren et al. 2012; Zarei et al. 2016; Jimenez et al. 2014; Leavitt et al. 2009; Wikramanayake et al. 2009; Avram et al. 2007; Kim et al. 2011; Kobielak et al. 2013; Kandyba and Kobielak 2013; Kandyba et al. 2013; Kobielak et al. 2003, 2007; Lee et al. 2011) (see Table 1).

The HairMax LaserComb© (Lexington International, Florida), a 3R class laser (safety level), was evaluated in androgenetic alopecia in multicenter, double-blind controlled study (against a non-active device). The clinical trial was performed in four centers and assessed 110 men with male AGA (Norwood-Hamilton: IIa-V, Fitzpatrick: I a IV) aged between 30 and 60 years (Jimenez et al. 2014).

The study subjects were instructed to use the device three times a week, during 15 min, over 26 weeks. The sites for application were marked with a circular tattoo, 2.96 cm in diameter, which was assessed after haircut. By means of computerized countdown, the scalp was evaluated via macroimage.

The study subjects treated with laser comb (655 nm) showed an increase in density of around 19.8 hairs/cm^2 in comparison to 7.6 hairs/cm^2 presented by the control group ($P < 0{,}0001$). No statistical improvement was observed in the investigator's overall evaluation.

In 2014, another group of researchers published a double-blind, randomized, controlled, multicenter study which had been performed to assess the clinical efficacy and safety of the same device in women and men with androgenetic alopecia.

A hundred and forty-one female volunteers ($n = 141$) and a hundred and twenty-eight male volunteers ($n = 128$) were randomized to receive the active device LaserComb or sham device (control) according to the following design: #1 with beams 9 X control, #2 with beams 12 X control, #3 with beams 7 X control, and #4 with beams 12 X control.

The application all over the scalp was performed three times a week throughout 26 weeks. Terminal hair density in the targeted area was assessed at the beginning and in the 16th and 26th weeks of the follow-up.

Both investigators and study subjects remained blind to the type of device used during the test. The specialist responsible for evaluating the digital pictures taken along the trial also remained blind to each branch of the study.

Table 1 Literature review about different devices and protocols

Home devices	Power	Treatment regimes	Studies	Subjects	Results	Peer reviewed?
Capillus™ 82 Laser Cap	410 mW	30 min 3–4×/week	Double blind RCT	44F	63.7% increase in terminal hair count vs sham	No
Capillus™ 202 Laser Cap	1010 mW	30 min 3–4×/week				
Capillus™ 272 Pro Laser Cap	1360 mW	30 min 3–4×/week				
HairMax™ Laser Band 41	205 mW	3 min 3×/week	Prospective cohort	28M, 7F	Total hair count and hair tensile strength increased	Yes (Satino)
HairMax™ Laser Band 82	410 mW	90 s 3×/week	Double blind RCT	110M	Mean terminal hair density increased by ~20 hairs/cm^2	Yes (Leavitt)
HairMax™ Prima7 Laser Comb	35 mW	15 min 3×/week	Case report	2M	No significant change in hair count or thickness	Yes (Rushton)
HairMax™ Ultima 9 Laser Comb	45 mW	15 min 3×/week	Retrospective Cohort	11M, 21F	Global photos – majority w/moderate improvement	Yes (Munk)
HairMax™ Ultima 12 Laser Comb	60 mW	8 min 3×/week	Double blind RCT	128M, 141F	Terminal hair density increased by ~15 hairs/cm^2	Yes (Jimenez)
iGrow™ Hair Growth System	255 mW	25 min every other day	Double blind RCT	41M	35–37% increase in terminal hair count	Yes (Lanzafame)
			Double blind RCT	42F		
iRestore™ Hair Growth System	255 mW	25 min every other day	Double blind RCT	18M, 18F	Pending, study in progress	N/A
Lasercap™ LCPRO	1120 mW	36 min every other day	Case series	7F	Improvement in hair volume and shine	N/A
			Case series	1M, 2F		
NutraStim™ Laser Hair Comb	60 mW	8 min 3×/week	N/A	N/A	N/A	N/A
Theradorme™ LH80 PRO	400 mW	20 min 2×/week	Double blind RCT	80M	Pending, study in progress	N/A

Source: Data obtained by consulting suppliers/internet/sales representatives. May 2017

At the end of study, the investigators observed an increase statistically significant in terminal hair density for subjects treated with active device against those treated with the sham device (control).

No serious adverse events have been reported. According to the authors, these results suggest that LLLT might be an efficient option for hair loss regarding both male and female patterns. However, the researchers recognized that the mechanism by which LLLT convert telogen into anagen follicles remains unknown.

Avram and Rogers conducted the first independent blinded study of LLLT and hair growth with seven volunteers and found that on average, there was a decrease in the number of vellus hairs, an increase in the number of terminal hairs, and an increase in shaft diameter. Nevertheless, these data were not considered statistically significant (Avram et al. 2007).

The first study involving a fractional Erbium glass fiber 1550 nm (Mosaic© Lutronic Co., Ltd., Seoul, South Korea) published is a non-clinic essay carried out in 2011. The investigators evaluated the effect of the device on hair cycle in a form of alopecia in rats. The radiation was applied over the shaved skin of C3H/HeN rats using various power and density configurations in different radiation intervals. Stimulation effects on hair were observed due to the level of power employed, density, and radiation interval. Histologic findings reveal the conversion of hair in telogen phase into anagen phase. The conversion into anagen hair and the increase of 5a Wnt, β-catenin were regarded as signs of therapeutic response.

Later, to assess the clinical effects of that same sort of laser, a study was performed involving 20 males with AGA (Kim et al. 2011). In the study involving humans, 20 male volunteers were treated in five sessions and in 2-week intervals. It was employed with 5 mJ power with a total density of 300 spots/cm^2.

According to the investigators, fractional laser can cause thermal injury or photothermolysis for each thermal microzone (TMZ), which induces collagen regeneration and thermal shock over proteins. Both events lead to the expression of growth factors, including vascular endothelium growth factor (VEGF), which induces neoangiogenesis. Other possible mechanisms are cytokine biomodulation and growth factors such as PDGF, KGF, and IGF.

Nowadays, it is known that there is a complex net of genes involved in the control of hair growth cycle and connected to Wnt and BMP signaling pathways, especially Wnt7 gene, which cause inadequate hair growth, if inactivated. Research data have already proved that, if BMP signaling pathways are reduced and Wnt pathways are increased, a hair growth phase is activated (Kobielak et al. 2013; Kandyba and Kobielak 2013; Kandyba et al. 2013; Kobielak et al. 2003, 2007).

During the study, incremental improvements in hair density and hair growth rate were observed, which suggested that fractional Erbium glass fiber 1550 nm might induce hair growth.

In that same year (2011), the investigators evaluated fractional Erbium glass fiber 1550 nm effect on female pattern alopecia (Lee et al. 2011). Twenty-eight South Korean volunteers took part into the study. The volunteers received laser application with intervals of 15 min, following the same parameters of the study conducted with male volunteers. Phototrichograms and global photos were taken at the beginning and at the end of the treatment. Changes in density and in the hair shaft diameter were analyzed. The global photos were evaluated by three independent dermatologists using a scale of seven points. Volunteers involved also answered an efficacy self-evaluation questionnaire. All adverse events were reported during 5 months of treatment.

After 5 months of study, the results demonstrated an increase in hair density of 157 ± 28/cm^2 ($P < 0.0001$) and in shaft thickness of 75 ± 13 μm ($P < 0.001$).

According to the global photos, out of the remaining 27 volunteers, 24 (87.5%) showed an improvement in their conditions. Two volunteers (7.4%) reported moderate pruritus after laser application, which was spontaneously solved 2 h later.

In 2013, a multicenter, double-blind, randomized, controlled study was performed to evaluate the efficacy and safety of LLLT in volunteers with androgenetic alopecia against a sham device, over 24 weeks, against sham device (control).

The study involved 40 volunteers with androgenetic alopecia. One group of volunteers was exposed to a helmet-like apparatus, which produces radiation in wavelengths of 630, 650, and 660 nm, and the other group was exposed to sham device (control) during 18 min per day.

A phototrichogram and overall evaluations were carried out. After 24 weeks, the results showed a significant increase in hair density in group of volunteers exposed to the active apparatus (LLLT) against the other group (sham device). The average diameter of hair shaft also increased significantly in the volunteers submitted to the intervention compared to sham device group.

According to the investigator's evaluation, a significant clinical improvement was observed in the group of volunteers exposed to the active apparatus. No adverse event was reported. In the investigators' opinion, LLLT was considered effective and safe concerning AGA treatment (Kim et al. 2013).

LLLT in Alopecia Areata

Alopecia areata is an autoimmune disease which is characterized by rapid and complete hair loss in one or many sites in the form of patches, generally located on the scalp. Available treatments are employed with variable success. These include pulsed high doses of oral or intravenous steroids, topical high-potency steroids under occlusion, photochemotherapy, and topical immunotherapy. Efficacy of treatments in patients with alopecia totalis and alopecia universalis is poor, with long-term complete regrowth in less than 20% of patients (Tosti et al. 2006).

In 1984, Trelles and collaborators investigated He-Ne laser action in alopecia areata (Trelles et al. 1984), and, from 2002 on, a series of studies were undertaken to evaluate the role played by different forms of light/laser as an alternative therapy to the types of alopecia (particularly alopecia areata) (Shukla et al. 2010; Touma and Rohrer 2004).

In 2003, a study assessed the effects of polarized linear infrared radiation produced by a commercial device denominated Super Lizer© in volunteers with alopecia areata. Fifteen volunteers over 18 years old diagnosed with alopecia areata and with multiple patches were engaged in this trial. Results showed that, out of 15 volunteers (46.7%), 7 presented hair growth in the radiated areas around 1.6 months earlier than those not radiated. Regarding the adverse events, only one patient complained about heat sensation over the radiated area (Yamazaki et al. 2003).

The most explored laser in the treatment of alopecia areata is the XeCL excimer 308 nm, better established by a vast number of studies conducted even in children, proposing as its mechanism of action apoptotic effect over T cells (Gundogan et al. 2004; Raulin et al. 2005; Al-Mutairi 2007, 2009; Ohtsuki et al. 2010, 2013; Byun et al. 2015).

In 2006, a study evaluated the efficacy of superpulsed Ga-As, 904 nm diode laser, in the treatment of alopecia areata. For this purpose, 16 volunteers with 34 alopecia areata patches refractory to other forms of therapy were selected. In each patient, there was a remaining patch without treatment as control lesion. Four sessions were held, one per week, with pulsed infrared diode laser (904 nm), pulse rate of 40/s. Photos were taken of each patient before and after the treatment, being 11 males (68.75%) and 5 females (31.25%). Concerning the volunteers' age, there was a range between 4 and 50 years of age with an average of 26.6 +/− SD of +/−m 13.8. The disease duration varied between 12 months and 6 years with an average of 13.43 +/− SD of +/− 18.34.

Results showed that hair regrowth was observed in 32 areas of alopecia (94%), whereas only two areas of alopecia did not show any response. On the alopecic patches, considered control, hair regrowth was not verified. On 29 patches (90.6%), terminal hair could be verified. Less pigmented vellus have been observed on three patches (Waiz et al. 2006).

In responders, the effect was earlier detected: 24 volunteers(75%) a week after the first session. At the end of the study, the researchers concluded that pulsed infrared diode laser is an efficient therapy with a high success rate in volunteers with alopecia areata (patches) refractory to various modalities of treatment.

In 2009, a group of researchers from the Department of Dermatology of Chung-Ang University College of Medicine, Seoul, SK, report the case of a 35-year-old man with several large-sized alopecia areata patches on frontal region of the scalp refractory to different methods/drugs (minoxidil topical solution 5%, topical steroids, and intralesional corticosteroid injections). Non-ablative laser (fractional Erbium glass fiber 1550 nm) applications were made once a week, during 24 weeks. A pulse energy of 10–15 mJ, with a density of 300MTZ/cm^2, was used in each application. Two applications were made in each session (Yoo et al. 2009).

The treatment was well tolerated, without any side effect reported. Firstly, hair growth was observed 1 month after the treatment was started. After 3 months, lesions were covered with terminal hair, mostly pigmented, in an average of 30–40%. Six months after the therapy began, new hair grew over all lesions. No relapse was reported during a 6-month clinical follow-up.

Regarding the LLLT's mechanism of action on AA, researchers assumed that one or more factors among improved microvascular circulation,

reduced inflammation, and increased cell energy in the form of ATP, working together, could explain the clinical benefits of LLLT on AA.

In conclusion, a LLLT offers a safe and effective option as monotherapy or in combination with other conventional therapy for non-scarring alopecia, such as male and female pattern hair loss, chemotherapy-induced alopecia, and alopecia areata, with available data to date demonstrating efficacy. We must consider that, regardless of these good results, the establishment of more consistent protocols requires the conduction of randomized, double-blind, sham-device-controlled trial with an adequate number of volunteers and longer follow-up.

Authors Experience: Case Studies

Our case studies (Figs. 2, 3, and 4) involving two patients with androgenetic alopecia using Erbium glass laser 1550 nm, energy of 8 mJ, density of

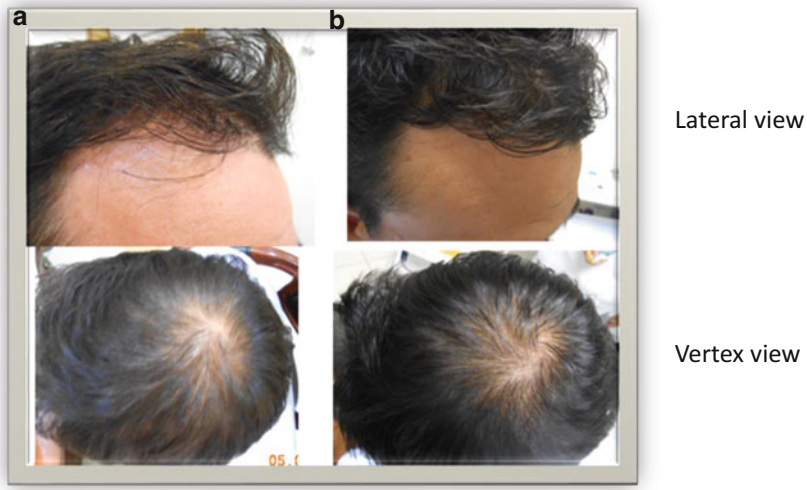
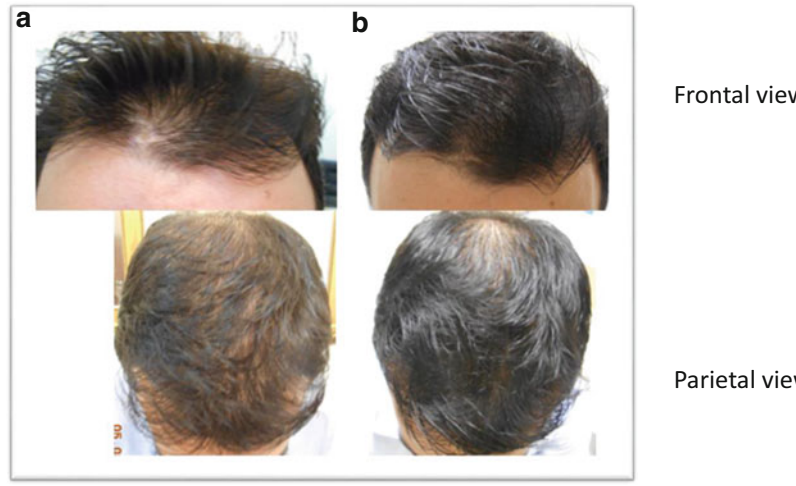


Fig. 2 Patient 1: Before (**a**) and 6 months after (**b**) 6 sessions, 1 month apart. Erbium glass laser 1550 nm; energy, 8 mJ; density, 9%

Fig. 3 Patient 2: Before (**b**) and 6 months after (**b**) 6 sessions, 1 month apart. Erbium glass laser 1550 nm; energy, 8 mJ; density, 9%



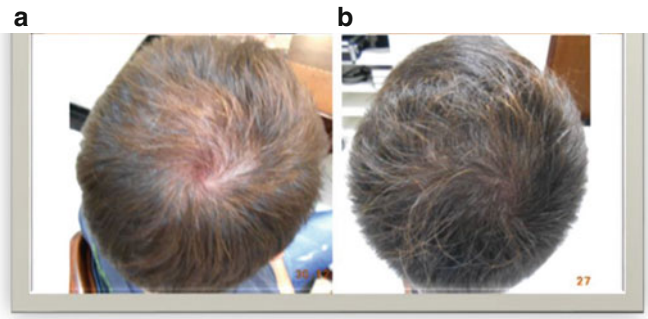


Fig. 4 Patient 3: Before (**a**) and 4 months after (**b**) 6 sessions, 1 month apart. Erbium glass laser 1550 nm; energy, 8 mJ; density, 9%

9%, and making 6 applications over the areas affected by alopecia. One-month interval between sessions.

Take Home Messages

1. LLL therapy offers a safe therapeutic option as monotherapy or in combination with other conventional therapies for non-scarring alopecia, taking into consideration the data available demonstrating efficacy up to date.
2. The interaction of laser light with tissues can lead to different results (stimulation or inhibition) depending on several factors, wavelength, dose, power, time, number of irradiations, optical properties of tissues, and type of irradiated cell, besides the physiological characteristics of the cells at the time of irradiation.
3. There has been a rapid increase in market availability of devices each with differing characteristics making both physician and patient/consumer navigation difficult.
4. Further investigation is needed to compare efficacy of LLLT devices to be able to address patient needs and expectations.

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Laser Lipolysis

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Abstract

Studies concerning laser's direct action on fat began in 1992. Two years later the first study of laser lipolysis was produced. The method was approved by the FDA in October 2006. Laser lipolysis is a minimally invasive procedure for the treatment of localized fat, improving the facial and body contour and flaccidity. It consists of the application of laser directly on the adipose tissue, based on the principle of selective photothermolysis. This method has the advantage to be less traumatic; to cause less bleeding, pain, ecchymosis, and edema; and minimizes side effects and complications. The postoperative recovery time is reduced when compared to conventional liposuction. There is induction of neocollagenesis, which leads to cutaneous retraction. Indications include the submental area, arms, abdomen, flanks, inner surface of thighs, knees, and elbows. Patients with irregularities after previous liposuction or other surgeries are also excellent candidates. For areas with more fibrous tissue, such as male breast (gynecomastia), flanks, and back, laser lipolysis maybe the only option. Recent articles described the use of laser lipolysis for the treatment of lipoma, as conventional surgery can result in disfiguring scars when treating lesions bigger than 10 cm. Other questionable indications are axillary hyperhidrosis and cellulite. There are no specific contraindications. Complications are rare, and when they occur they are not specific to the laser.

Keywords

Laser lipolysis • Fat • Localized fat • Body contour • Flaccidity • Cutaneous retraction • Cellulite • Liposuction • Neocollagenesis • Submental • Gynecomastia

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Introduction

In 1992, Apfelberg was the first to describe laser's direct action on fat. Two years later, he and collaborators produced the first study of laser lipolysis. However, its benefit was not significantly demonstrated. This equipment was not approved by the FDA, and the company Heraeus Lasersonics abandoned the technology (Apfelberg et al. 1994).

The first study to demonstrate the effect of laser on fat, as well as on the dermis, vessels, and apocrine and eccrine glands, was described between 2002 and 2003 by Bluggerman, Schavelzon, and Goldman, who introduced the concept of pulsed laser for laser lipolysis (Apfelberg et al. 1994).

In 2003, Badin founded these findings in one study titled "Laser Lipolysis: Flaccidity Under Control." The author demonstrated the histological changes after the thermal laser injury. The adipocytes' membrane was torn, vessels were coagulated, and collagen was reorganized. These histological changes were correlated with the clinical observation of reducing adiposity, ecchymosis, blood loss, and improvement of flaccidity. Badin concluded that laser lipolysis was less traumatic because of the cannula's smaller pitch and that this type of laser, Nd: YAG, produced a tissue reaction leading to cutaneous retraction (Badin et al. 2002).

In a subsequent study carried out by Goldman, 1734 patients were treated, including 313 men and 1421 women aged 15–78. In this group, less blood loss and ecchymosis, improvement of postoperative comfort, and better effectiveness of fat reduction in denser areas such as in gynecomastia, for example, were also documented (Kim and Geronemus 2006).

Table 1 Equipment available in the market

Commercial name	Wavelength (nm)	Laser type
SmartLipo (Cynosure, Westfort, MA) FDA 2006	1064/1320	Nd: YAG
ProLipo (Sciton, Palo Alto, CA) FDA 2007	1064/1319	Nd: YAG
CoolLipo (CoolTouch, Roseville, CA) FDA 2008	1320	Nd: YAG
LipoLite (Syneron, Yokneam, Israel) FDA 2008	1064	Nd: YAG
SlimLipo (Palomar, Burlington, MA) FDA 2008	924/975	Diode

In 2006, a study by Kim and Geronemus used magnetic resonance to evaluate the volume of fat reduction after Laser lipolysis. Seventeen percent of patients achieved a reduction of fat volume documented by magnetic resonance imaging, and 37% noticed an improvement in only 3 months, a quick recovery time and good cutaneous retraction (Kim and Geronemus 2006).

In this same year, the FDA approved the first laser lipolysis equipment, an Nd: YAG laser of 6 W (produced by DEKA and distributed by Cynosure, Westfort, Massachusetts). Soon after, several equipments with different wavelengths entered the market (Table 1).

In 2007, Morton et al. detailed a mathematical model that compared an equipment with a 980 nm laser diode to a 1064 nm Nd: YAG. This study suggested that regardless of the wavelength, what really drove the lipolysis and skin contraction was the heating. They have mentioned that the level of the internal temperature to achieve a contraction was from 48 °C to 50 °C (118–1222 °F) (Morton 2008).

In 2008, McBean and Katz studied an equipment which associated two wavelengths 1064 and 1320 nm, respectively, the SmartLipo®. The objectives of the study were to assess cutaneous safety and effectiveness. The effect of cutaneous retraction was documented by photographic documentation and measurement, as well as through histological studies and electron microscopy, which revealed study neocollagenesis. This was

the first study to demonstrate the clinical effects of cutaneous retraction produced by laser lipolysis, with objective measures proven by electron microscopy (Mcbean and Katz 2009).

In the same year, Palomar launched the Aspire™ platform (SlimLipo ®) in the market, a laser diode with two selective and safe wavelengths, respectively, the 924 nm for fatty cells and 975 nm, with greater selectivity for water in the connective tissue, promoting cutaneous retraction (Mcbean and Katz 2009).

Today, it became clear that laser lipolysis liquefies fat and promotes remodeling of collagen fibers, improving flaccidity. Currently, new research aims to standardize the methods that will optimize results, safety, and efficacy.

Laser lipolysis is a new technique, a minimally invasive procedure for the treatment of localized fat and laxity, improving facial and body contour. It consists of the application of laser directly on the adipose tissue, based on the principle of selective photothermolysis. This method has the advantage to be less traumatic and to cause less bleeding, reducing the postoperative recovery time when compared to conventional liposuction.

Since its approval by the FDA in October 2006, studies have corroborated for early clinic observation of the adipose tissue reduction, a rapid recovery, and flaccidity improvement.

Goldman has proposed that two properties must be considered to determine the effectiveness of laser lipolysis: wavelength and the energy employed. According to the theory of selective photothermolysis, these chromophores (fat, collagen, and blood vessels) preferentially absorb the laser energy based on the specific absorption coefficient, according to the wavelength. Many wavelengths, including 924, 968, 980, 1064, 1319, 1320, 1344, and 1440 nm, have been evaluated by their interaction with these chromophores. Many authors suggest that certain wavelengths are more effective for lipolysis (DiBernardo et al. 2009).

Parlette and Kaminer have documented that the 924 nm wavelength has a higher selectivity to absorb fat, but it is not effective to induce cutaneous retraction, improving laxity. They showed that 1064 nm wavelength has a good penetration in the tissue but low absorption by fat. However, its distribution of heating is superior with good cutaneous retraction effect. Finally, the 1320 wavelength has demonstrated great absorption by fat, but with low penetration in the tissue, so it is safe for treating more fragile skins, such as in the neck and arm areas (Parlette and Kaminer 2008).

The different wavelengths have variable absorption coefficients for fat, water, and hemoglobin. Fat contains approximately 14% of water, and collagen contains 60–70%; therefore the appropriate selection of the laser allows a preferential target of fat and/or water. When comparing light absorption by fat and by the dermis, we noticed that the highest selectivity to melt fat happens when 924 nm laser diode is used. Due to great absorption of light directly into fat, the heating effect is limited to the fibrous septum of fat and to the reticular dermis, preserving the underlying tissues, with less risks of thermal damage. Less trauma to the suction will be necessary due to great fat liquefaction (Parlette and Kaminer 2008).

There are multiple laser systems for lipolysis. Current technologies use small optical fibers 1–2 mm thick to transmit the laser directly into the subcutaneous tissue; the 924 nm has the highest affinity for fat and less heating of the collagen. Therefore, it promotes larger liquefaction of fat and less tissue retraction (McBean and Katz 2011).

Rupture and liquefaction of the adipose tissue, coagulation of small blood and lymphatic vessels, and collagenesis induction with tissue remodeling have been reported after laser lipolysis treatment. Other mechanisms of action such as photoacoustics and photomechanical effect have been purported (DiBernardo and Reyes 2009).

Indications and Contraindications

The primary indication of laser lipolysis is the treatment of localized fat through the liquefaction of the adipose tissue. Any location where there is localized fat and moderate flaccidity, including

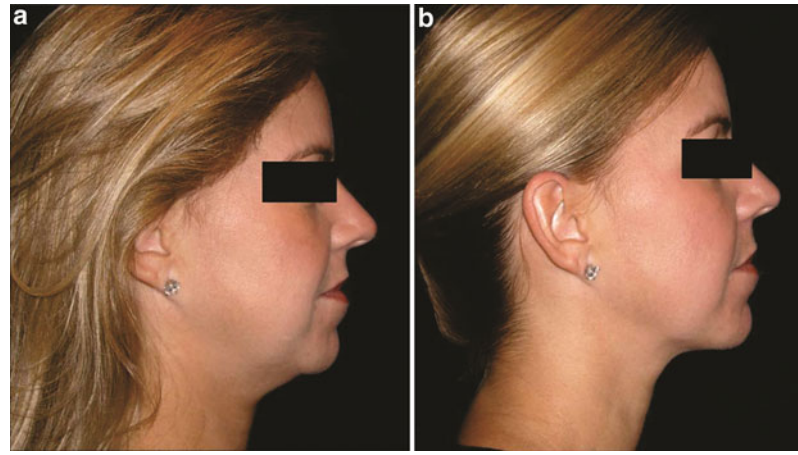

Fig. 1 (**a**, **b**) Before and after treatment with laser lipolysis

the submental, arms, abdomen, flanks, the inner surface of thighs, knees, and elbows, has an indication to this procedure because they simultaneously promote cutaneous retraction through neocollagenesis. It is very well indicated for face contour (Fig. 1a, b) (McBean and Katz 2011).

Patients with irregularities after liposuction and other surgeries are also excellent candidates. For areas with more fibrous tissue such as male breast (gynecomastia), flanks, and back, laser lipolysis may be the only option. The small size of the cannula facilitates the treatment in these fibrous areas without the additional trauma (McBean and Katz 2011; Palm and Goldman 2009).

Recent articles described the use of laser lipolysis for the treatment of lipoma, considering that conventional surgeries for lesions bigger than 10 cm can result in disfiguring scars. Laser lipolysis alone or associated with aspiration by suction facilitates the removal of these tumors with a better aesthetic result (Stebbins et al. 2011).

Other indications described are axillary hyperhidrosis and cellulite, still with questionable results. It can also be used in association with other technologies, such as fractional CO2, in the submental to increase neocollagenesis and cutaneous retraction internally and externally (Parlette and Kaminer 2008).

Careful patient selection is crucial before the procedure. The ideal candidate for laser lipolysis is a healthy patient with little localized fat. It is important to tell the patient that this procedure does not replace a healthy diet and physical exercises (McBean and Katz 2011).

There are no specific contraindications. Patients over 60 years old with cardiovascular disorders, hypertension, or diabetes should be carefully evaluated. Additionally, patients with liver disease, previous chemotherapy, and in use of antiretroviral medicine have risk of lidocaine toxicity (McBean and Katz 2011).

Preoperative Considerations

During the consultation, complete anamneses should be performed, and the real objectives regarding the procedure must be identified (McBean and Katz 2011).

Drug allergies must be investigated. Patients should be informed about drugs that should be avoided before the procedure, such as warfarin, clopidogrel bisulfate, aspirin, or other nonsteroidal anti-inflammatories, to avoid bleeding. Drugs that inhibit the cytochrome P450 liver enzymes, such as selective inhibitors of serotonin and antifungal azole agents, decrease the metabolism of lidocaine and should also be avoided (McBean and Katz 2011).

The laboratorial tests should be done to hold off some disorders in the liver, kidney, and blood. Some infections, such as HIV and hepatitis, and pregnancy are also contraindication (McBean and Katz 2011).

During the physical examination, the patient should be standing and without clothes. With the aim of obtaining better body contour, the patient may benefit from the treatment of adjacent areas, for example, to treat the abdomen and flanks, even when their initial complaint is limited to the abdomen (McBean and Katz 2011).

To assess the tonus and the elasticity of the skin on the area to be treated, the physician should perform the clamp test, in which the skin is gently pulled between the forefinger and the thumb and subsequently released. If the skin instantly returns, it indicates good elasticity. If the skin returns slowly, it indicates poor elasticity. Patients with excess flaccidity are not good candidates (McBean and Katz 2011).

Previous photographic documentation is important and mandatory to identify all irregularities, ripples, or previous scars and objectively evaluate the postoperative results (McBean and Katz 2011).

A preinformed consent form with guidance about the procedure and about postoperative cares should be signed by the patient before the procedure (Morton 2008).

Technique

Laser lipolysis can be performed under local anesthesia isolated or in association with intravenous sedation, epidural block, or general anesthesia. The type of anesthesia chosen depends on patient health and preference and should be decided with the doctor. The area to be treated must be marked with the patient in the orthostatic position. Once marked, the patient is taken to the sterile surgical environment (Palm and Goldman 2009).

Local anesthesia is performed through subcutaneous infiltration of tumescent solution of heated Klein or other similar solutions combining lidocaine and epinephrine. The total volume of the SC infiltration depends on the surgeon's preference and also on the size of the area to be treated. The solution is heated to minimize any discomfort associated with the difference of temperature between tissue and fluid, in addition to maintain the basal body temperature. The procedure should only be started after 20–30 min to allow a suitable fluid diffusion and adequate vasoconstriction. Besides promoting analgesia, the tumescent anesthesia also increases the selectivity and effectiveness of the laser (Klein 1993).

The use of suitable goggles in the operating theater for everyone in the team, including the patient, is a matter of safety (Palm and Goldman 2009).

The application of laser on the adipose tissue is performed through an 1.5 mm thick optical fiber directly on the tissue or inserted within a cannula 2–3 mm thick. The optical fiber leads not only the therapy light (924, 975, 1064, 1320 nm) but also a guiding light of neon-helium (634 nm), which allows the precise location of the tip of the fiber, so the doctor is constantly aware of the area of the laser operation (Palm and Goldman 2009).

The application technique happens through quick, constant, and back and forth movements, as if moving a fan, to avoid overheating of the treated area, preventing burns and consequently scars. The doctor will notice a decrease in tissue resistance to the cannula movement, indicating lipolysis. This parameter is used as a treatment endpoint. An infrared thermometer must be used throughout the entire treatment to measure the external temperature, taking care not to exceed 38–40 C (Palm and Goldman 2009).

The resulting content of lipolysis is an oil containing broken adipocytes and cellular debris, mixed with the tumescent solution. Aspiration of this content is optional and is the doctor's choice. The aspiration can be done through an external cannula 2–3 mm thick with negative pressure of 0.3–0.5 atm. Very small areas such as the submental, with small volumes, recover well without aspiration (Morton 2008).

Regardless of aspiration, a manual drainage must be performed while the patient is still in the operating theater, and the cannula's orifice must remain open to promote gradual output of the remaining content, which can occur up to 48 h after procedure (Palm and Goldman 2009; Stebbins et al. 2011).

Postoperative Care

It is recommended that patient uses compressive meshes placed at the end of the procedure and maintained for a period of 2–4 weeks. The return to routine activities occurs after the first 24 h, except for intense physical activities, which can be taken up within 15 days. The manual lymphatic drainage is initiated after 48 h, performed two to three times a week for 15 days (Palm and Goldman 2009).

Results

Although the initial clinical results can be similar to those obtained in a traditional liposuction, the histological findings show some differences such as rapid recovery due to blood vessel coagulation with peri- and post-procedure bleeding reduction. In addition it promotes neocollagenesis and reorganization of collagen in the reticular dermis, explaining the cutaneous retraction. This laser capacity of producing retraction is very important for the treatment of patients with some degree of flaccidity, who may not have indication of a traditional liposuction (DiBernardo and Reyes 2009; Palm and Goldman 2009; Morton et al. 2007; Goldman et al. 2011; Mann et al. 2008).

Complications

Complications are rare, and when they occur, they are not specific to the laser. Excessive energy or superficialization of the laser cannula can promote burn with unaesthetic scar. Adverse effects such as ecchymosis, edema, asymmetries, and temporary paresthesia are also reported and are similar to traditional liposuction (Katz and McBean 2008).

Conclusion

Laser lipolysis is a minimally invasive safe and effective procedure. It is a useful tool for body and facial contouring treatment. Through this technique, pain, ecchymosis, and edema are reduced, minimizing complications. In addition it promotes cutaneous retraction, avoiding laxity after lipolysis, and has a short downtime.

Take Home Messages

- Laser lipolysis is a minimally invasive safe and effective procedure.
- Any location where there is localized fat and moderate flaccidity, including the submental, arms, abdomen, flanks, the inner surface of thighs, knees, and elbows, has an indication to this.
- Induction of neocollagenesis and short downtime are the two major advantages.
- Complications are rare.

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Laser Treatment of Vascular Lesions

Andréia S. Fogaça

Abstract

Laser surgery has become the treatment of choice for many vascular lesions. The most common indications are vascular anomalies including port-wine stain and hemangiomas, as well as facial erythema and telangiectasias. In this chapter, we are going to approach different types of lasers and its indications, results, and side effects.

Keywords

Vascular lesions • Oxyhemoglobin • Deoxyhemoglobin • Methemoglobin • Pulsed dye laser • KTP laser • Near-infrared radiation

Contents

Introduction

One of the first indications of lasers in dermatology was the removal of vascular lesions, using the theory of selective photothermolysis, introduced by Anderson and Parrish in 1983 (Anderson and Parrish 1983). Three components are necessary for selective photothermolysis: (1) a laser wavelength with preferential absorption of the target

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chromophore, (2) appropriate pulse duration matched to the target size, and (3) a fluence that both treats the target and minimizes nonspecific thermal-related injury. The classic target chromophore for vascular lesions has been oxyhemoglobin, which has the greatest absorption peaks at 418, 542, and 577 nm. The laser light is absorbed by oxyhemoglobin and converted to heat, which is transferred to the vessel wall causing coagulation and vessel closure. Other hemoglobin species have more recently been recognized as appropriate targets, depending on the vascular lesion. They are deoxyhemoglobin and methemoglobin. In the case of deoxyhemoglobin, the greatest absorption peaks is 755 nm and has been used for refractory or hypertrophic PWS (port-wine stain), a venocapillary malformation.

The first lasers to treat vascular lesions were CO2 and argon lasers. The argon laser at 488 and 515 nm enjoyed a high absorption coefficient for hemoglobin (HgB), but the pulse durations (continuous wave) were longer than the thermal relaxation time of the targeted blood vessels, and in the absence of surface/epidermal cooling, the high absorption by epidermal melanin resulted in a high risk of hypopigmentation and scaring. In 1968, Dr. Leon Goldman e col. demonstrated the histopathology of the laser treatment of port-wine lesions (Solomon et al. 1968). Although Goldman accurately predicted that vascular lesions could be selectively heated, the pulsed dye laser (PDL) was the first laser, in 1986, to show that this selectivity was effective. Initially it was developed at 577 nm to target the yellow absorption peak of oxyhemoglobin. Currently, PDL lasers shifted to 585 nm and 595 nm, allowing for a depth penetration of approximately 1.16 nm.

In general, vascular laser technologies can be divided into three spectral ranges (Graphic 1):

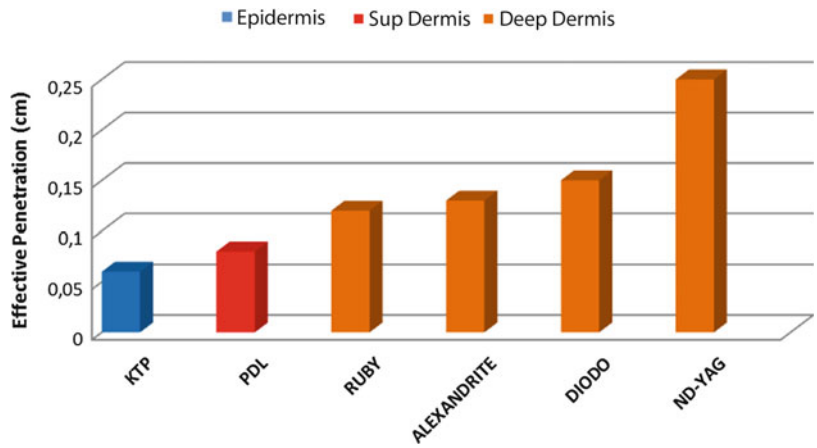
1. Green-yellow (GY) light sources, such as PDL (pulsed dye laser/585,595 nm) and KTP (potassium titanyl phosphate laser 532 nm)
2. The diode laser (800 nm) and alexandrite (755 nm) lasers
3. Near-infrared radiation (NIR), lasers with a smaller ratio of melanin to HgB absorption and deeper penetration (940, 980, and 1064 nm)

In summary, smaller lesions in lighter skin are treated with GY light sources, and larger lesions in darker skin are treated with NIR lasers.

Intense pulsed light (IPL) devices emit polychromatic noncoherent broadband light from 420 to 1400 nm with varying pulse durations, can cover all of the HgB peaks, and cannot be "framed" into one of the three aforementioned categories.

There are alternatives to treat vascular lesions, such as ablatives lasers (CO2) or photodynamic therapy (PDT).

The microanatomy of the vascular lesion should always be considered.



Graphic 1 Depth of penetration of different lasers

Laser Parameters

Wavelength

In general, the first parameter to be considered is wavelength, and it should be elected to achieve three goals: (1) to absorb the vascular target (O2 saturation of cutaneous blood ranges from 50% to 80%), the peaks of oxy-HgB absorption are 418, 542, and 577 nm with a smaller peak at 940 nm (Anderson and Parrish 1981a); (2) to avoid melanin target in darker-skinned patients, it is possible to use Nd:YAG laser 1064 nm (melanin absorption is much less than GY light); (3) to achieve desirable depth of penetration.

The lasers used to treat vascular lesions have wavelengths that are well absorbed by hemoglobin. However, we should be aware of concurrent absorption by melanin, which is maximal at short wavelengths (Anderson and Parrish 1981b). This may result in unwanted clinical effects such as hypopigmentation, especially when treating persons with dark skin types. As melanin in the normally pigmented skin is situated in the epidermis, overheating of the melanosomes may even induce epidermal necrosis, eliciting clinical blistering or at the long term even scaring.

In addition, penetration depth is also mainly determined by wavelength. As a rule, longer wavelengths have less scattering and a larger penetration depth. Theoretically, longer wavelengths may, therefore, be preferred for deeper and larger vascular lesions such as reticular veins, whereas shorter wavelengths may be suited for superficial vascular lesions such as telangiectasias.

Pulse Duration

The ideal pulse duration should be equal to or only slightly larger than the thermal relaxation time (time required for the heated tissue to lose about half of its heat). The very short pulses confine heat not only to the vessels but also to the erythrocytes. Accordingly, thermal confinement is excessive, and localized vessel rupture and intravascular thrombosis are observed in the treated area. With longer pulses (6–40 ms), intravascular thrombosis and spot-sized purpura are mitigated as gentle heating resulted in vessel wall stenosis and thrombosis of the larger vessels but not the microvessels that produce widespread purpura (Table 1).

Table 1 Thermal relaxation time of vessels with different diameters

Diameters (μm)	Tr (ms)
10	0.048
20	0.19
50	1.2
100	4.8
200	19.0
300	42.6

Spot Size

Larger spots increase the number of photons that penetrates deeper into the dermis, compared to smaller spots. However, with the same fluence, a larger spot will produce more epidermal damage and pain. The rule is larger spots should be accompanied by smaller fluences than their small spots counterparts.

Surface Cooling

Epidermal cooling was introduced in the 1990s to protect the epidermis, minimizing pigmentary changes and epidermal necrosis. In the treatment of all vascular lesions, cooling of the skin surface is crucial to minimize epidermal damage, to allow high radiant exposure, and to minimize discomfort associated with treatment (Nelson et al. 1995).

In resume, there are three types of surface cooling:

1. Cryogen spray (nitrogen or tetrafluoroethane), a significant reduction in pain score can be achieved when adequate dynamic cooling is used (on the order of tens of milliseconds). Disadvantages of the spray are the possibility of pigmentation changes (excessive cooling) and the need for purchasing cryogen canisters.
2. Contact cooling (sapphire windows or copper plate) that is placed on the skin during laser

treatment. The main caution is to avoid high compression of the vascular lesion. Risks of contact cooling are fogging and poor contact.

3. Refrigerated air cooling (cooling devices) works well but requires a second hand to hold near the surface or an accessory that allows one-hand operation. Air cooling has the advantage that the device can be used for different procedures and for large areas of the skin. However, caution is mandatory especially in patients with darker skin types. Post-inflammatory hyperpigmentation due to air cooling has been widely reported (Manuskiatti et al. 2007).

Physiological Influences

Superficial Vessels

Superficial vessels located over the deep vessels work as a shield reducing the efficacy of the treatment. Therefore, these vessels should be firstly treated for better results.

Skin Temperature, Vascular Dilatation, and Blood Flow

Low temperature of the skin on the area to be treated requires a slightly higher fluency to reach good effect (purpuric response). It is also described that high temperature with increased blood flow in the target can improve the treatment effect. On the other hand, vascular dilatation, suction, pressure, or erythema induced by UVB seems to not have any influence on clinical response (Paul et al. 1983; Aguilar et al. 2012).

Vascular Lasers and Light Sources

Pulsed Dye Laser (PDL: 577, 585, and 595 nm)

Pulsed dye lasers use a rhodamine dye dissolved in a solvent and pumped by a flashlamp. The PDL was the initial "test" for selective photothermolysis (SPT). The first PDLs were slow (0.5 Hz or less), equipped with only small diameter spot size (3–5 mm), lacked cooling, and used a 577 nm wavelength near one of the peaks of oxy-HgB absorption. Over the years from 1981 to 1990, the wavelength was changed to 585 nm. Later cooling devices were added and the laser wavelength was again increased to 595 nm to further enhance epidermal/vascular penetration.

Pulsed dye lasers have been proven safe and effective in the treatment of a variety of vascular lesions, including port-wine stains (Faurschou et al. 2011). Dierickx et al. identified the ideal pulse duration for PWS treatment to be 1–10 ms. In practice, treatment often begins at 1.5 ms, though this may be adjusted down to 0.45 ms and up to 6 ms. Parameters to consider include 7–10 mm spot size, pulse duration of 0.45–6 ms, and fluence of 5.5–9.5 J/cm^2 with appropriate epidermal cooling. Lower energies are used for larger spot sizes, with shorter pulse durations. Longer pulse durations are advisable in darker skin types. Treatment should start at lower energies, and this can be increased if treatment is tolerated well. The fluence is adjusted to achieve the desired end point. For the PDL, the desired end point is immediate purpura. Parameters vary by device.

Proper eye protection is essential and surgical lubricant may be placed on eyebrows and eyelashes to avoid singeing. Although hair often regrows, permanent hair loss can occur with PDL treatment, given the close proximity of the follicles to the surface.

Potassium Titanyl Phosphate Laser (KTP: 532 nm)

The lasers KTP are Nd:YAG with frequency doubled to 532 nm. This wavelength (532 nm) has a high absorption to oxy-HgB and melanin, therefore should be avoided in darker skin types because of the high risk of hypopigmentation (Foumier et al. 2002). The KTP laser penetration is approximately 1 mm, and it is more appropriately used to treat telangiectasias. The KTP laser may be used to treat individual vessels, with the advantage of no purpura.

There are many devices with this wavelength, all equipped with sapphire contact cooling.

Alexandrite Laser (755 nm)

The alexandrite is long-pulsed near-infrared laser. It was initially used for laser hair removal. There is strong absorption for deoxy-HgB, and overall blood absorption of 755 nm is 2× that of the 1064 nm Nd-YAG laser. However, melanin is highly absorbed by 755 nm; for this reason, it is better indicated in lighter skin types and darker vessels. There are many alexandrite lasers with long-pulsed capability. Cryogen spray, contact cooling, and refrigerated air are integrated into these devices. The alexandrite laser is typically used for PDL-resistant lesions, though it may be implemented as a first-line treatment for hypertrophic violaceous lesions in adults. The end point is a subtle gray-blue discoloration followed by deeper purpura. Care must be taken not to overlap pulses, as scarring can occur.

Diode Laser (800–983 nm)

Multiple diode lasers are now available, and different systems can emit infrared light at a variety of wavelengths, including 800, 810, 940, and 983 nm. Above 900 nm, absorption by melanin is lower than absorption by oxyhemoglobin. This makes diode lasers a safer treatment option for patients with darker skin types than the alexandrite laser. Like the alexandrite laser, 810 nm is better indicated for deeper vascular lesions in relatively fair-skinned patients (Wall et al. 2007).

Nd:YAG Laser (1064 nm)

The Nd:YAG laser has relatively poor HgB absorption, therefore this device should be used at higher fluences. These higher fluences necessitate epidermal cooling to achieve epidermal protection. Absorption by melanin at this wavelength is lower than for any other laser type used for vascular procedures. Nd:YAG laser treatment is supposed to be especially effective and safe in darker skin types. At 1,064 nm, penetration depth is at its peak at more than 4 mm. This makes the Nd:YAG laser a suitable treatment modality for deeply located veins (Meesters et al. 2013a). Although depth of penetration can be increased, there is a narrow therapeutic window with these devices, and caution is advised owing to the risk of scarring. It is recommended that only experienced laser surgeons use these devices.

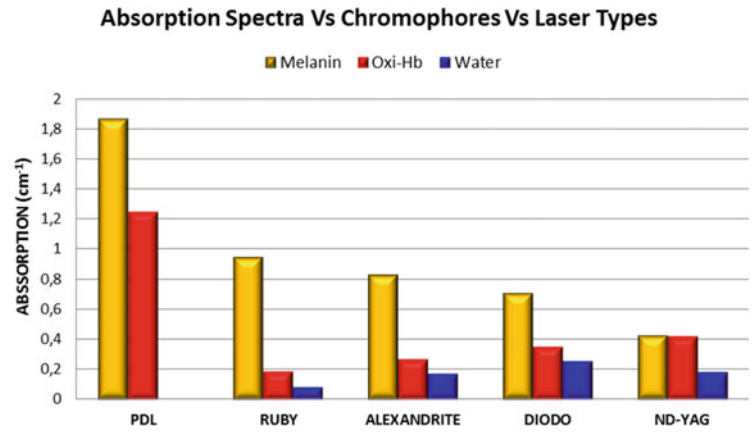
Intense Pulsed Light (IPL: 500–1200 nm)

IPLs rely on xenon flashlamp that emits high-intensity, noncoherent, and polychromatic broad-spectrum light (500–1200 nm), with varying pulse durations. By appropriate filtering, one can customize the spectrum for specific disorders. For most vascular applications, shorter wavelength ranges are applied. IPL devices are commonly used with the 550 and 570 nm filters to deliver primarily yellow and red light, with a minor component of near-infrared light. The use of IPL for vascular lesions have been increased because improvement in power supplies, in cooling, and in filtering is now available, and IPL devices are safer and more efficient (Ross 2006; Goldman et al. 2005; Goldman and Eckhouse 1996) (Graphic 2).

Vascular Lesions

Facial Telangiectasia and Spider Telangiectasia

Telangiectasias are small superficial vessels 0.1–1.5 mm in diameter that are commonly associated with sun damage, aging, and/or genetics (Goldman and Bennett 1987). Spider telangiectasia represents telangiectasia with a central feeding arteriole. Both can be treated with PDL, KTP, and IPL. Near-infrared lasers, specifically diode and Nd:YAG, have been used to treat deeper- or larger-caliber vessels (Fig. 1a–c). The laser treatment is efficient and is the gold standard to treat these lesions. The KTP laser produce better results



Graphic 2 Absorption spectra of chromophores (melanin, Oxi-Hb and water) Vs LASER Types

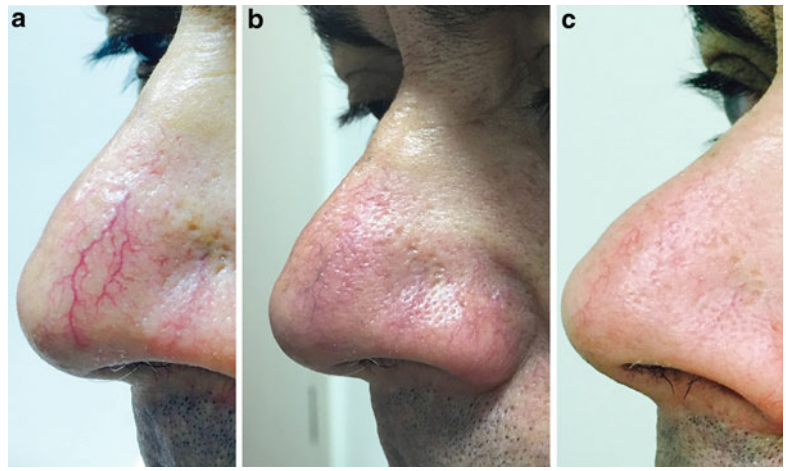


Fig. 1 (**a**) Telangiectasia before treatment, (**b**) Telangiectasia immediatly after treatment with Nd:YAG (Xeo Cutera) (100 J/cm^2; 3 mm; 30 ms), (**c**) Telangiectasia after 4 weeks-treatment with Nd: YAG (Xeo Cutera) (100 J/cm^2; 3 mm; 30 ms)

Table 2 Incidence rate (%) of Infantile Hemangiomas based on the depth of tissue involvement

Infantile hemangiomas	Incidence
Superficial hemangiomas	50%
Deep hemangiomas	15%
Combined hemangiomas	35%

than PDL laser when used to treat individual vessels, with the advantage of no purpura. There is relatively stronger absorption of hemoglobin at 532 nm, and care must be taken in patients with darker skin. Rule of thumb: for discrete, smaller (0.1–0.6 mm) telangiectasias, PDL, KTP laser, or IPL can be applied; for larger vessels (1 mm or more), Nd:YAG laser or Alexandrite laser is preferred, but care must be taken to apply the smallest fluence and smallest spot sufficient for vessel closure. The end point for treating vessels is vessel clearance, a transient blue coagulum, or purpura (Table 2).

Vessels around the nasal ala have more risk of scarring; therefore in this area, cooling is essential and overlap pulses should be avoided. We use epidermal cooling devices before and after shooting. The advantages of IPL are the relatively large spots sizes, which can minimize the polka dot effect common to PDL and KTP lasers.

Rosacea

Rosacea is a cutaneous vascular disorder associated with follicular inflammation. Patients with rosacea often have associated background facial

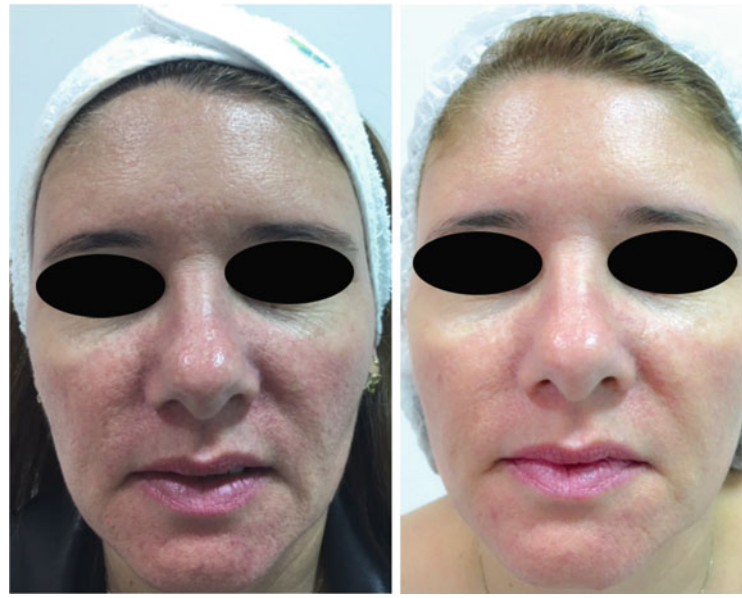


Fig. 2 Rosacea before and after treatment with Limelight (IPL) – 4 sessions/program A (19J, 20J, 21J, 21J)

erythema. Lasers and IPL are the first choice treatment for telangiectasias and facial erythema (Fig. 2). A comprehensive review of the literature finds that of the 18 histologic studies on rosacea, 14 showed an increase in *Demodex* mites (Schimidt and Gans 2004). It is hypothesized that these mites may play a role in the inflammation of rosacea. Studies have demonstrated thermal destruction of these mites after IPL therapy, which may contribute to the therapeutic effects of IPL (Prieto et al. 2002). Usually two to three sessions demonstrated good results; a certain percentage of patients (20%) do not respond to the IPL and need to be treated with PDL. PDL provides like IPL effective and relatively risk-free results.

In our experience, two treatments per year is the best method to control rosacea. Aminolevulinic acid-photodynamic therapy (ALA-PDT) or methyl aminolevulinate-photodynamic therapy (MAL-PDT) has also been reported to be resistant to rosacea (Baglieri and Scuderi 2011).

Poikiloderma of Civatte

Poikiloderma of Civatte presents in chronically sun-exposed areas, most commonly on the neck, chest, and lateral cheeks, with red-brown discoloration and associated telangiectasias. In our experience, the best results are achieved with IPL. Multiple sessions are necessary, and some cases are resistant to treatment. Several studies demonstrated that patients presenting typical changes of poikiloderma on the neck were treated with IPL at various settings every 4 weeks until desired improvement occurred. A 50–75% improvement in the extent of telangiectasia and hyperpigmentation comprising poikiloderma was observed in an average of 2.8 treatments. Incidence of hypopigmentation was 5%. Approximately 75% improvement occurs after one treatment. Side effects include transitory erythema from 24 to 72 h. Purpura occurs only 10% of the time and resolution occurs within 3–5 days (Weiss et al. 2000; Goldman and Weiss 2001). We advise our patients that "footprints" can be seen, it represents the shape of the contact crystal, and it is a normal transitory response. PDL has also been implemented to treat the vascular component of poikiloderma of Civatte with good results. Larger spot sizes and low fluences are advised for PDL to limit potential side effects like hypopigmentation or "polka dot". Fractional lasers have been studied to treat poikiloderma and showed to reduce the redness and hyperpigmentation (Behroozan et al. 2006; Tierney and Hanke 2009).

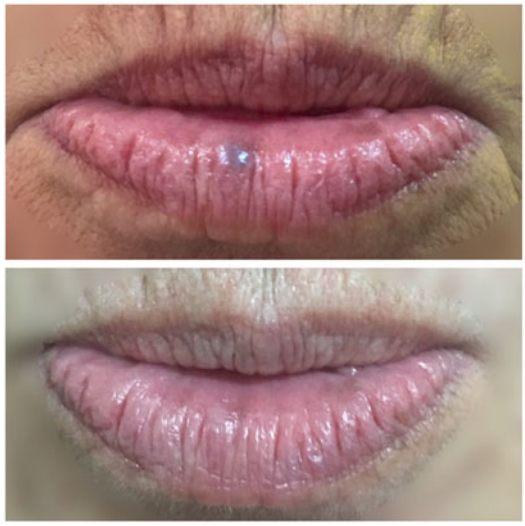


Fig. 3 Venous Lakes before and after treatment with Nd:YAG (Xeo Cutera), (90 J/cm^2; 5 mm; 30 ms)

Venous Lakes

Venous lakes are red-blue nodules, usually seen as a single lesion, typically occur on the lip, and can be treated successfully by PDL, KTP, or Nd:YAG lasers and/or IPLs. For superficial lesions, KTP and PDL are helpful. For deeper lesions diode, alexandrite, and Nd:YAG lasers are more effective. Often one treatment session will reduce the lesion by 80% in volume, and occasionally the lesions will disappear after one treatment (Fig. 3). Surface cooling is necessary to avoid epidermal injury. Any device with contact cooling should be held against the skin surface with only gentle pressure to avoid vessel collapse.

Infantile Hemangiomas

Infantile hemangiomas constitute the most common vascular tumors of early infancy. The estimated incidence of IHs ranges from 1% to 2.6% in healthy infants in the immediate newborn period to about 4–10% of infants by 1 year of age. A female predominance has been described ranging from 2:1 to 9:1 (Esterly 1996). Histopathologically, these lesions are composed of benign proliferations of plump endothelial cells with a unique vascular phenotype. Glutaminase transferase 1 staining of these lesions is positive and demonstrates small, scanty capillaries, a feature that persists throughout the natural progression of IH and can help confirm the diagnosis (North et al. 2000). Studies of the natural history of IHs reveal that complete resolution occurs in 50% of children by age 5 years and 70% by age 7 years, with continued improvement in the remaining children until 10–12 years of age (Bivings 1954; Garzon and Frieden 2000). IHs tend to be classified based on the depth of tissue involvement (Table 2) **(**Chiller et al. 2002**)**. Many studies demonstrated that PDL lasers are more effective and safe than KTP lasers and Nd:YAG (Leonard-Bee et al. n.d.; Raulin and Greve 2001). According to our experience, the best results are achieved with the following parameter: fluence 5–9 J/cm^2, spot size 7–10 mm, and pulse duration 0.45–1.5 ms. Alexandrite laser or Nd:YAG can be used to complement the results in the treatment of deeper lesions. Ablative fractional lasers are also being explored for their role in treating fibro-fatty residual from involuted hemangiomas and scars secondary to previous surgical excision. The alternatives to treat the IHs are imiquimod 5% cream or topical timolol maleate 0.5% gel (Jiang et al. 2011; Pope and Chakkittakandiyil 2010) (Fig. 4).

Port-Wine Stains Birthmarks

Port-wine stains are congenital, though in rare case they may be acquired. PWS are found in approximately 0.3% of newborns. They tend to occur on the head and neck, although they may appear anywhere on the body. PWS persist throughout life and many thicken with time. Early treatment may improve the responsiveness, decrease the number of treatments, and reduce the likelihood of permanent adverse sequelae (Reyes and Geronemous 1990; Chapas et al. 2007; Chapas and Geronemus 2005). PDL remains the gold standard of treatment for most PWS, although newer-generation IPL (narrow IPL) and KTP lasers have evolved as reasonable options. Anesthesia is an important concern when performing laser surgery in the pediatric

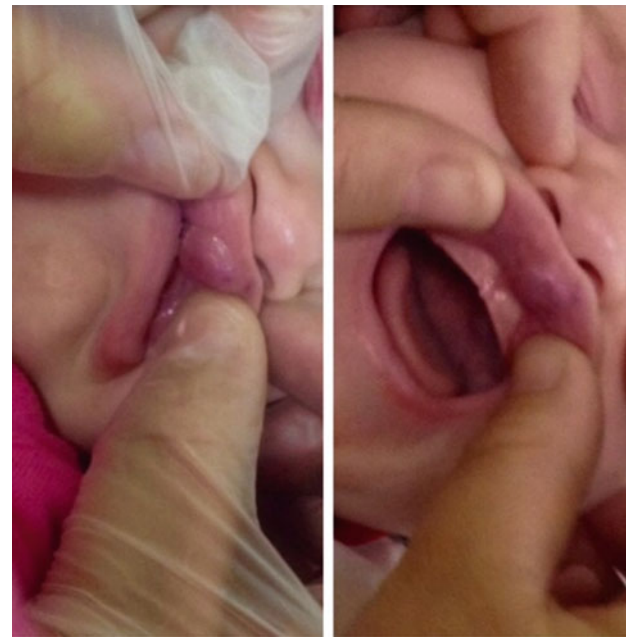


Fig. 4 Infantile Hemangioma before and after treatment (Timolol maleate 0,5 % gel; 2 times a day; 7 days)

population. While older children may tolerate the laser procedure using topical anesthetics only, infants and young children may require general anesthesia. Cooling the skin is crucial to minimize damage in surrounding tissue and to reduce the risk of postoperative complications such as swelling, scarring, and post-inflammatory pigmentary changes (specially in darker-skinned patients).

The PDL remains the most studied device in PWS treatment. Over the years, different parameters have been used to treat PWS, with significantly good results. The fluence is adjusted to achieve the desired end point. For PDL, the desired end point is immediate purpura. A confluent gray color signifies that the fluence is too high. The most commonly applied pulse duration is 1.5 ms. However, for lighter PWS, 0.45 ms has been advocated. Treatment intervals are normally about 3–6 weeks apart. A recent study showed that more frequent treatments might be preferable (Minkis et al. 2009; Chapas and Geronemus 2009). In general, improvement and clearance were gradual and require five to ten treatments.

The alexandrite laser is typically used for PDL-resistant lesions, though it may be implemented as a first-line treatment for hypertrophic violaceous lesions in adults. Care must be taken not to overlap pulses as scarring can occur. Note that the range of appropriate fluences for alexandrite laser use is quite broad. Nd:YAG laser and IPL can also be used for PWS. Photodynamic therapy (PDT) has been utilized successfully to treat PWS, primarily in China. The use of systemically administered hematoporphyrin photosensitizers results in prolonged photosensitivity (weeks), which limits its use. Alternative photosensitizers, such as benzoporphyrin derivative monoacid ring A and mono-L-aspartyl chlorin e6 (Npe6), have shorter periods of photosensitivity and maybe a good option (Eppley and Sadove 1994).

Laser treatment according to the vascular lesions is summarized in Table 3 part 1 and 2.

Pretreatment

- Clean the skin gently.
- Topical anesthesia should be avoided (blanching of the skin caused by anesthesia can decrease the results of the treatment). In some cases, it can be necessary taking into account the patient's age, extent of lesions, and preference.

Table 3 Correlation between vascular lesions and laser treatments

Diagnostic	Clinical characteristics	Laser	Parameters	End point	Interval of treatment	Tratment expectations	Comments
Facial telangiectasia	0.1–1 mm diameter; Red-purple; Macules or linear papules	KTP	7–16 J/cm^2, 3–7 mm, 10–30 ms	Vessel blanching or closure	4–6 weeks	1–2 treatments are indicated; vessels around nasal ala are more resistant and cannot disappear; new telangiectasias can appear	Hereditary hemorrhagic telangiectasias, lupus erythematosus, systemic sclerosis (CREST syndrome), rosacea, hyperstrogenic state, basal cell carcinoma
		PDL	5–8 J/cm^2, 10–12 mm, 0.45–6 ms				
		IPL	24–40 J/cm^2, 10–30 ms (550–570 nm)				
		Nd:YAG	90–115 J/cm^2, 3–5 mm, 20–30 ms				
Spider telangiectasia	Red-purple papules	PDL	5–8 J/cm^2, 7–10 mm, 1–5 ms	Vessel blanching or closure	4–6 weeks	1–2 treatments are indicated	Hyperestrogenic state, pregnancy
		Nd-YAG	90–100 J/cm^2, 3–5 mm, 20–30 ms				
Rosacea	Facial erythema; telangiectasias	IPL	24–45 J/cm^2, 10–20 ms (550–570 nm)	Homogeneous erythema	4 weeks	After 3–6 treatments, a clearance of 50–80% is usually achieved. Re-treatment once or twice a year	Hyperestrogenic state, tabagism, dietary habits, sun exposure, stress
		Nd-YAG (Genesis)	13–15 J/cm^2, 6,000–10,000 shots				
Venous lake	2–10 mm diameter; Blue-purple papules	KTP	7 J/cm^2, 4 mm, 14 ms	Vessel blanching or purpura	4–6 weeks	1–2 treatments are indicated	Associated to photo damage
		Nd-YAG	90–110 J/cm^2, 5–7 mm, 20–30 ms				
		Nd-YAG	100–150 J/cm^2, 3–7 mm, 20–30 ms				

Poikiloderma of Civatte	Telangiectasias; Hyperpigmentation; Hypopigmentation; Skin atrophy	IPL	17–24 J/cm^2, 20–30 ms (550–570 nm)	Homogeneous erythema	4–6 weeks	After 3–6 treatments, a clearance of 50–80% is usually achieved	Associated to photo damage
		PDL	5–7 J/cm^2, 7–10 mm, 0.45–2 ms	Purpura			
Port-Wine Stain	Pink-red-purple-blue macules or papules; Present at birth	PDL	6–8 J/cm^2, 10 mm, 1.5 ms	Purpura	4–12 weeks	Gradual lesion discoloration (10% per treatment)	Glaucoma, Sturge Weber syndrome, Klippel-Trenaunay, GLUT 1 negative
Infantile hemangioma	Pink-red macules; First few weeks of life	PDL	6–8 J/cm^2,7–10 mm, 0.45–1.5 ms	Purpura	2–8 weeks	Slow growth rate	Care must be taken when lesion is near ocular globe GLUT 1 positive
Pyogenic granuloma	0.5–2 cm diameter; Red-purple papules	PDL	6.5–9 J/cm^2, 7–12 mm, 0.45–3 ms	Subtle gray-blue discoloration followed by deeper purpura	3–4 weeks	1–3 treatments are indicated	Eletrosurgery and excision are the most indicated treatment
		Nd-YAG	100–150 J/cm^2, 3–7 mm, 20–30 ms				

- Intralesional lidocaine or nerve blocks may be required to treat deeper lesions such as venous malformations.
- Systemic anesthesia should be considered for children when treating hemangioma.
- Proper eye protection is essential.

Posttreatment

- Surface cooling is very important to stop the heating and minimize side effects (scaring, pigmentary changes).
- Physical sunscreen is recommended after treatment.

My Experience

In my experience, the success of vascular lesions treatment, with safety and efficacy, is related to surface cooling just before and after each session. Proper cooling is essential to protect the epidermis and minimize side effects (scaring).

I am therefore summing up the key points:

- Do not treat tanned skin
- Use longer pulse durations and/or lower fluences for darker skin.
- To treat port-wine stains, my first choice is pulsed dye laser.
- For hypertrophic lesions or PDL-resistant PWS treatment, we can use alexandrite laser.
- For venous lake, Nd:YAG is a good choice. One to two sessions will reduce 80–100% of the lesion.
- The use of 1064 nm long-pulse Nd:YAG laser requires fluences over ten times of that used with 532 and 595 nm lasers since the absorption of Hb and HbO2 at 1,064 nm is ten times less.
- My best results for treatment of rosacea include two to three IPL sessions per year.
- To avoid the polka dot effect in the treatment of vessels around the nasal ala, my best choice is IPL.

Conclusion

The laser treatment of vascular lesions was the first to use selective phototermolisys and nowadays is one of the most important treatments using this theory. The treatment is safe and efficient for most of vascular lesions. The parameters selection guarantees the treatment success (wavelength, spot size, pulse duration, surface cooling). New possibilities come up with technological advances and the increase of medical knowledge.

Take Home Messages

- Pulsed dye laser remains the gold standard treatment for port-wine stains.
- Early laser treatment improves port-wine stain response.
- The end point for treating vessels is vessel clearance, a transient blue coagulum, or purpura.
- Lasers and IPL are the first-choice treatment for telangiectasias and facial erythema.
- Multiple sessions are necessary to treat poikiloderma of Civatte, and some cases are resistant to treatment.
- Alexandrite laser or Nd:YAG can be used to complement the results in the treatment of deeper lesions.
- It is indicated to use longer pulse durations and lower fluences for darker skin.
- Do not treat tanned skin.

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Laser for Onychomycosis

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Abstract

Onychomycosis is a common fungal infection that affects the nail plate or the nail bed and is responsible for approximately 50% of the pathologies affecting the nails (Ghannoum Microbiology 157:3232–42, 2011). Its treatment remains a challenge, even though progress has occurred with the introduction of new antifungal drugs in the 1990s, since many cases linger for decades without a clinical cure (Sigurgeirsson J Europ Acad Dermatol Venerol 24:679–684, 2010). Most cases are caused by dermatophyte fungi; however, in recent years there has been a progressive increase of records of onychomycosis caused by nondermatophyte fungi (yeast and filamentous fungi) that do not respond to antifungal agents (Ranawaka et al. Dermatol Online Journal 18(1):7, (2012); Hwang et al. Ann. Dermatol 24(2):175–180, 2012). Photobiomodulation and photoinactivation studies indicate that lasers in the range of the infrared electromagnetic spectrum (870, 930, 1,064 nm), when applied with biochemical energy, are able to improve the microcirculation, to stimulate the metabolism of cells, and to inhibit the fungal and bacterial multiplication through the action in the wall of the microorganisms, by altering the electric charges and favoring the formation of ROS (singlet oxygen radicals, free radicals). This technique can be associated with the application in the nails of the fractional CO_2 laser so that in a drug delivery system it can be associated with antifungal and/or antibacterial agents in order to act synergistically and thus reduce the number of sessions of sub-millisecond 1,064 nm laser.

Keywords

Onychomycosis • Antifungal • Dermatophyte • Nondermatophyte • Biofilm • Photobiomodulation • Nd:YAG laser • CO_2 laser • Drug delivery

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Introduction

Onychomycosis is a common fungal infection that affects the nail plate or the nail bed and is responsible for approximately 50% of the pathologies affecting the nails (Ghannoum et al. 2000). Its treatment remains a challenge, even though progress has occurred with the introduction of new antifungal drugs in the 1990s, as many cases linger for decades without clinical cure (Sigurgeirsson 2010). It is estimated that the rate of clinical cure with oral medications reaches slightly over 50% of the cases, in the most optimistic statistics, while topical treatments do not reach 20% of cure rates (Scher et al. 2007).

Onychomycosis can complicate other foot problems in elderly persons, affect social interactions, impair employment in which there is direct contact with the public, and serve as a reservoir for potentially aggressive fungi in immunosuppressed individuals. Some factors are considered as predisposing factors, such as advanced age, diabetes, hyperhidrosis, immunocompromised individuals (tumors of hematologic origin, HIV/AIDS), alteration of peripheral circulation, and nail trauma (tight shoes, athletes, etc.), tinea pedis, and trauma from manicure or pedicure, in addition to family history (probably because of transmission) and nail psoriasis (Fig. 1) (Pariser et al. 2013).

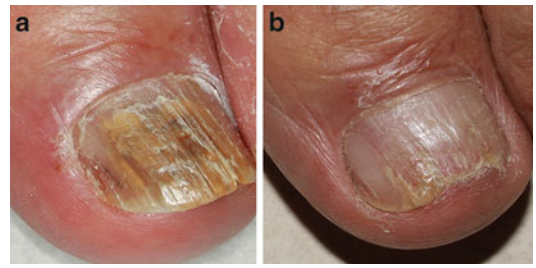

Fig. 1 (**a**) Diabetes. (**b**) Diabetes – 1 year after five sessions of Nd-YAG laser

Basic Concepts

The nails are keratinized plates of hardened consistency located on the distal ends of the fingers and toes. The first signs of the structure that will lead to the nails appear near the end of the first trimester of fetal life. The epidermis of the extremities of the fingers begins to proliferate and grow in the shape of a curved line toward the dermis. Next, the proliferative plate is divided into segments forming the *nail groove*. Cells in the deepest part of this groove give rise to the nail *matrix*, where the upper cells are keratinized and form the plate or body of the nail. As the mitoses in the matrix continue, the nail plate is displaced along the dorsal surface of the finger. This process in the hands precedes the one in the feet. Thus, approximately at the 32nd week, the fingernails reach the ends of the fingers, while, in the feet, this only happens at approximately the 36th week of intrauterine life.

The proximal part of the nail is called the *root*, where the *nail matrix* is located, which continues in the exposed part named *body*. Matrix cells become keratinized and, unlike the other parts of the body, do not come off; on the contrary, they become compact and move in the linear path of the *nail plate*, where they remain included. In the matrix, Merkel cells and melanocytes are also found. The dermis of that proximal part presents short papillae. The matrix is firmly attached to the dermis, so that, when the nail is extracted, the entire matrix cannot be removed. The root is covered with a small skinfold (*proximal nail fold*), which covers a small portion of the body of the nail, thus constituting the *eponychium*, formed by soft keratin.

Underlying the body of the nail, the epidermis differs from other anatomical regions by presenting only the Malpighian layer without cells containing keratohyalin granules, existing in the skin throughout the body. In this case, the nail plate performs the function of the cornea layer. The proximal portion of the nail bed has epidermis that is very thick, generating an opalescent image known as *lunula*, most evidenced in the thumb and which may appear in other fingers (Montagna and Parakkal 1974). The cells responsible for the production and the growth of the nail (*nail matrix*) are located there. On a layer of prismatic (basal) cells, 6–10 layers of polyhedral cells and 3–12 layers of flat cells can be found. It is assumed that the white discoloration is derived from this thick condition, which does not allow the indirect viewing of the blood inside the capillaries (Bloom 1977; Weiss 1977; Montagna and Parakkal 1974; Snell 1985); however, the lunula does not always coincide with the location of the matrix (Montagna and Parakkal 1974).

The nail plate contains a type of keratin that is very high in sulfurous amino acids (hard keratin), which explains its structural stability and chemical resistance. In this region, the cells have a thick cell membrane and are firmly attached to each other, with a large amount of thick and birefringent tonofibrils, measuring from 60 to 80 A, in their interior, and surrounded by dense amorphous material (Wiess 1977). On the surface of the nail plate, there are very evident longitudinal grooves in the elderly, but they are rarely present in the young population (Montagna and Parakkal 1974). Despite being thick and compact, the nail, as well as hair, is more permeable to water than the *stratum corneum* of the skin in general.

Underlying the body of the nail (*nail bed*), the dermis rests on the periosteum of the phalanx. In this segment, the dermal papillae form longitudinal and parallel ridges, which accompany the longitudinal axis of the nail. The vascularization is intense, which gives the pink opaque color observed through the nail plate. The side edges are involved by skinfolds, the *lateral nail folds*, separated from the bed where the body of the nail rests. The location that establishes the continuity of the epidermis of the finger with the distal end of the nail bed is named *hyponychium*, from where the free edge of the nail emerges.

Fingernails grow from 0.5 to 1.2 mm per week, while toenails show a slower evolution (Snell 1985). Several conditions can interfere in this growth: circadian rhythms (the growth is greater during the day than during the night and greater in summer than in winter), age group (greatly reduced growth after the seventh decade), hormonal factors (which speeds up during pregnancy, slowdown with hypothyroidism, etc.), nutritional conditions, and traumatic conditions.

Etiology and Epidemiology

Most cases of onychomycosis are caused by dermatophyte fungi, which are microorganisms found in soil (geophilic), animals (zoophilic), or humans (anthropophilic). The anthropophilic species are *Trichophyton*, *Microsporum*, and *Epidermophyton*. Dermatophytes are able to invade keratinized tissues (cornea layer, hair, and nails) and therefore are called keratinophilic microorganisms. Nondermatophyte fungi are not keratolytic, which is why they are found in the intercellular cement or fixed in the keratin previously destroyed by the dermatophytes, by trauma, or by other nail disease (Pariser et al. 2013; Hwang et al. 2012). Filamentous nondermatophyte fungi are most common in tropical regions (e.g., *Fusarium* and *Aspergillus*), as well as yeasts (especially *Candida* spp.). Nondermatophyte fungi have presented increasing incidence and are considered more difficult to be treated, because they often do not respond to antifungal agents (Fig. 2) (Ranawaka et al. 2012; Hwang et al. 2012).

A large-scale American study isolated dermatophyte fungi in 59% of the cases and nondermatophyte fungi and yeasts in approximately 20% of the cases. The *Trichophyton rubrum* and *Trichophyton mentagrophytes* are among the most frequently encountered dermatophytes, while the *Trichophyton tonsurans*, *Microsporum canis*, and *Epidermophyton floccosum* represented 0.8% of the dermatophytes. Among the isolated nondermatophytes, the *Acremonium*, the *Fusarium*,

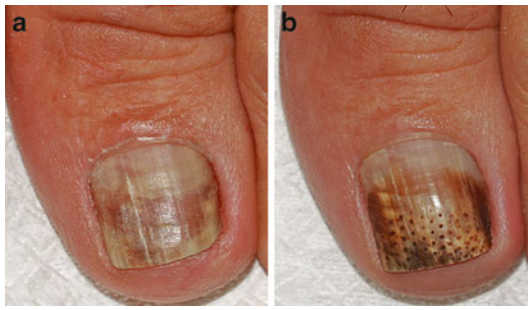

Fig. 2 (**a**) Onychomycosis by *Fusarium*. (**b**) Onychomycosis by *Fusarium* after treatment by Nd:YAG laser and CO_2 fractional laser plus topical amphotericin B

and the *Scopulariopsis* spp. deserve to be highlight with 29.5%, 34.1%, and 20% of frequency, respectively. Among the yeasts, *Candida parapsilosis* represented 66.7% and *Candida albicans* 16.7% of the cultures (Ghannoum et al. 2000). A study carried out in Rio de Janeiro in 2001 evaluated 2,271 patients and diagnosed 400 patients, being these diagnoses in 264 fingernails and 136 toenails, through direct mycological examination and culture; this study indicated the presence of dermatophyte fungi in 46.5% of the cases of onychomycosis in toenails, *Candida* in 49% of the fingernails of women, and 4.5% of emerging fungi (nondermatophytes and other microorganisms). Among the nondermatophyte fungi capable of causing onychomycosis, the *Scopulariopsis brevicaulis*, the *Fusarium* spp., the *Acremonium* spp., the *Aspergillus* spp., the *Scytalidium* spp., and the *Onychocola canadensis* were identified (Araujo et al. 2003). A study performed in Sri Lanka recorded onychomycosis by nondermatophyte fungi in 45.8%, *Candida* spp. in 34.1%, and dermatophytes in 20% of the cases. This variation of pathogens was attributed to the contact with soil, the habit of walking barefoot, the frequent immersion of the hands in water, and the moist and warm climate. The most encountered nondermatophyte fungi were *Aspergillus niger*, *Aspergillus flavus*, and *Fusarium* spp. Onychomycosis was accompanied by paronychia in 76% of the cases. Nondermatophyte fungi accounted for 22% of the onychomycoses in India, 35.5% in Malaysia, 51.6% in Thailand, and 68% in Pakistan (Ranawaka et al. 2012).

The *Fusarium* spp. have been highlighted as plant pathogens and can occasionally infect animals and humans. They can be found in soil, underground, and aerial parts of plants, organic substrates, and water, where they are part of the structure of biofilms. Among humans, they cause superficial infections (such as keratitis and onychomycosis), local invasive disease, or disseminated infections, the latter affecting severe immunocompromised patients (with deep and prolonged neutropenia and/or severe T cell immunodeficiency) and patients with hematologic diseases, mainly patients with acute leukemia. Furthermore, they can cause allergic sinusitis in immunocompetent individuals and mycotoxicosis in humans and animals from the intake of food contaminated by the toxin produced by these fungi. Among the 50 known species, 12 are capable of causing infection, and preexisting onychomycosis can be the source of the disseminated fusariosis (Nucci et al. 2007).

Biofilms

Since the seventeenth century, biofilms have been described in multiple systems. Most bacteria preferentially grow, as biofilms, in all self-sustaining aquatic ecosystems, and these sessile bacterial cells differ deeply from their planktonic counterparts (cells in suspension) (Costerton et al. 1995). The definitions of biofilm have evolved over the years, in parallel to the advances of the biology area and research studies on the subject. The definition used today was proposed by Donlan and Costerton (2002), and it describes biofilm as a microbial community in which the cells are connected to a substrate, or to each other, embedded in a matrix of extracellular polymeric substances (produced by themselves) and exhibit an altered phenotype regarding the rate of growth and transcription of genes (Fig. 3) (Donlan and Costerton 2002).

In fungi, the ability to colonize surfaces and to form biofilms was initially demonstrated for *Candida albicans* and *Saccharomyces cerevisiae*, in the 1990s and early 2000s (Hawser and Douglas 1994; Reynolds and Fink 2001).

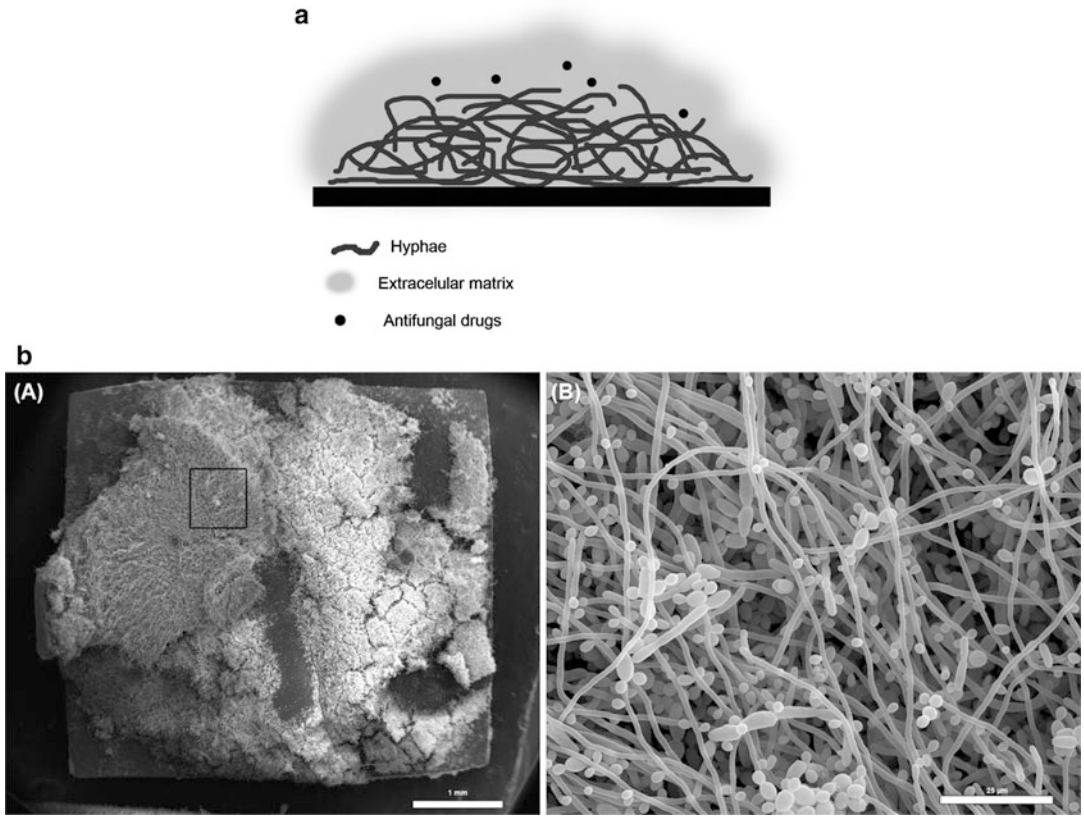

Fig. 3 (**a**) Biofilms. (**b**) Biofilms

However, the growing awareness on the importance of fungal biofilms can be seen in the increase in the number of publications describing the formation of biofilms by other species of *Candida* spp. (Bizerra et al. 2008; Lattif et al. 2010; Silva et al. 2011) as well as other yeasts that cause opportunistic infections and pneumonia in humans, such as *Malassezia pachydermatis* (Cannizzo et al. 2007), *Rhodotorula* sp. (Nunes et al. 2013), *Trichosporon asahii* (Di Bonaventura et al. 2006), *Blastoschizomyces* (D'Antonio et al. 2004) *Pneumocystis* spp. (Cushion et al. 2009), and *Cryptococcus neoformans* (Martinez and Casadevall 2007). Moreover, the ability to form biofilms has also been demonstrated in several filamentous fungi, including *Aspergillus fumigatus* (Mowat et al. 2009) and *Fusarium* spp. (Imamura et al. 2008); in fungi that cause endemic mycoses, such as *Histoplasma capsulatum* (Pitangui et al. 2012), *Paracoccidioides brasiliensis* (Sardi et al. 2014), and *Coccidioides immitis* (Davis et al. 2002); and in zygomycetes, such as *Mucorales* (Singh et al. 2011).

Biofilms in Dermatology

Despite the participation of biofilms in nail infections still being an open discussion, their involvement in other dermatological infections, including acne, miliaria, atopic dermatitis, and wounds, is quite accepted, especially related to bacterial biofilms (Vlassova et al. 2011).

Biofilms in Onychomycosis

During the course of the nail infection, the formation of a thick biomass can be observed, with fungal elements embedded in an extracellular

matrix (Burkhart et al. 2002). Several factors, including the firm adhesion of the fungi to the nail plate, the presence of persister cells, and the difficulty of eradicating the infection, suggest that biofilms are an important factor in the pathogenesis of onychomycoses (Nusbaum et al. 2012). Complementing this hypothesis, the ability to form biofilms was demonstrated in vitro for the primary causative agent of onychomycosis, the dermatophyte *Trichophyton* sp. (Costa-Orlandi et al. 2014). A model for biofilm formation in human nail fragments has recently been established using *Candida albicans* and *Fusarium oxysporum* (Vila et al. 2014) and may help to elucidate the involvement of biofilms in the pathogenesis of onychomycoses and to validate the antibiofilm activity of new molecules and new treatments (Fig. 4).

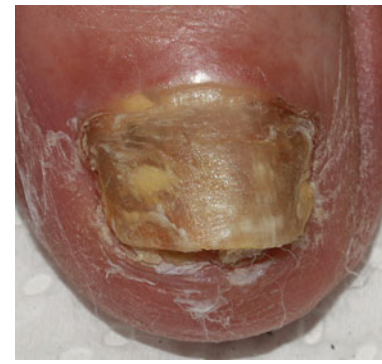

Fig. 4 Dermatophytoma

Antifungal Resistance Associated with Biofilms

According to the definition of a biofilm, the cells that make up its structure have altered phenotype and differ from the planktonic cells in the expression of genes, in the rate of growth, and, mainly, in the susceptibility to antifungal agents. The increase of antifungal resistance in the cells of *Candida* spp. grown as biofilms, in relation to their planktonic forms, is the most medically relevant behavioral change (Ramage et al. 2002). Multiple mechanisms have been suggested to explain the increased antifungal resistance of the biofilm, including cell density, alteration of drug targets, expression of drug efflux pumps, extracellular matrix, and presence of persistent cells (Kuhn et al. 2002a; Lattif et al. 2011; Mukherjee and Chandra 2004; Perumal et al. 2007; Ramage et al. 2002, 2012).

Role of the Extracellular Matrix of the Biofilm in Resistance

In most biofilms, the population of microorganisms corresponds to 10% of the total mass, and the extracellular matrix (ECM) corresponds to 90%. The matrix consists of a cluster of different biopolymers responsible for keeping the cells adhered to the surface and the cohesion of the biofilm, for restraining the cells, and for keeping them close, this way allowing cell-cell communication and diffusion of signaling molecules (Flemming and Wingender 2010).

The ECM, by definition, provides protection to cells against environmental factors, such as the immunity of the host and the antifungal agents (Seneviratne et al. 2008). One of the described key components of the ECM of *C. albicans* is a β-1,3-glucan responsible for abducting azoles, echinocandins, pyrimidines, and polyenes (Nett et al. 2010a, b; Vediyappan et al. 2010), behaving as a "drug sponge" and contributing to the increased resistance of biofilms of *C. albicans* (Nett et al. 2010a, b). The latest study published on the subject suggests that, in addition to the β-1,3-glucan, a polysaccharide complex formed by mannan-glucan (which is, in fact, the polysaccharide in greater abundance in the ECM of biofilms of *C. albicans*) is also capable of binding to fluconazole (and possibly to other drugs) and contributes to the resistance (Zarnowski et al. 2014). In this work, it is emphasized that, possibly, most polysaccharides of the ECM must act as drug sequestrants and contribute to the resistance of the biofilm to antifungal agents.

In addition to the polysaccharides, the extracellular DNA present in the ECM of biofilms of *C. albicans* also appears to have a role in the resistance to non-azole agents, as the addition of DNase increases the antibiofilm activity of polyenic agents and echinocandins, but not the activity of azoles (Martins et al. 2009, 2012).

Even though the resistance mechanisms associated with the lower susceptibility of biofilms to antifungals available are not fully elucidated,

several studies show that biofilms of *C. albicans*, *C. parapsilosis*, and *C. tropicalis* are resistant to treatments with different commercially available antifungals, among them fluconazole, nystatin, terbinafine, amphotericin B, voriconazole, and ravuconazole (Ferreira et al. 2009; Kuhn et al. 2002b). Moreover, in vitro studies with biofilms of *Fusarium* spp. also highlight its lower susceptibility to the commercial antifungal agents amphotericin B, voriconazole, itraconazole, and fluconazole (Mukherjee et al. 2012; Zhang et al. 2012).

Biofilms of *Candida* spp.

The in vitro development of biofilm of *Candida* spp. (in abiotic surfaces) can be didactically described in four sequential steps: (1) adherence, initial phase, in which the yeast in suspension and those circulating (planktonic cells) adhere to the surface; (2) intermediate phase, concerning the development of biofilm; (3) maturation phase, in which the polymer matrix completely soaks all layers of cells adhered to the surface in a three-dimensional structure; (4) dispersion, in which the most superficial cells leave the biofilm and colonize areas surrounding the surface (Chandra et al. 2001; Ramage et al. 2005; Seneviratne et al. 2008). At the end of the development, the biofilm consists of a dense network of cells in the form of yeasts, hyphae, and pseudohyphae soaked by polymeric extracellular matrix and with water channels between the cells, which facilitate the diffusion of nutrients from the environment through the biomass to the lower layers and which also allow the elimination of waste (Chandra et al. 2001; Ramage et al. 2001, 2005).

Biofilms of *Candida* spp., formed in in vivo models, seem to follow the same sequence of formation (Andes et al. 2004); however, the maturation occurs more rapidly and the final thickness is greater in these biofilms than those grown in in vitro systems.

The final architecture of the biofilm is variable and depends, in part, on the substrate on which it is formed and the growing conditions, such as culture medium used (in vitro), concentration and types of sugars, presence of serum proteins, pH, and temperature (Kumamoto 2002; Seneviratne et al. 2008).

Biofilms of *Fusarium* spp.

Species of the genus *Fusarium* are soil saprophytic and important pathogens of plants and humans. The clinical form of the fusariosis depends on the immune status of the host. In immunocompetent individuals, keratitis and onychomycoses are the most common infections. In immunocompromised individuals, the disseminated fusariosis is the second most common filamentous fungal infection, and it particularly affects patients treated with high-dose corticosteroids and with severe neutropenia, with mortality rate of up to 100% (Nucci and Anaissie 2007). The *Fusarium* spp. is an important causative agent of microbial keratitis, and the biofilm formation has been suggested as a contributing factor in recent outbreaks, mainly associated with the use of contact lenses (Mukherjee et al. 2012). The *Fusarium* spp. is also commonly isolated as a causative agent in onychomycoses (de Araújo et al. 2003; Morales-Cardona et al. 2014). In nails, fungal cells form thick fungal biomasses, with fungal elements embedded in an extracellular matrix (Burkhart et al. 2002); this behavior suggests the participation of biofilms in the pathogenesis of onychomycosis (Nusbaum et al. 2012). In the northern hemisphere, onychomycosis caused by dermatophytes, especially *T. mentagrophytes* and *T. rubrum*, are more prevalent (Ghannoum et al. 2000). However, in warmer and humid countries such as Brazil, the incidence of non-dermatophytic filamentous fungi (such as *Fusarium* spp.) and yeasts (such as *Candida* spp.) as causative agents of these infections is very significant (de Araújo et al. 2003; Morales-Cardona et al. 2014). These data are extremely relevant since, while most dermatophytes are sensitive to the terbinafine and azoles commonly used in the treatment of onychomycoses (ketoconazole, clotrimazole, and fluconazole), *Fusarium* spp. is often resistant to the available antifungals (Bueno et al. 2010; Ortoneda et al. 2004).

Diagnosis

The diagnosis of onychomycosis involves researching the involvement of the nail unit (nail plate, nail bed, and periungual tissues). Dermatophytes affect toenails more than fingernails, where the infections by *Candida* spp. are more frequent. The physical examination should be careful in order to register all the nail units involved and to observe the clinical signs of onychomycosis: onycholysis, material under the nail plate, subungual hyperkeratosis, change of color (white or yellow, brown), and intensity of the destruction of the nail plate (Fig. 5) (Pariser et al. 2013).

Clinical Evaluation

The clinic evaluation begins by gathering information such as age, sex, presence of vascular diseases, diabetes, hypertension, number of infected nails, duration of infection, history of previous treatment, type of onychomycosis, percentage of nail involvement, thickness of the nail, presence of dermatophytoma, involvement of the matrix, and exclusively lateral involvement (Ghannoum et al. 2000; Scher et al. 2007). In Brazil, there is also the need to include the family history of onychomycosis and the habit of removing the cuticles by manicures, which facilitates the involvement of the nails with mixed infections (bacterial and fungal). The examination of areas of intertrigo assists in the identification and treatment of fungal reservoirs. Individuals with a family history of diabetes, metabolic syndrome, peripheral circulatory problems, or immunodeficiency should be treated by a multidisciplinary team. Young individuals from 20 to 30 years with chronic infection that is difficult to treat should be investigated for family onychomycosis, because of the contamination of the nails in the infancy, the use of bathrooms with contaminated relatives and/or locker rooms, and fungi resistant to traditional treatment.

The identification of the clinical presentation is important for the choice of appropriate therapeutic approach for each case (Scher et al. 2007). The white-yellow or orange-brown spots may be caused by fungi that do not respond to the medication used, as in the case of nondermatophyte fungi. The brown spots are common in the fifth toe and should be differentiated from nail melanoma (although these two pathologies may occur at the same time). Patients with chronic onychomycosis should be examined for signs that indicate active infection, even if the culture is negative.

1. Change of more than 10% of the nail plate compatible with infection caused by dermatophytes by dermatoscopy
2. Presence of white, yellow, orange, or brown spots of plates on the nail
3. Lateral onycholysis with debris
4. Lateral hyperkeratosis on the nail plate or bed (Fig. 6) (Ortiz et al. 2014)

The following are some fungi that can cause melanonychia: *Scytalidium*, *Scopulariopsis*, *Aspergillus*, *Fusarium*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton soudanense*, *Candida albicans*, *Candida tropicalis*, *Curvularia*, etc. (Finch et al. 2012).

Differential Diagnosis

Irritant contact	Enamels, acrylics, or artificial nails
Nail trauma	Athletes, contusions
Psoriasis	Secondary infection by fungus
Lichen planus	
Neoplasms	Subungual
Bacterial infection	Gram-positive bacteria

Clinical Classification

Distal and lateral subungual onychomycosis – mixed infection by *Candida* and bacteria, dermatophytes

Proximal subungual onychomycosis – affects the base of the nail and can be caused by the genus *Fusarium* spp.

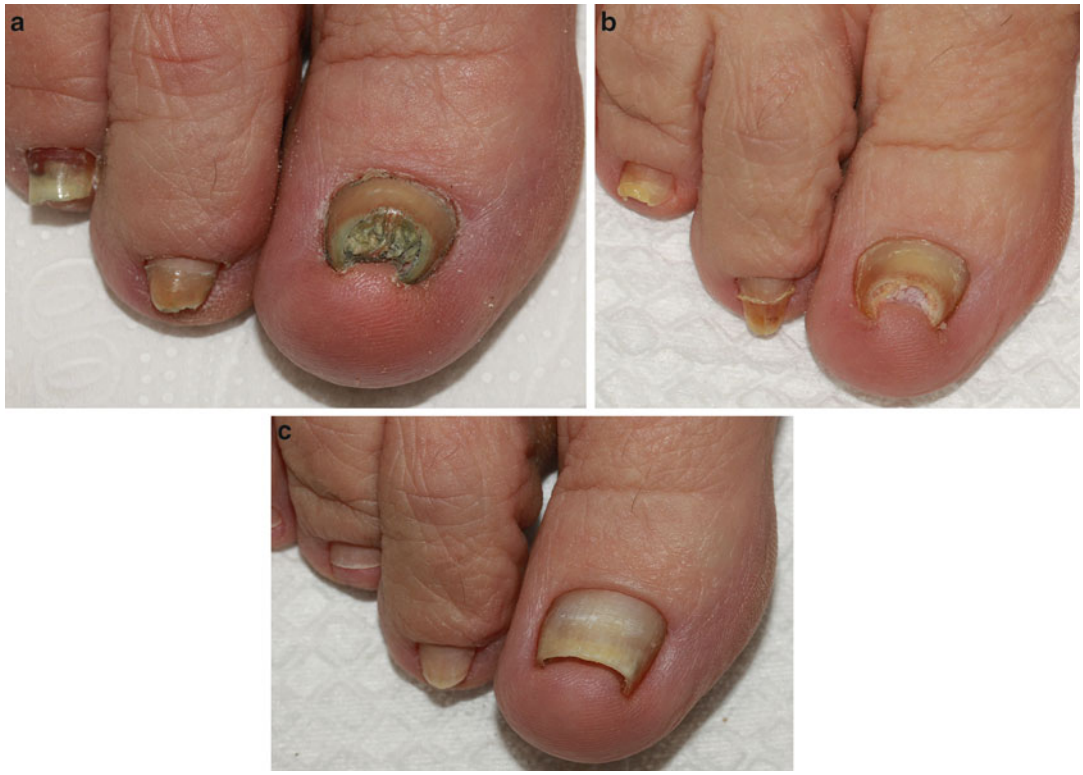

Fig. 5 (a) Traumatic onychodystrophy, negative culture, athletic runner. (**b**) Traumatic onychodystrophy, 7 months after first session of Nd:YAG laser. (**c**) Traumatic onychodystrophy 1 year and 4 months after first session of Nd:YAG laser

White superficial onychomycosis – *T. mentagrophytes*
Endonyx onychomycosis – dermatophytes
Total onychomycosis – dermatophytes and mixed infections with nondermatophyte fungi (Pariser et al. 2013; Hwang et al. 2012; Carney et al. 2011)

Prognostic Factors

Onychomycoses are under the influence of factors that make the prognosis grim. They act in the worsening of the nail infection. Their characteristics are:

Host – impaired peripheral circulation, diabetes, and immunosuppression (Figs. 7 and 8)
Nails – hyperkeratosis greater than 2 mm, lateral disease, dermatophytoma (biofilm), involvement of more than 50% of the nail plate, slow growth of the nails, total dystrophic onychomycosis, involvement of the matrix, and serious onycholysis
Microorganism – filamentous nondermatophyte fungi, yeasts, and mixed infections (Carney et al. 2011)

Clinically, it is not possible to identify or differentiate onychomycosis caused by dermatophytes, filamentous nondermatophytes, or yeasts (Ranawaka et al. 2012). The collection of samples is carried out with sterile instruments, with curettage after cutting part of the free edge of the nail, with curettage of the nail plate when white superficial onychomycosis is suspected, or with samples of the nail and the nail bed when the involvement is closer to the matrix. The material is collected after cleaning the nail with alcohol, stored and transported in sterile collector. Part of this material will be used for the direct

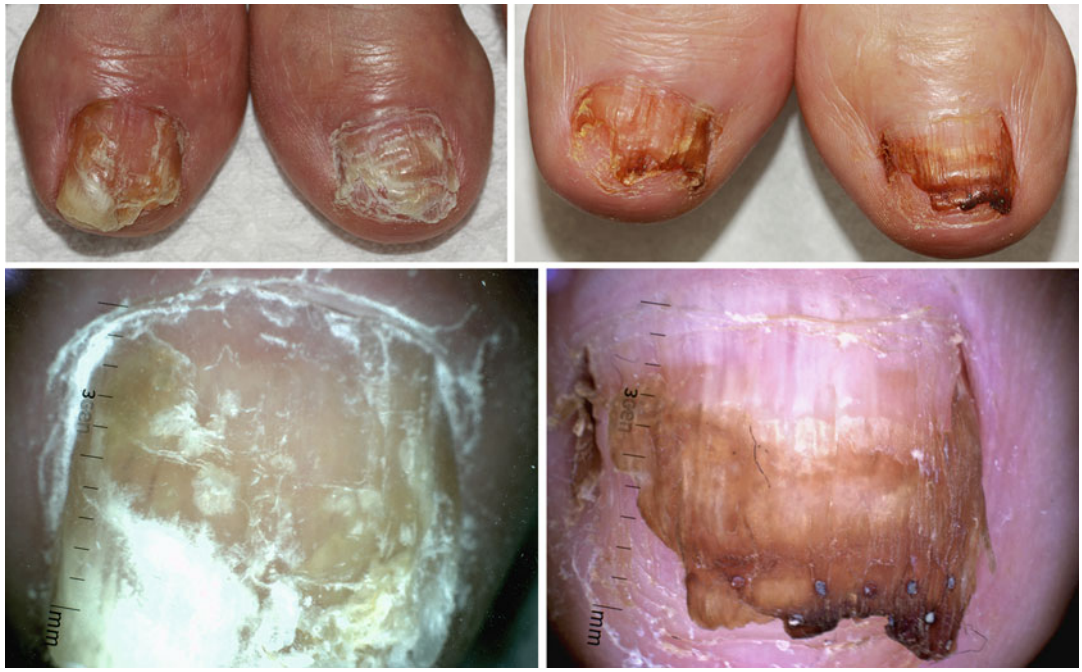

Fig. 6 (**a**) Dystrophic onychomycosis. (**b**) Dystrophic onychomycosis – after seven sessions of Nd:YAG laser. (**c**) Dermatoscopy – before treatment. (**d**) Dermatoscopy – after treatment

examination and another part for the culture in Sabouraud agar medium. The direct examination, although nonspecific, aids in the differential diagnosis from other diseases, such as psoriasis or lichen planus, although secondary bacterial and/or fungal infections may occur in relation to the other inflammatory pathologies. It is important to inform the laboratory when there is the need to research a nondermatophytic fungus and/or bacteria so that the material can be grown in suitable medium.

The culture is a method considered as gold standard for the diagnosis of onychomycosis in 3–4 weeks, although it can show a false negative in 15% of the cases (Pariser et al. 2013; Liu et al. 2000). The isolation of a nondermatophyte fungus or yeast can be considered as environmental contamination or from the local microbiota. The recommendation of the diagnosis of these pathogens is based on the lack of growth of the dermatophyte fungus in the culture and the growth of five colonies of the same microorganism in two consecutive samples (Araujo et al. 2003; Ranawaka et al. 2012).

The examination through the technology of nucleic acid amplification (PCR) has offered the opportunity to improve the quality and speed of diagnosis of dermatophytes by up to 4 h. It identifies species and subspecies of dermatophytes and sets them apart from nondermatophytes and *Candida* spp., and it does not require viable microorganisms for the test (Liu et al. 2000).

Treatment

Topical and Systemic Treatment

The treatment of onychomycoses faces several difficulties, among them the need for long-term monitoring, the side effects of systemic medications, and the difficulty of taking the medication to the target area to be treated (Vural et al. 2008). The traditional therapeutics of onychomycoses consists of palliative care, chemical or mechanical debridement (Chiacchio et al. 2004), and use of systemic or topical medications. The definition of "complete healing" by the US regulatory agency

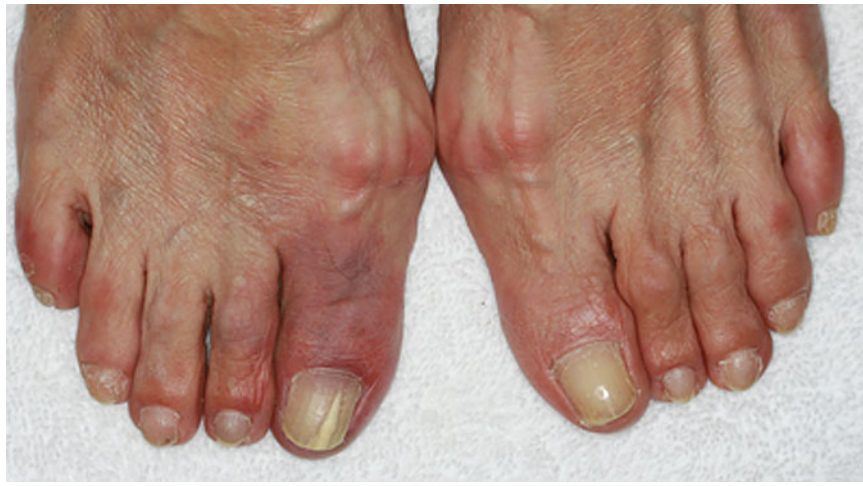

Fig. 7 Occlusion of right popliteal artery

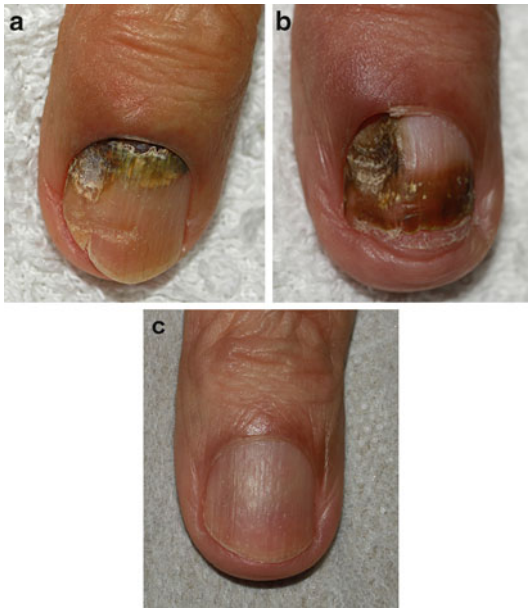

Fig. 8 (**a**) Mixed infection – *Trichophyton* sp. and *Pseudomonas* sp. – treatment with Nd:YAG laser plus topical garamycin and isoconazole. (**b**) Mixed infection – 3 months of treatment. (**c**) Mixed infection – 2 years after treatment

Food and Drug Administration (FDA), for evaluation of clinical results, are the negative results of the direct examination and culture, as well as completely normal appearance of the nail (Pariser et al. 2013).

The choice of treatment depends on the clinical presentation, the severity of the disease, and the cost and time of treatment. The systemic drugs used – terbinafine, itraconazole, and fluconazole – are associated with significant adverse effects, which hinder the prescription for patients with hepatic and/or renal problems. The topical medications are safer but are ineffective. In clinical practice, patients with long-term infections or chronic onychomycosis with serious changes of the nail plate, nail bed, and matrix can be observed. The study of Pariser et al. (2013) indicates that the cure rate with ciclopirox topical 8% for 48 weeks is 5.5–8.5%. Therefore it is not recommended as monotherapy. The cure rates with therapeutic treatment with systemic medications range from 14% to 54%, according to the used medication, the dose, and the administration time.

Treatment with Light and Laser

The application of lights in tissues and organisms can have both stimulatory and inhibitory responses according to the parameters used. Some terms are used to determine these effects, such as biostimulation, low-level laser (or light) therapy (LLLT), low-intensity laser therapy, low-power laser therapy, cold laser, soft laser,

photobiostimulation, and photobiomodulation. The most used term is the low-level laser therapy (LLLT), a term that is often mentioned in the Medical Subject Heading (MeSH) in the controlled vocabulary thesaurus of the National Library of Medicine. The conference of the North American Association for Light Therapy and the World Association for Laser Therapy in September 2014 determined in consensus that the term that better designates it is photobiomodulation, proposed to be included in the MeSH Section at the National Library of Medicine (Anders et al. 2015).

The photodamage of the ultraviolet light in bacteria and fungi without the use of a photosensitizing agent was demonstrated in the beginning of the decade of 1903 with lamps that radiated a wavelength between 226 and 328 nm (UVC + UVB). The germicidal activity against prokaryotic and eukaryotic pathogens was observed in 2002; however, its use was abandoned because of the photocarcinogenic effect in human cells (Bornstein et al. 2009a). Since then, other wavelengths in the near-infrared range (NIR) of the electromagnetic spectrum have been studied in order to identify the photoinactivation of pathogens, both with the use of light and photosensitizing agent, and with the use of laser (Vural et al. 2008; Kosarev et al. 2010).

The studies of lights and lasers with antimicrobial objective have walked parallel paths in the areas such as physical-chemical, microbiology, and clinic. Although studies on the electromagnetic spectrum are unraveling the behavior of certain wavelengths and some tests with the use of the laser in the culture of *T. rubrum* and bacteria indicate the photoinhibition of certain microorganisms, there is still a lack of in vitro studies that mimic clinical conditions and clinical studies with broader sampling. One of the difficulties is the wide variety of clinical presentations of onychomycoses and the combinations of mixed infections that form biofilms (Meral et al. 2003; Vural et al. 2008; Knappe et al. 2004; Pasquini 2003; Landsman et al. 2010).

Interaction of the Laser with the Skin

The extent and the intensity of the action of the laser on the skin depend on the structure of the tissue determined by its water content and blood circulation that influences the absorption, scattering, reflection, thermal conductivity, heat capacity, and density, which in turn are influenced by the parameters of the laser beam (energy intensity and wavelength). Depending on the duration of the irradiation of the laser in the tissues, there are different energy densities that will lead to three types of interaction: photochemical effects (10s–1000s; 10^{-3}–1 W/cm^2), photothermal effects (1 ms–100 s;1–10^6 W/cm^2), and photoionization and photomechanical effects (10 ps–100 ns; 10^8–10^{12} W/cm^2). The photothermal and photochemical effects are obtained using less energy and with pulses greater than those used for the photoionization and photomechanical effects. These physical parameters are important to classify the type of laser equipment available and their purposes. In this way, the same type of wavelength may be indicated for different clinical conditions according to the energy of the equipment and its ability to generate short or long pulses (Knappe et al. 2004).

The increase in temperature and its distribution in the place exposed to laser radiation depend on the energy absorbed by the tissue and its thermal properties. According to the temperature achieved, different effects will happen. When the temperature reaches 45 °C, there is no irreversible tissue damage. Temperatures between 50 and 45 °C generate alterations of enzymes and edema. Temperature above 60 °C for a few seconds generates denaturing coagulation of the tissue proteins, and the temperature between 90 and 100 °C causes the vaporization of the plasma cell (as with the CO_2 laser) (Knappe et al. 2004). Currently, there are studies on the effects of lasers whose wavelength of the electromagnetic spectrum lies on the near-infrared range (NIR). Lasers in this range between 700 and 1,400 nm have in common the ability to penetrate deeply into the dermis with virtually no dispersion of the light beams. A study performed with the diode laser

system of 870 nm and 930 nm indicates the in vitro photoinactivation in physiological temperatures of *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Trichophyton rubrum* by reducing the membrane potential and increasing the generation of reactive oxygen species (ROS) without harmful effects to human cells.

A clinical study with laser diode of 870 nm and 930 nm performed by Landsman et al. (2010), based on previous studies of Bornstein, obtained improvement in cases of onychomycosis in 63% of the cases accompanied during 180 days through the growth of 3 mm of treated nails and culture examined by periodic acid-Schiff being negative in 30% of the cases (Landsman et al. 2010; Bornstein 2009; Bornstein et al. 2009). The exposures were done with two applications with duration of 2 min and accompanied with the measurement of the temperature with infrared thermometer.

The 1,064 nm Nd:YAG Laser

The 1,064 nm Nd:YAG laser has been used for the remodeling of collagen (Dang et al. 2005; Koh et al. 2010; Dayan et al. 2003a, b; Schmults et al. 2004; Tan et al. 2004), treatment of pseudofolliculitis barbae (Ross et al. 2002), pyogenic granuloma, stimulation of angiogenesis (Kipshidze et al. 2001), and as antibacterial and antifungal agent as noted in photobiomodulation performed with visible light and near-IR (Guffey et al. 2014).

A new in vitro model was created to study the effectiveness of the Nd:Yag laser through the irradiation of nails previously sterilized and subsequently contaminated by biofilms of *Candida albicans* and *Fusarium oxysporum*. The evaluation of the colonies in electron microscopy showed 50% inhibition of the biofilm of *Candida albicans* and 100% of the biofilm of *Fusarium oxysporum*, even with the presence of holes in the wall of the latter microorganism and emptying of contents, which would indicate injury of the wall of the fungus. The tests indicated reduction of viability of the colonies of *Candida albicans* and *Fusarium oxysporum* studied (Vila et al. 2014).

The Nd:YAG laser is used in cases in which the systemic medication is contraindicated, such as when the growth of the nail is slow (because of circulatory problems, diabetes, trauma, etc.). The 1,064 nm Nd:YAG laser belongs to a range of the electromagnetic spectrum that is characterized by the ability to penetrate deeply into the skin with little dissipation and dispersion, and it has hemoglobin and water as known target chromophores and little affinity for melanin. In this way, it is possible to use safely in high phototypes (IV, V, VI). (Dayan et al. 2003b) indicates that the Nd:YAG laser stimulates the formation of collagen fibers and improves microcirculation (Bornstein 2009; Dayan et al. 2003a, b). The 1,064 nm Nd:YAG laser facilitates the revascularization of the extremities through a nonthermal effect. Clinically, there is a stimulus for the growth of the nail and improvement of its structure and vascularization, which is why it is used in cases of slow growth of the nails or onychoschizia.

When there is the presence of dermatophytomas (adherent fungal abscesses protected by biofilms and refractory to oral antifungal therapy), the chemical and/or surgical debridement is recommended. It can be done with the use of urea at 40% or trimming of the nail with CO_2 laser.

The sub-millisecond Nd:YAG laser can be used in the treatment of the nails. According to the equipment, it can be used with a 5 or 6 mm spot, which allows a good dispersion of the laser in the treated area with reduced Gaussian curve (which concentrates the energy in the center of the spot), forming a top hat, with less joules and deeper penetration than the smaller spots.

Although clinical studies use a small sampling, the treatment with the Nd:YAG laser can be an alternative that can be used alone or in combination with other treatments (Sá Guimarães 2014). Currently, some neodymium-doped yttrium aluminum garnet (Nd-YAG) laser devices have been approved for temporary whitening of the nails:

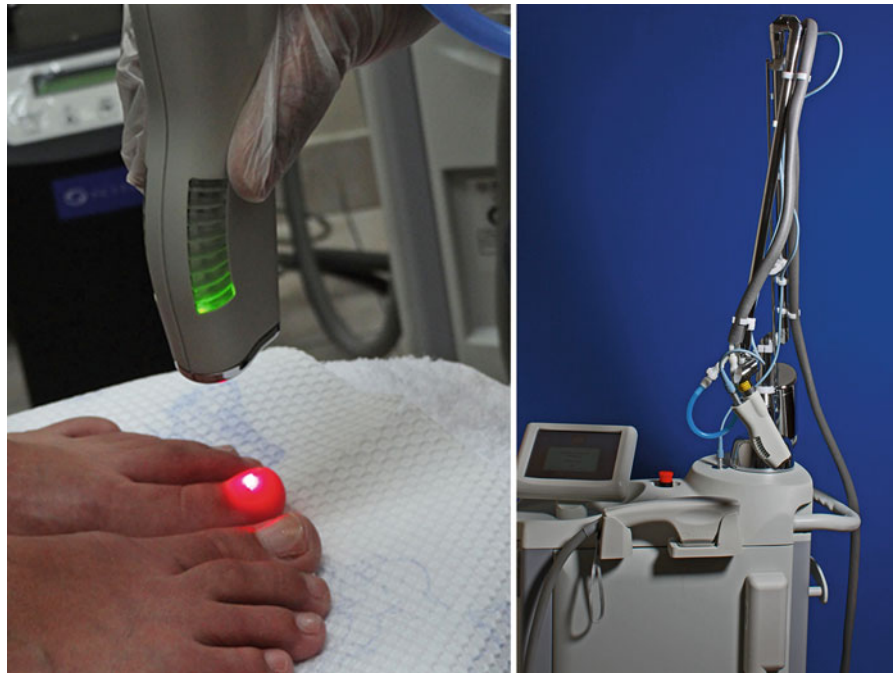

Fig. 9 Nd:YAG application and equipment

Pinpointe Footlaser (Nuvolase), GenesisPlus (Cutera), Q-Clear (Light Age), CoolTouch VARIA (CoolTouch), and Joule ClearSense (Sciton) (Ortiz et al. 2014; Kimura et al. 2012; Hochman et al. 2011). The Joule ClearSense tip (Sciton equipment) emits a 6 mm spot, with proficiency ranging from 5 to 6 j/cm^2, with pulse duration of 0.3 ms, 4.0 Hz, and with real-time temperature control, measured through the infrared thermometer built into this handpiece.

The application is done in concentric circles repeated until reaching the temperature between 42 and 44 °C. Three initial sessions are performed with an interval of a week, and then there is the monitoring until the total growth of the treated nails with intervals ranging from 1 to 3 months according to the intensity of the nail involvement and clinical improvement (Fig. 9).

The prevention of recurrences can be done with the application of antifungal powder with miconazole 2% on the feet and shoes at the long term (Warshaw et al. 2005). This measure treats and prevents tinea pedis in mocassin, usually caused by *T. rubrum* or *T. mentagrophytes* (interdigitalis).

The 10,600 nm CO_2 Laser

The CO_2 laser has water as its main chromophore. In the continuous mode, it is used in parallel points (with 3 or 4 W, in a continuous mode with the control of the cutting perpendicular to the pedal) in order to cut the plate with the preservation of the nail bed. The cutting of the hyperkeratotic nail facilitates the collection of material for culture and surgical debridement.

The experimental use of fractional CO_2 laser as a way of drug delivery was described by Haedersdal et al. (2010). In this experiment, methyl 5-aminolevulinate (MAL) was used, which is a precursor of porphyrin as drug test. It was observed a significant absorption in the depth of the skin with the creation of intradermal channels created by the 3 mm laser and increased concentration of porphyrin in the hair follicles because of the diffusion of MAL in the area tested (Haedersdal et al. 2010).

The fractional CO_2 laser can be used in the treatment of onychomycosis caused by *Fusarium* spp. with application (12 W, 1,000 μm of spacing, 700 μs of pulse duration, and five stacks,

Smartxide, Deka laser) in the entire length of the nail plate and eponychium followed by the application of cream with tetracycline and topical amphotericin B (occlusive dressing at night) (Lurati et al. 2011) followed by morning brushing with hydrogen peroxide 10 vol (Garcez et al. 2010) until the total growth of the nail. The application of amphotericin B produces a brown pigmentation on the sick part of the nail where there is debris of dehydrated appearance. This coloration serves as an auxiliary chromophore for the application of Nd:YAG laser causing a higher concentration of heat in these areas.

Conclusions

Anders et al. (2015) suggest that the term photobiomodulation therapy would be "a form of light therapy which uses non-ionizing forms of light sources, including lasers, LEDs, and broadband light, in visible light and infrared. It is a nonthermal process that involves endogenous chromophores that promote photophysical and photochemical events in multiple biological scales." This therapy is applied to reduce pain, inflammation, and immune modulation, and it promotes wound healing and tissue regeneration (Anders et al. 2015). Meral et al. (2003), Ortiz et al. (2014), Vila et al. (2014), and Vural et al. (2008) found that the lights and lasers used in photobiomodulation are able to inhibit bacterial and fungal growth. Research studies are just beginning, and they certainly will bring new solutions to the infections caused by biofilms from different sources.

Take Home Messages

- Rate of clinical cure with oral medications reaches slightly over 50% of the cases, while topical treatments do not reach 20% of cure rates.
- Nondermatophyte fungi have presented increasing incidence and are considered more difficult to be treated.
- Form biofilms was demonstrated in vitro for the primary causative agent of onychomycosis.
- Nd:YAG laser stimulates the formation of collagen fibers, improves microcirculation, and is antibacterial and antifungal agent.
- Fractional CO_2 laser can be used for drug delivery.

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Lasers for Aesthetic and Functional Vaginal Rejuvenation

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Abstract

Vaginal rejuvenation has been popped up recently due to the increase in life expectancy and the search for a better quality of life. Nowadays, women live one-third of their lives after menopause, demanding efforts to keep their sexual life up to their body and mind's health. Advances in laser therapy have made this possible, reversing vulvovaginal atrophy and its symptoms, known as genitourinary syndrome of menopause, including vaginal dryness, dyspareunia, decrease in sexual arousal and orgasm, stress urinary incontinence, and vaginal bleeding. Carbon dioxide laser (CO_2) and the erbium laser (Er:YAG) are the most common lasers used for female rejuvenation. They promote neocollagenesis and neovascularization in the connective tissue of the vaginal wall, as well as recover the mucosal epithelium, restoring lubrication and elasticity of vaginal walls.

Keywords

CO_2 laser • Erbium laser • Er:YAG • Genitourinary syndrome of menopause • Intimate laser • Menopause • Radiofrequency • Urinary incontinence • Vaginal laxity • Vaginal rejuvenation • Vulvovaginal atrophy

Contents

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Introduction

Vaginal rejuvenation is commonly defined as a combination of minimally invasive procedures that stimulate regeneration of female lower genital tract, aiming to regain aesthetic and functional features lost with the aging process in menopausal women. It is also indicated to treat vagina relaxation in young women.

Vagina relaxation, for example, is one of the biggest responsibilities for sexual dissatisfaction. It represents the loss of the optimum structural architecture of the vagina, generally associated with natural aging and specially affected by childbirth, whether vaginal or not. Multiple pregnancies increase the alteration of these structures, making vaginal muscles relaxed with poor tone, strength, control, and support. The vaginal canal becomes wider and stretched, and sexual gratification consequently diminishes, since it has been attributed to frictional forces generated during intercourses. Therefore, many women, especially after menopause, seek for vaginal treatments to regain their sexual health and well-being (Sturdee et al. 2010).

As we know, menopause is the cessation of menstruation for more than 1 year, reflecting the depletion of ovarian function. As the life expectancy of women has increased, nowadays, approximately one-third of a woman's life is postmenopausal (NAMS 2013). The progressive cessation of estrogen circulating levels leads to metabolic and tissue changes, more evident in the genital tract due to its particular sensitivity to variations in sexual hormone levels. Together with menopause, the vaginal epithelium starts to get thinner and vaginal walls become less elastic with loss of rugations, looking more pale, dry, and friable at the specular exam, often bleeding after minimal trauma. The entire vaginal canal becomes shorter and narrower. The vulvar area, particularly the clitoris, becomes atrophic and more vulnerable (Mehta and Bachmann 2008). These alterations lead to a constellation of symptoms grouped as genitourinary syndrome of menopause (GSM).

The GSM is a new term in substitution to vulvovaginal atrophy as agreed by the North American Menopause Society and the International Society for the Study of Women's Sexual Health (Portman et al., 2014). This syndrome is characterized by a combination of symptoms such as vaginal pain during sex intercourse (dyspareunia), itching, urinary incontinence, dysuria, and the main complaint of aging women: vaginal dryness, an early symptom. The GSM affects around 20–45% of women (Santoro and Komi 2009) and reflects directly in the general quality of life, mostly causing a profound negative impact in the sexual field.

Vaginal health can be objectively assessed by the vaginal health index score (VHIS). The VHIS evaluates the appearance of vaginal mucosa (elasticity, pH, vaginal discharge, mucosal integrity, and moisture). Each parameter is graded from 1 to 5; the higher the score, the better the vaginal health. If the total score is smaller than 15, the vagina is considered atrophic (Bachmann et al., 1992) – see Table 1.

There are several treatment options to minimize GSM symptoms, including nonhormonal products for mild cases, local vaginal hormone therapy for persistent symptoms, and systemic hormonal replacement therapy (HRT) as a broader approach for severe symptoms (Sturdee et al. 2010).

The nonhormonal therapy is mostly based on the use of vaginal lubricants and moisturizes in a regular basis, providing only temporary relief prior to intercourse. Lubricants have been demonstrated to decrease vaginal irritation during sexual activity but do not provide a long-term solution (Bygdeman and Swahn 1996).

Low-dose local estrogen therapies can be useful for women with GSM symptoms without systemic climacteric complaints, in the absence of contraindications, such as personal history of either endometrial or breast cancer. The major disadvantage of this approach is the recurrence of symptoms once it has been suspended, generating a dependency relation among women.

The systemic HRT relieves not only the vaginal symptoms but also general complaints like hot flushes, mood lability, and sleep disturbances. It is not indicated for exclusive GSM, since it has more contraindications and side

Table 1 Vaginal health index score (VHIS)

	1	2	3	4	5
Elasticity	None	Poor	Fair	Good	Excellent
Vaginal discharge (fluid volume)	None	Scant amount, vault not entirely covered	Superficial amount, vault entirely covered	Moderate amount of dryness (small areas of dryness on cotton tip applicator)	Normal amount (fully saturates on cotton tip applicator)
pH	>6.0	5.6–6.0	5.1–5.5	4.7–5.0	<4.7
Musosal Integrity	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable – thin epithelium	Normal
Moisture	None, surface inflamed	None, surface not inflamed	Minimal	Moderate	Normal

Adapted from Bachmann et al. (1992)

effects than the local HRT, like the increased risk of thrombosis and breast/endometrial cancer (Santoro and Komi 2009).

In this context, the vaginal laser (an acronym for "light amplification by stimulated emission of radiation") therapy appears as a feasible option for women desiring nonhormonal therapy with a longer efficacy compared to the topic local therapy. The laser device is a coherent, collimated, and monochromatic source of light, which is absorbed by tissue according to its light absorbance coefficient. Considering vaginal indications, the most used kind of lasers are the fractional carbon dioxide (CO_2) and Erbium-doped yttrium aluminum garnet (Er:YAG) lasers, both of them targeting the water of the tissue through different wavelengths: 10,600 nm for the CO_2 and 2940 nm for the Er:YAG lasers (Vizintin et al. 2012).

History

The concept of stimulated light was conceived by Albert Einstein back in 1905, in a phenomenon called the photoelectric effect. The first laser was constructed in 1960, a chromium-ruby device. The first carbon dioxide (CO_2) laser was built in 1964 by Patel and his team.

Laser is considered one of the most versatile therapeutic instruments in several medical fields. In dermatology, fractional lasers like Er:YAG and CO2 lasers have been used mainly for resurfacing, rejuvenation, and scar improvement, with significant effects in the connective tissue, stimulating tissue remodeling, with similar effects being reproducible within the vaginal epithelium (Sasaki et al. 2009).

Gynecologists have been using lasers successfully to treat vaginal and cervical pathologies over the past five decades (Kaplan et al. 1973). In this last decade, a wave of publications involving vaginal rejuvenation has caught attention of the scientific community worldwide. The mechanism of action involves neocollagenesis and restoration of the trabecular architecture of the vaginal wall, regaining the appearance observed in premenopausal women.

The CO_2 and the Er:YAG lasers are among the most studied and spoken technologies aiming vaginal rejuvenation. More recently, radiofrequency has also gained some strength in treating this area, with prominent findings, specially using a transcutaneous temperature-controlled radiofrequency for vulvovaginal rejuvenation (Vanaman et al. 2016).

Mechanisms of Action

The medical use of Laser technology is based on the interaction between the light emitted and tissue chromophores, including hemoglobin, melanin, connective tissue, and water (Alexiades-Armenakas et al. 2008), which depends on the

different absorption of light in the electromagnetic spectrum.

The vaginal wall is composed of four layers: squamous epithelium, lamina propria, muscular layer, and the adventitia. Like the epidermis, the squamous epithelium has basal and suprabasal layers, and differentiates to form a cornified envelope comprised of a flattened layer of specialized cells. Electron microscopy shows lipid lamella, but they do not form an impermeable intercellular lipid envelope as they do in the epidermis, making vaginal wall permeable to water and soluble proteins. Also unlike epidermis, the vaginal epithelium usually is not keratinized and stores glycogen. The synthesis of glycogen is diminished by estrogen cessation after menopause, as well as the epithelial thickness already mentioned (Anderson et al. 2014).

The CO_2 laser is a fractional, ablative laser that emits light at the wavelength of 10,600 nm, which is strongly absorbed by tissue's water (Fisher 1992), promoting microthermal ablation of the epithelium (the so-called microthermal zones – MTZ), with preservation of healthy tissue islands between the ablated area. This ablation induces the body to repair and promote re-epithelization of the vaginal tissue, restoring the flora, the thickness, and lubrication. It also causes an important heating deep in the dermis surrounding the ablated tissue, which, in turn, promotes neocollagenesis and reorganization of the elastic and collagen fibers of the connective tissue, restoring the healthy architecture of the vagina. Fractional CO_2 laser, differently from local therapies, can act in deep layers stimulating collagen synthesis (Gaspar et al. 2011).

The Er:YAG laser is a fractional, nonablative laser that emits light at the wavelength of 2940 nm, which is also absorbed by tissue's water, with 15 times more affinity than the CO_2, with less recovery downtime but also less collagen production, since its rays reach smaller depths. It induces photothermal heating of the vaginal wall without ablating its surface, which boosts neocollagenesis and remodeling of the connecting tissue and also stimulates regrowth of the epithelium, but with comparatively less thermal injury and less mucosa swelling than the CO_2 laser (Gaviria and Lanz 2012).

The Er:YAG 2940 nm Smooth Mode is a modified Erbium 2940 nm in which laser energy is delivered onto the mucosa tissue in a fast sequence of low-fluence laser pulses inside an overall super-long pulse of several hundred milliseconds. The delivered laser energy thus results in an overall nonablative buildup of heat and creates a temperature increase within the mucous tissue. With this Er:YAG laser (*IntimaLase™, Fotona®*), human tissue can get nonablatively heated to a depth of 100 microns, which is just what is required for a depth-controlled thermal treatment of vaginal mucosa tissue (Vizintin et al. 2012).

However, through diverse ways, Er:YAG and CO_2 lasers share some similarities in their mechanism of action, since both target the water resulting in tissue heating. This mechanism involves a controlled heat-shock response that stimulates the production of a small family of proteins called the heat-shock proteins. Heat-shock proteins 43, 47, and 70 (a protein subtype as chaperone of collagen, which is overexpressed after laser irradiation) appear to play an important role, stimulating the production of many growth factors. Among these factors are: transforming growth factor-A (stimulates matrix proteins synthesis such as collagen), basic fibroblast growth factor (stimulates angiogenic activity with endothelial cell migration and proliferation), epidermal growth factor (stimulates re-epithelization), platelet-derived growth factor (stimulates fibroblasts to produce extracellular matrix components), and vascular endothelial growth factor (regulates vasculogenesis and angiogenesis). Therefore, the laser stimuli activate fibroblasts to produce new collagen, other components of the extracellular matrix (proteoglycans, glycosaminoglycans, etc.), and new vessels, with specific effects on epithelial tissue (Prignano et al. 2009). Such body response of recovery results in a thicker epithelium, neocollagenesis, reorganization of the trabecular architecture of the collagen, neovascularization with recovery of the papillary disposition of the subepithelial connective tissue, and regain in production of mucopolysaccharides

by the extracellular matrix (Salvatore et al. 2015). These alterations lead to reestablishment of the vaginal health, with return of lubrication, ameliorate in epithelial pallor, reverse of vaginal laxity, return of vaginal pH and microbiota, improvement in elasticity of the vaginal wall, and elevation of sexual arousal and satisfaction for both the woman and her partner.

In our practice, we often use the CO_2 Laser *Femilift*™ from *Alma Lasers* for vaginal rejuvenation, which has a special sterile, disposable, and individual cover for each patient. This facility makes the procedure more hygienic and allows the operator to perform multiple laser sessions subsequently, without the long wait for sterilization (Fig. 1). The Er:YAG laser we often use is either from *Fotona (IntimaLase*™ and *IncontiLase*™*)* or from *LMG (Solon Femina*™*)*, and both of them have a laser speculum that avoids the contact between the laser device and the vagina, but needs to be sterilized before the next patient. The former, *IntimaLase*® and *IncontiLase*®, emit, respectively, a circumferential and an angular laser beam, to reach either the whole vaginal wall or selectively the anterior wall (for urinary incontinence) – Fig. 2.

Indications

The vaginal laser is indicated to women between 20 and 80 years old with one of the following symptoms (Salvatore et al. 2014; Zerbinati et al. 2015; Gambacciani and Levancini, 2015; Vizintin et al. 2015; Perino et al. 2016; Gambacciani et al. 2015):

- Hypotrophy and/or vaginal atrophy
- Mild to moderate urinary incontinence
- Sexual dysfunction such as dyspareunia, dryness, low vaginal sensitivity, and vagina wall bleeding during intercourse
- Postpartum and lactation (temporary estrogen-reduced levels)
- Vagina relaxation/laxity
- Posttreatment for gynecological cancers (breast and endometrial), to improve vaginal symptoms of the lack of estrogen

Contraindications

- Pregnancy
- Bacterial or fungal vaginal infection – laser treatment can be performed only 30 days after vaginal infection treatment
- HPV infection
- Active herpes viral infection - laser treatment can be performed without active infection and during prophylaxis treatment
- Gynecological oncology pathologies
- Previous surgical orthesis implant for urinary incontinence, like transvaginal mesh/sling
- Impaired immune system or chronic corticoid therapies

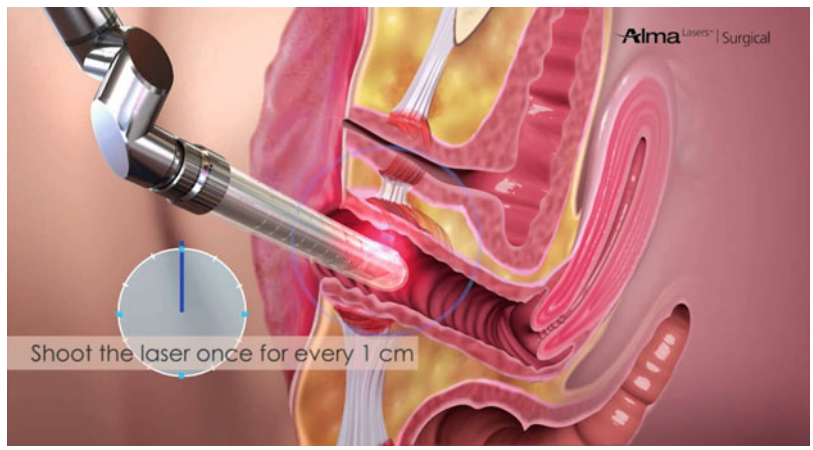

Fig. 1 CO_2 vaginal laser – Femilift from Alma Lasers, with its disposable cover and its marks signaling the 1 cm distance of each shot, circumferentially

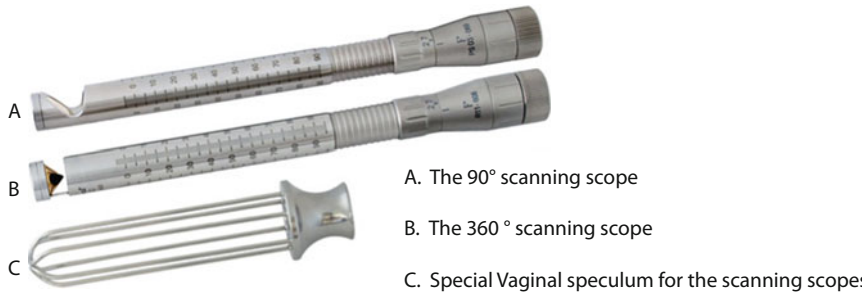

Fig. 2 Er:YAG vaginal laser: Fotona accessories needed for application of the laser beam to the vaginal mucosa, consisting of, from the bottom to the top, a sterile laser speculum, a circular 360° (IntimaLase), and an angular 90° (IncontiLase) adapter. (**a**) The 90° scanning scope. (**b**) The 360° scanning scope. (**c**) Special vaginal speculum for the scanning scopes

- Scleroderma, lichen sclerosus, vitiligo, or psoriasis
- Uncontrolled diabetes
- Anticoagulant therapy
- Patients who have used isotretinoin in the last 12 months (Salvatore et al. 2014; Zerbinati et al. 2015; Gambacciani and Levancini 2015; Vizintin et al. 2015; Perino et al. 2016; Gambacciani et al. 2015)

Orientations Prior to Treatment

Prior to the treatment, patients should fill the pretreatment questioner and sign the Informed Consent Form. It is highly recommended that the physician take a detailed patient medical history, including previous treatment modalities, to examine the gynecology condition for treatment suitability with the vaginal laser (Salvatore et al. 2014; Zerbinati et al. 2015; Gambacciani and Levancini 2015; Vizintin et al. 2015; Perino et al. 2016; Gambacciani et al. 2015).

It is also important to determine why the patient is seeking treatment and to understand her expectations. It is advisable to warn the patient that there may be very mild discomfort associated with the treatment.

Patients shall perform a pregnancy test at least 1 day before the session, and show a recent cervical screening test result (best if within less than 30 days).

Patients with personal history of previous genital herpes simplex infection should undergo the prophylaxis protocol, which is valacyclovir 500 mg every 12 h for 7 days, starting 24 h prior to the laser session. Acyclovir or fancyclovir can also be used (Beeson and Rachel 2002).

Procedure

1. The patient should be in lithotomy position.
2. Insert a disposable or sterile vaginal speculum to look for active lesions, signs of infection, or alterations of either the vaginal fluid or the mucosa. If the normal aspect is observed, dry the pathway with sterile gauze to avoid burning from water absorption.
3. After taking out the speculum, carefully introduce the laser device completely, until you feel touching the cervix or the patient complains of pain. Some lubricant oil, like mineral oil, might be used in the introit if it is too dry, avoiding the laser window. Usually, the laser probes are marked circumferentially and have a sign that represents the vaginal depth, between 7 and 13 cm. They also have a security distance from the tip to the laser window, which prevents the patient from cervix irradiation.
4. Some devices have a 360° laser-beam delivery system, enabling 360° irradiation of the vaginal canal, whereas others carry a limited laser window, which needs to be clockwise rotated systematically to reach the totality of vaginal

wall circumference. These last devices are also assigned to make rotation easy and patterned, so the doctor is sure to perform the 360° irradiation.

5. After the first circumferential deep shot, pull back the device as marked (1 cm), making subsequent shots until the whole marked area is outside the vagina. Patients usually report some heating sensation when the laser window is coming closer to vaginal introit. This is when you shall fully insert it again and perform a new pass, starting from the deep to the introit.
6. The number of subsequent passes and laser sessions are also described by the manufacturer's protocol, depending on the patient's complaints and the results achieved by each session (Salvatore et al. 2014; Zerbinati et al. 2015; Gambacciani and Levancini 2015; Vizintin et al. 2015; Perino et al. 2016; Gambacciani et al. 2015).

Treatment Protocols

Each laser device has its own protocols, with the right fluency and power indicated for the patient's needs. Nevertheless, one rule is always true: the higher the power, the bigger is the depth and the magnificence of the thermal injury provoked.

If the main objective is tightening, for example, higher energies are required. The doctor must perform three consecutive passes, throughout the whole vagina wall, circumferentially, in each laser session, with a total of three sessions spaced by a period of 30 days for the best outcomes.

The same protocol with high energy is also applied to urinary incontinence treatment. However, in these cases, at least two passes should be applied focusing on the anterior wall of the vagina (using a clock as a reference, the laser window must be focused between 10:00 and 02:00 o'clock), and one circumferential pass.

When vaginal dryness and atrophy are the main complaints of the patient, lower energy is indicated. One or two circumferential passes are enough for each session. Three sessions are necessary for better results.

Posttreatment – What Is Recommended or Expected

- No sexual intercourse for 3–7 days
- No tampons for 3 days
- No healing cream is needed
- Some translucent or blood discharge might occur within the following 3–7 days after the procedure
- Be available for patients' contact. Ask them to notify you in case of any bleeding, fever, or other unusual side effects (Salvatore et al. 2014; Zerbinati et al. 2015; Gambacciani and Levancini, 2015; Vizintin et al. 2015; Perino et al. 2016; Gambacciani et al. 2015)

Vaginal Laser Rejuvenation – Literature Review

Over the last few years, much has been studied about the use of lasers for vaginal aging. In a 12-week treatment with fractional CO_2 laser for GSM, this treatment has been proved to be efficacious, feasible, and safe to ameliorate the GSM symptoms (Salvatore et al. 2014). In 2015, researches have revealed restoration on vaginal mucosa by the remodeling and neosynthesis of collagen in the lamina propria (Zerbinati et al. 2015). In the same year, Gambacciani and colleagues showed that vaginal erbium laser (VEL) induced subjective improvement in dryness, dyspareunia, and the overall VHIS in 65 postmenopausal women (PMW) after three monthly sessions. Twenty-one of them who also had mild-moderate stress urinary incontinence reported improvement, which was measured by their score at the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) (Gambacciani and Levancini 2015). Also in 2015, another group demonstrated the improvement in vaginal laxity, stress urinary incontinence, and GSM symptoms after Er:YAG laser treatment (Vizintin et al. 2015).

In 2016, a study involving 30 postmenopausal women complaining about GSM and overactive bladder (OAB) symptoms showed that, after three

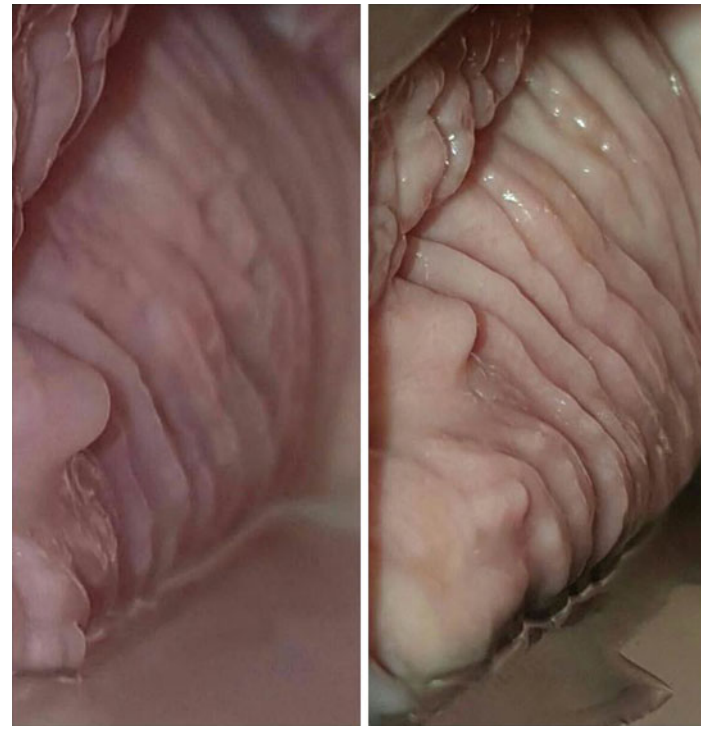

Fig. 3 Case 1: Before (*left*) and after (*right*) three CO_2 Femilift™ laser sessions, showing improvement in vaginal thickness and rugations. Courtesy of Dr. Ana Lucia Sayeg

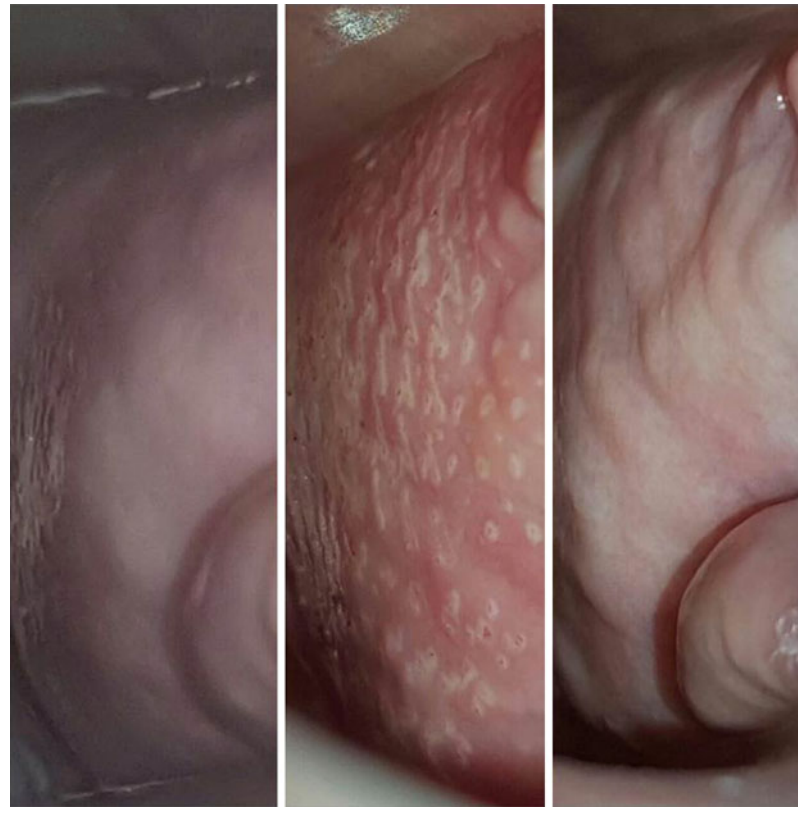

Fig. 4 Case 2: Before (*left*), immediately after (*middle*), and 30 days after (*right*) CO_2 laser. In the middle figure, note the microthermal zones (MTZ) provoked in the mucosa, representing epithelium vaporization. After healing (*right*), see the improvement in palor and rugations of the vagina wall. Courtesy of Dr. Andre Vinicius

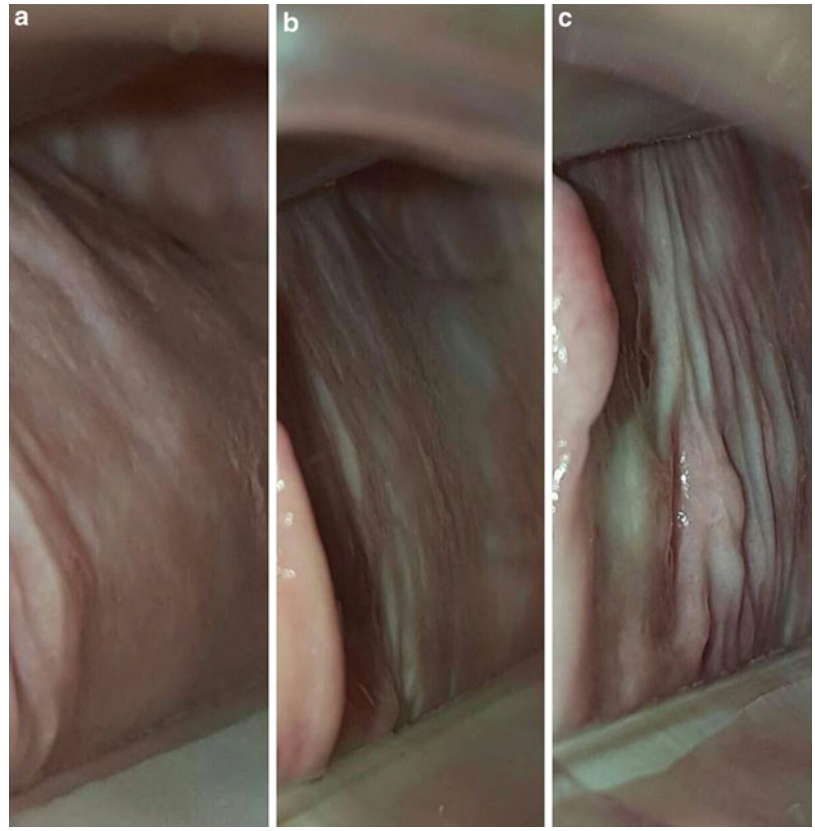

Fig. 5 Case 3: (**a**) Before, (**b**) after 1 CO_2 laser session, and (**c**) after two laser sessions. Observe the gain in vaginal wall rugae and loss of palor. Courtesy of Dr. Andre Vinicius

sessions of CO_2 vaginal laser, there was significant improvement on OAB symptoms, such as reduction in the number of micturition and of urge episodes (Perino et al. 2016). In the same year, 70 women with GSM and vestibulodynia were studied by Murina and colleagues. Patients underwent three sessions of treatment with microablative fractional CO_2 laser, applied on the vulva and vestibular surface, resulting in statically significant improvement in dyspareunia and pain scores (Murina et al. 2016). The benefits of CO_2 laser treatment on the vaginal flora were also documented: there was restoration of the postmenopausal vaginal flora equilibrium, with the predominance of *Lactobacillus*, and the low pH, protecting women from vaginal infections (Athanasiou et al. 2016).

In 2017, a study presented 1-year results with fractional CO_2 laser for genitourinary syndrome of menopause. It emphasized the advantages of positive effects duration and the low risk of adverse events, concluding that CO_2 laser therapy was safe and effective for GSM (Sokol and Karram 2016).

Authors Experience

In our practice, we experienced different technologies, but most of our results were performed with the CO_2 Laser Femilift™, from Alma Lasers. These results are shown in the case reports below.

In case 1 (Fig. 3), a 62-year-old postmenopausal woman was submitted to three monthly sessions of CO_2 Femilift™ laser, with the following parameters: 100 mJ per pixel, long-pulse, Power: high, three circumferential (360°) passes per section.

Case 2 (Fig. 4) shows the specular exam of a 44-year-old woman with premature menopause and a family history of breast cancer. The figure on the *left* shows the vagina walls before the laser session: note the palor, the dryness, and

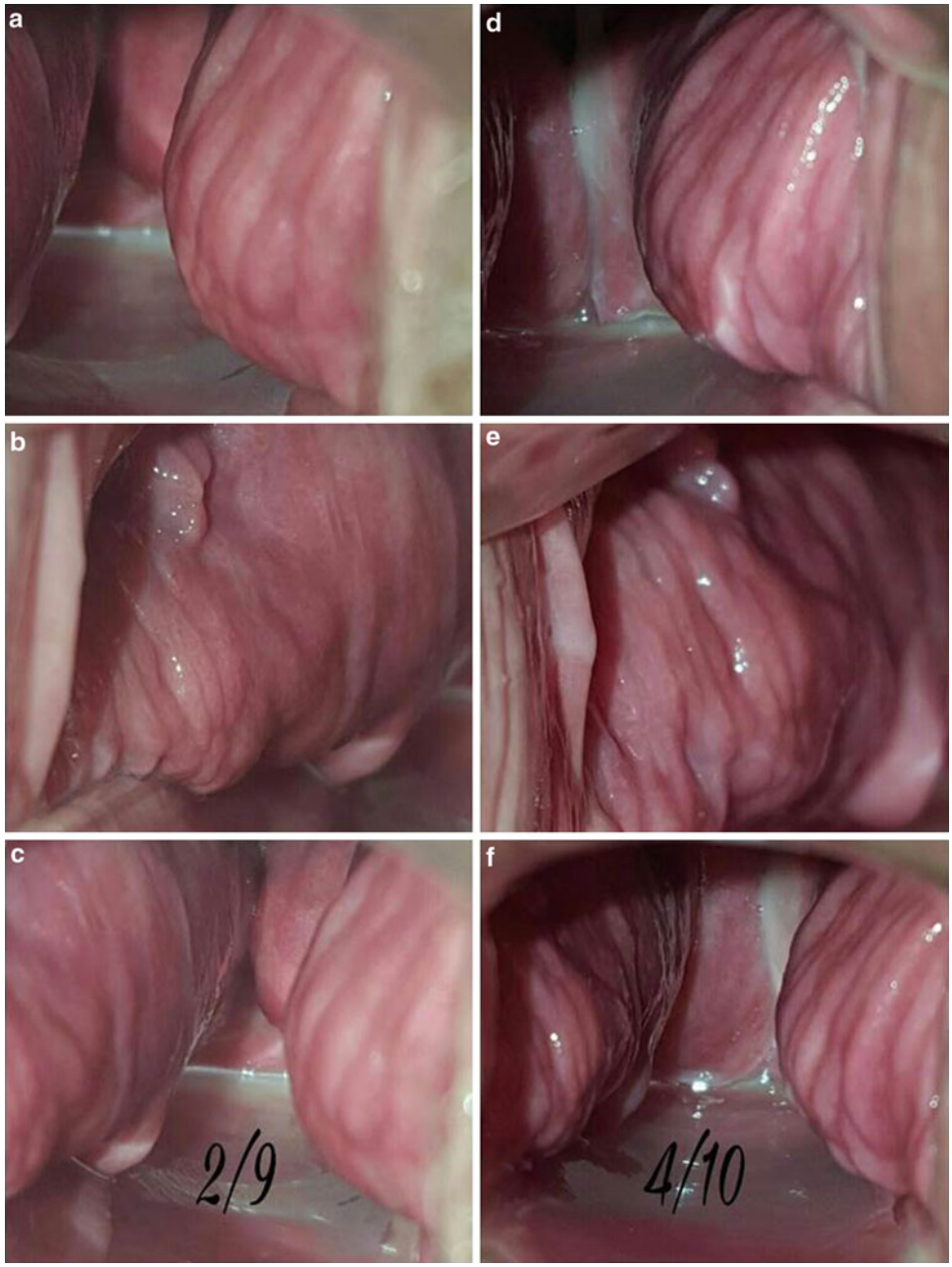

Fig. 6 Case 4: 47-year-old woman before (*left* pictures) and after (*right* pictures) three Er:YAG Femina™ monthly sessions. **a**–**c** show, respectively, the right, the left, and both vagina walls, before the laser treatment. **d**–**f**, on the right side, show the same vagina walls 30 days after the last laser session. Courtesy of Dr. Andre Vinicius

the absence of rugations. Three circumferential passes of the CO_2 Femilift™ laser were performed, with the parameters: Energy: 75 mJ per pixel, long-pulse, Power: medium. The middle figure shows the vagina wall immediately after the three laser passes: note the microthermal zones (MTZ) ablated in the mucosa, representing epithelium vaporization. After healing (*right*), see the improvement in pallor and rugations, 1 month after the first laser session.

In case 3, we show the specular exam of a 58-year-old postmenopausal woman, with vaginal dryness and dyspareunia (Fig. 5a–c). In Fig. 5a, vaginal wall before any treatment: observe the pallor, the lack of rugae, and dryness. In Fig. 5b, vaginal wall after the first session of CO_2 laser, starting to present rugae and increased mucous secretion. In Fig. 5c, observe the vaginal wall 15 days after the second session of CO_2, with the healing areas (in *white*), significant increase in vaginal rugae, and improvement in pallor and in lubrication. The laser used was the Femilift™ with the parameters: Energy: 100 mJ per pixel, long-pulse, Power: high, three circumferential passes per section.

Case 4 (Fig. 6) illustrates a 57-year-old postmenopausal woman's specular exam, showing, in Fig. 6a–c, the right, the left, and both vagina walls, respectively, before the Er:YAG 2940 Femina™ laser treatment. On the right, in Fig. 6d–f, we can see the same walls 30 days after one laser session, with the 360° scope in multiple micropulse mode, 1.7 J delivered per shot, 3 multishots, 3 passes per session.

Conclusion

According to the literature review and our experience, laser treatment is a new and effective tool for vaginal rejuvenation. It is able to improve symptoms such as vaginal dryness, itching, urinary incontinence, dysuria, as well as vaginal pain during sex intercourse.

Take Home Messages

1. Almost half of menopaused women experiment some symptoms of the genitourinary syndrome of menopause (GSM), including vaginal dryness, dyspareunia, urinary incontinence, and loss of sexual pleasure.
2. The GSM is due to the ovarian failure and consequent lack of estrogen, which reposition is not always a comfort and feasible option for the patient.
3. The vaginal lasers were developed to stimulate, via deep tissue heating, the regrowth of epithelium, and dermis structures, with reorganization of collagen and elastin fibers, regain in mucosal thickness and irrigation, and recovery of vaginal wall elasticity and lubrication, with consequent increase in sexual pleasure.
4. The CO_2 and the Er:YAG lasers are the most studied and proven to be efficient technologies. Radiofrequency has also been used with promising results.
5. The candidate to the treatment must perform a Pap smear at least 30 days to the first laser session, as well as a nonpregnancy status warranty at the days of the laser sessions.
6. There cannot be any sign of active infection or neoplasia at the sessions, making the specular exam an essential tool before the laser procedure.
7. Herpes simplex previous infections require a prophylaxis treatment, starting 24 h prior to the laser session, and kept for 7 days (until re-epithelization).
8. Patients are oriented to refrain from sexual intercourse from 3–5 days after the laser. No healing cream is needed. Tampons are not recommended!
9. The treatment consists of three monthly laser sessions, with a maintenance protocol of annual single sessions.

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Laser Safety

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Abstract

This chapter will describe the laser security aspects from the classification of laser's risk until the preventive measures. The main risks such as eye risks, skin risks, teeth risks, plume risks, fire risks, and electrical risks will be discussed, and preventive measures since protective equipment until behavioral aspects will also be addressed.

Keywords

Laser • Safety • Hazards • Risk • Preventive • Eye risk • Skin risk • Teeth Risk • Plume Risk • Fire Risk • Electrical Risk • Home-use devices

Contents

Introduction

The International Electrotechnical Commission (IEC) is a global organization that prepares and publishes international standards for all electrical, electronic, and related technologies. The IEC document 60825-1 is the primary standard that outlines the safety of laser products (Smalley 2011).

The IEC published some documents that represent international benchmarks of laser safety. These documents are 60601, 60825, and 60825-Part 8. The national regulatory agencies usually combine these international recommendations with national legislation to produce local laser safety guidance and/or regulation.

Classification is based on calculations and determined by the Accessible Emission Limit (AEL) also incorporating viewing conditions as follows:

- **Class 1 lasers** products that are very low risk and "safe under reasonably foreseeable use," including the use of optical instruments (eye loupes or binoculars) for direct intrabeam viewing. There is risk of glare, dazzling, and reduction in color vision due to afterimages:
  - Examples: laser printers and compact disk players

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- **Class 1 M lasers** have wavelengths between 302.5 nm and 400 nm and are safe except when used with optical aids (e.g., microscopes, loupes, binoculars):
  - Safe under reasonably foreseeable conditions of operation (unaided eye) but may be hazardous if the user employs optics within the beam
  - Examples: optical fiber communication systems
- **Class 2 lasers** have visible wavelengths (400–700 nm) safe if viewed for less than 0.25 s (safe for momentary exposures but hazardous if deliberately staring into the beam). Do not permit human access to exposure levels beyond the Class 2 AEL for wavelengths between 400 nm and 700 nm. Any emissions outside this wavelength region must be below the Class 1 AEL:
  - Emitting visible laser beams.
  - Not inherently safe for the eyes, but protection by natural aversion responses, such as blink reflex, is usually adequate.
  - Example: amusement laser guns, laser pointers, and barcode scanners.
- **Class 2 M lasers** have wavelengths between 400 nm and 700 nm *and are potentially hazardous when viewed with an optical instrument*. Any emissions outside this wavelength region must be below the Class 1 M AEL:
  - Emitting visible laser beams
  - Eye protection normally by aversion responses including blink reflex but may be more hazardous if the user employs optics within the beam
  - Example: level and orientation instruments for civil engineering applications
- **Class 3R lasers** are marginally unsafe for intrabeam viewing of beams and are potentially hazardous, but the risk is lower than that of Class 3B lasers because the accessible emission limit is within five times the Class 2 AEL for wavelengths between 400 nm and 700 nm and within five times the Class 1 AEL for wavelengths outside this region:
  - Direct intrabeam viewing is potentially hazardous, but the risk is lower than Class 3B lasers.
  - Fewer manufacturing requirements and control measures for the user than for Class 3B lasers.
  - Example: laser pointers and alignment lasers.
- **Class 3B lasers** are normally hazardous under direct beam viewing conditions but are normally safe when viewing diffuse reflections. May produce minor skin injuries or even pose a risk of igniting flammable materials:
  - Output power of continuous wave not exceeding 0.5 W
  - Examples: lasers for physiotherapy treatments
- **Class 4 lasers** are hazardous under both intrabeam and diffuse reflection viewing conditions. They may cause also skin injuries and are potential fire hazards:
  - High-power output devices
  - Output power of continuous wave exceeding 0.5 W
  - Capable of producing hazardous reflections
  - May cause eye and skin injuries
  - Could constitute a fire hazard
  - Requires extreme caution in using
  - Examples: laser projection displays, laser surgery devices, and laser metal-cutting devices

Most of the lasers used in medicine are Class 3 or 4, which means that risks are greater in every application.

Well-stablished routines that consider these risks can prevent mistakes such as described below.

Preventive Measures

The preventive measures are always the gold standard choice on laser safety.

The control measures are engineering nature, administrative nature, procedural nature, and protective equipment.

These measures are listed and described below:

1. Engineering measures manufactures safety measures built into the systems to prevent accidental emission of laser radiation. Some examples are

guarded foot switch, key lock, housing interlocks, audible and visible emission indicators, beam stops, aperture covers or shutters, standby mode, foot + hand operative switches, and contact switches and sensors.

2. Administrative measures are continuous monitoring of the safety program by responsible physician, compliance with the laser security measures and laser safety officer or committee; formal audits; written policies (safety setup checklists, procedure log sheets), procedures, and documentation tools; mandatory education and training programs; and a reporting mechanism for complications.
3. Procedural measures are perioperative activities or work practices adopted by all the laser personnel in order to prevent complications. This includes controlled access to laser room, preparing a laser-safe operative site (nonflammable antiseptics and prep solutions, nonreflective material, fire-retardant drapes, avoid oxygen source near laser application, bowel preparation in the case of perineal and perianal laser application), controlling of electrical hazards, eliminating smoke from the surgical site intraoperatively, setting up, checking and testing the laser system and accessory equipment before usage (test the laser beam firing in a tongue blade before the first use of the day), and assisting the physician and the patient before, during, and after the laser application.
4. Protective equipment: window barriers, mirror coverage, signs on room access door, labels, protective eyewear (Figs. 1, 2, and 3), teeth protection (Fig. 3), fire extinguishers, nonflammable drapes, anodized instruments, skin protection, masks, and smoke evacuation systems with filters (Smalley 2011; Smalley and Goldman 1998).

Fig. 1 Eyes protection

Hazards Area

It is extremely advisable that signs posted visibly indicate the area where there are laser hazards. In some countries it is a legal obligation. These signs will alert the staff and patients about the area where laser security measures are necessary, such as control access and wearing safety glasses. It is also advisable that in each entryway to this area, there are always available protective goggles during laser operation in case of emergency entry in this area.

The doors must always be closed but never locked during laser use.

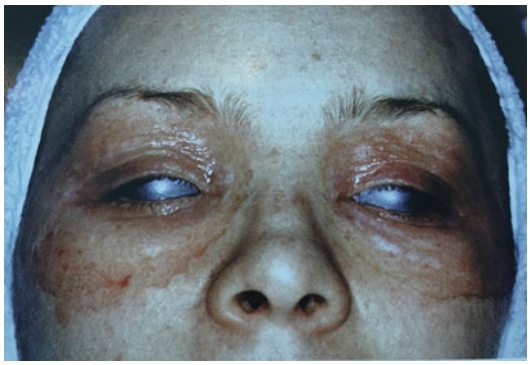


Fig. 2 Intraocular protection (eyeshield)

Beam Hazards: Related to Direct or Reflected Impact of the Laser Beam to Tissue

Eye Risks

The human eye has as the only defense system the "blink reflex." This reflex takes one-fourth of a second to be effective. As the lasers work in milli-, nano-, and picoseconds scale, it is not possible to the "blink reflex" to protect against the lasers. Furthermore, some lasers do not work with wavelengths of bright visible light, such as infrared ones, which does not elicit the reflex.

Even with eyelids closed, some lasers can cause damage to the eyes that makes us emphasize even more the importance of eye protection.

The eye lens is capable to focus light in a very small point in retina that makes the coherent light of lasers even more dangerous (Dudelzak and Goldberg 2011).

As known even a laser pointer with an output greater than 5 mW can induce permanent eye injury. So many professional laser devices and home-use devices are able to cause eye damage.

Some laser variables are related to intensity of eye injury.

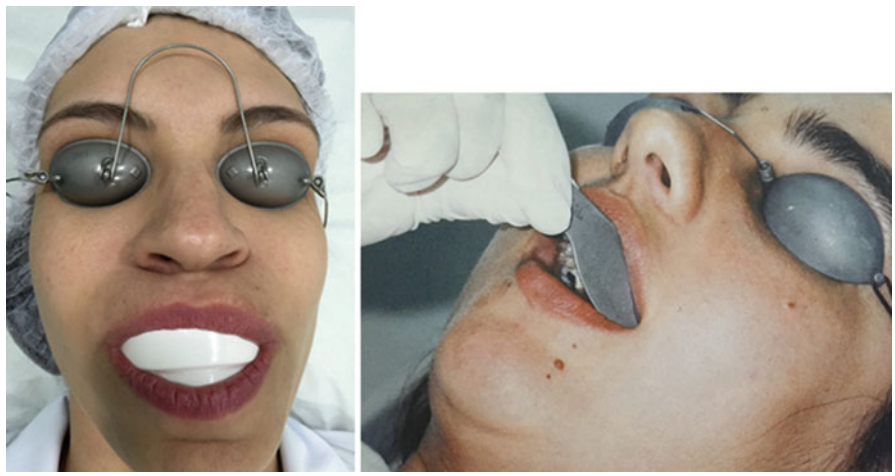


Fig. 3 Teeth protection

Laser variables are:

1. Wavelength

Lasers operating with wavelengths of ultraviolet (200–400 nm), mid-infrared (1400–3000 nm), and far-infrared (3000–10,600 nm) are absorbed by the anterior ocular segment inflicting damage on the lens and cornea.

Visible light lasers (400–760 nm) and near-infrared ones (760–1400 nm) are absorbed in the posterior ocular segment by the retina and vascular choroid.

Wavelengths above 700 nm and below 400 nm may cause photochemical damage for the cornea and lens cataract, and above 1400 nm can cause corneal burn.

Blind spots and glaucoma due to damage to retina vessels and pigmented iris are also possible.

The chromophores of the eyes are the same of daily use in dermatology such as water, melanin, and hemoglobin.

The lasers such as CO2 (10,600 nm), Nd-YAG (1320 and 1064 nm), alexandrite (755 nm), Diodo (810 nm), Er-YAG (2940 nm), and Q-switched ones (alexandrite, ruby, and Nd-YAG) can cause damage to multiple structures of the eye through mechanisms of photochemical, photothermal, and photoacoustic damage.

2. The pulse duration

The pulse duration of almost all lasers used in dermatology is smaller than the blink reflex elicit time (0.25 s), which makes almost all pulse durations of risk.

The shorter the pulse duration, the faster the delivery of the energy defined in the parameters.

3. The energy/fluence

The higher the energy defined in the parameters, the greater the risk of eye damage.

4. The beam diameter

The beam diameter can influence more or less according to the wavelength and the position of incidence on the eye.

The damage is also modified by eye variables. The eye variables are:

1. The location of damage in the eye (foveal ones are worst).
2. The iris color (dark-skinned ones are worst).
3. If the pupil is dilated (night lesions or lesions in the dark can be more dangerous than in daylight).
4. The state of refraction of the eye at the moment of injury (if the focus is before or after the retina, the damage can be less or more intense) (Barkana and Belkin 2000).

After being damaged by a laser, the primary eye injury can evolve with secondary eye injuries that are caused by shock wave, heat, and release of various noxious agents by the directly injured neurons (Lee et al. 2011).

If the damage occurs, the treatment options are few. Corticosteroids are the main choice, but anecdotal case reports used antioxidant vitamins and vasodilator drugs. There are drugs under development that intend to block secondary injury. These drugs are called neuroprotective compounds. Some reports also suggest the use of growth factors (Lin et al. 2011; Jewsbury and Morgan 2012).

Sometimes surgery may be necessary for the treatment.

Because of the above exposed, the eye protection is one of the most important topics in laser training, laser use, and laser security.

The eye protection may be thought for the patient, for the physician, and for the support personnel. The goggles are the main component in eye protection, and the goggles for protection against laser wavelengths are specially designed for that.

These patient goggles may be of heatproof stainless steel with smooth polished concave surface and anodized convex surface without any transparency (external or topical usage). The

staff goggles are generally of other material such as coated glass or polymeric material with selected transparency. The selected transparency is chosen according to the laser that will be used, because they can have a central rejected wavelength or a band of wavelengths. Another characteristic of these goggles is the optical density (OD) that is the log of attenuation of the light transmitted through the lens. So lens with an ODof 4 allow $1/10^4$ of the laser energy to penetrate. These goggles also may have side shields and no front surface reflection.

All goggles may have permanent labels indicating wavelengths and optical density, side shields, adequate visible light transmission, and proper fit and be comfortable.

When the goggles are cracked, scratched, discolored, or with any other damage to lens, frame, or straps, they may be replaced.

Abrasive cleaning methods and alcohol-based cleaning solutions can degrade the optical coating on the lenses and decrease the optical density, resulting in eye injury.

As the eye injury may be caused also by reflected laser and not only by direct light emission, all jewelry should be removed, glass of windows and mirrors should be covered, and all instruments should be anodized, roughened, or ebonized with fluoropolymeric coating. The reflection is not related to instrument color as black can be as reflective as silver.

Chlorhexidine should not be used to disinfect eye contact goggles because this substance may cause keratitis and corneal opacification.

According to national regulations, door warning signs may be placed outside the laser operation rooms to alert visitors about risks.

Some technologies to transform lasers in eye-safe machines have been suggested such as the use of efficient wide-angle forward scattering diffusers that would change the coherent nature of lasers and intense pulses lights (IPLs) in noncoherent. This is theoretically justified because the biological effect of lasers and IPLs occurs after the light of these sources is scattered in the skin before acting in its final target (the chromophores). So the coherent nature of these light sources is not essential for the efficiency of the treatment. However, this technology is not applicable for all types of lasers and still must be further developed (Slatkine and Elman 2003).

It is important to remember that goggles protection is also necessary to protect the eyes from splatter of biological material that can occur after laser impact in the tissue.

Skin Risks

Skin risks are related to inappropriate selection of patients, energy, pulse duration, or any other laser controllable parameter or inadvertent firing of the laser.

To avoid skin risks, the continuous education and training programs are essential once the incorrect use of one laser variable may cause great damage to the skin.

Understanding the physics, the laser-tissue interaction, the laser parameters, and variables, knowing the characteristics of that specific machine that will be used in that treatment and the patient skin, and tailoring theses variables according to each case are the best ways to prevent accidental damage to the skin.

Cooling is also a good way to prevent laser damage in some cases. Depigmenting skin prior to laser therapy with topical hydroquinone 4 weeks before is a method to diminish some risks.

The skin damages can result in temporary or permanent lesions such as erythema, edema, crusting, blistering, scarring, atrophy, or hyper- or hypopigmentation (Dudelzak and Goldberg 2011).

Table 1 shows which damage each kind of radiation can cause in the skin and eyes.

Teeth Risks

Dental enamel is vulnerable to ultraviolet and infrared light. When using laser near the mouth, the patient should be alerted to maintain closed mouth, and some protection may be used as moistened gauze and protective mouthpiece (Fader and Ratner 2000).

Possible teeth damage is charring, cracking, flaking, and craters.

Table 1 Tissue changes caused by different radiations

Wavelength range	Spectrum	Eyes	Skin
200–280 nm	UVC	Photokeratitis (inflammation of the cornea, equivalent to sunburn)	Erythema, burns, and skin cancer
280–315 nm	UVB	Photokeratitis (inflammation of the cornea, equivalent to sunburn)	Tanning, burns, and skin cancer
315–400 nm	UVA	Photochemical cataract (clouding of the eye lens)	Photoaging, tanning, and skin cancer
400–780 nm	Visible	Photochemical damage to the retina, retinal burn	Burns, photosensitivity reactions, and increasing pigmentation
780–1400 nm	Infrared A	Cataract, retinal burn	Burns
1400–3000 nm	Infrared B	Aqueous flare (protein in the aqueous humor), cataract, corneal burn	Burns
3000–10,000 nm	Infrared C	Corneal burn	Burns

Adapted from Mattos (2012)

Non-beam Hazards: Secondary Hazards Not Related to Beam Directly

Fire Hazard

The combustible materials above are of risk of ignition when exposed to certain lasers:

- Gauze
- Towels
- Drapes
- Dry sponges
- Plastics
- Rubber
- Tape removers
- Skin degreases and skin preparation solutions
- Foam devices
- Respiratory devices (face masks, nasal cannulae)
- Methane gas (perianal area)
- Makeup, hair spray, alcohol-based mousse or gels, nail polish
- Oil-based eye ointments
- Products with alcohol
- Solutions with iodophors
- Hair-bearing areas

Some of this kind of risk materials can be prepared with saline solution prior to the procedure to reduce risk of ignition. Other materials may be avoided in the laser room.

When using CO2 laser on tissue, it is important to notice that generally a carbonized tissue layer is built up during application. This layer blocks laser penetration and continuously heats. If not removed this carbon layer can heat to temperatures over 1000 °C making possible to fire ignition, burns, and extensive tissue damage (Fader and Ratner 2000).

Hair and cotton can be ignited by lasers in an enriched oxygen atmosphere or when not soaked with saline solution.

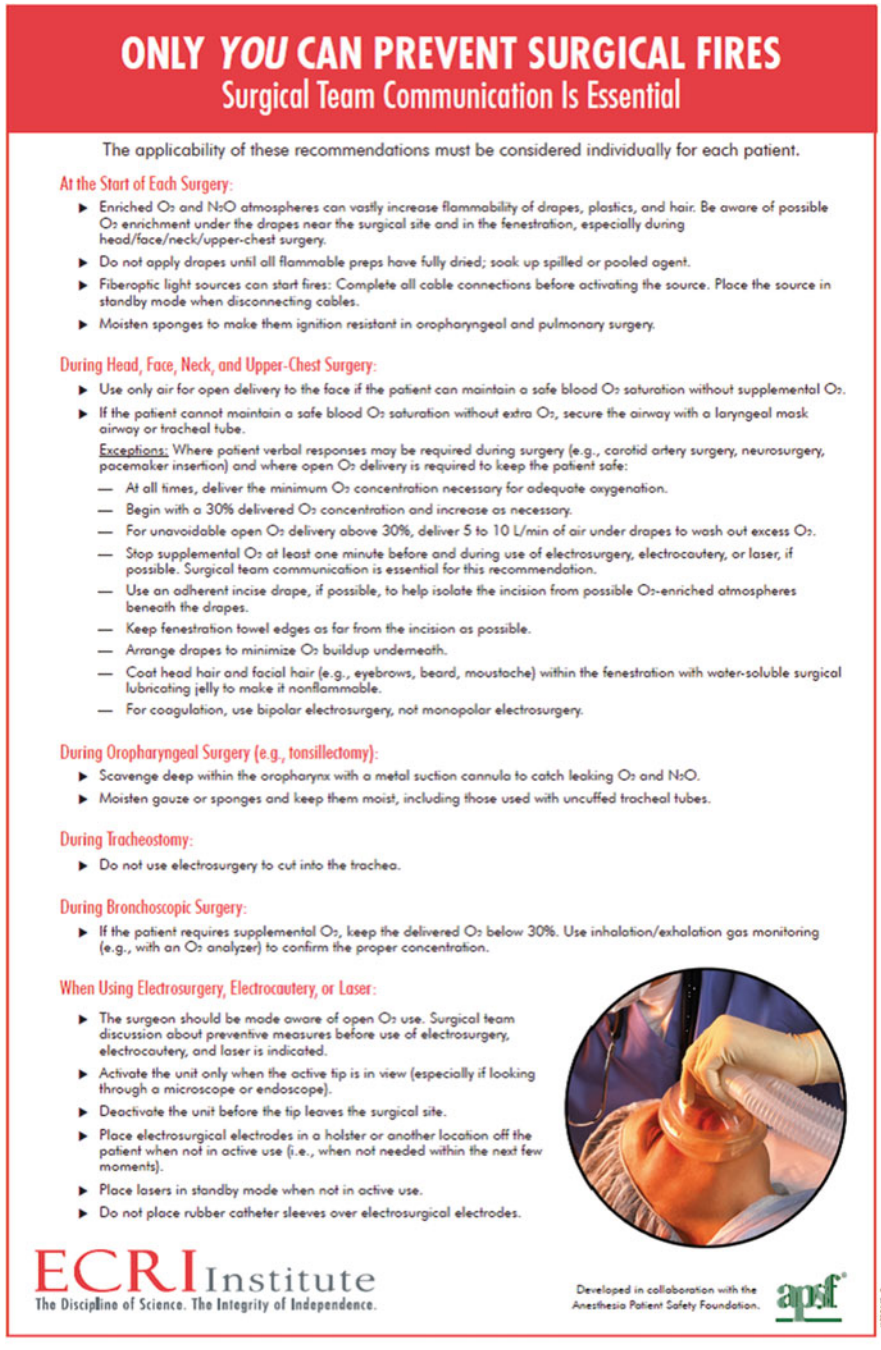
A fire extinguisher for standard electrical equipment and a water container must be available to any emergency when working with fire hazard.

The O_2-enriched atmosphere is the most common cause of fire in laser use (Sheinbein and Loeb 2010). The fire ignition can occur even out of laser treatment field (remote fire) as reported in literature (Waldorf et al. 1996) (Fig. 4).

Electrical Hazard

The laser devices are high-voltage, high-current instruments, and there is great risk of circuity fire and electrocution. Only trained personnel may operate these devices.

Correct installation and grounding are very important in preventing electrical hazard.



ONLY *YOU* CAN PREVENT SURGICAL FIRES
Surgical Team Communication Is Essential

The applicability of these recommendations must be considered individually for each patient.

At the Start of Each Surgery:

- Enriched O_2 and N_2O atmospheres can vastly increase flammability of drapes, plastics, and hair. Be aware of possible O_2 enrichment under the drapes near the surgical site and in the fenestration, especially during head/face/neck/upper-chest surgery.
- Do not apply drapes until all flammable preps have fully dried; soak up spilled or pooled agent.
- Fiberoptic light sources can start fires: Complete all cable connections before activating the source. Place the source in standby mode when disconnecting cables.
- Moisten sponges to make them ignition resistant in oropharyngeal and pulmonary surgery.

During Head, Face, Neck, and Upper-Chest Surgery:

- Use only air for open delivery to the face if the patient can maintain a safe blood O_2 saturation without supplemental O_2.
- If the patient cannot maintain a safe blood O_2 saturation without extra O_2, secure the airway with a laryngeal mask airway or tracheal tube.

  Exceptions: Where patient verbal responses may be required during surgery (e.g., carotid artery surgery, neurosurgery, pacemaker insertion) and where open O_2 delivery is required to keep the patient safe:
  - At all times, deliver the minimum O_2 concentration necessary for adequate oxygenation.
  - Begin with a 30% delivered O_2 concentration and increase as necessary.
  - For unavoidable open O_2 delivery above 30%, deliver 5 to 10 L/min of air under drapes to wash out excess O_2.
  - Stop supplemental O_2 at least one minute before and during use of electrosurgery, electrocautery, or laser, if possible. Surgical team communication is essential for this recommendation.
  - Use an adherent incise drape, if possible, to help isolate the incision from possible O_2-enriched atmospheres beneath the drapes.
  - Keep fenestration towel edges as far from the incision as possible.
  - Arrange drapes to minimize O_2 buildup underneath.
  - Coat head hair and facial hair (e.g., eyebrows, beard, moustache) within the fenestration with water-soluble surgical lubricating jelly to make it nonflammable.
  - For coagulation, use bipolar electrosurgery, not monopolar electrosurgery.

During Oropharyngeal Surgery (e.g., tonsillectomy):

- Scavenge deep within the oropharynx with a metal suction cannula to catch leaking O_2 and N_2O.
- Moisten gauze or sponges and keep them moist, including those used with uncuffed tracheal tubes.

During Tracheostomy:

- Do not use electrosurgery to cut into the trachea.

During Bronchoscopic Surgery:

- If the patient requires supplemental O_2, keep the delivered O_2 below 30%. Use inhalation/exhalation gas monitoring (e.g., with an O_2 analyzer) to confirm the proper concentration.

When Using Electrosurgery, Electrocautery, or Laser:

- The surgeon should be made aware of open O_2 use. Surgical team discussion about preventive measures before use of electrosurgery, electrocautery, and laser is indicated.
- Activate the unit only when the active tip is in view (especially if looking through a microscope or endoscope).
- Deactivate the unit before the tip leaves the surgical site.
- Place electrosurgical electrodes in a holster or another location off the patient when not in active use (i.e., when not needed within the next few moments).
- Place lasers in standby mode when not in active use.
- Do not place rubber catheter sleeves over electrosurgical electrodes.

Fig. 4 Security measures to prevent surgical fires

The clamps, connecting cords, power cords, fuses, circuit breakers, and plugs integrity may be checked before use (Dudelzak and Goldberg 2011).

Plume Hazard

Plume and smoke are frequently produced during laser usage, and the mutagenic and carcinogenic capacity of these subproducts is already recognized.

The disease transmission of plume and smoke has also been described and should be of concern of healthcare professionals and support staff (Sawchuk et al. 1989).

Red blood cells, cellular clumps, bacteria, HIV, and HPV DNA have been recovered of laser plume. Carbon particles, benzene, formaldehyde, acrolein, and over 41 toxic gases have been proved to be liberated by tissue after laser thermal disruption of cells (Andre et al. 1990; Ulmer 2008).

A laser surgeon infected in nasal anterior nares and another one with laryngeal papillomatosis after treating anogenital papillomatosis were reported in literature (Hallmo and Naess 1991).

The carbon and toxic compounds such as formaldehyde and benzene that exist in the plume and can cause (Ulmer 2008):

- Asthma
- Anemia
- Anxiety
- Bronchiolitis
- Carcinoma
- Cardiovascular dysfunction
- Colic
- Congestive interstitial pneumonia
- Dermatitis
- Dizziness
- Emphysema
- Eye irritation
- Headache
- Hepatitis
- HIV
- Hypoxia
- Lacrimation
- Leukemia
- Light-headedness
- Nasopharyngeal lesions
- Nausea or vomiting
- Sneezing
- Throat irritation
- Weakness

The common surgical masks are not able to filter the very small particles produced during laser application. The laser masks are made of synthetic fibers electrostatically charged and should be replaced periodically because the smoke eliminates their polarity after a period of usage. However, masks are not considered the first-line protective devices, once their chance to fail after 20 min of usage is high. The fit and wearing technique also interferes in masks efficiency.

Smoke aspiration and elimination is extremely necessary in the site and room of laser application and is the first-line protective device (Bigony 2007). The device should employ a triple-filter system. The high-efficiency particulate air filter that removes particles larger than 0.3 μm is not sufficient; an *ultralow particular air filter*, which is capable of removing particular matter up to 0.1 μm in size, is necessary and a charcoal filter to remove toxic chemicals within the smoke.

Some aspects to be evaluated before choosing the smoke aspirator are:

- Cost and operating expenses
- Effectiveness
- Filter and canister design
- Filter monitoring
- Fluid removal capabilities
- Foot pedal activation versus automatic activation
- Noise production
- Single use versus reusable
- Size

The distance between laser-treated site and the suction tip recommended is 1 cm, and the effectiveness drops from 99% to 50% when this distance is changed from 1 to 2 cm.

After laser use the room atmosphere may take 20 mins to return to normal concentration of particles.

Q- switched lasers present a particular challenge because they generate high-speed tissue fragments and particles that may escape capture by the smoke evacuation device. Some specific safety measures have been recommended in these situations such as splatter shields or collecting cones, treatment through a transparent membrane, appropriate eye protection, gloves, gowns, and laser surgical masks.

Some laser surgeons cover lesions with optical clear biological dressings and shoot through them, sacrificing 5–10% of energy drop for a clean and elegant protective barrier.

The recent application of lasers in treatment of fungal infections like onychomycosis turned on the alert to the possibility of viable fungi in smoke (Karsai and Däschlein 2012).

More intriguing is the suggestion by some authors that plume can spread viable malignant cells like melanoma cells to other sites (Lewin et al. 2011).

The American Academy of Dermatology recommends the use of face masks, eye protectors, gloves, gowns, caps, and shoe covers (Dover et al. 1999).

After the surgery one may remember that the smoke may have contaminated the covered and uncovered body surfaces. So washing hands and other body parts is advisable.

Smalley PJ and Goldman MP 1998 wrote: Of all safety hazards, *complacency* is by far the most dangerous. Accidents happen when we adopt the attitude: "I have been using lasers for years; we've never had a problem and it won't happen here."

This attitude makes that the surgeon and the staff relax on preventive measures opening the way for mistakes and accidents.

Home-Use Intense Pulsed Light (Ipl) and Laser Devices Safety

The home-use epilation devices use the same principle of selective photothermolysis of professional devices. Although some differences are important in home-use devices compared to professional ones:

- Low energy
- Few energy settings
- Fixed pulse duration
- Single fixed filter
- Small treatment areas
- Parallel skin cooling not possible
- Cover fewer skin tones

These differences should alert the manufactures and healthcare providers to not carry the clinical experience and knowledge of published studies about professional devices to the home-use ones (Town et al. 2012).

However, it is reasonable to expect similar side effects but with different incidences between these two kinds of devices.

The most common adverse effects reported in some studied devices were erythema, edema, pain, pigmentary changes, skin abrasion, folliculitis, skin irritation, pruritus, stinging, tingling, skin dryness, and blistering.

Although these adverse effects were not too frequent, the studies selected the subjects with inclusion and exclusion criteria in order to diminish risks. From the moment the devices are available to general population with no control of "inclusion and exclusion criteria," it is expected that the incidence of adverse effects will be higher in real-life daily use.

Home-Use Devices Desirable Characteristics

- Eye safe
- Easy to use without training

- Clinically effective (causes follicular biological damage without causing epidermal or ocular damage)
- Cost-effective in mass production

The manufactures developed different technologies to achieve these characteristics such as contact switches or sensors, auto-standby, and low-energy preset, and then they claim in some countries to reclassify of these devices as Class I laser category not requiring the use of safety glasses. The reclassification is under evaluation and not approved yet (Thaysen-Petersen et al. 2012).

Many of them do not inform the claimed fluence, pulse duration, wavelength, and homogeneity or spectral output (in case of IPLs) that complicates safety evaluation.

Some studied home-use devices showed risks of skin and eye damage regardless of safety mechanisms adopted by manufactures. Moreover, patients can misclassify their skin tones and can apply on tanned skin, and the safety mechanisms can fail. All these variables may be considered when classifying home-use devices safety (Town and Ash 2010).

The regulatory standards are not well defined on many countries, and some important measures regarding users education should be adopted as:

- Comprehensive education materials (e.g., user manuals)
- Consumer care support (e.g., telephone helpline support)
- Detailed instructions for use
- DVDs
- In-store trained sales consultants
- Physician-directed use of home-use devices
- Web-based tutorials

Once the home-use devices will be used as appliances, safety measures include those as electrical safety, assembling, maintenance, disposal, labeling, and categorization of consumer risk (as children).

Other issues may be considered when using home-use devices by nonprofessional users such as:

- Treating areas with melanocytic nevi.
- Treating areas with tattoos.
- Treating individuals with polycystic ovarian syndrome or ovarian hyperandrogenism.
- Treating pregnant woman.
- Treating tanned skin.
- Treating still healing skin.
- Treating individuals using photosensitizers or phototoxic drugs (specially in IPL devices).
- Treating face and eyebrows.
- Treating with suboptimal energy may induce paradoxical hair growth on home-use devices that typically work with lower energies compared to professional ones.

Take Home Messages

- The lasers used in medicine can be generally high-risk devices.
- Preventive measures will be effective if all involved staffs follow security routines that take the risks into account.
- The intrabeam most dangerous risk is the eye risk that may lead to complete blindness.
- The non-beam hazards are diverse and most reported is related to plume.
- The home-use devices are not free of risks, and consumers should be aware of the risks.

Cross-References

- ▶ CO_2 Laser for Other Indications
- ▶ CO_2 Laser for Scars
- ▶ CO_2 Laser for Stretch Marks
- ▶ CO_2 Laser for Photorejuvenation
- ▶ Erbium Laser for Photorejuvenation
- ▶ Erbium Laser for Scars and Striae Distensae
- ▶ Fractional Ablative and Non-Ablative Lasers for Ethnic Skin

- Intense Pulsed Light for Photorejuvenation
- Intense Pulsed Light for Rosacea and Other Indications
- Lasers for Aesthetic and Functional Vaginal Rejuvenation
- Laser on Hair Regrowth
- Laser for Hair Removal
- Laser Lipolysis
- Laser for Onychomycosis
- Laser Treatment of Vascular Lesions
- Light-Emitting Diode for Acne, Scars, and Photodamaged Skin
- My Personal Experience with Laser
- Non-ablative Fractional Lasers for Scars
- Non-ablative Lasers for Photorejuvenation
- Non-ablative Lasers for Stretch Marks
- Photodynamic Therapy for Acne
- Photodynamic Therapy for Photodamaged Skin
- Q-Switched Lasers for Melasma, Dark Circles Eyes, and Photorejuvenation
- Transepidermal Drug Delivery with Ablative Methods (Lasers and Radiofrequency)

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My Personal Experience with Laser

Neal Varughese and David J. Goldberg

Abstract

During the last 30 years, I have witnessed first-hand the advances and innovations in laser and energy-based technology. The pioneering work of Anderson and Parrish in 1983 was instrumental in powering this evolution. Anderson and Parrish lead the industry to develop energy-based systems that were more precise, thus allowing clinicians to target specific chromophores with minimal adjacent tissue damage and thereby decreasing the risk of complications. In 1985 upon completion of my dermatologic training, there were limited devices available, and their application was limited to a specific clientele. Fast forward to 2015, the array of devices that are now accessible to the everyday consumer is nothing short of miraculous. The single most effective treatment modality for conditions such as photodamage, acne scars, melasma, and stretch marks is difficult to define. The following chapter outlines my approach to treating these conditions based on my own clinical practice and research.

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Keywords

Acne scars • Melasma • Photorejuvenation • Stretch marks • Laser dermatology • Cosmetic dermatology • Radiofrequency • Intense pulsed light • Light emitting diode

Contents

Photorejuvenation

Photorejuvenation encompasses treatments that address the quality, tone, and texture of the skin and uneven pigmentation associated with photodamage. Initially, the only lasers available were *ablative* laser devices (CO2 and Er:YAG), which were effective, but had the disadvantage of requiring a high level of operator skill in addition to increased side effects and downtime for patients. In line with new technological developments, there has been a revolution in *non-ablative* modalities that address photorejuvenation leading to epidermal improvement and dermal collagen remodeling. These modalities include vascular lasers, mid-infrared lasers, intense pulsed light

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systems, radiofrequency devices, and light-emitting diode (LED) techniques. Epidermal lesions that remain after treatment are amenable to multiple treatment modalities. In such cases, the Q-switched lasers, such as 532 (KTP) and 694 nm (ruby) wavelength, are appropriate.

I treat many of my patients with intense pulsed light (IPL) (Fig. 1a, b). IPL encompasses wavelengths from 400 to 1,200 nm which permits the simultaneous treatment of broken capillaries and mottled pigmentation by targeting the chromophores of hemoglobin and melanin (Raulin et al. 2003). Often, the clinical results and patient satisfaction tend to be more impressive when I combine IPL treatments with adjunctive LED treatments. Various LED wavelengths have been shown to improve wound healing and promote human tissue growth. With the application of these techniques, caution needs to be taken in patients with a history of photosensitivity or who take medications that can increase the risk of photosensitivity.

The new IPL devices are very safe; however, scarring and hyperpigmentation still remain a risk. The clinical pearl, especially with darker skin types, is to employ a bleaching cream prior to performing treatment. In treating patients with dark skin types, the use of longer wavelengths or higher cutoff filters as well as longer-pulse durations and lower fluence is recommended. Otherwise, treatment with a mid-infrared laser (1,064–1,450 nm) is an option, as postoperative complications including scarring and postinflammatory hyperpigmentation are minimal when conservative parameters are used (Goldberg 2000).

Additionally, I use more conservative parameters when another device (i.e., KTP, QS ruby) is used in conjunction with IPL.

The ideal patient is 35–55 with mild to moderate photodamage. Although early indications are that results may last for several years, patients who are young may not appreciate the subtle improvement they are receiving from non-ablative resurfacing. Moreover, older patients with severe photodamage and deep wrinkles may require more aggressive surgical and laser cosmetic treatment.

Melasma

Melasma presents a unique challenge to the dermatologic surgeon. Current therapies include topical therapies with bleaching creams, oral medications, chemical peels, and light-based therapies. Although several lasers have demonstrated some potential, they are complicated by transient improvement or rapid recurrence of melasma (Pooja et al. 2012).

The devices that have shown the most consistent results include IPL, Q-switched and picosecond Nd:YAG lasers, and non-ablative fractional lasers (Fig. 2a, b).

Fractional lasers can be applied to achieve partial pigment improvement but only produce temporary resolution (Goldberg et al. 2008). Low-fluence,

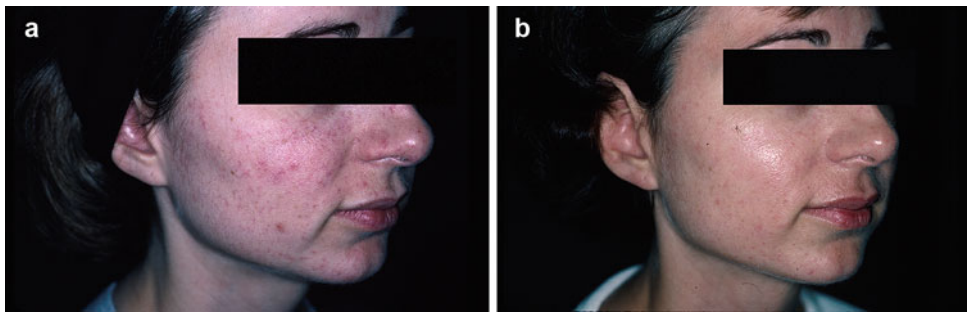

Fig. 1 (**a**, **b**) Pre- and post-IPL treatment

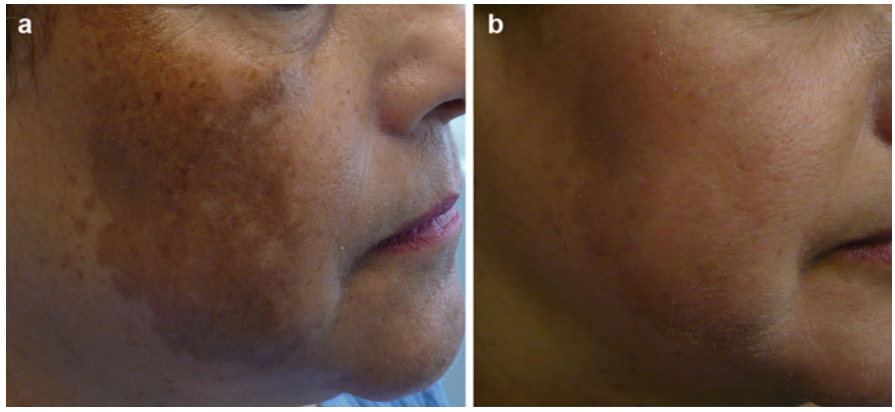

Fig. 2 (**a**, **b**) Pre- and post-melasma treatment

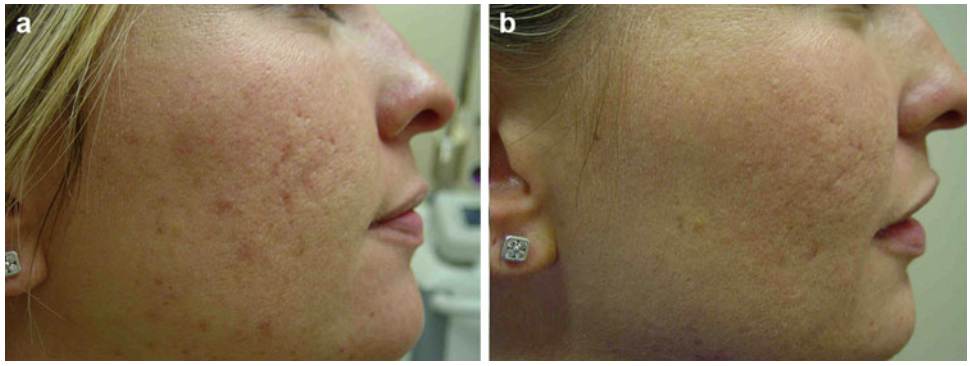

Fig. 3 (**a**, **b**) Pre- and post-acne scar treatment

long-pulse-duration, high-filter IPL tends to have more lasting results in the treatment of melasma, as the cutoff filter permits the use of longer wavelengths to target deeper melanin. I combine each treatment with LED lights, which have been shown to significantly reduce melanin production and tyrosinase expression.

The effects of postinflammatory hyperpigmentation are mitigated with hydroquinone application 4–8 weeks prior to laser treatment and thereafter as a maintenance therapy.

Acne Scars

Acne scarring is another difficult dermatological condition to treat. We have found that deep seated scars respond well to ablative lasers. For patients unable to tolerate ablative lasers, non-ablative laser and radiofrequency devices are devices that offer significant improvement in acne scars and skin texture (Fig. 3a, b).

When it comes to treating acne scars in darker skin types, radiofrequency devices play an important role in my practice. Postinflammatory hyperpigmentation (PIH) may be a complication of fractional laser treatments that persists for months, especially in skin types IV–VI (Ong 2012; Hu et al. 2009). To avoid this complication, I utilize a fractional bipolar RF device which generates fractional deep dermal heating to induce skin injury. This subsequently elicits a wound healing response, thereby stimulating the remodeling of dermal collagen. Although the clinical improvements may be more modest as compared to fractional resurfacing, this approach

involves extremely rapid recovery and less risk for PIH (Rongsaard and Rummaneethorn 2014).

Stretch Marks

Early in my career, topical retinoids were the gold standard in treating stretch marks. However, lasers have shown much efficacy in treating both early and advanced stretch marks.

In the early stages of stretch marks, changes are more inflammatory in nature, and thus they appear pigmented purple to red. Although there are multiple treatments available for red stretch marks, I prefer the long-pulsed 532 nm KTP and 595 nm pulsed dye lasers in lighter skin types and 1,064 nm Nd:YAG in darker skin types. Conversely, older stretch marks are hypopigmented and atrophic. We have found that the excimer laser is a wonderful option to restore pigmentation (Goldberg et al. 2003). It is important to remember that stretch marks are "dermal scars," and therefore IPL, fractional photothermolysis, and radiofrequency devices are several options to improve the texture of stretch marks in all skin types.

Conclusion

Laser dermatology continues to evolve at a startling pace. My 30 years of clinical practice have led to me specific treatment regimens for the myriad of conditions previously outlined. Although a variety of treatment options currently exist, the definitive treatment for each condition remains elusive. In my own clinical practice, I have found that the best patient outcomes often occur when energy-based devices are combined with topical or adjunctive therapies.

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Part II

Photodynamic Therapy

Daylight Photodynamic Therapy and Its Relation to Photodamaged Skin

Beni Moreinas Grinblat

Abstract

Photodynamic therapy (PDT) with artificial red or blue light is an option for treating actinic keratosis and field cancerization. In this chapter, we present a new option of photodynamic therapy, with natural daylight as the light source. The method, called as daylight-PDT, is a safe, effective, and almost painful treatment for thin actinic keratosis and an option for patients with multiple lesions.

Keywords

Daylight photodynamic therapy • Actinic keratosis • Photodynamic therapy • Red light • Blue light • Photodamaged • Photorejuvenation

Contents

Introduction

Daylight photodynamic therapy (DL-PDT) is an option for treatment of thin actinic keratosis. It was developed by Wiegell in 2006 (Wiegell et al. 2008) and since that several studies were published around the world. The principles of DL-PDT are similar to the conventional PDT, with activation of photosensitizers resulting in the formation of reactive oxygen species and cell death. Most of the studies of DL-PDT were performed using aminolevulinate cream (MAL) as photosensitizer. MAL is a prodrug that is converted to protoporphyrin (PpIX) inside the cell.

Protoporphyrin is activated by visible light, and in DL-PDT the visible light of the natural sunlight spectrum makes the activation.

DL-PDT is indicated for treating thin actinic keratosis (grades I and II, according to Olsen (Olsen et al. 1991)), mainly in patients with multiple lesions on the scalp and/or face.

Besides treating AKs, DL-PDT seems to improve other aspects of photodamage, such as fine wrinkles and pigmentation.

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Daylight Photodynamic Therapy

Pre-procedure

There is no specific preparation before treatment with PDT. Patients should keep using daily sunscreens.

Protocol of Procedure

Several studies and internationals consensus (Morton et al. 2015; Gilaberte et al. 2015; Grinblat et al. 2015a) established the protocol of daylight-PDT (Fig. 1).

1. The first step is the skin preparation. The objective is to remove scales and crusts and roughen the surface of the skin to enhance the MAL penetration. The curettage of the field is the most used method, but there are other options as slightly abrasive pads and microdermabrasion. Microneedling and ablative lasers might be used but with caution, using smooth parameters.
2. An organic sunscreen must be applied in the whole area before or after the skin preparation. The sunscreen (SPF $\geq$ 30) must be used to block the ultraviolet radiation and, hence, prevent sunburn during the 2 h of daylight exposure.
3. In order to block only UV and not visible light needed to activate PpIX, a chemical sunscreen must be used. Sunscreens containing physical filters such as zinc oxide or titanium dioxide must not be used, because they reflect some visible light and thus may reduce the activation of PpIX by daylight.
4. Fifteen minutes after the skin preparation/sunscreen application, the photosensitizer should be applied. Applying a thin layer in the whole area and a thicker one over the AKs is recommended. As mentioned before, the majority of the published studies were performed with MAL as the photosensitizer and it is not a recommended occlusion. Usually, 1–2gr of MAL cream is sufficient to treat the whole face.
5. Up to 30 min after the MAL application, the patient has to be exposed to daylight, for 120 min. He must stay outdoors but can stay under a shadow. In Brazil, the procedure can be performed in the whole year, even in the winter (Grinblat et al. 2016). It is recommended to avoid treatment in very cloudy days and, obviously, if it is raining.
6. After the illumination (2 h of daylight exposure), the MAL is removed, and the patient has to avoid the sun exposure for the rest of the day.

Post-Procedure

The erythema after treatment is usually mild and topical steroids are not recommended in routine. Patients should keep using daily sunscreens, and the use of moisturizers is indicated.

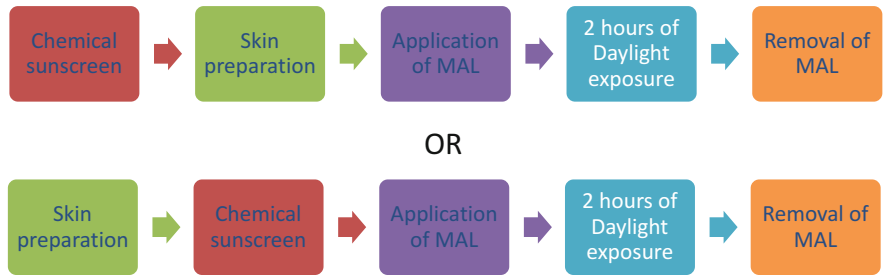

Fig. 1 Protocol of DL-PDT with MAL

Side Effects

DL-PDT is usually not painful, and the erythema after treatment is usually mild. Blistering and crusting are very rare.

Discussion

Several studies were published about DL-PDT in different countries, and they showed similar results when DL-PDT was compared to conventional MAL-PDT, when treating thin AKs. The main advantages of DL-PDT are:

1. The possibility of treating large areas (face and scalp)
2. There is no equipment involved in the treatment
3. DL-PDT is almost painless

During conventional photodynamic therapy, the pain can be intense. Pain occurs when there is a great amount of PpIX into the cells and in DL-PDT that does not happen. During the treatment with DL-PDT, there is a continuous activation of few amounts of porphyrin; there is no accumulation of PpIX into the cells.

In an Australian study (Rubel et al. 2014), DL-PDT was compared to conventional PDT and the clinical results were similar. But, most of the patients considered DL-PDT much less painful and most of them preferred DL-PDT.

Australian study showed similar results when DL-PDT was performed in sunny or cloudy days, and a Brazilian study (Grinblat et al. 2015b) showed good results even if DL-PDT was performed during winter. The Latin-American consensus (Grinblat et al. 2015a) recommends 2 h of daylight exposure under comfortable temperatures.

For most of the authors, one single treatment of DL-PDT is sufficient, but sometimes another session is indicated and the authors recommend 3-month interval till the second treatment. In our experience, patients with intense photodamage need more than one session.

Daylight-PDT is usually indicated for patients with multiple thin AK (types I and II). Treating the whole area, DL-PDT can be considered as a "field cancerization treatment."

In 2016, Philipp-Dormston and colleagues published a study about DL-PDT for "field cancerization" (Philipp-Dormston et al. 2016). They defined "field cancerization" as an area with photodamage and AK. For those authors,

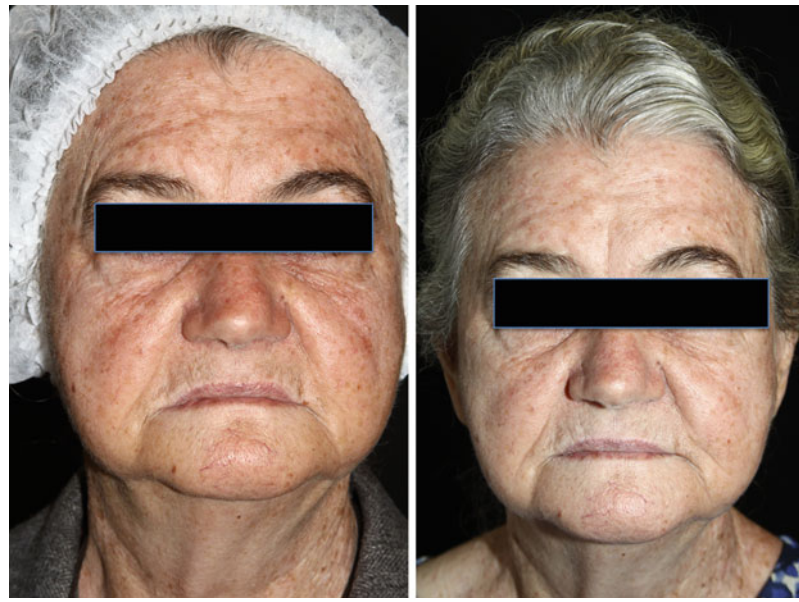

Fig. 2 Before and after one session of MAL- DLPDT

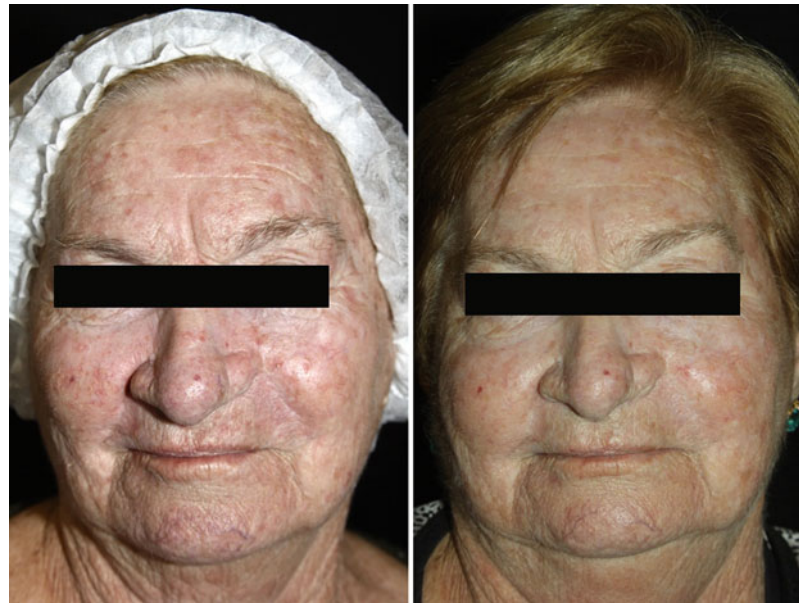

Fig. 3 Before and after one session of MAL- DLPDT

DL-PDT is effective and could prevent the appearance of new AK lesions in a photodamaged skin.

We observe reduction of the number of AK lesions and improvement of the photodamaged skin (skin texture and pigmentation) in our patients after treatment with only one MAL-DL-PDT with 2 h of daylight exposure (Figs. 2 and 3).

DL-PDT x Photorejuvenation

Besides treating multiple AKs, DL-PDT seems to improve other aspects of photodamage.

Kohl and colleagues published a study about photodynamic rejuvenation. The authors observed improvement of hyperpigmentation, fine wrinkles, and skin tightness after conventional PDT, with IPL, blue light, and red light (Kohl et al. 2010). Issa and colleagues showed skin remodeling induced by conventional PDT, with increase expression of metalloproteinase 9 in the dermis and also of collagen type I (Issa et al. 2009). In 2010, the same group showed an increase of collagen and reduction of elastic fibers after conventional MAL-PDT (Issa et al. 2010).

In 2015, a group of experts published that besides the clearance and prevention of AK, most studies after conventional PDT showed improvement of skin texture (tactile roughness), pale skin, wrinkles, mottled pigmentation, facial erythema, and elastosis (Philipp-Dormston et al. 2016).

There is no data in the literature about photorejuvenation with daylight-PDT, but in our experience patients treated with DL-PDT showed improvement of skin texture. As mentioned, there are several published studies about skin rejuvenation after conventional PDT, and in our experience, we can observe improvement of fine wrinkles with DL-PDT, although lower than the one observed after conventional PDT. According to some authors (Philipp-Dormston et al. 2016), daylight photodynamic therapy could be a complementary and convenient treatment option to already existing rejuvenation procedures for patients with actinic field damage.

Conclusion

DL-PDT is safe, effective, almost painless and can be considered a first-line option in the treatment of multiple and thin AKs. Besides the excellent cure rate of AK lesions, an improvement in the texture, pigmentation, and fine wrinkles can be observed.

Take Home Messages

- DL-PDT is an option for treatment of thin AK.
- DL-PDT maintains the efficacy of conventional PDT for AK treatment.
- DL-PDT is almost painless. Erythema and edema are very discreet comparing to conventional PDT.
- The use of a chemical sunscreen is recommended before the application of the photosensitizer.
- DL-PDT seems to improve signs of photodamage.

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Actinic Cheilitis: Efficacy and Cosmetic Results

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Abstract

Actinic cheilitis (AC) is a common disease caused by long-term solar exposure and is considered a premalignant lesion of the lips. AC has potential to develop into squamous cell carcinoma (SCC) and metastasis. SCC of the lip arising from AC is more prone to metastasis than cutaneous form with rates of the former varying between 3% and 20% and is the most common malignancy of the oral cavity. AC affects especially pale-skinned individuals with poorly pigmented lower lips. The overall survival rate in 5 years is less than 75%. Treatments are difficult because surgical treatment can have significant adverse effects, whereas less invasive procedures may not be as efficient. A high degree of clinical suspicion should be maintained, given the malignant nature of the condition. We emphasize the need for regular follow-up, rigorous clinical exam, and accurate pathologic analysis. The chapter will discuss the efficacy of therapy with photodynamic therapy (PDT) using methyl aminolevulinate and 5-aminolevulinic acid, application times, skin preparation techniques, pain, cosmetic outcome, and patient satisfaction.

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Keywords

Actinic cheilitis • Solar cheilitis • Photodynamic therapy • 5-Aminolevulinic acid • Methyl aminolevulinate • Cosmetic outcome • Lip cancer • Squamous cell carcinoma

Contents

Introduction

An understanding of the nature of actinic cheilitis can be achieved by studying and reflecting on comments about it by three dermatologists, namely, Dubreuilh in1896, Freudenthal in 1926, and Sutton Jr. in 1896 (Heaphy and Ackerman 2000). Actinic cheilitis is a very frequent disease of the lips (Dufresne and Curlin 1997). This ominous precursor of cancer occurs specially on lower lip due to chronic sunlight exposure and

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Table 1 Relationship between the various risk factors in actinic cheilitis

Major risk factors:
Genetic predisposition
Skin pigmentation
UV radiation history
Minor risk factors:
Smoking
Alcoholism
Organ transplantation
Lupus discoid
Chronic scars
Poor oral hygiene

outdoor activities of people such as fishermen, farmers, beachworkers, golfers, and surfers (Dufresne and Curlin 1997; Martins-Filho et al. 2011; Lucena et al. 2012; Ribeiro et al. 2014).

Basic Concepts

Actinic cheilitis, or solar cheilosis, attracts a number of clinical definitions from malignant lesions to relative mild descriptions of the sun-damaged lips. This occurrence is sunlight dose dependent (Table 1) and is cumulative over a 5–20-year exposure to ultraviolet radiation, immune status (organ transplantation), age, genetic predisposition (xeroderma pigmentosum, porphyria cutanea tarda, oculocutaneous albinism), drugs (voriconazole), geographic latitude (countries close to equator), and use of lip protection (lipstick, lip sunscreen) (Rogers and Bekic 1997; Savage et al. 2010; Lucena et al. 2012; Jadotte and Schwartz 2012a). Other factors like tobacco, alcohol, poor oral hygiene, and chronic scarring in discoid lupus erythematous are involved (Table 1) (Jadotte and Schwartz 2012a).

As with actinic keratosis, the exact transition rate to most common lip cancer, the squamous cell carcinoma (SCC), is unknown, but the relative risk is felt to be 2.5 times higher. SCC is, however, the most frequent oral cavity cancer and head and neck malignant tumor, with an incidence in the United States of 1.8 per 100.000 (Ulrich et al. 2007). SCC is considered a disease of low aggression and favorable prognosis because it tends to progress slowly. Estimated occurrence of SCC is 89% on the lower lip, 3% on the upper lip, and 8% at the oral commissures (Picascia and Robinson 1987).

When diagnosed early it has a cure rate of 80–90% and a mortality rate between 10% and 15%. Metastases tend to occur in between 3% and 20%; of these cases the mean survival for 5 years decreases to 25% (Kwon et al. 2011; Lim et al. 2014).

As already noted, AC occurs more often on the lower lip. Two forms exist, acute which is less common in the elderly which occurs after prolonged sunlight exposure. Edema and redness are characteristic of the mildest forms. Severe congestion, fissuring, and ulceration typify the most severe form. At times vesicles may appear on the vermilion edge. These vesicles rupture causing superficial erosions and vary from days to weeks to heal (Nico et al. 2007).

The chronic form of AC usually manifests itself as slight scaling involving the whole area of the lower lip up to the commissures and is present in all seasons of the year. The scaling is not always uniform and some areas may display more intensive hyperkeratosis than others (Picascia and Robinson 1987; Nico et al. 2007). Leukoplakia, scale plaque with a sandpapery feel on palpation with a gloved finger, is a common presentation (Jadotte and Schwartz 2012a).

White-gray or brown changes may appear. The vermilion edges lose their usual plasticity which can be assessed by the appearance of marked folds. These wrinkles are parallel to one another and are perpendicular to the long axis of the lip (Picascia and Robinson 1987; Nico et al. 2007).

The differential diagnosis (Table 2) of CA covers a spectrum of neoplastic, inflammatory, eczematoid, and photosensitive disorders, along with a few rare but important diseases (Picascia and Robinson 1987; Jadotte and Schwartz 2012b).

Evaluation of ultraviolet ray-induced lesions of the lower lip can be difficult, as often clinical aspects do not correspond to the severity of the microscopic epithelial alterations. When clinical signs are present in well-demarcated area of the lip, it is supposed that the most severe histological changes occur at this point.

However, AC frequently presents as diffuse and poorly demarcated alterations along the

Table 2 Differential diagnosis of actinic cheilitis

Squamous cell carcinoma
Amelanotic melanoma
Discoid lupus erythematous
Oral lichen planus
Metastatic cancer
Plasma cell cheilitis
Cheilitis glandularis
Angular cheilitis
Granulomatous cheilitis
Eczematous cheilitis
Nutritional cheilosis
Actinic prurigo cheilitis
Factitious cheilitis
Necrotizing sialometaplasia
Sweet syndrome

vermilion, and choosing an area for incisional biopsy in these cases may be challenging (Nico et al. 2007). The carcinomatous transformation generally is characterized by induration, infiltration, or ulcers in actinic area (Samimi 2016). Sometimes two or more biopsies are required.

Currently, reflectance confocal microscopy seems to be a promising diagnostic tool for actinic cheilitis as it allows noninvasive evaluation in real time and in vivo (Ulrich et al. 2011).

Treatment of actinic cheilitis provides relief of symptoms, improves the cosmetic appearance, but, more importantly, prevents the development of squamous cell carcinoma (Picascia and Robinson 1987).

Surgical scalpel vermilionectomy offers the most definitive treatment to date for actinic cheilitis, followed by carbon dioxide laser (Nelson et al. 2007). There are various options to treat actinic cheilitis; however, these options very often have disabling side effects (Sotiriou et al. 2008).

Treatments have been used for the treatment of actinic cheilitis, as shown in Table 3 (Robinson 1989; Dufresne et al. 2008; Lima Gda et al. 2010; Shah et al. 2010; Ulrich et al. 2011; Jadotte and Schwartz 2012b; Barrado Solís et al. 2015).

The treatment options for actinic cheilitis are diverse and each modality has both distinct advantages and disadvantages. Each treatment can be safely performed in an outpatient setting, although

Table 3 Cheilitis actinic treatments

3% diclofenac gel
5% 5-fluoracil cream
5% imiquimod cream
Carbon dioxide laser
Cryosurgery
Dermabrasion
Electrodesiccation and curettage
Er-YAG laser
Ingenol mebutate gel
Surgery (scalpel excision, vermilionectomy, Mohs Micrographic Surgery)
Trichloroacetic acid peel

each therapy option comes with different potential adverse effects. Some of them requires operator expertise to perform. Apart of therapeutic option, actinic cheilitis can potentially recur. There are effective methods well established for actinic cheilitis treatment. Each modality has its own inherent risks, benefits, and anticipated sequelae. To determine the treatment of choice, age, comorbidities, mental health, previous carcinomas, and immunosuppression should be considered. About the area, single or multiples lesions, localization, extension, induration, as well as ulcerated lesions should be considered. Isolated and well-defined lesions can be treated with destructive methods such as cryosurgery, dermabrasion, electrodesiccation and curettage, and lasers, while extensive areas can be fully treated with field treatment as diclofenac, 5-fluoracil, imiquimod, lasers, dermabrasion, ingenol mebutate, photodynamic therapy, surgery, or trichloroacetic acid peel as presented in Table 3.

The photodynamic therapy can be used in localized lesions or in all entire lip.

Photodynamic Therapy:

PDT Mechanism of Action

Photodynamic therapy has been introduced as a therapeutic modality for epithelial skin tumors revealing a high efficacy rate and satisfactory outcomes in cutaneous actinic keratosis, superficial

basal cell carcinoma, and Bowen's disease. Regarding actinic cheilitis, photodynamic therapy is considered a relative new off-label therapeutic option (Rossi et al. 2008).

The advantages of PDT are its high efficacy and tolerability coupled with excellent cosmetic outcomes (Morton et al. 2008; Sotiriou et al. 2011). As the lip is a cosmetically sensitive site, treatments for actinic cheilitis must consider cosmetic outcomes (Morton et al. 2008; Sotiriou et al. 2011; Calzavara-Pinton et al. 2013).

Despite these facts, PDT for actinic cheilitis is not very common: there are only a few case series and studies that report the applicability and efficacy of this treatment modality for actinic cheilitis. In most of them, treatment outcome was assessed only by clinical evaluation (Sotiriou et al. 2010).

PDT Indications and Contraindication

Off-label clinical indications for PDT in actinic cheilitis are generally poor and based on individual case reports or small cases series, and the few randomized clinical trials performed enrolled small number of patients with short follow-up.

All authors agreed that cosmetic outcome was excellent, and the tolerability was acceptable in the majority of patients (Calzavara-Pinton et al. 2013). In one study the cosmetic results were rated by the investigators as excellent in 81.8% of cases (Sotiriou et al. 2010).

If the cosmetic outcome only is considered, PDT offers positive cosmetic outcomes observed by the investigators when compared with conventional treatments.

Ulceration, nodularity, atrophy, nodularity, bleeding, blurred demarcation, and friability (especially when prolonged) indicate malignancy (Jadotte and Schwartz 2012a; Yazdani Abyaneh et al. 2015). In these cases, biopsy is mandatory and PDT should be avoided until histopathological elucidation.

All of the studies are descriptive series without control arms. A bias toward reporting and publishing series with positive findings should also be considered. Furthermore, various treatment parameters were used and lengths of follow-up ranged widely. Clinical responses were assessed subjectively by nonblinded investigators; a histological confirmations of cure were established in only half of the subjects (Yazdani Abyaneh et al. 2015).

Furthermore results are generally based on visual assessments without controlled parameters, such as histopathology and/or noninvasive imaging procedures (Calzavara-Pinton et al. 2013).

These factors led to a wide range in clinical response and histological cure rates. There is a need for randomized controlled trials with long-term follow-ups to evaluate the clinical and histological response of actinic cheilitis to PDT. More studies are also needed to determine the optimal number of treatment sessions and techniques (Yazdani Abyaneh et al. 2015).

PDT: Use and Doses:

PDT is a noninvasive and precisely directed treatment. Patients are prepared for PDT first with gentle removal of scale and crust from the lips (Fig. 1). The procedure involves the topical application of photosensitizing agents most often 20% 5-aminolevulinic acid (ALA) or 16% methyl 5-aminolevulinate cream (MAL) on the lip (Fig. 2). The area is occluded (Figs. 3 and 4) after preestablished time of 3 h, and visible light irradiation (usually red or blue) is applied with subsequent promotion of reactive oxygen species, which in turn produces local tissue destruction (Barrado Solís et al. 2015; Choi et al. 2015).

Daylight PDT (DA-PDT) is a novel modality in which the activation of the topical photosensitizer is induced by the exposure to natural daylight without requiring preliminary occlusion. In two studies enrolling 12 patients, the use of DA-PDT showed benefits decreasing the pain level (Levi et al. 2013; Fai et al. 2015).

There is no specific data that explains exactly about cosmetic outcome of the lip treated with photodynamic therapy. In our experience we observed overall lip rejuvenation with a younger appearance (Figs. 5 and 6), uniform color, best

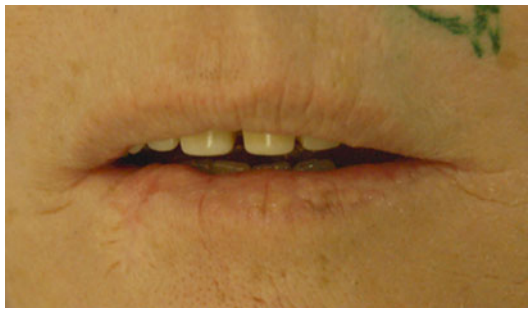

Fig. 1 Actinic cheilitis in lower lip

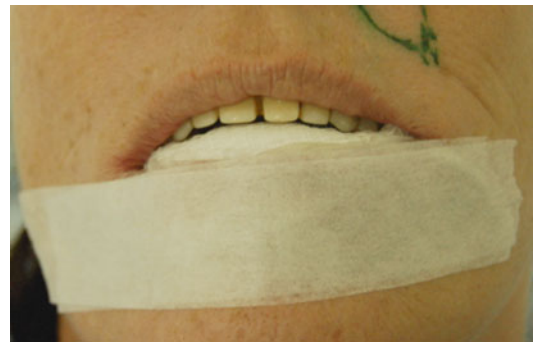

Fig. 4 Dressing light protection for 03 hours

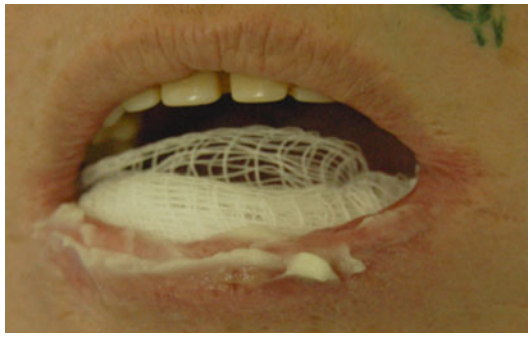

Fig. 2 MAL application in lower lip

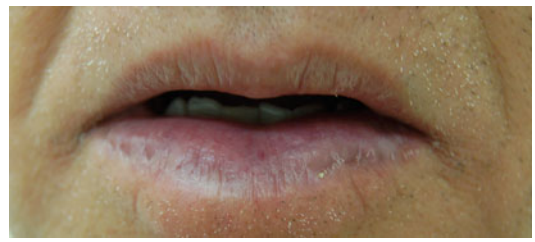

Fig. 5 Lower lip before photodynamic therapy

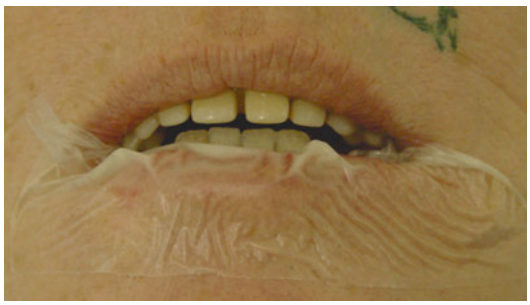

Fig. 3 MAL occlusion in lower lip with adhesive tape

delimitated vermilion transition, soft and thinner epithelium, and less flaking.

PDT: Side Effects and their Management

The pain and burning sensation during the irradiation is always present in different levels. Edema, erythema, blistering, hemorrhagic crusting, itchiness, erosions, paresthesias, scaling, and mild dryness can occur. These reactions resolved 5–14 days after the treatment and cold dry helps in pain control (Sotiriou et al. 2010; Yazdani Abyaneh et al. 2015). After PDT treatment occurs, selective destruction of unhealthy tissue, increase local immune response and advantages of short-term treatment as minimal erythema, reduced scaring risk and renewal skin epithelium (Alexiades-Armenakas 2007; Kodama et al. 2007; Sotiriou et al. 2008; Rossi et al. 2008; Castaño et al. 2009).

Conventional PDT for actinic cheilitis has been reported in a number of publications with clinical and histological cure rates ranging between 47% and 100%. This wide variability in efficacy can partly be explained by different study designs including differences in biological endpoints, light sources, and follow-up periods (Levi et al. 2013; Kim et al. 2013). Despite of observational clinical results, it is important to keep in mind the significantly higher histological recurrence rates

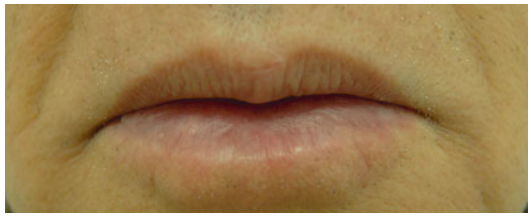

Fig. 6 Lower lip after photodynamic therapy

(Sotiriou et al. 2010). Inadequate uptake of the photosensitizer owing to dilution by saliva and rapid regeneration of mucosa epithelium compared with the skin may result in a lower efficacy of the treatment. PDT offers a promising treatment option supported by excellent cosmetic outcome posttreatment with the need for further study (Kim et al. 2013; Yazdani Abyaneh et al. 2015).

Authors' Experience

The author always performs lip biopsy before all actinic cheilitis treatment. It is possible to treat isolated lesion as well as all entire lip. When the photodynamic therapy is the treatment of choice, there is careful curettage of crusts and scales from the lip; a 1 mm thick layer of 20% methyl 5-aminolevulinate cream is applied over the entire lip. Cotton roll is placed in the gingival transition and the lip is covered by an occlusive bandage for 3 h. After the removal of the cream, lesions are irradiated with 37 J/cm^2 of red light (635 nm). Two treatment sessions are conducted 1 week apart.

Conclusion

Cheilitis actinic is a chronic premalignant condition affecting the lip. Untreated lesions may become squamous cell carcinoma, and treatment options can be ablative, surgical and topical modalities. Photodynamic therapy is focal and also a field-directed treatment for actinic cheilitis. The cosmetic outcome and results suggest that photodynamic therapy may offer comparable rate response. The pain and high cost sometimes turns the method unfeasible. However, increasing the efficacy of PDT through optimization of treatment parameters is still necessary.

Take Home Messages

- As with actinic keratosis, the exact transition rate to squamous cell carcinoma relative risk is felt to be 2.5 times higher
- Treatment of actinic cheilitis should provide relief of symptoms, improve the cosmetic appearance, but, more importantly, prevent the development of SCC.
- As the lip is a cosmetically sensitive site, treatments such as PDT for actinic cheilitis must consider cosmetic outcomes.
- PDT is advantageous in that it has transient and mild to moderate cosmetic adverse effects and minimizes patient discomfort.

Cross-References

- ▶ Daylight Photodynamic Therapy and Its Relation to Photodamaged Skin
- ▶ Photodynamic Therapy for Photodamaged Skin
- ▶ Transepidermal Drug Delivery and Photodynamic Therapy

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Photodynamic Therapy for Photodamaged Skin

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Abstract

Photodynamic therapy (PDT) is a well-established therapeutic modality for non-melanoma skin cancer (NMSC). It is based on a photochemical reaction, which causes destruction of the target tissue associated with an inflammatory response. In the last years, PDT has been indicated for some dermatosis in cosmetic dermatology, such as acne, sebaceous hyperplasia, rosacea, and photoaging. Although PDT's mechanism of action in these dermatoses is not totally clear, some histological studies had shown dermis remodeling induced by PDT in photodamaged skin. In this chapter, we are going to discuss about photoaging and PDT treatment, comparing literature review and authors' experience.

Keywords

Photodynamic therapy • Photosensitizer • Nonmelanoma skin cancer • Actinic keratosis • Basal cell carcinoma • Bowen disease • Photodamaged skin • Collagen fibers • Elastic fibers • Skin remodeling • Dermis • Aging • Photoaging • Photorejuvenation • Rejuvenation

Contents

Introduction

Aging is a complex and multifactor process that occurs in all individuals, influenced by environmental, hormonal, and genetic elements, resulting in functional and aesthetical skin changes. Photoaging is clinically manifested by wrinkles,

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roughness, dryness, sagging, pigmentary spots, telangiectasias, and, in some cases, premalignant and malignant lesions (Ferolla 2007; Issa 2008; Gilchrest 1989).

PDT is based on a photochemical reaction, which causes destruction of the target tissue associated with an inflammatory response. For this reaction, a photosensitizer agent in the target tissue is necessary, a source of light and oxygen. It is approved for NMSC treatment, including actinic keratosis (AK), basal cell carcinoma (BCC), and Bowen disease (squamous cell carcinoma – SCC in situ) (Issa and Patricia-Azulay 2010; Kalka et al. 2000; Szeimies et al. 1996a; Casas et al. 2001; Nestor et al. 2006). The two main photosensitizers are aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), which were approved to be used with light-emitting diode (LED) that emits visible light. PDT with ALA-blue light is very well indicated for superficial lesions, mainly AK. PDT with MAL-red light is recommended for deep lesion treatment because of MAL's lipophilicity and deeper penetration of the red light in the skin (Hurlimann et al. 1994; Szeimies et al. 1994, 1996b, 2002a, 2005; Fink-Puches et al. 1998; Salim et al. 2003; Lee and Kloser 2013; Babilas et al. 2005).

The global improvement of the skin around AK lesions after PDT called attention to a new possibility for photoaging treatment. Many clinical studies had reported improvement in texture, pigmentation, wrinkles, and laxity in the field of cancerization treated with PDT (Nestor et al. 2006; Hurlimann et al. 1994; Szeimies et al. 1994, 1996b, 2002a, 2005; Fink-Puches et al. 1998; Salim et al. 2003; Lee and Kloser 2013; Babilas et al. 2005; Bruscino and Rossi 2010; Park et al. 2010; Issa et al. 2010; Shamban 2009; Bjerring et al. 2009; Almeida Issa and Piñeiro-Maceira 2009). However, only in the last years, some histological and immunohistochemical studies described some factors involved in the mechanism of skin rejuvenation induced by PDT (Issa et al. 2010; Almeida Issa and Piñeiro-Maceira 2009; Szeimes et al. 2012).

Some other *off-label* indications include acne, rosacea, sebaceous hyperplasia, vulgar warts, psoriasis, granuloma annulare, necrobiosis lipoidica, and mycosis fungoides (Morton et al. 2013; Alster and Tanzi 2003; Calvazara-Pinton et al. 2010; Bissonnette et al. 2002; Szeimies et al. 2002b; Gold and Goldman 2004a).

Photoaging

Concept

Aging is a continuous process that affects the skin function and its appearance. The chronological aging affects all organs similarly, but environmental (extrinsic) and inherited (intrinsic) processes overlap to produce skin aging. There are evidences that the inherent and extrinsic aging processes have, at least in part, biological, biochemical, and molecular common mechanisms. Chronic sun exposure has been identified as one of the main environmental injuries. Other environmental aggressions, such as smoking, wind, and chemical agent exposure, are also involved (Issa 2008).

Pathogenesis

The UVB radiation (290–300 nm) is responsible for sunburn, while the UVA (320–400 nm), which penetrates more deeply in the skin, promotes collagen and elastic fiber damage. Both UVA and UVB are involved in the pathogenesis of skin cancer and photoaging. The UV radiation causes genetic and molecular changes in the cells of the epidermis, leading to cell atypia (Ferolla 2007; Issa 2008; Gilchrest 1989).

The response to UV radiation involves complex paths, which start in the cell surface receptors that activate transcription factors, AP-1, and NF-kappaB. These factors regulate synthesis of cytokines and interleukins (IL-1, IL-6, IL-8, TNF-alpha) and metalloproteinases, such as MMP-1, MMP-9, MMP-3, and MMP-10. These cytokines and interleukins stimulate an inflammatory process, and on the other hand, they mediate some antioxidant enzymes, balancing the damage. MMP-1 is increased in photodamaged skin and is

responsible for breaking collagen types I and III into high molecular fragments of collagen, which change the extracellular matrix, inhibiting synthesis of new collagen. MMP-9 breaks these fragments into smaller fractions of collagen, modifying the relationship between the fibroblasts and the extracellular matrix, allowing neocollagenesis (Kang et al. 2001; Chung et al. 2001; Naderi-Hachtroudi et al. 2002; Dougherty et al. 1998; Fisher et al. 2002).

Clinical and Histopathologic Aspects

The clinical findings about photodamaged skin include wrinkles, roughness, dryness, pigmentation, telangiectasias, and, in some cases, premalignant lesions (actinic keratosis) and malignant lesions (BCC and SCC). In the epidermis, cellular atypia is observed, as well as loss of polarity of keratinocytes and reduced number of Langerhans cells. In the dermis, eosinophilic material (elastosis solar) is observed, as well as thick and curly elastic fibers and thin and flat collagen fibers (Ferolla 2007; Issa 2008; Gilchrest 1989; Kalka et al. 2000).

Treatment

Photoaging treatment includes topical medicaments and cosmeceuticals, oral nutraceuticals, and cosmetic procedures. Chemical peelings, microneedling, transepidermal drug delivery, lasers, botulinum toxin, and fillers are the most important procedures in aesthetic dermatology (discussed in another chapter). If premalignant and malignant lesions are present, a different approach is necessary.

The benefits of PDT for photodamaged skin were realized during the field of cancerization treatment, when the improvement of texture, pigmentation, and wrinkles was observed. PDT's protocol for photodamaged skin varies a lot in literature with different numbers of sessions, using ALA or MAL and different sources of light (blue and red light-emitting diode (LED), intense pulsed light (IPL), and laser) (Issa 2008; Palm and Goldman 2011; Sanclemente et al. 2012; Bjerring et al. 2002; Karrer et al. 1999a; Dover et al. 2005; Alster et al. 2005; Alexiades-Armenakias and Gernemus 2003; Gold et al. 2006; Togsverd-Bo et al. 2012; Ruiz-Rodriguez et al. 2002).

Photodynamic Therapy

Concept and Mechanism of Action

Photodynamic therapy is based on a chemical reaction activated by light, in the presence of a photosensitizer in the target tissue, light, and oxygen. ALA and MAL are the most important photosensitizers used ▶ Daylight Photodynamic Therapy and Its Relation to Photodamaged Skin. In fact, they are prodrugs, absorbed by the target cell and then transformed into protoporphyrin IX (Pp IX), inside the cytoplasm and mitochondria (Ferolla 2007; Issa 2008; Gilchrest 1989; Issa and Patricia-Azulay 2010; Kalka et al. 2000; Szeimies et al. 1996a; Casas et al. 2001). Different sources of light can be used, but LED with red or blue light (Fig. 1) is the most important source for premalignant and malignant lesion treatment. The selective destruction of target tissue occurs through a chemical reaction, where the photosensitizer agent in the tissue absorbs the light, becoming excited and then transferring the energy to the oxygen. That sequence of chemical reactions promotes reactive oxygen species (ROS) production, especially the *singlet* oxygen, which is cytotoxic to malignant cells (Ferolla 2007; Issa 2008; Casas et al. 2001; Hurlimann et al. 1994; Szeimies et al. 1996b, 2005; Palm and Goldman 2011; Sanclemente et al. 2012; Bjerring et al. 2002; Karrer et al. 1999a; Dover et al. 2005; Alster et al. 2005; Alexiades-Armenakias and Gernemus 2003; Gold et al. 2006; Togsverd-Bo et al. 2012; Ruiz-Rodriguez et al. 2002). PDT causes an inflammatory response, activating nuclear factors that control the expression of many cytokine and interleukin genes (IL-1, IL-2, IL-6, IL-10, α-factor of tumoral necrosis – TNF-α) (Ferolla 2007; Issa 2008).

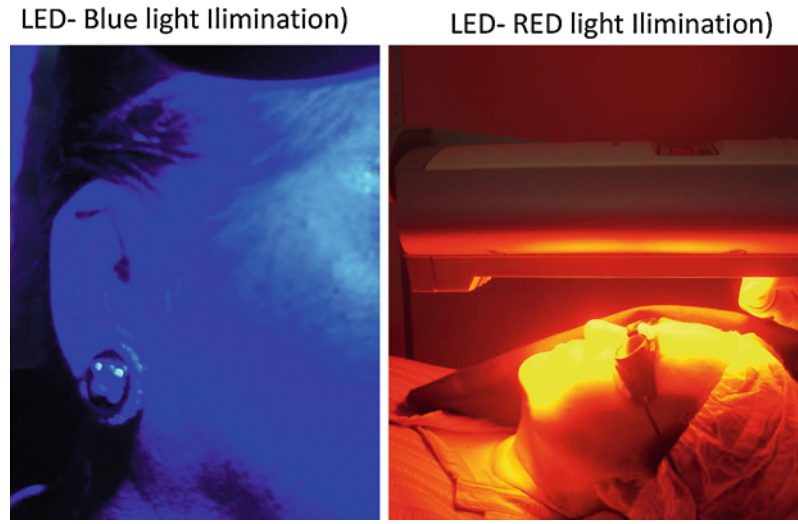

Fig. 1 Source of lights

Light Sources

Light-Emitting Diode (LED): Visible Light

PpIX exhibits maximum light absorption (the Soret peak) at 405 nm (blue light) and a weaker absorption band at 635 nm (red light). Blue light is better absorbed, but it penetrates more superficially, around 1–2 mm. Red light penetrates around 4 mm, and it is considered the best choice for deeper lesions (carcinoma) treatment. Both blue and red light can be used for AK lesions and for photoaging treatment (Issa 2008; Naderi-Hachtroudi et al. 2002; Palm and Goldman 2011; Sanclemente et al. 2012).

Other Light Sources

Laser or IPL can be used for PDT treatment, but they are expensive devices without advantages comparing to LED for AK lesion treatment. For this reason, they are better indicated for photorejuvenation and acne treatment, as they can act directly in vessels, pigments, and collagen (Bjerring et al. 2002; Karrer et al. 1999a; Dover et al. 2005; Alster et al. 2005; Alexiades-Armenakias and Gernemus 2003; Gold et al. 2006; Togsverd-Bo et al. 2012; Ruiz-Rodriguez et al. 2002).

Photosensitizers

Aminolevulinic Acid (ALA)

In the USA, ALA was approved by the FDA in 1999 associated with blue light for AK treatment. It is available as a stick, called Levulan Kerastick (DUSA Pharmaceuticals) (Fig. 2), in a solution with 20% of ALA and 48% of ethanol. This stick has two glass bottles inside. One of them contains powder of ALA and the other contains ethanol (solvent). The bottles should be broken with a slight manual pressure in the tube, which is shaken to mix the powder and the solvent. After mixing, ALA is ready to be used through an applicator in one of the stick's extremities.

The incubation time of ALA on the skin varies in literature, but at least 3 h are necessary for NMSC treatment. When ALA is used for photorejuvenation, 1 or 2 h are enough, but usually more than one session is necessary (Ferolla 2007).

Methyl Aminolevulinate (MAL)

MAL is a methyl ester derivative of ALA. It is lipophilic and therefore has a better permeability through the cell membrane. It is well recommended for NMSC treatment, not only for AK lesions but also for carcinomas (BCC and Bowen disease). For NMSC, an incubation time

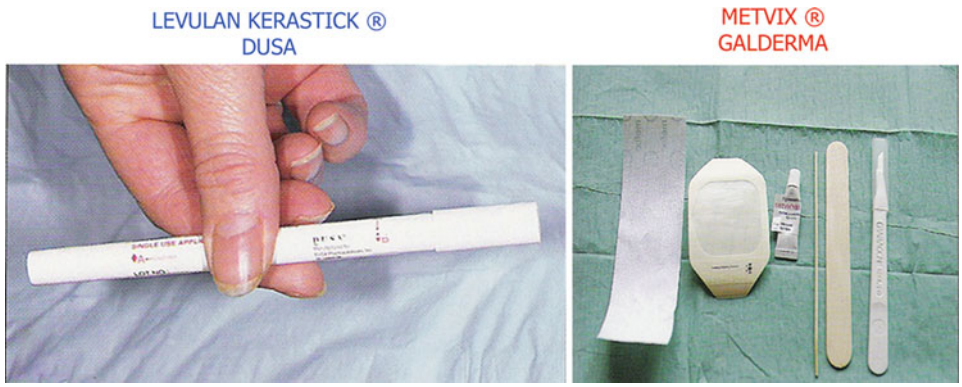

Fig. 2 Photosensitizers

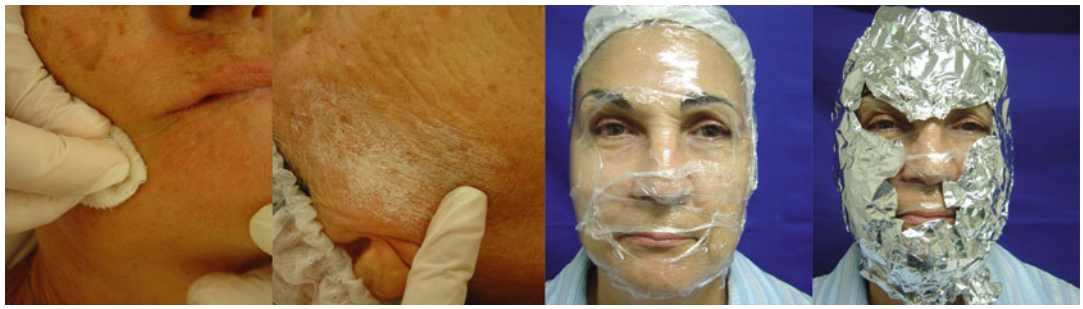

Fig. 3 Steps of procedure: (**1**) cleaning the skin; (**2**) applying the photosensitizer; (**3**) oclusion with plastic film; (**4**) light protection during incubation time

of 3 h is necessary. Otherwise, when MAL is used for skin rejuvenation, 1 or 2 h are enough (Issa 2008; Issa et al. 2010). Different from ALA, MAL has its distribution all over the world, including Brazil. Its commercial name is Metvix (Galderma) (Fig. 2), and it is available in a tube containing 2 g of a lipophilic cream. In many countries it is approved for AK and BCC. In the USA, it is approved for AK, and in Brazil and some other countries, it is approved for AK, BCC, and Bowen disease. The cure rate of MAL-PDT for AK ranges from 70% to 100%, up to 95% for superficial basal cell carcinomas, and 70–93% for Bowen disease (Issa 2008; Issa and Patricia-Azulay 2010; Hurlimann et al. 1994; Szeimies et al. 2005; Fink-Puches et al. 1998; Salim et al. 2003).

Procedure

PDT's protocol is well established for NMSC treatment. Photosensitizer's incubation time is 3 h with an occlusive dressing (Fig. 3). ALA-blue light is approved for AK treatment, and MAL-red light is approved for AK, BCC, and Bowen disease. One session is recommended for AK lesions, and two sessions with 1-week interval are indicated for BCC and Bowen disease. The protocol for rejuvenation varies a lot in literature, regarding skin preparation, photosensitizer incubation time, source of light, and number of sessions (Ferolla 2007; Issa 2008).

In the standard protocol for NMSC, a slight curettage should be done over the lesion to prepare the skin before applying the photosensitizer.

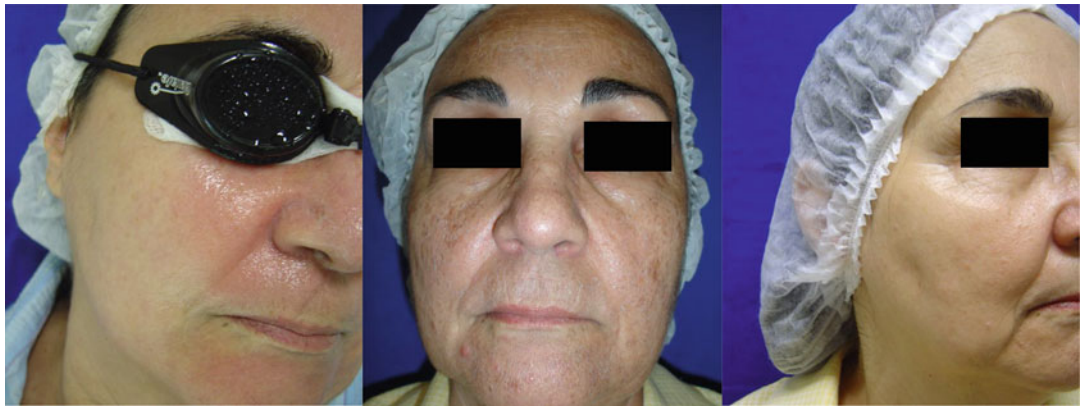

Fig. 4 (**1**) Erythema just after procedure; (**2**) scales and dryness after 48 h; (**3**) completely recovery after 8 days

Recently, in order to increase the photosensitizer penetration, some other methods, as ablative lasers and microneedling, have been evaluated. This technique is called transepidermal drug delivery (TED). TED + PDT is an option for photoaging treatment (discussed in another chapter ▶ "Transepidermal Drug Delivery and Photodynamic Therapy") (Kassuga et al. 2012; Torezan et al. 2013).

MAL is ready to be applied 10 mm around the lesion. ALA should be prepared when it is to be used, as explained before. An occlusive dressing is maintained during the photosensitizer's incubation time to increase the penetration and to avoid ambient light exposure before 3 h. The excessive drug is removed with a physiologic solution before illumination. The time of light exposure depends on the LED to be used. After session, patients should be advised to avoid sun exposure for 48 h and to use sunscreen after this period. Cold compress and moisturizing cream can be used. Analgesics can be prescribed, but steroids should be avoided (Issa 2008).

Side Effects

Side effects of topical PDT are limited to the area treated, and it includes pain and burning sensation, during the illumination up to 24–48 h after treatment. Erythema, edema, and crusts occur in the first week (Issa 2008; Issa and Patricia-Azulay 2010; Kalka et al. 2000; Szeimies et al. 1996a; Casas et al. 2001; Nestor et al. 2006) (Fig. 4). The skin peels after 3 days, but is completely recovered after 7–10 days. On extra-facial region, it takes more time to start peeling and to recover. Erythema can be present after 2–4 weeks on the face and up to 3 months on extra-facial region. Dyschromia is very rare, but if it occurs it is temporary. Herpes simplex can occur after 2 or 3 days, and antiviral prophylaxis is recommended for patients with past history of herpes. Bacterial infection is rare, and antibiotic prophylaxis is not necessary. Sterile pustules are described after acne treatment (Ferolla 2007; Issa 2008).

Photodynamic Therapy for Photorejuvenation

Possible Mechanisms Involved

The effects of light on the skin involve complex mechanisms. The balance between the dermal damage and induction of repair seems to define the final effect. Photoaging is mediated by direct absorption of UV radiation and by photochemical reactions mediated by ROS. They play an important role in the pathogenesis of aging and also participate in mechanism of action of PDT (Issa 2008).

Recently, it has been reported that PDT can modulate the expression of interleukins (IL-1, IL-2, IL-6, IL-10) in tumors and in normal tissue; some of them are also produced after UV radiation. These

interleukins activate an inflammatory response, causing injury to the tissue, but at the same time they stimulate antioxidant response, limiting the damage and allowing dermis repair (Brenneisen et al. 2002; Karrer et al. 2003; Kolh et al. 2010).

Some authors reported an increase of MMP 1 and 3 and a reduction of collagen type I in an in vitro study in which culture of fibroblasts from normal and scleroderma skin was submitted to PDT (ALA and red light). The result suggests an anti-sclerotic effect of the PDT on the skin (Kolh et al. 2010). This effect is undesirable for skin rejuvenation and motivates new studies to evaluate possible mechanism involved in PDT for skin rejuvenation.

Issa et al. (2008) studied the effects of MAL-red light (two sessions) in patients with photodamaged skin. They evaluated MMPs (1, 3, 7, 9, 12), MMP inhibitors (TIMP 1, TIMP 2), and collagen types I and III. They reported an increase of MMP-9 in the first 3 months, followed by an increase of collagen type I after 6 months, which was statistically significant, measured by morphometry (Issa et al. 2010; Almeida Issa and Piñeiro-Maceira 2009). Authors concluded that MMP-9 degraded the broken collagen (degraded by UV radiation) and changed the extracellular matrix, allowing fibroblasts to synthesize new collagen type I. These histological findings corroborate clinical improvement in texture, wrinkles, pigmentation, and firmness, noticed after 3 months of treatment, with progressive improvement up to 6 months.

Clinical Reports

Ruiz-Rodriguez et al. (2002) treated 17 patients with different degrees of photoaging with AK lesions (a total of 38 lesions) with two sessions of PDT with ALA, with 1-month interval. ALA's incubation time was 4 h. IPL was used as light source. A total of 33 AK lesions had a complete resolution within 3 months. The technique was well tolerated, and an excellent global improvement was achieved in all patients.

Gold et al. (2006) evaluated ten patients with severe photoaging with AK. The protocol for PDT was application of 20% ALA solution on the face, with an incubation time of 30 min. The light source was IPL. Patients were submitted to three sessions of treatment with 1-month interval. AK cure rate was 85%, and 90% of the patients had a global improvement (texture, pigmentation, and facial erythema).

Alster et al. (2005) compared ALA-IPL and IPL isolated for photoaging treatment and reported a better clinical result, without increasing side effects with ALA-IPL. Marmur et al. (2005) reported clinical improvement with an increase of collagen type I in photodamaged skin after ALA-IPL.

Touma and Gilrescht (2003) compared different time of light exposures and reported improvement in photoaging even with a short period of illumination. In another study, Touma et al. (2004) evaluated the use of 40% urea before PDT with ALA-blue light, but no significant clinical effects were observed.

Alexiades-Armenakias et al. (2003) reported the use of vascular laser 585 nm, after 3–18 h of ALA incubation time in 35 patients with AK. They evaluated 2.561 AK lesions on the face, scalp, and extremities. The cure rate was 99.9% after 10 days, 98.4% after 2 months, and 90.1% after 4 months on the face and scalp. The lesions located on the extremities had a poor response with complete resolution of 49.1% after 2 months. Authors concluded that when using not purpuric parameters of PDL for PDT, it is possible to reach good cure rate with minimum discomfort, low downtime, and excellent aesthetical results.

Palm et al. (2011) treated 18 patients with photoaging, using MAL-PDT, comparing blue light with the red light. There was no statically significant difference between them.

Sanclemente et al. (2012) studied histopathological findings after PDT treatment with MAL-red light and reported an increase of collagen and elastic tissue, although not statistically significant.

Ferolla et al. (2007) demonstrated the global clinical improvement of skin (pigmentation, fine wrinkles, sagging, AK lesions) after three sessions of ALA-red light (Fig. 5). The incubation time was 2 h, followed by the red light

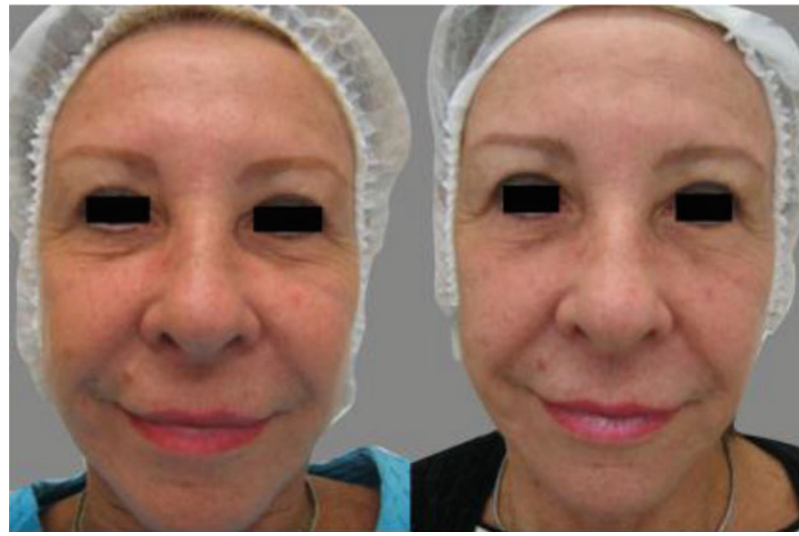

Fig. 5 Before and 21 days after two sessions of ALA-PDT- red light

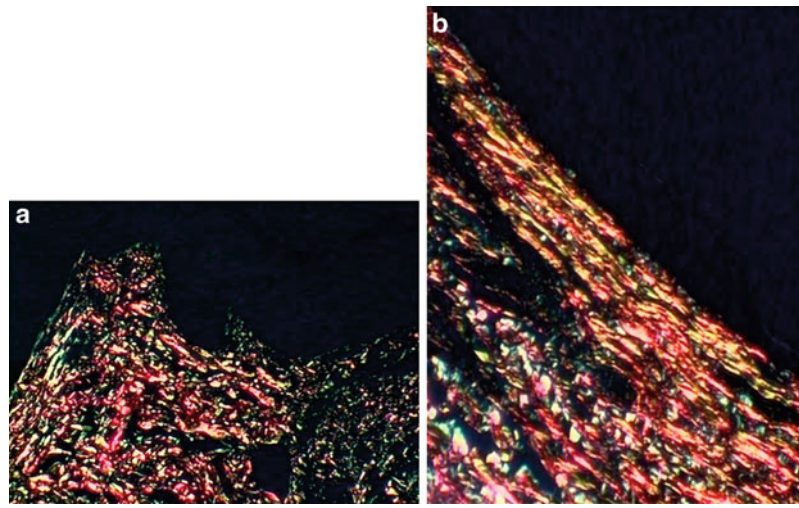

Fig. 6 (**a**) Before treatment: collagen fibers disorganized (picrosirius with polarized light × 340). (**b**) After treatment: collagen fibers better organized (picrosirius with polarized light × 340)

illumination for 20 min. Histological studies showed improvement in collagen fibers organization (Fig. 6a, b).

Issa et al. (2008) evaluated the therapeutic response of PDT for photodamaged skin in 14 women with and without AK. Two sessions of MAL-red light were done with 30 days of interval. MAL incubation time was 2 h under occlusion. The light source was a LED (Aktilite – Photocure) with a dose of 37 mJ/cm^2. Clinical results included texture, pigmentation, and wrinkle improvement observed after 3 and 6 months of follow-up (Fig. 7). After 6 months, reduction of skin sagging was more evident (Fig. 8). Side effects included edema, erythema, and crusts. Authors also evaluated histological and morphometric changes in those patients mentioned above and observed a statistically significant increase of collagen and elastic fibers mainly 6 months after treatment (Figs. 9 and 10).

Le Pillouer-Prost and Cartier (2016) reported that PDT is an effective method for photoaging treatment, improving fine wrinkles, skin roughness, and laxity. They consider patients with past

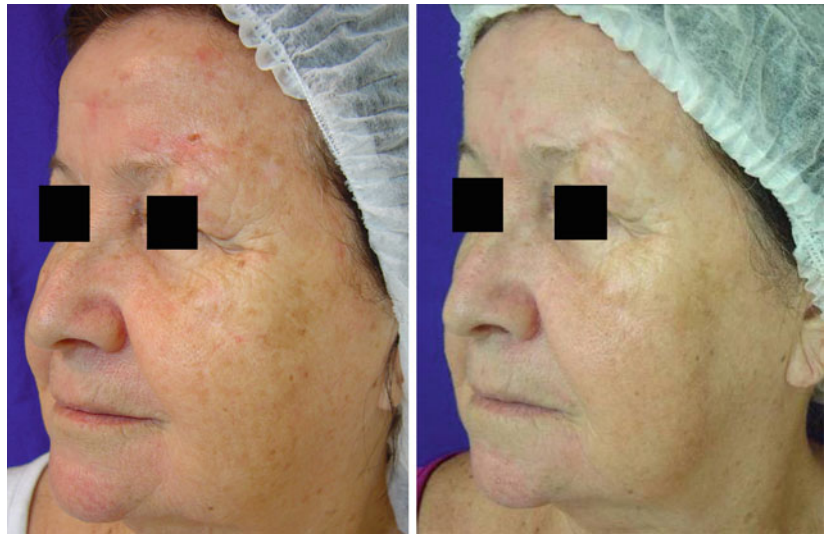

Fig. 7 Before and 6 months after treatment (two sessions of MAL-PDT) with red light (dose: 37J/cm^2). MAL incubation time of 2 h

history of significant sun exposure and with multiple AK lesions as the best indication for PDT photorejuvenation.

Protocol of Treatment (PDT × Photorejuvenation) and Author's Experience

1. Advise patients regarding the benefits and the limits of the technique.
2. Take pictures for further comparison.
3. Prophylaxis with aciclovir, if patient has past history of herpes.
4. Remove makeup, and then apply alcoholic chlorhexidine to clean the skin.
5. Do a slight curettage of AK lesions.
6. Apply ALA or MAL on the area to be treated. When using MAL, a thin layer of the cream should be applied throughout the area and it is also recommended to put a thicker layer on the top AK lesions.
7. Occlusive dressing with plastic film and aluminum paper can be done or not. ALA or MAL incubation time ranges from 1 to 3 h.
8. If AK is visible, it is better to do occlusion for 3 h with one session or for 1 or 2 h within two or three sessions (3–4 weeks of interval).
9. LED is better than IPL for AK lesions for a longer follow-up.
10. Remove the dressing and the excessive photosensitizer agent, before starting light exposure.
11. Time of light exposure depends on the lamp used. Usually it is programmed to deliver light dose and turn off automatically. If IPL or laser is used, protocols are going to vary according to the device based on its irradiance and fluence.
12. Analgesic before light exposure and during 24 h, if incubation time is 3 h.
13. Avoid sun exposure for 48 h. After this period, patients are advised to use sunscreen.
14. The use of moisturizing cream and cold compresses with thermal water is indicated. Corticoid should be avoided, but can be used if necessary.

Take Home Messages

1. The light effects on the skin involve complex mechanisms. The balance between dermal damage and induction of repair seems to define the final effect.
2. Photoaging is mediated by direct absorption of UV radiation and by photochemical

Fig. 8 Before and 6 months after treatment (two sessions of MAL-PDT) with red light (dose: 37J/cm^2). MAL incubation time of 2 h

reactions mediated by ROS. They play an important role in the etiopathogeny of photoaging and participate in the mechanism of action of PDT.

3. PDT protocols for photodamaged skin are reported with ALA or MAL and with different sources of light: IPL, laser, and LED.
4. Protocols vary in literature: different incubation times of ALA or MAL (30 min to 3 h), with or without occlusive dressing, number of sessions (average of 2–3), and interval between the sessions (2–4 weeks).
5. Clinically, a global improvement of skin is observed, with the improvement of texture, actinic keratosis, pigmentation, wrinkles, and sagging.
6. Histologically, there is an improvement in the organization of elastic and collagen fibers, with a statistically significant increase of those fibers at morphometry.

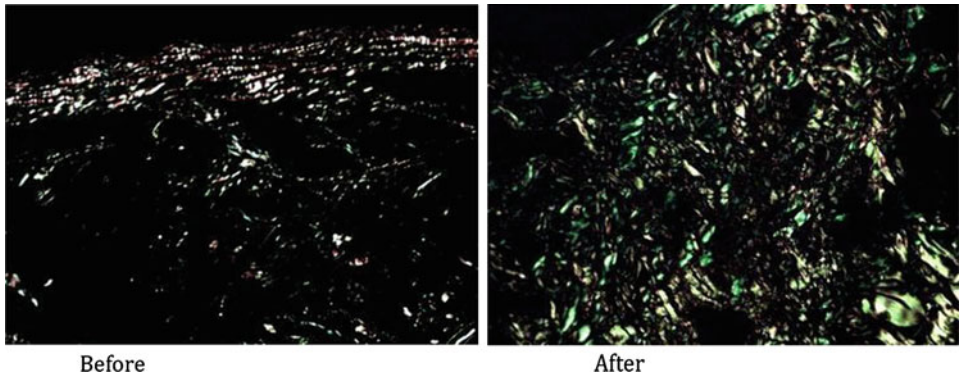

Fig. 9 Solar elastosis before and new collagen fibers in reticular dermis, 3 months after MAL-PDT treatment (Picro sirius × 400)

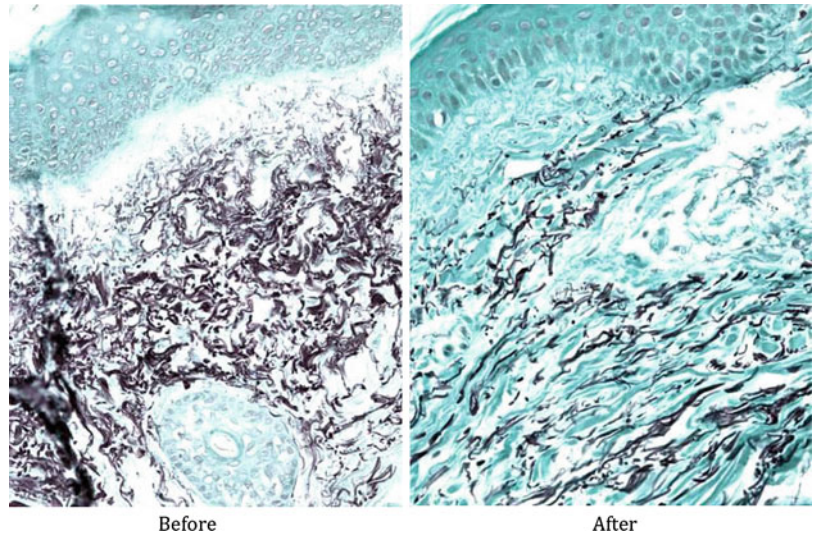

Fig. 10 Elastic fibers are compacted and disorganized before and organized 3 months after MAL-PDT treatment (Orcein × 400)

7. A possible mechanism of action related to photorejuvenation involves the increase of MMP-9 after PDT treatment, which modifies the extracellular matrix, inducing dermis remodeling with neocollagenesis.

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Photodynamic Therapy for Acne

Ann-Marie Wennberg Larkö

Abstract

Acne is a common disease that affects a large part of the young population. Common treatments for moderate acne include the use of oral antibiotics. However, there is an increased risk of antibiotic resistance. Furthermore, the environmental effects of these drugs may be severe. Hence there is an alternative for treatment of moderate acne. Photodynamic therapy (PDT) seems to have a good effect. However, treatment parameters need to be elaborated upon as possibly the choice of photosensitizer in the future. Pain is a cumbersome side effect but may be controlled by easy measures.

Keywords

Acne • Antibiotics • Photodynamic therapy • Bacterial resistance • Environmental hazards

Contents

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Introduction

Acne is a common skin disorder affecting mainly adolescents but also adults. Comedones become inflamed and sometimes cystic acne appears. Acne leads to severe suffering at a sensitive age. Patients with acne have a higher unemployment rate compared to the person with a healthy skin (Cunliffe 1986).

There is no generally accepted grading system for acne. However, in clinical practice this is less of a problem.

Moderate to severe acne is often treated with systemic antibiotic, especially tetracyclines. This may lead to bacterial resistance and have impact on environmental issues as tetracyclines do not degrade easily in nature. There seems to be an association between bacterial resistance and poor treatment results (Thiboutot 2011).

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Relevant Etiology

The pilosebaceous unit is the target organ. The secretion of sebum is increased, and *P. acnes* produces lipase that degrades triglycerides to glycerol and fatty acids which have inflammatory properties. *P. acnes* also excretes porphyrins which are light sensitive. Hence, visible light and photodynamic therapy can induce a photochemical reaction and less *P. acnes* (Hongcharu et al. 2000). However, this has been debated (Guffey and Wilborn 2006).

Photodynamic Therapy (PDT)

The basic principle is that a photosensitizer is concentrating in rapidly proliferating cells. The sensitizer is then converted to light-sensitive porphyrins. When exposed to light, a photochemical reaction occurs together with oxygen via energy transfer producing singlet oxygen. Hence, free radicals are formed and cell death occurs (Dougherty et al. 1978).

The most common photosensitizer used is delta-aminolevulinic acid (ALA). Several other derivatives are also used or tried (Song et al. 2014). See below.

ALA and its derivatives are mainly used for treating skin cancer or its precursors, actinic keratosis, superficial basal cell carcinoma, and squamous cell skin cancer in situ. Clinical results are good for thin lesions, but thicker tumors are harder to treat, e.g., nodular basal cell carcinomas (Sandberg et al. 2008).

The methyl ester of ALA (MAL) is probably most often used today. MAL is deesterified to ALA. MAL is more lipophilic than ALA and suggested to be more selective. However, it is questionable if there is a significant difference in transdermal penetration between ALA and MAL. Recently, a new formulation was introduced, BF-200. It may be more effective than ALA in tumor treatment (Neittaanmaki-Perttu et al. 2014).

The rate-limiting steps in heme formation are ALA synthetase and ferrochelatase. Exogenous application of ALA bypasses the first rate-limiting enzyme. Accordingly, accumulation of protoporphyrin IX (PpIX) takes place as ferrochelatase probably is downregulated. This process occurs in sebocytes. It seems that the intracellular target is the mitochondria (Peng et al. 1992). The process is oxygen dependent and oxygen depletion leads to less tissue damage (Ericson et al. 2003).

Mechanism of Action in Acne

P. acnes itself produces small amounts of porphyrins (Romiti et al. 2000). This can be seen as fluorescence when irradiating a skin area with UVA.

Irradiation with blue or red light leads to excitation of the endogenously produced porphyrins and formation of singlet oxygen. This results in bacterial death.

Applying ALA or its derivatives leads to formation of PpIX and accumulation in sebocytes. Again, singlet oxygen is formed in the presence of oxygen and the sebocytes are affected. In some studies sebum production has decreased, and in other studies this has not been found (Hongcharu et al. 2000; Horfelt et al. 2007).

More than 15 years ago, PDT treatment of acne was discussed (Hongcharu et al. 2000). They reported good effects of PDT for acne and showed a decreased sebum excretion due to damaged sebaceous glands. Others have not found a reduced sebum excretion (Horfelt et al. 2007; Pollock et al. 2004). Mouse studies have also indicated that ALA is taken up by sebaceous glands preferentially (Divaris et al. 1990).

Red light has a better tissue penetration than blue light or UV. Red light has been suggested to have anti-inflammatory properties on acne as well (Na and Suh 2007).

Blue light seems to be the most effective wavelength in photoactivating *P. acnes*. It seems that blue light alone may be beneficial against acne (Morton et al. 2005). Red and blue light might also be combined (Papageorgiou et al. 2000).

Jeong et al. have demonstrated that topical ALA-PDT for acne can induce apoptosis of sebocytes (Jeong et al. 2011).

Kosaka et al. demonstrated that focused damage of sebaceous glands may be achieved with ALA-PDT (Kosaka et al. 2011).

Light Sources for PDT

Both lasers and noncoherent light sources may be used (Zheng et al. 2014). The advantage of noncoherent light sources is that they are cheap and simple. However, LED light sources have become more common in everyday life and extremely cheap as pointers, LED lightning at home, headlights for cars etc. Unfortunately, LED light sources for treatment are rather expensive for various reasons. One can argue in favor of broadband light sources but also against. One advantage is that a bigger part of the absorption spectrum is used, one disadvantage that they produce more heat.

Lasers produce coherent, monochromatic light which exactly can match the absorption spectrum of porphyrins. The irradiated area is usually small which is a disadvantage. Also, the special properties of laser radiation, e.g., coherency, are not necessary.

Exposure to different wavelengths has been claimed to have a beneficial effect (Sadick 2009). The effect of sunlight is probably due to bacterial destruction as well as immunosuppression by its effect on Langerhans cells. It is probably mainly the UVA portion that is active. UVB has a poorer penetration in tissue and does not match the absorption band of porphyrins.

Visible light alone has proved to have an effect on acne (Sigurdsson et al. 1997).

Clinical Results

Several authors have reported good results after ALA-PDT for acne (Hongcharu et al. 2000; Horfelt et al. 2007).

Recently, a new LED device was introduced with green and red light (Dong et al. 2015). The overall effectiveness rate was 90% in 46 patients with moderate to severe acne. They argue that pulsed light sources may be less effective as there is not sufficient oxygen. Using shorter wavelengths may decrease pain.

Ying et al. recently published good results after PDT treatment of acne. They used 5% ALA in 21 patients with severe acne and a LED light source emitting at 633 nm. Total effectiveness rate was 85%.

Japanese studies have demonstrated a good effect of PDT on acne, but broadband light sources may cause more pain (Asayama-Kosaka et al. 2014).

Recently Das and Reynolds have discussed advances in acne pathogenesis and implications for therapy (Das 2014). They discuss different wavelengths and different light sources. Infrared lasers may minimize the sebaceous glands or affect lipids (Das and Reynolds 2014).

Both visible light and ALA have been proven to have an effect on acne. Pinto et al. compared the efficacy of red light alone and MAL-PDT for mild and moderate acne. MAL-PDT had a quicker action and a higher response rate than red light alone (Pinto et al. 2013).

Mei X et al. compared ALA-IPL-PDT photodynamic therapy with IPL in a recent study. ALA-IPL-PDT was shown to be superior both in terms of global lesion count and inflammatory and non-inflammatory lesion count (Mei et al. 2013).

Acne treatment by MAL-PDT with red light versus IPL has also been compared. Patients responded earlier to red light, but both therapeutic regimens were effective (Hong et al. 2013).

Haedersdal, Togsverd-Bo, and Wulf in 2008 studied different light sources in a review. They concluded that many therapeutic regimens may be active but that results are better for MAL-PDT than optical therapies (Haedersdal et al. 2008).

On the other hand, Hörfelt et al. a year later found that single low-dose red light is as efficacious as MAL-PDT for treating acne (Horfelt et al. 2009).

Zheng et al. recently made a review of photodynamic therapy in acne (Zheng et al. 2014). They studied 14 randomized clinical trials involving 492 patients. They concluded that several photosensitizers may be used. Probably ALA plus red light is the optimal choice but further studies are warranted.

Linkner et al. evaluated the efficacy of ALA-PDT and microdermabrasion for acne

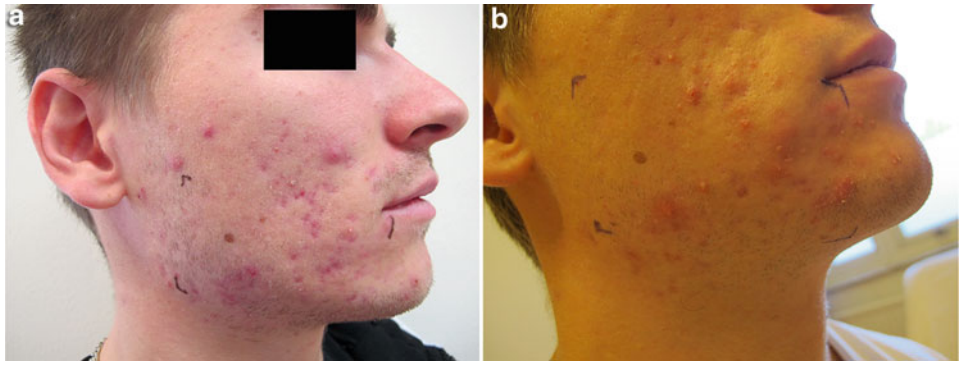

Fig. 1 (**a**) Before PDT. (**b**) Four weeks after two sessions of PDT

scarring. They found a good effect (Linkner et al. 2014). First, microdermabrasion was carried out, then PDT. Side effects were small.

A combination of ALA-PDT and ablative fractional Er:YAG laser has also been tried in severe acne (Yin et al. 2014). They evaluated the efficacy of combining ALA-PADT and fractional Er:YAG laser for scarring lesions in severe acne. Initially patients were treated with ALA-PDT four times at 10-day intervals. Then they got laser treatment five times at 4-week intervals. Scarring was significantly reduced.

Liu et al. (Liu et al. 2014) demonstrated good effect on acne with PDT, intense pulsed light (IPL), and blue-red light-emitting diode (LED) treatment of moderate to severe acne (Liu et al. 2014). One hundred fifty patients were enrolled. PDT gave faster clearance but was associated with more pain than IPL.

Interestingly, ALA-PDT seems to have an antibacterial effect (Li et al. 2013). ALA-PDT may be able to use in antibiotic resistance to reduce the biofilm.

A typical case is resented in Fig. 1a, b, before and after two PDT treatment sessions.

Adverse Effects of PDT

Short-term side effects include erythema and pain. This is often experienced as stinging and burning. The pain sensation is often individual but the larger the area treated, the worse is the pain (Grapengiesser et al. 2002). Men also seem to have more pain. Sometimes blisters occur.

The pain mechanism is not fully understood. Pain control is often achieved by a fan or cold water. Paoli et al. have used nerve blocks with good results (Paoli et al. 2008). MAL-PDT may be less painful than ALA-PDT (Wiegell and Wulf 2006).

Long-term side effects have not been observed so far, but a certain carcinogenic effect cannot be excluded although there is no convincing evidence (Ibbotson 2011).

Other Photosensitizers Than ALA

Other derivatives than ALA are also used. A recent study demonstrated a good effect of chlorophyll-a as the photosensitizer (Song et al. 2014). Also, side effects were minimal. Absorption peaks for chlorophyll are 430 and 662 nm. Hence, in this study blue and red light were used to match the absorption peaks of chlorophyll. Even sebum production decreased. Incubation time is significantly shorter with chlorophyll compared to ALA and MAL.

Indole-3-acetic acid (IAA) using green light has also been used, and the effect is good and the procedure relatively painless. Twenty-five patients were enrolled in the study. IAA was left 15 min under occlusion and green light was given for 15 min. Sebum excretion was also reduced (Jang et al. 2011).

Also, indocyanine green has been used with favorable results (Jang et al. 2011). Thirty-four patients were engaged. Half of the face was treated with indocyanine green with 805 nm radiation and the other half with indole-3-acetic acid and green light (520 nm). Few side effects occurred.

Place in Therapy

Acne may be treated in several ways. For mild to moderate acne, topical preparations may suffice. For more severe acne, antibiotics are often advocated. Unfortunately, bacterial resistance has become a major problem as well as environmental issues.

Hence, there is a need for treatment alternatives to antibiotics. PDT may be such an alternative. Most data are collected concerning ALA-PDT and MAL-PDT but new photosensitizers seem to emerge as an alternative. More studies are needed to elucidate proper dosage regimens and proper light delivery. PDT may well be used more frequently for acne in the future.

Take Home Messages

- *P. acnes* itself produces small amounts of porphyrins. Irradiation with blue or red light leads to excitation of the endogenously produced porphyrins and formation of singlet oxygen, resulting in bacterial death.
- PDT promotes focused damage of sebaceous glands, decreasing sebum excretion.
- Red light has a better tissue penetration than blue light or UV. Red light has been suggested to have anti-inflammatory properties on acne as well.
- Blue light seems to be the most effective wavelength in photoactivating *P. acnes*. It seems that blue light alone may be beneficial against acne. Red and blue light might also be combined.
- Photodynamic therapy seems to be effective against moderate acne and may prove to be an alternative to oral antibiotics in the treatment of acne.

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New Substances and Equipment Developed in Brazil: Photodynamic Therapy

Cristina Kurachi, Kleber Thiago de Oliveira, and Vanderlei Salvador Bagnato

Abstract

Photodynamic therapy (PDT) is an attractive technique to treat cutaneous lesions, especially basal cell carcinoma (BCC). The development of topical photosensitization PDT was a great advance to enhance its clinical dissemination, even though there is still limitation for a widespread use, especially in emerging economy countries, due to a high cost of the available drugs. In Brazil, as in worldwide, the main cancer type is BCC, and the present public healthcare services fail to provide an efficient treatment. Surgical resection is the elected treatment, and the available surgical facilities are not sufficient, resulting in long waiting list. For patients living far from the medical centers, the waiting between diagnosis and treatment can be of several months, besides long distance travels. Our strategy to overcome this reality and assist to promote the establishment of PDT centers in the Brazilian territory is to bring together the scientific expertise developed in academia and the technology sector. The Brazilian program is funded by the Brazilian Development Bank (BNDES), coordinated by the University of São Paulo, and has the partnership with MMOptics and PDT Pharma companies. We present our strategies, the Brazilian PDT device and compounds, and the partial results of this multicenter clinical trial.

Keywords

Photodynamic therapy • ALA • MAL • Basal cell carcinoma • Brazilian technology

Contents

Introduction

Photodynamic therapy (PDT) has been presented as an attractive therapeutic technique for basal cell carcinoma and potentially malignant cutaneous disorders (Lehmann 2007; Morton et al. 2008; Soini et al. 2015; Zouboulis et al. 2015).

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Dermatology is the medical area with the major PDT indications including local treatment of infected and inflammatory lesions, acne vulgaris, benign lesions, and facial resurfacing (Ma et al. 2015; Sakamoto et al. 2012; Issa et al. 2010; Hu et al. 2015; Monfrecola et al. 2004), especially due to its selective effect and cosmetic results. The main PDT protocols in dermatology use the topical application of 5-aminolevulinic acid hydrochloride (ALA) or their ester derivatives such as methyl 5-aminolevulinate hydrochloride (MAL) or prodrugs that improve the production of the endogenous photosensitizer protoporphyrin IX (PpIX), resulting in a superficial therapeutic response, without the overall skin photosensitivity side effect of the systemic administration.

Following the worldwide trend, Brazil also presents the nonmelanoma skin cancer as the most common cancer type. According to the Brazilian National Cancer Institute (INCA), around 182,130 new nonmelanoma skin cancer cases would be diagnosed in 2014. Brazil is the biggest country in South America, considering its continental area and population that is presently of around 206 million people. Any health policy in Brazil for a widespread and efficient diagnosis and treatment procedures is complex, especially for those pathologies that require higher-complexity facility and specialized personnel. The number of hospital beds for each 1,000 people was of 2.26, being the rate of public beds of only 0.8 in the last publication of 2012 (Resources indicatives, Brazilian Ministry of Health). During the years between 2005 and 2012, the Brazilian public health system cut approximately 42,000 of hospital beds, and until 2014, additional 7,000 beds were lost.

This situation goes in the wrong direction if it is considered the increasing population and also the increasing needs for health care. Considering the current numbers of new cases of nonmelanoma skin cancer and the available beds, if all patients require the hospitalization for the surgical removal of the lesions, the waiting list for the treatment procedure will never close. As a consequence of this reality, a late diagnosis and long waiting period for cancer treatment are observed. In some regions, this waiting can be of years.

Photodynamic therapy can constitute the first treatment option for non-infiltrative basal cell carcinoma (BCC) lesions. For this, early diagnosis is essential, as well as a small interval between diagnosis and treatment. Topical ALA/MAL-PDT has been already approved for BCC in several countries, including Brazil, and constitutes a highly attractive therapy for public health policies especially because it is an ambulatory procedure and, compared to the surgical resection, with reduced costs. Those are relevant features when considering public health. Metvix™ (Galderma, Switzerland) is approved by the Brazilian Health Surveillance Agency (ANVISA) as a PDT drug. A widespread use of MAL-PDT in Brazil is still prevented by the involved costs, being mainly present in private practice.

Our group in Brazil began to work with PDT in 1999, combining experimental studies, instrumentation, and clinical research. Since then, several protocols and devices have been tested in cell culture, animal models, and clinical trials for cancer, premalignant lesions, and infectious diseases (Melo et al. 2004; Bagnato et al. 2005; Souza et al. 2005, 2007, 2009a, b; Ferreira et al. 2006, 2007; Inada et al. 2012; Takahama et al. 2013; Silva et al. 2013; Andrade et al. 2014). Based on our experience and achieved results, we believe that topical PDT for BCC may contribute to decrease the waiting time for skin cancer treatment, improve patient satisfaction, and reduce treatment costs. Another factor that must be pointed out is that great majority of the patients has to travel long distances to get cancer treatment, in some cases even thousands of km. Bringing the skin cancer treatment to low clinical settings reduces the costs of medical care and of patient transportation and decreases the long waiting times.

The only feasible way to achieve a wide and diffuse PDT application in the Brazilian territory is to reduce the costs and improve the education and training of the medical teams on the photodynamic concepts, especially on indications and clinical protocol.

Based on these aspects, a Brazilian program for PDT of superficial BCC was established. For this, we have adopted a model combining public and

private sector interests using the needs as the opportunity for study, technological development, and commercial activity.

Brazilian Program and Strategies

The Brazilian program for PDT of superficial BCC has been financed by the Brazilian Development Bank (BNDES) and started on 2011. This program is coordinated by São Carlos Institute of Physics, University of São Paulo, and has the two Brazilian partner private companies; one is MMOptics responsible for the device, and the other is PDT Pharma that produces the ALA and MAL compounds.

The main aims of this multicenter clinical trial were (1) evaluation of the PDT response using the Brazilian device and drugs, (2) establishment of PDT centers in different regions, and (3) dissemination of PDT for medical doctors. Within these three main aims, other specific objectives were set, as to compare the feasibility and the tumor control efficacy of the PDT between an experienced and non-experienced center and to evaluate the PDT response depending on tumor site and skin phototypes, among others.

Our strategy for a higher success potential was to set a multidisciplinary team involving different expertise and experience necessary for the project execution: medical doctors, physicists, chemists, pharmacists, nurses, and engineers. Since the beginning, the collaboration with the Amaral Carvalho Cancer Hospital was essential for the clinical trial. Dr. Ana Gabriela Salvio, dermatologist, is the responsible medical doctor for the project, and the multicenter trial is approved by the Brazilian Ethics Committee on Human Research (CONEP, Comissão Nacional de Ética em Pesquisa) and institutional local Internal Review Boards.

Presently 70 PDT units were installed in 20 Brazilian federal states, 9 centers in Latin America, and 1 in Europe (Scotland). The establishment of each PDT unit included the training of the local team on the clinical protocol and the device use. Basic concepts on PDT mechanisms, light-tissue interactions, and ALA-protoporphyrin biosynthetic metabolism are discussed. The clinical protocol, indications, potential side effects and risks, and PDT equipment hands-on practice are also addressed during the training. The treatment of two patients with non-infiltrative BCC lesions is performed, so the medical team can observe and discuss all the procedure steps together with the specialized personnel of our group. The training is finished with the discussion of any questions left or other comments, and the local team receives support educational materials containing the handout of the clinical protocol. An open communication is stimulated to a frequent discussion on patient indication and follow-up. A 3-month report is asked to be sent to the principal investigator.

In this Brazilian program for the multicenter clinical trial, only BCC lesions up to 20 mm in diameter and 2 mm in depth are included, and the resumed MAL-PDT protocol is presented at Fig. 1. It is interesting to note that the established protocol uses a fluorescence-guided treatment, which has shown to allow an optimized result.

ALA and MAL Production

As mentioned before, 5-aminolevulinic acid hydrochloride (ALA) and their ester derivatives such as methyl 5-aminolevulinate hydrochloride (MAL) have occupied a special position in PDT treatments, not because they are photosensitizers, but because they are well-known direct biosynthetic precursors of protoporphyrin IX in cells which is the real photosensitizer with ALA derivatives. Basically, when ALA or their ester derivatives are used as topical cream formulations, a protoporphyrin IX accumulation is observed after 1–2 h, thus allowing the use of local PDT treatments by red light (630 nm) (Kennedy et al. 1990). The biosynthetic mechanism of production and accumulation of protoporphyrin IX is currently well established wherein the excess of ALA inside the cells can also promote an inhibition of some steps for heme production, thus resulting in a protoporphyrin IX localized accumulation (Fig. 2) (Kennedy et al. 1990).

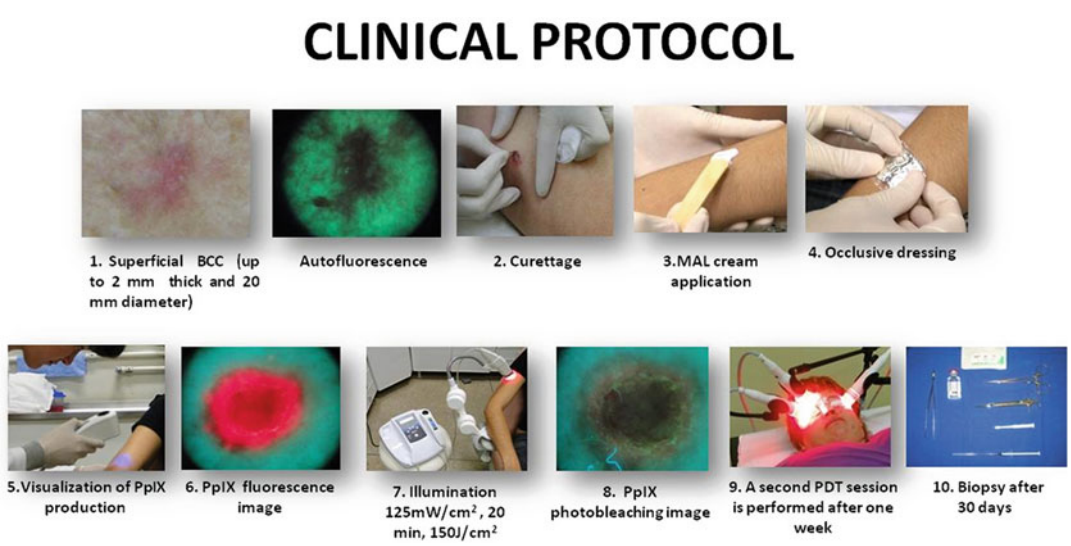

Fig. 1 Schematic chart of the resumed clinical protocol investigated in the Brazilian program

This alternative method was introduced in the literature in 1990 by Kennedy and coworkers (Kennedy et al. 1990), and an outstanding increase in PDT indications has been developed since this discovery. It is important to highlight that this treatment allowed the possibility to perform many local treatments with only localized photosensitivity instead of the overall skin and ocular photosensitivity caused by systemic administrations. Many scientists consider the local photosensitivity as one of the main advantages of this technique; however, the most important is the safety of the treatments. Systemic drugs may cause side effects, since complex issues are involved. A number of protocols should be considered before a new systemic drug is designated as an approved medicine, in which not only the effects of drug have to be studied but also the effect of metabolites, the population variability, and many other factors.

Definitively, ALA-PDT has the potential to act against many bacterial, fungal, precancer lesions, BCC, condyloma by human papillomavirus virus (HPV), and cervical intraepithelial neoplasia, as well as a fluorescent marker in cancer diagnosis (Tetard et al. 2014; Gold and Goldman 2004; Fotinos et al. 2006).

Another growing field for applications of ALA-PDT is the dermatology. In fact, PDT is essentially a technique for causing cellular damage. Therefore, the use of ALA in dermatology is well established since many inflammatory processes can be treated, thus selectively eliminating the abnormal cells and also killing pathogen microorganisms present in dermal infections.

Over the last 25 years, the ALA-PDT protocols have definitively proven to be useful for many treatments; therefore, the main question we have is: Why is ALA-PDT not a routine treatment in hospitals and clinics?

This is a highly complex question to address since many factors are involved. Economically, ALA therapies may involve millions of US dollars, which correspond to a large market. On the other hand, for many years, big pharmaceutical companies have systematically worked to develop systemic drugs and have spent millions of USD on research involving anticancer drugs (chemotherapeutical), and someone has to pay the bill. However, it is most important to convince the edge of the pyramid (the doctors) that PDT treatments present several advantages and can contribute to improve health around the world. As the pharmacist is directly responsible for promoting free medicine into the pharmacy, for example, vitamins and energy supplements, the doctors are also pivotal for the diffusion and success of PDT, and they should be the first ones convinced

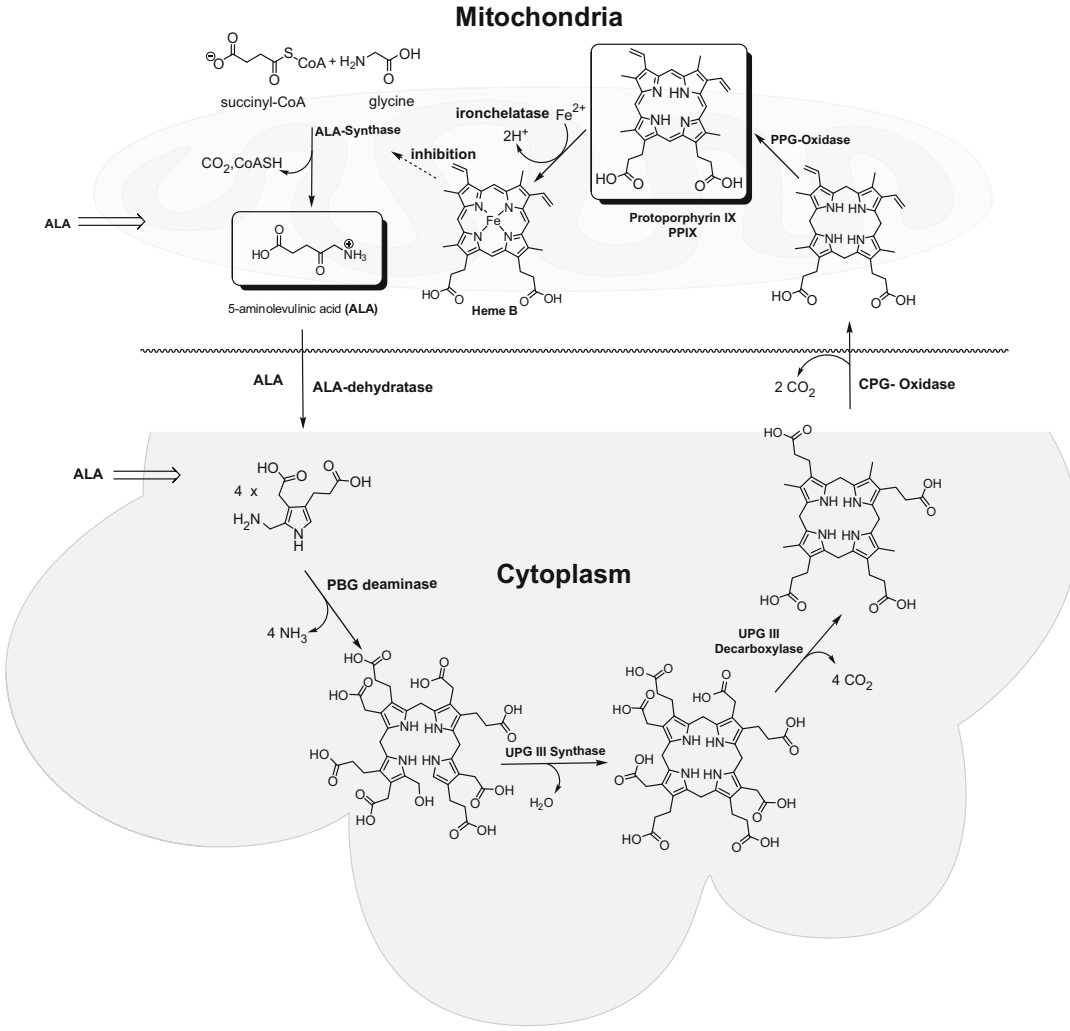

Fig. 2 Biosynthesis of heme group

that PDT is in fact effective. However, once, again it is not an easy assignment and involves many issues.

Fortunately, the diffusion of PDT treatments has grown around the word, and Brazil has figured out very useful contributions in this field. A successful example is the work developed by Optics and Photonics Research Center (CEPOF) located at the University of São Paulo in São Carlos City and also by two Brazilian associated companies, namely, PDT Pharma and MMOptics. The MMOptics started many years ago manufacturing optical devices, and PDT Pharma is the youngest initiative in Latin America working with the synthesis of photosensitizers and photomedicines (Fig. 3). Both companies are currently committed to establish protocols and commercial solutions involving mutually the photomedicine cream and the light device.

One of the main challenges for both companies is to turn this technology attractive considering PDT costs, and it has meant a number of investment and work. The PDT Pharma was born as a spin-off company due to the need of a provider which could allow the offering of ALA and their derivatives with a feasible price and considering the Latin America economical reality. The first challenge was to establish a facility to synthesize ALA and their

Fig. 3 One of the laboratories of PDT Pharma – with the permission of the company

derivatives fulfilling all the pharmaceutical requirements, from the active pharmaceutical ingredient (API) production until the formulation of a new cream, both respecting all the patent issues and the international protected marked. Since then, almost 7 years were spent, and according to information from the PDT Pharma company, in the beginning of 2017, a full solution will be technically available for the market.

The PDT Pharma example is very useful to illustrate the discussion established before where we mentioned the difficulty to make the PDT treatments more popular and accessible for the people due to the bureaucracy and also economical barriers. Obviously, as scientists we also completely understand all the market issues and the business market size which some systemic drugs can mean, and the objectives of the PDT team/companies are by far to fight against it. In this case it is important to mention that both companies are devoted to make the PDT closer to the people that need health assistance, thus allowing alternative solutions especially for public health consumers.

PDT Device Development

To the best of our knowledge, the LINCE (MMOptics, São Carlos, Brazil) was the first commercial system available for PDT with a widefield fluorescence visor and illumination probe combined in the same device (Fig. 4). The development of this device was performed by our group at the University of São Paulo and MMOptics financed by the Brazilian Funding Authority for Studies and Projects (FINEP, Financiadora de Estudos e Projetos), a government federal organization of the Ministry of Science, Technology and Innovation.

The main technical characteristics of the PDT system are presented at Table 1. LINCE is a portable device that has two probes, one for fluorescence visualization and another for the PDT illumination. Both probes have LED-based light sources, and optical components to provide a uniform illumination area. The system contains a photodetector in the front panel for the irradiance checking and an electronic visor and push bottoms for the irradiance and illumination time selection.

One of the main limitations of the use of ALA or MAL as a topical prodrug is the variability of production of protoporphyrin IX (PpIX) as a result of the surface and metabolic differences of the tumor lesions. As a consequence, the resulted PpIX production may be highly heterogenous, resulting in an overall ineffective PDT response. There is no way to predict the adequate PpIX concentration and distribution within the tumor, but the monitoring of the tissue fluorescence can

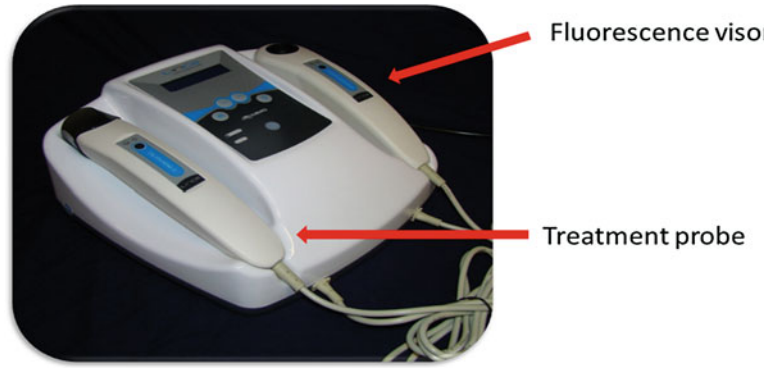

Fig. 4 LINCE PDT device. The portable dual system combines the use of a widefield fluorescence visor and the illumination treatment probe

Table 1 Main specifications and technical features of LINCE (2011)

Equipment	
Input voltage	100–240 V/50–60 Hz
Electric classification (EN 60601-1)	Class II, type B
Operating mode: treatment probe	Continuous
Operating mode: evidencer probe (fluorescence)	Intermittent (on, 15 min) or (off, 2 h)
Treatment LED spot diameter	(20 ± 2) mm
Fluorescence LED spot diameter	(20 ± 2) mm
Treatment LED wavelength	(630 ± 10) nm
Fluorescence LED wavelength	(400 ± 10) nm
Treatment LED irradiance levels	50, 75, 125, and 150 mW/cm^2 ± 20%
Fluorescence LED irradiance	Maximum at 40 mW/cm^2 ± 20%
Protection goggles	1 (evidencer), 2 (treatment)

be used to indirectly detect the presence of the PpIX. The skin autofluorescence shows a higher emission at the green spectrum, the cancer lesion shows a decreased autofluorescence, and the PpIX emits a red fluorescence. The possibility to qualitatively assess the production of PpIX is a great advantage for the medical doctor to evaluate if this PDT step has been adequately taken place. If there is no PpIX production after the cream incubation time or if it is heterogenous, the resulted photodynamic response will be poor. In this case, the medical doctor should reevaluate the lesion preparation or even the further illumination.

Another relevant clinical information that can be obtained using the widefield fluorescence imaging is the analysis of the resulted photobleaching after the completion of the illumination exposure (Fig. 1, steps 6 and 8). This is a qualitative evaluation of the induced photodynamic reaction since there is a direct correlation between the PpIX photobleaching and the production of the singlet oxygen. The PpIX photobleaching can be assessed by the decreased red fluorescence when compared to the before illumination red emission.

Overall Partial Results of the Multicenter Study

From the beginning of the PDT applications in this present multicenter clinical trial in March 2011 until June 2015, around 4,000 BCC lesions were treated using the proposed protocol. This database is constantly updated with the partial reports from the PDT units. Partial results have been already published (Ramirez et al. 2014; Blanco et al. 2015; Buzzá et al. 2016), but the main results

evaluated until now demonstrate that the investigated MAL-PDT protocol is effective for over 85% of the treated lesions (complete tumor response in a punch biopsy at 30 days after treatment). One important feature was observed when considering the complete response rate; when the PDT was performed by an experienced dermatologist, the rates could reach 95%, but for the ones that had no previous experience, the achieved rates were lower. Our hypothesis, based on the analysis of the treated cases, is that the experienced doctors are more restricted on the MAL-PDT indication, since they already know which lesions will respond better. This fact points out the relevance on the training as well as on a closer follow-up of the medical team, especially to discuss the lesion selection.

There was only one report of an unexpected side effect where one patient with a lesion at the nose showed a moderate/severe inflammatory condition after the first PDT session, which was controlled with a topical corticosteroid cream, but prevented the second session at the seventh day.

On the PDT center at the Amaral Carvalho Hospital, a double-bind study comparing the treatment efficacy of ALA-PDT, MAL-PDT, and surgery has been performed in 600 patients. The clinical steps were completed; the results are under analysis and will be presented in a scientific paper.

Non-oncological Protocols

In order to evaluate the efficacy of the photodiagnosis and PDT for the treatment of potentially malignant lesions, but also to develop protocols for local microorganism inactivation in infected lesions, other research and instrumentation development was also performed. Examples of targeted potentially malignant lesions are condyloma acuminatum by *human papillomavirus* (HPV) in women (Inada et al. 2012) and actinic cheilitis (Takahama et al. 2013), and ongoing clinical trials are for cervical intraepithelial neoplasia (CIN), actinic keratosis, and field cancerization.

Considering photodynamic therapy for infectious diseases, our group and collaborators have been investigating and determining protocols for onychomycosis (Silva et al. 2013), denture stomatitis (Mima et al. 2011), pythiosis (Pires et al. 2012, 2014), pharyngitis, and infected cutaneous ulcers.

Final Considerations

Photodynamic therapy has been showing effective results for the local treatment of cancer and infected lesions. Even though, PDT presents several advantages when compared to surgical resection for the treatment of superficial BCC, its widespread use has been prevented due to limitations mainly considering the involved costs of the illumination equipment and photomedicine compound. In Brazil, through a national program funded by BNDES (Brazilian Development Bank), scientists, clinicians, and technological companies could work together to establish a multicenter clinical study. The achieved results showed that the PDT protocols have similar response when compared to literature presented with foreign drug and devices. Analyzing the results and comparing the established centers, it was possible to infer the relevance of the training of the medical team, as well as a closer monitoring of the non-experienced teams. The proper indication of the MAL-PDT was the main factor contributing to the higher complete response rates, which was mostly observed at the centers with indicated previous experience with PDT. This program resulted in the implementation of 70 PDT centers, including the ones in low setting clinical facilities.

Take Home Messages

- The Brazilian program to implement PDT centers, using national technology, is presented.
- A clinical MAL-PDT protocol was tested in 70 centers for the treatment of superficial BCC.
- The illumination device has a dual platform, a widefield fluorescence visor and an illumination probe, both LED-based light sources.

– Tumor complete response was of 90% in experienced teams and around 65% for the teams without any previous experience on PDT. The uncorrected indication of some lesions was the main factor attributed to this lower response.

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Part III

Ablative and Non-ablative Radiofrequency

Non-ablative Radiofrequency for Facial Rejuvenation

Célia Luiza Petersen Vitello Kalil, Clarissa Prieto Herman Reinehr, and Celso Alberto Reis Esteves Jr.

Abstract

Over the last decades, non- or minimally invasive skin rejuvenation techniques have shown continuous and growing demand. Although surgical procedures are the "gold standard" for facial and body skin sagging treatment, many patients choose procedures with lower downtime, even if it means more subtle results, because they don't want to be away from their work and social activities. In order to fulfill this need, a range of non-ablative devices was introduced, such as lasers, devices using light sources – as intense pulsed light (IPL) – and radiofrequency. This chapters discuss radiofrequency, an extremely valuable therapeutic for rejuvenation, as it allows patients to keep realizing their activities and also provides "natural" results.

Keywords

Radiofrequency • Rejuvenation • Collagen • Skin aging • Non-ablative devices • Skin laxity

Contents

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Introduction

Over the last decades, non- or minimally invasive skin rejuvenation techniques have shown continuous and growing demand (Mulholland 2011). Although surgical procedures are the "gold standard" for facial and body skin sagging treatment, many patients choose procedures with lower downtime, even if it means more subtle results, because they don't want to be away from their work and social activities (Mulholland 2011; Bogle and Dover 2009; Brightman et al. 2009; DeHoratius and Dover 2007; Afrooz et al. 2014; Elsaie 2009; Sadick et al. 2009). In order to fulfill this need, a range of non-ablative devices was introduced, such as lasers, devices using light sources – as intense pulsed light (IPL) – and radiofrequency (Mulholland 2011; Alexiades-Armenakas et al. 2008).

The use of radiofrequency as a treatment of periorbital rhytides and sagging was described in 2003 by Fitzpatrick et al. with more than 80% of the treated patients showing improvement after a monopolar radiofrequency session (Fitzpatrick et al. 2003).

Further studies have evaluated its use in the treatment of sagging neck skin, improvement of lower third face contour, management of atrophic acne scars, and treatment of body laxity and cellulite (Brightman et al. 2009).

Radiofrequency

The devices used for laxity treatment work producing heat in enough amount to warm up the dermis (DeHoratius and Dover 2007; Hodgkinson 2009). Beyond radiofrequency, ultrasonic waves and infrared radiation devices also act through dermal heating (DeHoratius and Dover 2007).

Radiofrequency is a form of electromagnetic energy in which electrons move in an electric field and change its polarity up to six million times per second. The alternating electric current generated fluctuates between 3 kHz and 300 MHz (Bogle and Dover 2009; Osório and Torezan 2009). When trying to move into the tissue, the resistance to the rotational movement of electrons generates high-frequency oscillation in the water molecules of the dermis (Goldberg et al. 2008). This energy oscillation is eventually transformed into thermal energy (Ohm's law) (Mulholland 2011; Hodgkinson 2009; Osório and Torezan 2009). The resistance to the passage of electrons depends on the tissue's characteristics, such as its temperature and the concentration of water (Abraham and Mashkevich 2007).

The formula that represents the total energy follows:

$$\text{Energy(J)} = \text{I}^2 \times \text{R} \times \text{T}$$

I = current
R = tissue impedance
T = time of application

The principle that guides the process is called reverse thermal gradient: protective epidermal cooling occurs and dermal heating as well (Goldberg 2004). The epidermal cooling is applied before, during, and after the application of the radiofrequency handpiece (Goldberg 2004). This protection of the epidermis results in lower risk of infection, scarring, and pigmentary changes when compared to ablative procedures.

The heating of dermal collagen between 50 and 70 °C (Celsius degrees) results in the rupture of hydrogen bonds and in changes in the conformation of collagen fibers, which lose their three-dimensional structure and assume an amorphous form, causing it to contract by 30% and thickening the fiber (immediate tissue retraction) (Hodgkinson 2009; Bogle et al. 2007). The collagen contraction is a time- and temperature-dependent process, every 5° of temperature reduction, a 10 min increment is required to obtain the same amount of retraction (the Arrhenius equation) (Brightman et al. 2009). In monopolar radiofrequency, the dermis heating is expected to reach around 65–75 °C, and the epidermis must be maintained at a temperature below 40 ° C. If dermal heat produced is suboptimal, it will not improve sagging and rhytides. In the event of an

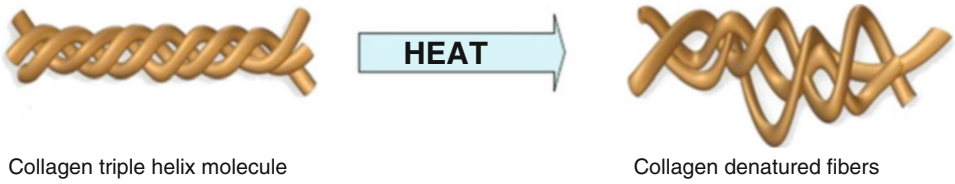

Fig. 1 Representation of the immediate effect of dermal heating on the collagen fibers

excessive heat production, atrophy, scars, erosions, and skin discoloration may occur (Royo de la Torre et al. 2011) (Fig. 1).

After that begins the subepidermal inflammatory reaction process resulting in neocollagenesis and a gradual improvement seen in 6–12 weeks (late effect) (Steiner and Addor 2014).

Moreover, the heat delivered to the deeper tissues stimulates adipose tissue capillary blood flow and accelerates lipid metabolism (Hodgkinson 2009).

Types of Radiofrequency Delivery (Monopolar/Multipolar (Bipolar and Tripolar)/Fractional)

Monopolar Radiofrequency

First generation of radiofrequency. Volumetric heating (three dimensional) of the dermis and subcutaneous occurs in a short period of time. Maximum depth reached is 20 mm, and it depends on the size and geometry of the handpiece (Steiner and Addor 2014). The type of handpiece used and the amount of energy delivered through it are the main determinants of depth reached (Hodgkinson 2009; Alster and Lupton 2007). Handpieces with larger contact areas on the treated surface obtain deepest dermal heating (Goldberg et al. 2008).

There is only one active electrode in contact with the skin surface to be treated (dipole in the device handpiece) in this type of radiofrequency, and the current flows from this electrode toward a neutral or return electrode placed in a distant location, usually in the back (Hodgkinson 2009). Most of the heat is produced in the area located below the active electrode (Steiner and Addor 2014) (Fig. 2).

Thermage CPT System (ThermaCool®)

1. Radiofrequency generator: alternating current (AC) 6.78 MHz, maximum flow 225 J/cm^2, with a display through which current, energy, number of sections, duration of treatment, and impedance can be monitored. At the display the energy can be selected according to the area to be treated (Hodgkinson 2009; Abraham and Mashkevich 2007).
2. Pulsed cryogen within the treatment handpiece: cooling system before, during, and after the application of radiofrequency (Goldberg 2004).
3. Cable connected to disposable treatment handpiece containing treatment electrode inside: single use, with duration limited by the number of shots (200, 400, or 600) and time ("one handpiece, one patient, one treatment") (Hodgkinson 2009; Abraham and Mashkevich 2007).
4. Microprocessor: located on the handpiece which controls pressure, current flow, and skin temperature in contact with the handpiece (Abraham and Mashkevich 2007).

There are 0.25 cm^2 handpieces used to treat the upper eyelid and fine wrinkles and 3.0 cm^2 handpieces used to lower eyelid, periorbital wrinkles, and bottom of the eyebrow region. In addition there is the DC handpiece body and a specific body handpiece for cellulite treatment (Hodgkinson 2009).

A complete cycle of radiofrequency emissions ranges from 1.5 to 1.9 s (Steiner and Addor 2014).

The treatment is performed in the clinic with no need of topical anesthetic since it is slightly painful and also because heat intensity evaluation by the

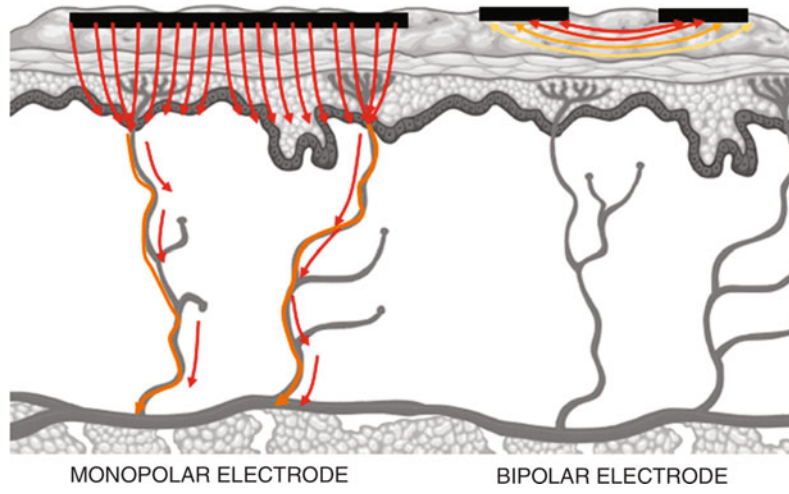

Fig. 2 Representation of affected depth of the tissue by monopolar and bipolar radiofrequencies, respectively

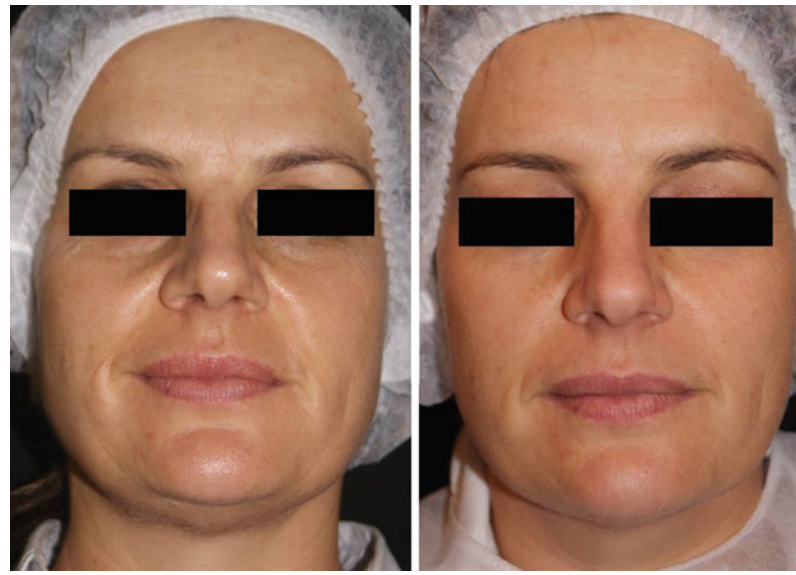

Fig. 3 Patient 1 – ThermaCool. One session – treatment for contouring and facial sagging improvement (before and after 8 months)

patient is necessary to reduce the risk of possible complications. The postoperative does not require specific care and one session gives good results (Steiner and Addor 2014) (Figs. 3, 4, and 5).

Multipolar Radiofrequency

Bipolar

In this type of radiofrequency, there are two active electrodes in contact with the area to be treated, located at a fixed distance, and the current flows only in the space between them (closed power circuit) (Sadick 2007). This type of radiofrequency shows a more superficial dermal heating and reaches a maximum depth of 2–4 mm, and this maximum depth is half the distance between electrodes. More sessions are necessary to achieve similar results to those obtained with monopolar radiofrequency (Steiner and Addor 2014). Among the RF devices that use bipolar energy, we quote Aluma™/Lumenis®, Santa Clara, and Accent® and Accent XT®, Alma Lasers.

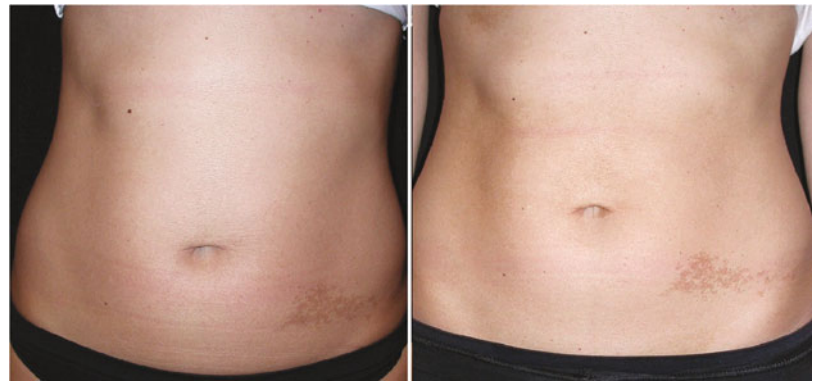

Fig. 4 Patient 2 – ThermaCool. One session for abdominal contour improvement (before and after)

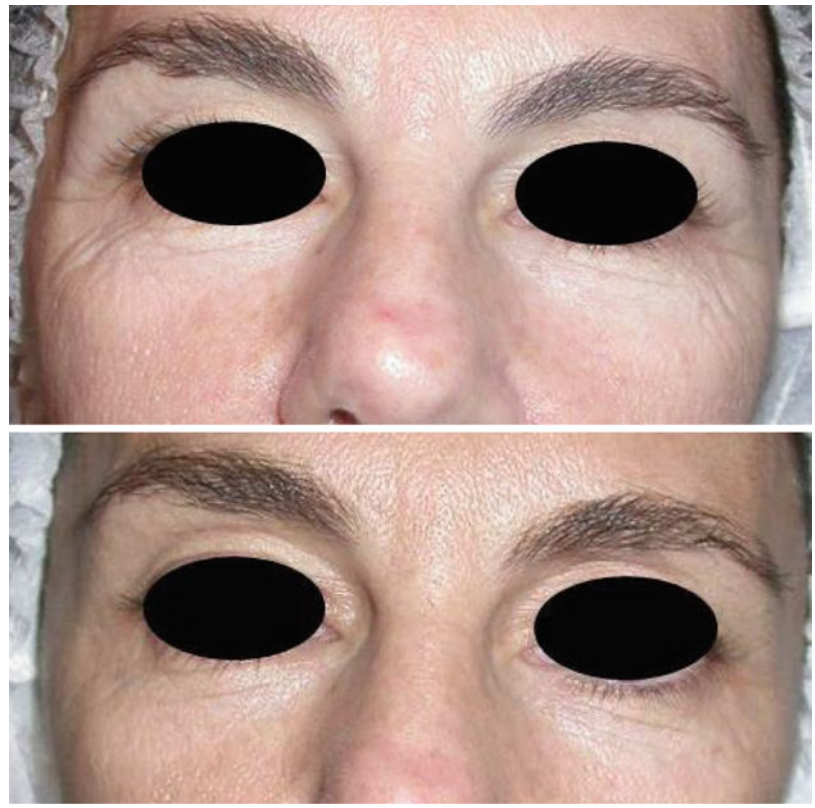

Fig. 5 Patient 3 – ThermaCool. One session, 0, 25 cm tip, eyelids and periorbital treatment, improvement of the side and upper eyelid sagging

Tripolar

It is the third generation of radiofrequency, which has three active electrodes that deliver energy and enhance the flow. Although smaller, the energy released is more concentrated when compared to the mono- or bipolar radiofrequency (Steiner and Addor 2014). This technique allows homogeneous heating of the dermis and hypodermis, reaching 20 mm deep with the use of lower power, approximately 50 W (Steiner and Addor 2014). An example of this technology is found in the device Apollo TriPollar®, Pollogen LTDA.

Fractional Radiofrequency

Fractional radiofrequency consists of minimally invasive technique of bipolar radiofrequency wherein the heat generated by an electromagnetic current results in cellular evaporation in the

epidermis (Reddy and Hantash 2009). Electromagnetic waves cause oscillations of the water molecules and produce thermal energy in the dermis. This controlled volumetric heating of the dermis will finally stimulate the neocollagenesis. The device comprises electrodes or microneedles arranged in pairs. The technique combines non-ablative coagulative effect on dermis with areas of controlled ablation in less than 5% of the treated epidermis (Taub and Garretson 2011). This RF mode allows intermediate areas of treated skin with untreated areas that function as a cell reservoir and accelerate the healing. Fractional radiofrequency can be used in facial rejuvenation and treatment of acne scars (Steiner and Addor 2014; Taub and Garretson 2011).

Plasma

Newest type of radiofrequency uses the state of matter called plasma. Plasma pulses are created when very high radiofrequency energy passes through inert nitrogen and oxygen gas and generates ionized gas. The handpiece directs this formed energy to the treated surface. The operating principle is the same as other types of radiofrequency with dermal heating and stimulating neocollagenesis (Rivera 2008; Spandau et al. 2014).

Key features of the types of radiofrequency

	Multipolar	
Monopolar	Bipolar	Tripolar
1 active electrode	2 active electrodes	3 actives electrodes
Depth 20 mm	Depth 2–4 mm	Up to 20 mm
Deeper	More superficial, multiple passages, greater number of sessions	Deeper; energy is more concentrated than monopolar radiofrequency

Histopathological Changes

According to what was reported by Zelickson et al. and Meshkinpour et al., denaturation of collagen fibers and mRNA expression of collagen I are observed after the radiofrequency. The increase in collagen III occurs at a higher intensity than that of type I collagen, with a peak between the sixth and tenth weeks post procedure (Meshkinpour et al. 2005; Zelickson et al. 2004). Javate et al. demonstrated an intact epidermis with increased thickness and amount of collagen fibers in the superficial and deep dermis post-radiofrequency non-ablative biopsies (Javate et al. 2011).

In 2011, El-Domyati et al. observed that after six biweekly interval monopolar radiofrequency sessions, skin biopsies showed epidermal hyperplasia that continued to increase 3 months after the end of the treatment, increase of granulosa layer, and increase in the epidermal organization degree. Besides that, the study showed elastosis reduction in the papillary dermis and increase in the amount of collagens I and III, 3 months after treatment that were statistically relevant (El-Domyati et al. 2011).

Study with non-ablative lasers (Pulsed Dye Laser and Nd:YAG) observed similar effects in stimulating collagen production and in the elevation of crucial enzymes for dermal proteins remodeling of the extracellular matrix (MMPs) (Orringer et al. 2005).

Table with the main radiofrequency non-ablative devices

Radiofrequency devices/ manufacturer	Radiofrequency (RF) technology
Thermage™/Thermage	Monopolar RF
Aluma™/Lumenis®, Santa Clara	Bipolar RF and vacuum
Accent®, Accent® XL/Alma Lasers	Unipolar and bipolar RF
Apollo TriPollar®/Pollogen LTDA	Tripolar RF
Polaris ReFirme™/Syneron	Bipolar RF and diode laser
ReFirme™/Syneron Medical	Bipolar RF and optical energy
Reaction™/Viora	Multipolar RF and vacuum
PowerShape™/Eunsung Global Corp.	Multipolar/bipolar RF and vacuum
Apollo®/Pollogen LTDA	Bipolar RF
Venus Freeze®/Venus Concept	Multipolar RF
Triniti E-max®/Syneron Candela	Bipolar RF + diode laser

Table with the main radiofrequency ablative devices

Radiofrequency devices/ manufacturer	Radiofrequency (RF) technology
Scarlet RF™/Viol Co., LTDA	Fractional bipolar RF
HF Fraxx®/Loktal	Fractional RF with microneedles
Matrix RF®/Syneron	Fractional bipolar RF
Renesis®/Primaeva Medical, Inc.	Fractional bipolar RF
ePrime®/Syneron Candela	Fractional bipolar RF
Duet RF PowerShape®/ Eunsung Global Corp	Fractional and thermal RF

Indications

As a result, in general, facial contour (jaw) and sagging are improved.

The technique can be used in the treatment of moderate submental shrinkage and sagging in the neck region.

The middle third of the face may also benefit, with attenuation of the nasolabial groove and reduction of sagging of the treated area (Sukal and Geronemus 2008).

Other Indications:

Treatment of body cellulite – associated with bipolar radiofrequency vacuum (VelaShape® – Syneron Candela) (Brightman et al. 2009)
Waist circumference reduction – bipolar radiofrequency associated with vacuum (VelaShape® – Syneron Candela) (FDA approved in 2007) (Brightman et al. 2009)
Treatment of atrophic acne scars – all types of radiofrequency may be used (monopolar, multipolar, and fractionated) (Taub and Garretson 2011; Rivera 2008)
Body treatment: laxity in the upper limbs, abdomen, and buttocks (Hodgkinson 2009) (FDA approved in December 2005)
Treatment of active acne – report with Thermage® (Dierickx 2004)
Radiofrequency in drug delivery (Subramony 2013; Gratieri et al. 2013)

The radiofrequency may be used as an adjunct in the treatment of gynoid lipodystrophy (Osório and Torezan 2009; Site Thermage). Goldberg et al. evaluated the efficacy of monopolar radiofrequency treatment of cellulite in the thigh in six sessions with biweekly intervals in 30 patients showing a circumference reduction of the thighs and improvement in cellulite degree, with no changes in lipid metabolism (Goldberg et al. 2008).

Patient Selection

The ideal patient for radiofrequency facial rejuvenation should be between 30 and 60 years old, presenting with mild to moderate skin sagging and facial rhytides, and should have realistic treatment expectations (Abraham and Mashkevich 2007; Goldberg 2004). Patients who underwent face lift surgery who present recurrent mild laxity 2–3 years after the procedure are, in general, good candidates for radiofrequency (Hodgkinson 2009; Abraham and Mashkevich 2007).

Patients presenting sagging after weight loss and abdominal sagging after pregnancy also benefit for body radiofrequency.

The correct patient selection is a major determinant of the response level to treatment (Suh et al. 2013). Patients with advanced age, who are obese, and with marked sagging will present mild results (Abraham and Mashkevich 2007). However, explained the limitations, if the patient does not wish to be submitted to more invasive procedures, radiofrequency is an interesting option (Goldberg 2004).

The correct selection of patients is a major determinant of the level of response to treatment (Suh et al. 2013). Patients with advanced age, obese, and with marked sagging will have less satisfactory results (Abraham and Mashkevich 2007). However, if the patient does not wish to be subjected to more invasive procedures and even after the limitations have been explained still wants to be subjected to radiofrequency, it is possible to do it (Goldberg 2004).

Benefits of the Procedure (Pros and Cons)

If we compare radiofrequency, a non-ablative technique, with ablative and surgical procedures, the procedure allows faster recovery and lower risk of complications. The results, however, are more discrete (Goldberg 2004). Another benefit regards the possibility to realize the procedure in all skin types, since radiofrequency operating mechanism differs from lasers and there is no absorption or scattering by the tissue melanin (Abraham and Mashkevich 2007). Moreover, it can be used on hairy areas without risks, because it does not damage the follicle.

Contraindications

Monopolar RF

Absolutes (Abraham and Mashkevich 2007)
Patients with cardiac pacemaker or defibrillator
Patients with other implantable electronic devices
Skin pathologies on the application area
Infection at the application site
Presence of permanent fillers in the area to be treated, especially polymethyl methacrylate (PMMA)
Relatives
Smoking
Autoimmune disease
Previous radiotherapy at the application site
Pregnancy
Chronic use of corticosteroids or nonsteroidal inflammatory
Other conditions that can impair healing

It is not recommended to use monopolar radiofrequency on areas with metal plates or on tattoos (Abraham and Mashkevich 2007).

Multipolar RF

Absolutes
Patients with cardiac pacemaker or defibrillator
Patients with other implantable electronic devices
Skin pathologies on the application area
Infection at the application site
Presence of permanent fillers in the area to be treated, especially polymethyl methacrylate (PMMA)
Inelastic scars
The use of photosensitizing medication
Systemic neoplasm
Venous thrombosis in use of anticoagulants

(*continued*)

Fractional RF

Absolutes
Patients with cardiac pacemaker or defibrillator
Patients with other implantable electronic devices
Skin pathologies on the application area
Infection at the application site
Presence of permanent fillers in the area to be treated, especially polymethyl methacrylate (PMMA)
Silicone prothesis in the area to be treated
Use of copper IUD (in the case of treatment in the lower abdomen)
Dental abscess if applied in the area of the face
Active rosacea

Contraindication to Radio in the Eyelid Region

Patients who underwent prior cornea surgery can't be submitted to radiofrequency in the eyelid region because of the need to use intrapalpebral protector that could injure the cornea (Steiner and Addor 2014).

Pre-procedure Care

The pre-procedure standardized photographs are essential. There are systems that allow, in addition to the standardization of photographs, the examination of variations in pigmentation and in epidermal thickness and the number and depth of rhytides, enabling the assessment of therapeutic response (Suh et al. 2013).

Application Techniques

For monopolar and multipolar radiofrequency, the following precautions should always be followed:

1. Fulfillment of consent form with the necessary explanations, expected results, and side effects and possible complications. The term should be applied by a dermatologist and all the patient's questions must be clarified. **Make sure the patient does not have any of the contraindications to the procedure.**
2. Before the procedure, it is necessary to remove all metals that are in contact with the patient's skin (jewelry, costume jewelry, watches).
3. Clean the area of the skin that the application of radiofrequency will be held, remove makeup and perform antisepsis of the skin with isopropyl alcohol (Steiner and Addor 2014).

After, for **monopolar radiofrequency**, proceed to the following steps:

4. Position the dispersive plate on the back of the patient.
5. Apply the temporary marking grid, accompanying the individual handpiece, on the area to be treated.
6. If the procedure is performed in the eyelid area, it is essential to use intrapalpebral protector that should be of plastic material to prevent its heating. This measure seeks to protect the eye globe from heat, from the electric field, and from mechanical damage.
7. Apply generous amount of specific fluid to monopolar radiofrequency, provided by the equipment company, over the area to be treated to occur correct docking of the handpiece on the skin. The handpiece should remain completely in contact with the skin at the time of application (Steiner and Addor 2014).

After completing the steps above, treatment is started. The equipment automatically calculates the impedance of the patient (Hodgkinson 2009). The energy levels are adjusted as the treated area changes according to the tolerance of the patient (Jacob and Kaminer 2008).

It is recommended that, when defining the area to be treated, the area adjacent to the one presenting sagging and loss of shape will also be treated so as to assist in support of dermal process (Jacob and Kaminer 2008).

Since its introduction, algorithms' application has been modified. Today are proposed treatment protocols with lower energy and greater number of passages, as opposed to what was initially described (individual passages with high energy), with better results (Bogle et al. 2007).

Current techniques allow less discomfort to the patient and more meaningful and homogeneous results (Sukal and Geronemus 2008).

By making the procedure without requiring anesthesia there is the possibility tolerable of interaction with the patient during the procedure as to the degree of warming sense. This fact made it possible to avoid overheating the epidermis and its complications (Sasaki et al. 2007).

During the execution of the procedure, the patient will refer feeling warmth in the treated area. Ideal heat is the one reported by the patient as "warm" and it is not intolerable (Hodgkinson 2009).

There are three techniques described for the application of monopolar RF:

1. Two simple passages
2. A scaled passage
3. A superimposed passage: recommended use in the Thermage CPT® device (Thermage, Inc., Hayward, California)

In the technique described as two simple passages, a row of passages is realized following the squares marked by the temporary grid, and then a second passage is performed on the marked circles in a staggered grid manner, alternating rows (Abraham and Mashkevich 2007). Following the completion of two passages, we proceed to the vectors' application, which consists of additional passages following the direction in which the elevation of the skin is desired (lifting effect) (Abraham and Mashkech 2007).

The technique with multiple passages (staking), maintaining the tissue heated, shows more efficient results, since the heating of the dermis diminishes

the tissue's resistance to the electrical current passage (Hodgkinson 2009). In the multiple passage technique, the energy required is reduced at each subsequent passage at the same location. Furthermore, the technique allows freedom to the operator, who can perform higher number of passages in areas that are more lax than in less affected areas (Jacob and Kaminer 2008).

The study of Dover et al. compared the single passage technique with the multiple one in 5,700 patients. In the group undergoing single passage, 54% of patients had improvement in skin laxity after 6 months. On the other hand, in the multiple passage group, improvement was observed in 84% of patients, which also reported less pain during the procedure and greater satisfaction with the results (Dover and Zelickson 2007).

The number of shots ranges from 400 to 800 for facial treatment session and from 1,000 to 1,200 on body section. On the face, many practitioners choose to perform one side and then the other. A session is performed in about 1 h. One may proceed to treatment of the entire surface or only a localized area, such as the mandibular region and the forehead (Jacob and Kaminer 2008). The expected effects of the session are erythema and immediate contraction of the treated surface, being able to also have local edema (Hodgkinson 2009).

The **multipolar radiofrequency** differs from the monopolar for not having marking grid and dispersive plate. Glycerin fluid is used on the application area of the skin, and there are specific handpieces for each region (the face, lower eyelid, and body). It is important to use an external infrared thermometer to monitor the temperature of the epidermis, which should not exceed 40 °C, to avoid burns (Steiner and Addor 2014).

Expected Results, Number of Sessions, and Session Intervals

The result can take up to 6 months to be noticed, since it is dependent of neocollagenesis and dermal remodeling, starting on average between 2 and 3 months (Abraham and Mashkevich 2007). Some patients also referred improvement of skin color and texture with smoothed scars (Abraham and Mashkevich 2007). Moreover, the results are highly variable, and even the application with suitable technique, some patients with show better results than others. The photographic record pre- and post-standardized procedure is essential in the evaluation of these patients (Steiner and Addor 2014).

In monopolar radiofrequency with one session, the results are obtained depending on time described above. In individual cases, two to three sessions with 6–12-month intervals between them are required.

In order to study the effect of subsequent sessions of monopolar radiofrequency, the study of Suh et al. evaluated eight patients who underwent monopolar radiofrequency sessions with Thermage CPT® apparatus for facial rejuvenation over a period of 7 years. The patients had an average of four sessions, with intervals between them ranging 4–45 months. During this period, there was no worsening in the assessment by the Glogau scale in eight patients, and seven patients reported satisfaction with treatment outcomes. Randomized studies with larger numbers of patients are needed to confirm the findings (Suh et al. 2013).

Regarding multipolar RF, a larger number of sessions, most often five to six sessions every 10–15 days, are required (Steiner and Addor 2014).

Therapeutic response is also dependent on the area being treated. The middle and lower third of the face respond faster than the neck because they have higher amounts of subcutaneous fat (Bogle et al. 2007).

Immediate Effects

Soon after the procedure, local edema can be observed, which is responsible for the "lifting" effect immediately observed. Mild erythema also occurs and remains for a few minutes after the procedure and resolves spontaneously (Abraham and Mashkevich 2007). Erythema and mild swelling the endpoints are expected immediately after the procedure (Sadick 2007).

FDA-approved uses for: Monopolar RF – ThermaCool System (Thermage, Inc., Hayward, California): (Abraham and Mashkevich 2007)

Treatment of periorbital skin sagging (FDA approved 2002)
Treatment of periorbital rhytides (FDA approved 2002)
Treatment of perioral rhytides (FDA approved 2002)
Treatment of facial rhytides (FDA approved 2004)
Treatment of generally rhytides (FDA approved 2005)

Adverse Effects

Edema	May persist for up to 1 week
Acneiform eruption	
Linear surface crusts	
Hypersensitivity of the neck	In general up to 2–3 weeks after the procedure
Moderate erythema	
Burns overlying skin	Bad-quality technique, high energy application
Nodosities in the cervical region (Site Thermage)	Disappear in 1–2 weeks
Irregularities of jaw and temporal contour (Hodgkinson 2009)	Monopolar radiofrequency, occur with older equipment
Mild to moderate pain (Site Thermage)	During the procedure, disappears shortly after
Temporary paresthesia	Perineural edema in sensitive nerves, disappears in weeks (Abraham and Mashkevich 2007)

According to the manufacturer ThermaCool System® (Thermage, Inc., Hayward, California), 99.8% of monopolar radiofrequency non-ablative procedures performed show no adverse effects (Abraham and Mashkevich 2007). Mild erythema and edema generally disappear in less than 24 h (Sukal and Geronemus 2008).

The day after the procedure, the patient can resume the skin care, as well as treatments previously used (Hodgkinson 2009).

Regarding the fractional RF, hypopigmentation can occur if the fluence used is too high and also postinflammatory hyperpigmentation in predisposed patients (Mulholland 2011).

Clinical Cases

Picture 3: Patient 1 – ThermaCool. One session – treatment for contouring and facial sagging improvement ((before and after 8 months)

Picture 4: Patient 2 – ThermaCool. One session for abdominal contour improvement (before and after)

Picture 5: Patient 3 – ThermaCool. One session, 0, 25 cm tip, eyelids and periorbital treatment, improvement of the side and upper eyelid sagging

Combined Treatments

Supplementation with other treatments such as IPL, fillers, botulinum toxin, chemical peels, and microdermabrasion is beneficial and should be individualized according to the needs of each patient (Abraham and Mashkevich 2007).

Some devices combine optical energy to electrical energy, in general the association of radiofrequency with laser (Laser Diode – Polaris WR system) or light source (LIP – Aurora®, SR, Syneron) and allow the treatment of vascular injuries and pigmented hair removal and treatment of rhytides' addition and sagging (Lanigan 2008). The combination of the two types of energy has a synergistic effect, allowing the use of lower doses of both, with less risk of adverse effects (Sadick 2007). In combined systems, in which the optimal energy used is lower than that usually required, there is the possibility of use in patients with higher phototypes with less risk of adverse effects (Alster and Lupton 2007).

We also found in the market devices for treatment of gynoid lipodystrophy linking bipolar RF vacuum and ultrasound (Syneron Candela VelaShape®) (Brightman et al. 2009).

Take Home Messages

– Radiofrequency is extremely valuable in the therapeutic arsenal for rejuvenation as it allows the patients to keep realizing their activities and also provides "natural" results.

– The correct knowledge of the technique and the proper selection of patients are extremely important to the treatment success, since it is dependent on these variants for the best results.
– Radiofrequency can be combined to others rejuvenation techniques with synergistic effects.

Cross-References

► Intense Pulsed Light for Photorejuvenation
► Non-ablative Lasers for Photorejuvenation

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Non-ablative Radiofrequency for Cellulite (Gynoid Lipodystrophy) and Laxity

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Abstract

Cellulite, also known as gynoid lipodystrophy, is a multifactor disorder of the dermis, epidermis, and subcutaneous cellular tissue (Goldman et al. Pathophysiology of cellulite. New York: Taylor & Francis; 2006). In most cases, this alteration occurs in postpubertal women with a prevalence of 80–90% (Goldman and Hexsel. Cellulite: pathophysiology and treatment. 2nd ed. Florida: Editorial Informa, Healthcare; 2010; Emanuele. Clin Dermatol 31(6):725–30, 2013). Clinically, cellulite presents irregularity of the skin surface with depressions, lumps, and nodules associated with laxity. Usually, cellulite is located in the abdomen, buttocks, and lower limbs, but it can also occur on the arms and the back. Histologically, cellulite is caused by subcutaneous herniated fat within the fibrous connective tissue (Rossi and Vergnanini. JEADV 14: 251–62, 2000; Khan et al. J Am Acad Dermatol. 62(3):361–70, 2010; De Peña and Hernández-Pérez. Rev Cent Dermatol Pascua 3:132–5, 2005). An increase in the thickness of the subcutaneous cellular tissue is also observed. Although cellulite is still considered as an unclear etiological condition, there are many hypotheses trying to explain this disorder. Treatments can be invasive and noninvasive. Invasive methods include subcision and mesotherapy, as well as liposuction when patients also want to remove excessive localized fat. Noninvasive treatments include topical treatments, controlled diets, cryolipolysis, focused ultrasound, endermology, laser, and non-ablative radiofrequency. In this chapter we are going to discuss the treatment with non-ablative radiofrequency. Radiofrequency (RF) contracts collagen and stimulates neocollagenesis by thermal heat, promoting thickening of the dermis, avoiding fat herniation. It can also promote improvement in local circulation due to the vasodilatation and lymphatic drainage. Clinically it improves the laxity and the irregularity of the skin surface (Coringrato et al. Radiofrecuencia ablativa en dermatología quirúrgica: Una revisión, Rev. dermatología argentina, vol. XIV, Julio–Septiembre 2008, Número 3; Brightman et al. Lasers Surg Med 41:791–8, 2009).

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Keywords
Cellulite • Gynoid lipodystrophy • Noninvasive radiofrequency • Neocollagenesis • Laxity • Fat herniation • Dermis thickness

Contents

Introduction

The skin is the most external organ and its appearance contributes to the patient's personality. Skin diseases and cosmetic problems significantly affect the self-esteem. The psychological effects of the cellulite (gynoid lipodystrophy) are frequently more serious than the physical alteration observed in this dermatosis. It can affect interpersonal relationships in a social, affective, and sexual way. It can affect normal daily activities, such as going to the beach, practicing sports, or using certain type of clothing. In the last years, the idea of having an ideal sculpting body changed the concept of cellulite from a cosmetic problem to a disease. Nowadays, women look for all types of treatments with the hope of reducing cellulite or making it disappear (Goldman and Hexsel 2010; Goldman et al. 2006). Different mechanisms are involved in cellulite's pathogenesis, and many different treatments are developed with aim to fight against each mechanism. There is no ideal treatment, but there are many therapeutic alternatives to reduce the physical appearance of this condition. Recently, noninvasive devices such as nonablative radiofrequency (RF) and the combination of RF with other technologies have gained strength and have been very successful. The most used RFs for cellulite are the unipolar, bipolar, and the combination of RF with infrared light, vacuum, and mechanical massage.

Cellulite (Gynoid Lipodystrophy)

Concept and History

Cellulite, also known as gynoid lipodystrophy, nodular liposclerosis, adiposis edematosa, dermopaniculosis deformans, edematous fibrosclerotic panniculopathy, panniculosis, and cellulite hypodermosis, is a multifactor disorder of the dermis, epidermis, and subcutaneous cellular tissue (Goldman et al. 2006). In most cases, this alteration occurs in postpubertal women with a prevalence of 80–90% (Goldman and Hexsel 2010).

Alquier and Paviot described cellulite for the first time in 1920 (Rossi and Vergnanini 2000). They described a non-inflammatory complex cellular dystrophy of the mesenchymal tissue caused by a water metabolism disorder, which produces the saturation of the adjacent tissues by interstitial fluid (Rossi and Vergnanini 2000). In the same decade, Laguese described cellulite as changes in the subcutaneous tissue characterized by the increased fatty tissue and interstitial edema (Goldman et al. 2006; Laguese 1929). In 1958, Merlem defined cellulite as an angiopathy, and in 1978, Benazzy and Curri suggested the term "sclerotic-fibrous-edematous panniculopathy" (Goldman et al. 2006). In 1978 Nüremberg and Müller (1978) found differences in the structure of the skin and the subcutaneous tissue of men and women that would partially explain the prevalence of cellulite in women (Nürnberger and Müller 1978). Currently, the terms cellulite and gynoid lipodystrophy are the most used terms in medical literature.

Clinical Manifestations

Usually, cellulite is located in the abdomen, buttocks, and lower limbs, but it can also be located on the arms and the back. Cellulite is caused by subcutaneous herniated fat within the fibrous connective tissue, with a typical dimpled appearance (with alternated depressions with lumps) or orange skin appearance (due to swelling of the flat surfaces and dilation of the follicular openings) (Rossi and Vergnanini 2000; Khan et al. 2010; De Peña and Hernández-Pérez 2005). The majority of the injuries have an oval shape, where the axis of the injuries is parallel to the tension lines of the skin (Goldman and Hexsel 2010). Cellulite is more evident with laxity, therefore getting worse with aging. During palpation, pinching the skin in a cellulite area, we can feel an increasing in the thickness of the subcutaneous cellular tissue and in its consistency and a decreasing in its mobility by adhesion (De Peña and Hernández-Pérez 2005).

In general, cellulite is an asymptomatic alteration; however, painful nodules can accompany it in the severe stages, suggesting an inflammation in dermis and adipose subcutaneous underlying tissue (Goldman and Hexsel 2010; Emanuele 2013).

Cellulite is different from obesity; obesity is characterized by hypertrophy and hyperplasia of the adipose tissue that is not necessarily limited to the abdomen or the lower limbs(Rossi and Vergnanini 2000). The presence of cellulite should not be confused with obesity, even though adipogenesis aggravates this condition (Emanuele 2013).

Etiopathogenesis

The etiopathogenesis of cellulite has been widely discussed in the last decades. Although cellulite is still considered as an unclear etiological condition, there are many hypotheses with respect to its origin, such as vascular changes and edema, architectural difference of the skin related to gender, inflammatory alterations, and hormonal variations.

Vascular Changes and Edema

The first document about the pathophysiology of cellulite reported the increasing in the glycosaminoglycan amount in the dermis and extracellular matrix and on the capillary dermal vessels of the skin in the cellulite area. This could explain the amount of water retained in the skin, attracted by glycosaminoglycans. Based on these findings, edema in cellulite was related to the changes in the composition of the extracellular matrix (Emanuele 2013). Some degree of damage in the skin vasculature with an alteration in the precapillary arteriole sphincters was also reported. Other findings, such as the presence of new capillary formations, telangiectasia, microthrombi, and micro-hemorrhages, related cellulite to a chronic venous insufficiency (Rossi and Vergnanini 2000). These contribute to capillary permeability and excessive retention of fluids in the dermis, as well as in the fat layer, between the adipocytes and the lobular septa, increasing the interstitial pressure due to the hydrophilic properties of glycosaminoglycan.

Vascular alterations, edema, and decreased venous return cause hypoxia of the tissue which leads to the thickening of the fibrous septa in the superficial adipose tissue and deep dermis, which causes the padded aspect of cellulite (Curri and Bombardelli 1994).

Architectural Difference of the Skin Related to Gender

This theory was described by Nüremberg and Müller in 1978 when they reported cellulite as a fat herniation called "papillae adiposae." In this condition, fat penetrates from the subcutaneous tissue through the interior surface of a weak dermis in the dermo-epidermal interface, which is considered a characteristic of female anatomy (Nürnberger and Müller 1978). This alteration has been confirmed through ultrasound, spectroscopy, and magnetic resonance imaging (MRI) (Bravo et al. 2013). It has been observed that the herniation of the tissue is typical in women because the fibrous septa are different in this gender than in men. In men, septa are distributed in an intersecting way forming small polygons that generate a type of cell that does not move forward

facially toward the dermis and are not placed perpendicularly as what occurs in women. This particularity helps to understand why cellulite can occur both in skinny and in obese women (Nürnberger and Müller 1978).

Querleux et al. (2002) reveal the three main orientations of the septa, which are parallel, perpendicular, and angular (approximately 45°). They describe that women with cellulite have a higher percentage of perpendicular septa than women or men without cellulite.

Inflammatory Alterations

Inflammatory alterations were cited as one of the main pathophysiology factors of cellulite. Kligman concluded that cellulite is a blurred appearance of swollen chronic cells (Nürnberger and Müller 1978); also there is evidence of lymphocyte and macrophage infiltration in the fibrous septa, resulting in adipocytes and cutaneous atrophy (Nürnberger and Müller 1978; Bravo et al. 2013). This hypothesis would explain why some patients with cellulite have pain and sensitivity to compression. Other authors do not consider inflammation as part of this process (Piérard et al. 2000).

Hormonal Variations

Other authors suggest that cellulite is a connective tissue abnormality that results from estrogen activity over fibroblasts to produce matrix metalloproteases which damage the connective tissue, degrading collagen fibers in the trabeculae inside adipose tissue (Bravo et al. 2013).

The physical manifestations of cellulite are due to the destruction of the normal architecture of the collagen trabeculae that keep the adipose tissue confined in only two layers: superficial and deep layers of fat (Pugliese 2007). Therefore, the correlation between cellulite and hormones is justified by its appearance after puberty, worsening during pregnancy and with estrogen treatments, as well as in obesity, in which estrogen level is increased.

On diet with excessive fat and carbohydrate, a hyperinsulinemia is produced, increasing lipogenesis and inhibiting the lipolysis, generating fat accumulation. It has also been described that prolactin increases water retention in the adipose tissue generating edema (Isidori 1983).

Other hormones involved are the thyroid hormones that increase lipolysis and reduce the activity of phosphodiesterase and decrease antilipolytic receptor activity. Patients with hypothyroidism have more cellulite due to a reduction of lipolysis (Rosenbaum et al. 1998).

Predisposed Factors

Cellulite occurs in all races, although white women tend to show more cellulite than Asian or black women (Draelos 2001). It is said that Latin women have more cellulite in the hips and gluteus, while Anglo-Saxon and Nordic women have more cellulite in the abdomen, influenced by their biotype.

Diet, as mentioned previously, is also an influential factor. Diets based on high level of carbohydrates, fats, and salt promote cellulite. Tight clothes and high-heel shoes make the venous return difficult, alternating the pumping mechanisms and thus increasing cellulite (Goldman et al. 2006).

Smoking is considered a predisposed factor as it can modify skin's microcirculation and can increase elastic fiber and collagen fiber degradation (Morita 2007). Some contraceptives and beta blockers may make cellulite worse.

There is another series of circumstances that can aggravate cellulite such as obesity, localized fat accumulation, and laxity.

Cellulite can be aggravated or begin after surgeries, mainly liposuction, that cause subcutaneous fibrosis or atrophy (Goldman et al. 2006).

Clinical Evaluation

The patient must be questioned about trauma history, liposuction or injections in the affected area, chronic diseases, pregnancies, surgeries, family history, type of usual diet, and consumption of oral contraceptives or hormones (Goldman and Hexsel 2010).

The physical exam must be conducted with the patient standing and with relaxed muscles. Cellulite is observed better with a pinching test, which consists of taking a piece of the skin between the thumb and the index finger along the natural vertical fold of the skin until forming a skinfold. The palpation must be conducted to assess the elasticity of the skin and the subcutaneous tissue. The venous or lymphatic insufficiency and the degree of obesity or overweight of the patient must be assessed using the body mass index (BMI). Laxity and other aggravating conditions should be evaluated (Goldman and Hexsel 2010; Bertin et al. 2001).

Cellulite Classification

The clinical classification of cellulite is a key element before starting any specific medical treatment, regarding the mechanism of action, number of sessions, and session interval.

Clinical Stages

Grade I: the patient is asymptomatic and there are no clinical alterations (Goldman and Hexsel 2010; Rossi and Vergnanini 2000).

Grade II: cellulite is evident only after compression or muscle contraction, paleness, decrease of temperature, and decrease of elasticity.

Grade III: the mattress appearance of the skin and/or orange skin is evident while resting, fine granulation of palpable sensation in deep levels, pain during palpation, decrease of elasticity, paleness, and decrease of temperature.

Grade IV: has the same characteristic as the third degree with more palpable, visible, and painful nodules, adhered to deep levels and wavy appearance of the surface of the skin.

Clinical Description

Limited or hard cellulite: the skin has a very pronounced thickness and is more prominent in superficial tissues (Goldman et al. 2006; Rossi and Vergnanini 2000; De Peña and Hernández-Pérez 2005). Normally, hard or limited cellulite occurs in young women who practice exercises. Since this cellulite is hard, it is limited and occupies less space. The aspect of cellulite is compact and firm and does not change according to the position. It is usually associated with stretch marks. When a piece of the infiltrated skin is squeezed between the fingers, a roughness similar to the skin of orange with dilated follicular pores will appear on the surface. When rotating a piece of skin between the fingers, small nodules of hard consistency can be seen. Also, there is an impossibility to slide the superficial layer of the skin over a deeper layer. It has a good response to the treatment.

Soft or diffuse cellulite: the tissue is not attached to a deeper layer; it's the most frequent. It usually occurs in women who do not practice exercise. It is associated with muscular hypotonia and laxity. The diagnosis is generally made through visual inspection. It is characterized by a modification of the anatomy, provoking a deformation of the pelvic area. Usually, it is present in women over 40. The skin can have a thickness of 5–8 cm. When standing, the padded appearance can be observed, and the skin shakes with movements and changes in position. When touching, the soft tissue can be felt as well as the presence of small and hard nodules. With respect to mobility, the superficial and deep layers of the skin can slide easier. It can be accompanied by circulatory complications such as varicose veins, ecchymosis, telangiectasias, heavy sensation, fatigue, feet numbness, and night pains, as well as orthostatic hypotension due to blood ectasia in peripheral zones. It is normal to find soft and hard lipodystrophy association.

Edematous cellulite: is the most severe and least frequent, usually accompanied by obesity. In this classification the positive Godet sign is observed. In this sign, a pressure on the tissue with the finger will produce a depression on the skin surface, lasting some minutes to disappear. The infiltration is harder compared to the previous one; this characteristic is due to the composition of the interstitial fluid that is viscous and with high molecule weight proteins, with lymphedema appearance. It also associates vascular symptoms. The patient experiences a heavy and painful sensation.

Treatments

The demand for therapeutic options to improve this alteration is very high, and in the past years, the offer of therapeutic alternatives has increased. Among them are invasive treatments such as:

- Liposuction: removing localized fat, not indicated to cellulite (Draelos 2001).
- Subcision is a surgical technique that does not require incisions and leave no scars. Through this technique, fibrous septa are cut and the depressions are reduced.
- Carboxitherapy increases vascular tone and produces active microcirculatory vasodilatation due to the action of CO_2 on arteriole smooth muscle cells (Goldman and Hexsel 2010).
- Mesotherapy comprises injections composed by some active substances. These substances have lipolytic action (Goldman and Hexsel 2010).

Noninvasive treatments are the following:

- Topical treatments: which work mainly in four objectives: increasing microvascular flow, reducing lipogenesis and promoting lipolysis, restoring the normal structure of the dermis and the subcutaneous tissue, and preventing or destroying the formation of free radicals (Goldman et al. 2006)
- Oxygen therapy: promotes superficial lipolysis
- Controlled diets: to avoid overweight
- Cryolipolysis approved by the FDA to eliminate localized fat, producing a crystallization of the fats in adipose cells at above freezing temperatures, leading to an apoptosis of adipose cells and an inflammatory process that results in the reduction of the fat layer in 2–4 months
- Focused ultrasound: produces heating of the adipocytes, generating coagulative necrosis and death of the cells in the adipose tissue
- Endermology: consists of motorized rollers with vacuum suction between them to lift the skin and reach deeper structures, producing stimulation of the metabolism and vascularization with lymphatic drainage (Goldman and Hexsel 2010)
- Laser
- Ablative and non-ablative radiofrequency

In this chapter we will discuss in detail the treatment of cellulite with non-ablative radiofrequency.

Radiofrequency

Radiofrequency (RF) is a form of electromagnetic energy (Shapiro et al. 2012). Its frequency ranges from 3 kHZ to 300 GHz (Lapidoth and Halachmi 2015). When applied to skin tissue, rapidly oscillating electromagnetic fields cause movement of charged particles within the tissue resulting in heat generation proportional to the tissue's electrical resistance (Shapiro et al. 2012). The idea of using heat to cauterize comes from Egyptian era. Nevertheless, only in the nineteenth century, a device using a galvanic current was built. Lee de Forest (http://www.newworldencyclopedia.org/entry/Lee_De_Forest) was an American inventor and engineer who created the thermionic valve or vacuum tube that allowed RF amplification (Kotcher Fuller 2005). William Bovie, in 1920 (O'Connor et al. 1996), developed the electrocautery for electrosurgery, which could cut, coagulate, cauterize, and fulgurate tissues. In 1939, the hyfrecator was introduced in the market. It is a device that uses low frequencies and high AC (alternating current) electrical voltage. This device is used for tissue destruction and for bleeding control (Lapidoth and Halachmi 2015).

RF is currently used in medicine in several treatments with different spectrum variations, including aesthetic medicine where it is considered a simple, effective, and minimally invasive method (Lapidoth and Halachmi 2015). RF is used in aesthetic medicine with applications for ablative and non-ablative applications (Lapidoth and Halachmi 2015).

The tissue effects achievable using RF energy depend on the applied energy density; the

following are several RF-induced thermal changes of tissue that are commonly used in medicine (Lapidoth and Halachmi 2015):

- Ablation of tissue: this effect is used for cutting or removing tissue and is based on thermal evaporation of tissue.
- Coagulation: this provides hemostasis for controlling bleeding. Coagulation may be applied to soft tissue as well, to induce necrosis.
- Collagen contraction: high temperatures induce immediate transformation in the tertiary structure of proteins. For noninvasive cosmetic procedure, this effect is produced with lower temperatures to avoid skin necrosis.
- Tissue hyperthermia: it is to use subnecrotic temperatures to stimulate natural physiological processes in attempts to modify skin appearance and to reduce subcutaneous fat; an example of this is ThermaCool.

The first device based on non-ablative RF was approved by FDA (Food and Drug Administration) in 2002. It is a monopolar device called ThermaCool (Thermage, Hayward, CA). It was developed to treat photodamaged skin on the face, reducing wrinkles and improving laxity (Lolis and Goldberg 2012; Alexiades-Armenakas et al. 2008).

Non-ablative RF does not absorb or disperse epidermal melanin; therefore, it can be used in all skin phototypes, without risk for epidermis injury. RF contracts collagen fibers and stimulates neocollagenesis by thermal energy, improving laxity and wrinkles. For cellulite treatment, synthesis of new collagen by fibroblasts promotes dermis thickening, improving the clinical aspect of cellulite (Coringrato et al. 2008; Brightman et al. 2009).

Radiofrequency Frequency

The frequency of electrical current characterizes how many times per second an electrical current changes its direction and is reported in hertz. This change in direction is associated with a change of voltage polarity. Frequencies in the range of 200 kHz to 6 MHz are the most common in medicine (Lapidoth and Halachmi 2015).

Radiofrequency Waves

The energy generated by RF can spread in a tridimensional way in the area treated with a controlled depth. The depth of the RF depends on the RF electrode configuration, the device parameters, and the tissue to be treated (Alan and Drover 2010).

The electric conductivity in RF is variable according to the tissue. Tissues with few amount of water have less electric conductivity. Therefore, good results can be reached when RF is used to treat tissues with high water concentration, as sweat or sebaceous glands (Alan and Drover 2010).

The RF energy can be delivered in continuous wave (CW) mode, burst mode, and pulsed mode. For gradual treatment of large areas, the CW mode is most useful as it allows a slow increase in temperature in bulk tissue as in cellulite or skin tightening (Lapidoth and Halachmi 2015). The burst mode delivers RF energy with repetitive pulses of RF energy, and it is used, for example, in blood coagulation (Lapidoth and Halachmi 2015). Pulsed mode is optimal when the goal is to heat a small tissue volume while limiting heat conduction to the surrounding tissue and is effective for fractional skin ablation (Lapidoth and Halachmi 2015).

In RF the impedance matching systems are a combination of several capacitors and inductors (Lapidoth and Halachmi 2015). The challenge in these devices is that they must distinguish the different impedances of different parts of the human body (Lapidoth and Halachmi 2015). The impedance matching system must compensate for these differences (Lapidoth and Halachmi 2015). An impedance matching system may be variable (Thermage) or broadband (Accent) (Lapidoth and Halachmi 2015).

Table 1 RF properties and its indications

Types of RF	Properties	Mechanism/indication
Monopolar	Capacitive coupling Active tip + return electrode Heat depth depends on size and geometry of the tip Heat decreases as distance increase from the electrode Depth: 3–6 mm	Tissue ablation Coagulation Subnecrotic heating (collagen remodeling Laxity/cellulitis Wrinkles
Unipolar	No eletric current Eletromagnetic field is produced by RF (high rotating frequency of water molecules) Penetration depth: up to 20 mm	Body countour Cellulits
Bipolar	Two active electrode in the tip Low penetration depth: 3 mm	Promotes fibers contraction: collagen remodeling Cellulits Laxity wrinkles
Tripolar	Combines the effects of monopolar and bipolar in one applicator Heats superficial and deep skin Very low power, safer	Laxity Cellulits

Radiofrequency Power

The most important characteristics of RF energy are its peak and average power. Peak power is important to estimate the thermal effect produced, while average power affects the speed at which the heating is induced (Lapidoth and Halachmi 2015).

High-power density applied to a large skin surface may create only gentle warming, but when applied through a needle electrode, the small power is applied over a small contact point, leading to high-power density (Lapidoth and Halachmi 2015).

Penetration Depth and Radiofrequency Energy Distribution Between Electrodes

Penetration depth is a parameter broadly used in laser dermatology to mean the distance below the skin, which is heated. In RF current decreases at a distance from the electrode due to the divergence of current lines (Lapidoth and Halachmi 2015). The depth of penetration can be affected by altering the topology of the skin and optimizing the electrode system and can be affected by the anatomical structure of treated area (Lapidoth and Halachmi 2015).

Types of Radiofrequencies

The energy used for RF is calculated with the following formula (Table 1):

$$\text{Energy(J)} = I^2 \times z \times \text{t}, I = \text{current},$$
$$z = \text{impedance}, t = \text{time(seconds)}.$$

Monopolar Radiofrequency

The first monopolar RF (MRF) device was approved by the Food and Drug Administration for the improvement of periorbital rhytides in 2002, followed by full-face wrinkles in 2004, as well as the temporary improvement in the appearance of cellulite when vibration was added to the delivery system (Carruthers et al. 2014). Since then, the monopolar radiofrequency is an important part of the treatment of cellulite (Carruthers et al. 2014).

The MRF devices release energy using a localized dipole in the tip and another in contact with the patient's skin, acting as a ground or return electrode. The electrode is designed to disperse

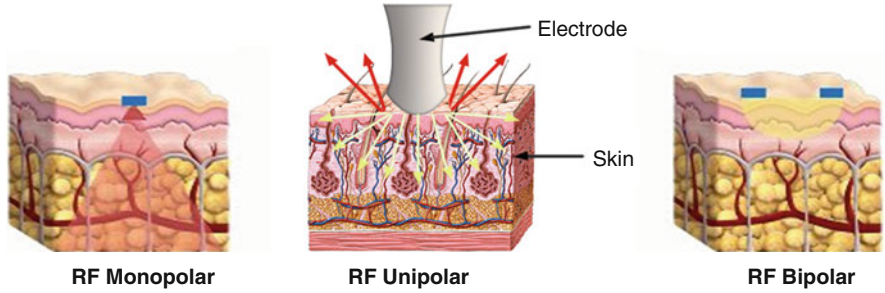

Fig. 1 Types of radiofrequency: mechanism of action proposed

energy uniformly through the skin by a process called capacitive coupling that creates a zone of higher temperature to controlled depth of 3–6 mm.

The tissue exposed to an electric field promotes resistance to the RF waves, generating heat, which modifies micro- and macromolecular structure of the tissue (Alan and Drover 2010). The electromagnetic energy (RF) is transformed into thermal energy (Fig. 1). The heat promotes collagen denaturation and collagen fiber contraction, stimulates new fibers of collagen synthesis, and increased fibroblast activity, improving laxity and wrinkles. On the other hand, monopolar RF can also be used in electrosurgery because of its ablative potential (Bravo et al. 2013; Carruthers et al. 2014). The amount of newly produced collagen seems to be dependent on the intensity of heating of connective tissue and time that the tissue is heated (Carruthers et al. 2014). Depending on the MRF system used, energy can be delivered in a "stamped" mode, a continuously gliding movement, or internally along the dermal–hypodermal interface through a fiber or electrode (Carruthers et al. 2014).

The heat generated by RF current near the active electrode does not depend on the size, shape, or position of the return electrode when the return electrode is much larger in size than the active electrode and is located at a distance which is much greater than the size of the active electrode (Lapidoth and Halachmi 2015). Heating decreases dramatically as distance increases from the electrode (Lapidoth and Halachmi 2015). Monopolar devices have a more deeply penetrating effect than bipolar or unipolar devices (Carruthers et al. 2014). The depth of heating depends on the size and geometry of the treatment tip (Bravo et al. 2013). Typically, the device heats the dermis from 65 °C to 75 °C, the temperature at which collagen denatures (Lolis and Goldberg 2012).

Monopolar devices are most commonly used for tissue cutting (Lapidoth and Halachmi 2015) like the electrical bistoury; this is an electromedical apparatus that uses the heat generated by the passage of high-frequency current, of the order of 1 MHz, between an active, punctiform electrode and an electrode of greater surface area placed in close contact with the skin. Its function is to perform tissue ablation (International Electrotechnical Commissio).

Treatment effects with monopolar devices depend on the density of RF energy, which can be controlled with RF power, and the size of active electrode (Lapidoth and Halachmi 2015):

- Tissue ablation: very high-density energy is required.
- Cutting instruments: a needle-type electrode is used to concentrated electrical current on a very small area.
- Coagulation hand pieces have a larger surface area than ablative devices.
- Subnecrotic heating is usually used for treatments related to collagen remodeling.

Monopolar RF can be used on all types of the skin because it is not reflected or absorbed by epidermal melanin or vasculature, as it passes through the skin, making it safer to use (Carruthers et al. 2014); also monopolar RF can

be used in different parts of the body such as the thighs, arms, neckline, neck, jowls, eyebrows, eyes, midfacial, cheeks, nasolabial folds, and melolabial folds.

Some devices of monopolar radiofrequency are available in the market, including Thermage ThermaCool, Exilis, and Pellevé S5. Each of them brings different advantage, as speed, vibration, cooling system, and progressive heating (Lapidoth and Halachmi 2015).

The most common adverse effects are burning sensation and heat in the area during the procedure. Edema and erythema usually disappear within hours after the procedure. Less frequent are burns, crust formation, erosion, depigmentation, scar, and dysesthesia (Bravo et al. 2013; Lapidoth and Halachmi 2015).

Unipolar Radiofrequency

The mechanism of action of unipolar RF differs from monopolar radiofrequency. In unipolar RF, no electric current is produced in the tissue (Bravo et al. 2013). Instead, a high-frequency electromagnetic radiation is produced, resulting in a fast alternating polarity of the electromagnetic field, inducing high rotating frequency in water molecules (considered as chromophore). Such superfast oscillations produce heat and later that heat dissipates in the tissue. The electromagnetic wave phase produced by this device is controlled in such a way that it allows for the penetration of heat in the tissue to a depth of up to 20 mm. The heat produced by the movement of water molecules allows the superficial temperature of the skin to stabilize in approximately 40° centigrade, while the highest temperatures of 50–75° centigrade are obtained in the reticular dermis (Bravo et al. 2013).

Unipolar RF with high frequency is more appropriate to define body contour, as it penetrates deeper (20 mm) and reaches higher temperatures. Unipolar RF is considered more effective than bipolar RF for the treatment of cellulite because of its penetration depth, as the penetration bipolar RF from 2 to 4 mm (Alexiades-Armenakas et al. 2008). On the other hand, bipolar RF induces dermal thickening, contributing to the skin irregularity, a component of cellulite.

Bipolar Radiofrequency

Bipolar RF consists of two active electrodes placed within a short distance. In this type of device, the current has a flow between electrodes, which means that the treatment is symmetric and is limited to the tissue between them. The penetration depth is low, approximately half the distance between the two electrodes (Lapidoth and Halachmi 2015).

It can be used in all types of skin, as other RF. The mechanism of action is similar to the monopolar RF. The heat promoted by RF induces extracellular fiber contraction and then stimulates new collagen fiber production in the dermis, increasing dermis thickness, which contributes to avoid fat herniation into the dermis. Clinically it is observed as a smoother skin.

The association of bipolar with unipolar is very useful to treat body contour, laxity, and cellulite by the fact that they can reach different depth. A new technology in which the same device promotes RF energy able to reach different depths of skin at same treatment session was developed, called HD 3D (Alma Lasers, Israel). This device has a special tip in which rollers promote a massage with the rollers, improving local circulation and lymphatic drainage.

The most common adverse effects are hot sensation during the procedure, erythema, and light edema, which last some minutes after the procedure. Burn and post-inflammatory hyperpigmentation are rare and operator dependent.

TriPollar RF

TriPollar RF produces homogeneous and deep volumetric heating of tissue, thus combining the effects of monopolar and bipolar RF modalities in one applicator. The RF current flows between three poles (electrodes). This arrangement of electrodes causes each to act as a common pole, eliminating the need for cooling of the electrodes and skin, optimizing safety and simultaneously heats superficial and deep skin layers at the same time. The densely focused current between three poles results in a high-power density in the treatment area and therefore low-power consumption, providing clinical effects with longer-term results over successive treatment sessions without

discomfort (Manuskiatti et al. 2009; McKnight et al. 2015). This novel technology has a special electrode configuration that produces high density and focused RF energy of approximately 18 W/cm (Goldman et al. 2006) deep into all skin layers (Manuskiatti et al. 2009). The total maximum power of the TriPollar RF powered system is 30 W compared to 200–300 W in unipolar systems. This relatively low-power consumption enables the TriPollar configuration to achieve safe and effective results without any active cooling (Manuskiatti et al. 2009).

Studies demonstrate in ex vivo human skin statistically significant increases in collagen synthesis in the superficial and mid-dermis, a lipolytic activity, a draining activity, and a firming effect on the skin (Boisnic 2008). The adverse effects like erythematous papules, papular urticaria, primary degree burns, blisters, and bruising could be provoked by an inadequate amount of glycerin oil used (Manuskiatti et al. 2009).

Combination of Radiofrequency with Other Technologies

Some devices, as VelaShape (Syneron Medical Ltd.), combine bipolar RF energy, vacuum, and infrared light. The combination improves collagen contraction and neocollagenesis. The vacuum stimulates the lymphatic (Alexiades-Armenakas et al. 2008; Sadick and Magro 2007; Adatto et al. 2014). The effects seem to be long lasting, but new sessions of treatment are required for further improvement (Alster and Tanzi 2005). Temporary side effects include erythema, edema, and bruising. Blisters, peeling, infection, hypopigmentation, and hyperpigmentation can rarely occur (Sadick and Magro 2007).

The mechanical manipulation generated by vacuum and rollers in the special tip increases local and lymphatic drainage(Adatto et al. 2014).

Cellulite and Radiofrequency: Clinical Studies

Bravo et al. (2013) conducted a study in eight female patients, with II and III grade of cellulite in buttocks and legs. These patients were submitted for four sessions of unipolar radiofrequency (Accent RF system – Alma Lasers) with 2 weeks interval. Patients were clinically evaluated through comparative before and after pictures, as well as through laboratorial tests and ultrasonography (US) images. Pictures and US images were performed before starting the treatment and 30 days after the last session. Laboratorial tests to evaluate possible side effects were done before and after the first and the last session of treatment. All of the eight patients showed clinical improvement, and US images showed increasing in the thickness of the dermis in seven of the eight patients. No alteration in the laboratorial exams was reported. Authors concluded that this type of unipolar RF was an efficient and safe method in the treatment of cellulite (Figs. 2 and 3). These authors also reported good results for photodamaged skin treatment, as demonstrated in Fig. 4 the improvement of the laxity in the neck.

Hexel et al. (2011) conducted a pilot study with a device combining bipolar RF technology, infrared light, vacuum, and mechanical massage. They evaluated nine patients that had a body mass index (BMI) of 18–25 kg/kg and at least 6° in the severity scale of cellulite (CSS) (Hexsel et al. 2009). The scale used in this article was described by Hexel and consists in five key clinical morphologic features of cellulite: (A) the number of evident depressions; (B) depth of depressions;

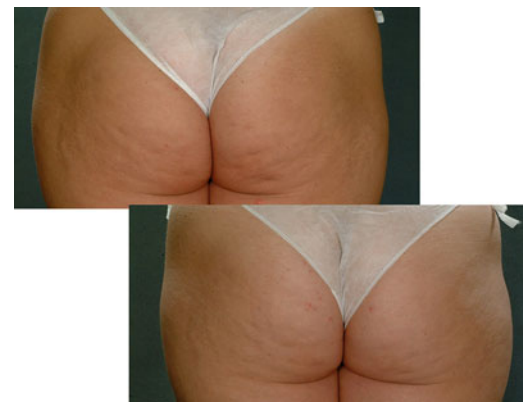

Fig. 2 Before and after five sessions (RF – Accent – Alma Lasers). Improvement of the skin depressions in number and depth on the buttocks

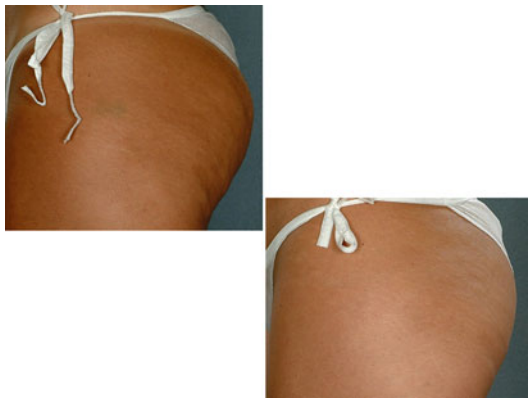

Fig. 3 Before and after five sessions (RF – Accent – Alma Lasers). Improvement of the irregular appearance of the skin surface on the buttocks

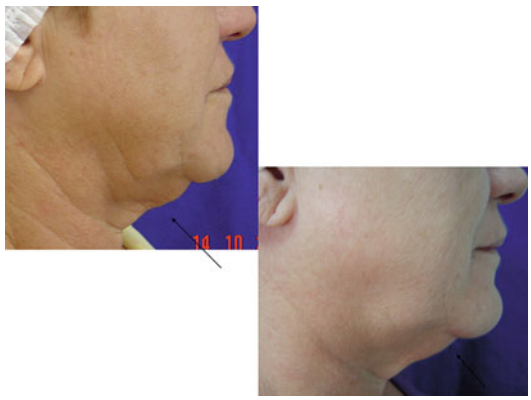

Fig. 4 Before and after five session (RF – Accent – Alma Laser). Improvement of the skin laxity on the neck area

(C) morphological appearance of skin surface alterations; (D) grade of laxity, flaccidity, or sagging skin; and (E) the classification scale originally described by Nürnberger and Müller (Hexsel et al. 2009). Authors reported reduction on cellulite severity and on corporal circumference of the buttocks in all patients. Poor results were observed in the thighs with the same treatment (Hexsel et al. 2011).

Goldberg et al. (2008) evaluated the efficacy of the unipolar device (Accent RF system – Alma Lasers) in 30 patients with III/IV cellulite grade in the upper part of the thigh. They were treated with six sessions every 15 days and were evaluated 6 months after the treatment. Clinical circumference measurements, skin biopsy, MRI, and blood lipid evaluation were performed. Twenty-seven patients showed clinical improvement. The reduction on the circumference of the thighs was 2.45 cm in average. Histological changes showed dermal fibrosis. No changes in the lipids blood level were observed nor in the MRI of the treated patients.

Sadick and Magro (2007) conducted a study in 20 patients aging from 28 to 59, phototypes I to VI, in which he used different intensities of bipolar RF, infrared light, and levels of vacuum. Sixteen of the 20 patients remained in the study. Twelve sessions of 30 min were performed twice a week, 3 days a part, for 6 weeks. The RF energy, the optic energy, and the levels of vacuum were adjusted from patient to patient to ensure that the optimum parameters of the treatment were reached. Clinical results were evaluated through photographies, circumference measurements of the leg, and dermatological exams by the researchers. A total of 65% of the patients had a reduction in the circumference of the leg; 50% of the patients had an improvement greater than 51%. In most patients, some degree of improvement could be observed in the appearance of cellulite.

Adatto et al. (2014) conducted a study with 35 healthy female patients with skin laxity and subcutaneous fat deposits localized in the abdomen, buttocks, or thighs, using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation. Sixty percent of the patients showed improvement of 24.1%; 27% of the patients showed improvement between 25% and 49% and 5% showed improvement between 50% and 74%, while only 8% of the patients did not show any improvement.

Take Home Messages

- Cellulite, also known as gynoid lipodystrophy, is a multifactor disorder of the dermis, epidermis, and subcutaneous cellular tissue.
- Although cellulite is still considered as an unclear etiological condition, there are many hypotheses trying to explain this disorder.

- In the last years, the idea of having an ideal sculpting body changed the concept of cellulite from a cosmetic problem to a disease.
- Treatments can be invasive and noninvasive. Noninvasive treatments include topical treatments, controlled diets, cryolipolysis, focused ultrasound, endermology, laser, and non-ablative radiofrequency.
- Radiofrequency (RF) or RF spectrum is the name given to one of the parts of the electromagnetic spectrum, with frequencies from 3 kHZ to 300 GHz.
- The energy generated by RF can spread in tridimensional volumes of the tissue, to controlled depths.
- The depth of the RF depends on multiple factors such as the tissue over which it is applied (dermis, epidermis, subcutaneous tissue), the configuration of the electrodes if desired (monopolar, bipolar, tripolar), the programming of the RF waves, and the applied temperature.
- RF does not have absorption or dispersion due to epidermic melanin and therefore cannot be used in all types of skins and generate significant heat without a risk for the epidermis.
- Radiofrequency (RF) contracts collagen and stimulates neocollagenesis by thermal heat, promoting thickening of the dermis and avoiding fat herniation.
- RF can also promote improvement in local circulation due to the vasodilatation and lymphatic drainage. Clinically it improves the laxity and the irregularity of the skin surface.
- New RF devices have been developed associating other technologies to reach different layers of the skin and to improve lymphatic drainage.
- Many studies report efficacy with RF for cellulite and body laxity with few sessions and minimal side effects.

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Non-ablative Radiofrequency for Hyperhidrosis

Mark S. Nestor, Alexandria Bass, Raymond E. Kleinfelder, Jonathan Chan, and Michael H. Gold

Abstract

Hyperhidrosis is the most common sweating disorder and can cause significant interference on quality of life. Current treatment options include topical aluminum chloride, lasers, tap water iontophoresis, oral glycopyrrolate, botulinum A toxin, surgical excision of the skin and sweat gland layer, or sympathetic nerve blocks. In recent years, thermotherapy has emerged as an alternative treatment option. Radiofrequency thermotherapy (RFTT) utilizes electromagnetic radiation to produce electric current. When this current meets resistance within the tissue, it produces heat to denature proteins and permanently destroy sweat glands. Fractional radiofrequency differs from monopolar, unipolar, and bipolar radiofrequency as it allows unaffected regions to serve as a reservoir of cells to accelerate healing and maintain skin integrity. When compared to other types of radiofrequency, fractional delivery causes less patient discomfort and less downtime. Studies have shown a significant decrease in the amount of sweating and improvement in quality of life. Radiofrequency is a promising alternative treatment method to those with hyperhidrosis.

Keywords

Hyperhidrosis • Thermotherapy • Radiofrequency

Contents

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Introduction

Sweating is a mechanism that occurs in humans to maintain homeostasis, prevent overheating, and is necessary for survival. The process is activated by the autonomic nervous system. Triggers include but are not limited to heat, emotions, gustatory sensations, and axon reflexes. All of these triggers stimulate the eccrine glands to produce sweat (a 99–99.5% aqueous solution in healthy individuals). However, some individuals experience disturbances in the sweating process and they are categorized into two groups: hypohidrosis/anhidrosis (diminished or absent sweat production) and hyperhidrosis (excessive sweat production). Hyperhidrosis is the more common complaint and affects 0.5% of the United States' population to an extent that it interferes with their quality of life and activities of daily living. It can occur anywhere on the body but most commonly affects the axilla, face, palms, and soles. It affects both sexes equally, but women often seek treatment more frequently and especially for axillary hyperhidrosis (Hurley 2003; Schick et al. 2016; Solish et al. 2007).

There are several current treatment options available to people who suffer from hyperhidrosis. Conservative methods include application of aluminum chloride, lasers, tap water iontophoresis, systemic anticholinergic agents such as oral glycopyrrolate, and frequent botulinum A toxin injections. Many patients find these conservative treatments unsatisfactory due to the need for continuous maintenance. On the contrary, there are more permanent and effective surgical options available. These include surgical excision of the skin and sweat gland layer or sympathetic nerve blocks, but many patients find these methods too invasive (Hurley 2003; Schick et al. 2016).

Radiofrequency Thermotherapy

Due to this gap in current treatment, thermotherapy has emerged as an alternative treatment option over recent years. Using lasers, microwaves, and now radiofrequency waves, thermotherapy uses heat at a temperature greater than 56 °C to denature proteins and permanently destroy sweat glands. Radiofrequency thermotherapy (RFTT) is performed by using a device, either using electrodes or microneedles, to give off thermal energy. It does this by using electromagnetic radiation to produce electric current in the frequency range of 3 kHz–300 MHz. When this current meets resistance within the tissue, it produces heat (Lolis and Goldberg 2012). The advantage of using radiofrequency over lasers is that it is not affected by tissue diffraction or chromophore absorption. The energy can be delivered to the target tissue more precisely than previous methods without damaging the epidermis like older ablative methods. Depending on the penetration depth used and type of radiofrequency, this non-ablative technique has been approved for wrinkle reduction, skin tightening, treating striae, and, when penetrated deeper, for hyperhidrosis (Schick et al. 2016; Elsaie 2009) (see chapter ▶ "Non-ablative Radiofrequency for Facial Rejuvenation," this volume).

Types of Radiofrequency

Monopolar Radiofrequency

Radiofrequency was first developed in the 1920s to be used for electrocautery. It evolved and is used most extensively now in dermatology for skin rejuvenation. It was first approved by the FDA in 2002 for facial wrinkle reduction and was known by the names *Thermage*® and *ThermaCool*®. These devices use monopolar radiofrequency, meaning they use one electrode to deliver current and another electrode to contact the skin and act as a grounding pad. This device heats the dermis to 65–75 °C to cause partial denaturing of collagen which enables retraction and thickening of the collagen. A cooling spray is used simultaneously to protect the epidermis and keep it between 35 °C and 45 °C. Since its development, this device has now been used to treat rhytids, acne scars, and cellulite. The main reported limitations to monopolar radiofrequency are patient discomfort and results that are more modest when compared to more invasive procedures (Lolis and Goldberg 2012; Elsaie 2009).

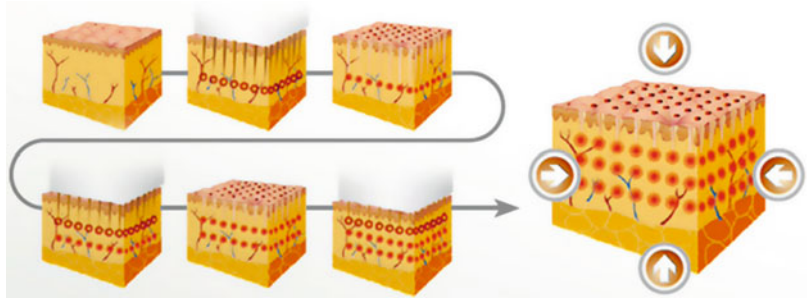

Fig. 1 Fractional microneedle radiofrequency demonstrating how microneedles cause small precise fractional dermal injury at multiple levels (Weiner 2013)

Unipolar Radiofrequency

Unipolar radiofrequency is another form of radiofrequency used in dermatology. In contrast to monopolar radiofrequency, unipolar uses high-frequency electromagnetic radiation at 40 MHz to produce heat, rather than electric current. This method allows deeper penetration of the skin to depths of 15–20 mm, which is helpful in treating disorders of the dermis such as cellulite (Lolis and Goldberg 2012).

Bipolar Radiofrequency

Bipolar radiofrequency is performed by using two active electrodes over the treatment area rather than only one electrode that is used in monopolar. The current flows between the electrodes to a depth that is half the distance between the electrodes. Compared to monopolar radiofrequency, bipolar cannot penetrate as deep but produces less pain and more controlled energy. It is commonly used with light-based systems, electro-optical synergy (ELOS), vacuum systems, or functional aspiration controlled electrothermal stimulation (FACES), to help control the energy depth through the skin. Bipolar devices are used to treat facial laxity, rhytids, pigmented and vascular lesions, acne and acne scarring, hair removal, and cellulite (Lolis and Goldberg 2012; Elsaie 2009).

Fractional Radiofrequency

Fractional radiofrequency is a newer approach that delivers bipolar energy either via electrodes or microneedles arranged in pairs. The microneedle method allows for even more precise delivery of energy to the targeted tissue by creating zones of affected skin adjacent to non-affected skin (Fig. 1; Weiner 2013). This energy, like the other techniques, results in thermal damage in order to stimulate collagen remodeling but differs by allowing the unaffected regions to serve as a reservoir of cells to accelerate healing and maintain skin integrity. When compared to other types of radiofrequency, fractional delivery causes less patient discomfort and less downtime. In addition, this delivery technique has been studied for its usage in treating hyperhidrosis (Schick et al. 2016; Lolis and Goldberg 2012).

Clinical Trials Using Radiofrequency for Hyperhidrosis

In 2012, Hong et al. (2012) found that using microwaves to treat axillary hyperhidrosis could provide long lasting effects. Since then, studies evaluating the efficacy of using radiofrequency waves to treat primary axillary hyperhidrosis (PAH) have been conducted.

Kim et al. (2013) conducted one of the first pilot studies in 2013 looking at fractional microneedle radiofrequency (FMR) for PAH. Twenty subjects with severe hyperhidrosis were enrolled and treated with two sessions of FMR at 4-week intervals. Outcome assessments were performed using starch-iodine tests to outline the area of excessive sweating and quantify sweat reduction. Eight weeks after the second treatment they found a significant decrease in the amount of sweating and 70% of subjects said they experienced greater than a 50%

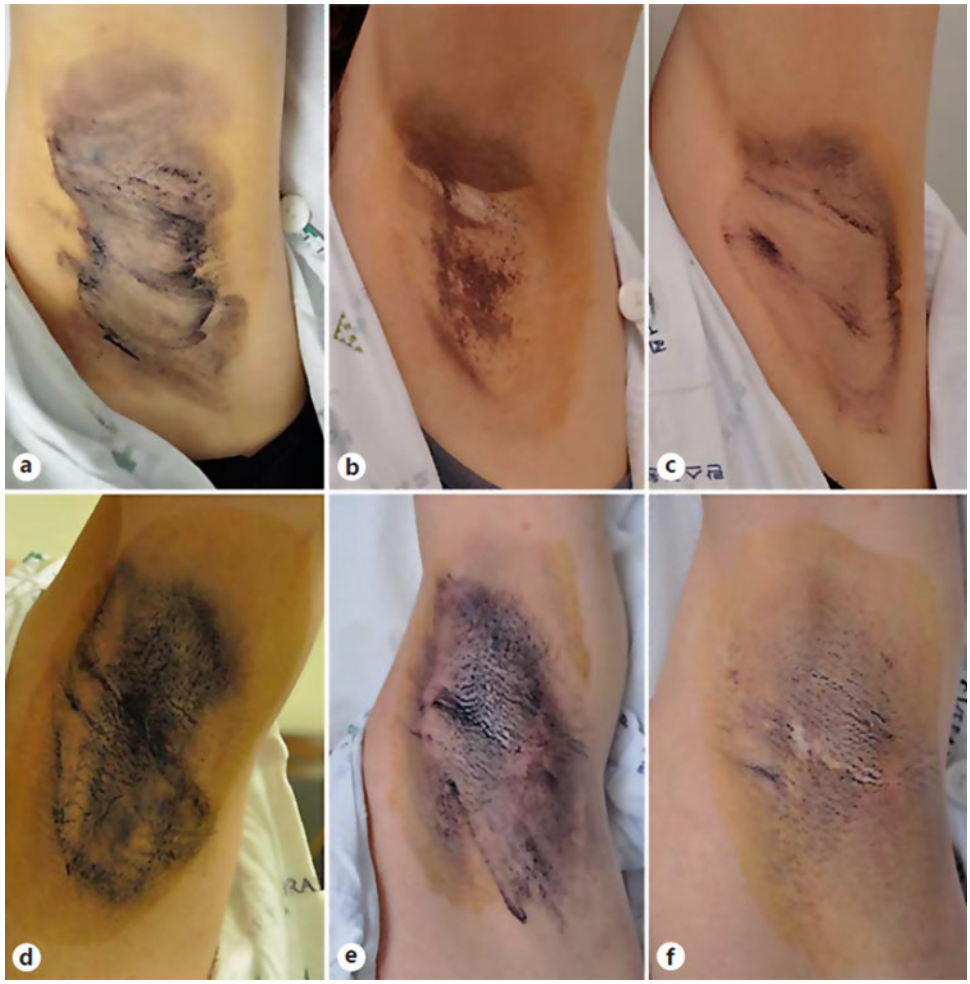

Fig. 2 Starch-iodine photographs before and after FMR treatment. Patient 1 (**a**–**c**) and patient 2 (**d**–**f**) at baseline (**a**, **d**), 1 month after the first treatment (**b**, **e**), and 2 months after the second treatment (**c**, **f**) (Kim et al. 2013)

improvement in sweating (Fig. 2). Histologic samples retrieved before and after the treatment sessions showed that the glands being targeted were at a depth between 2 and 4 mm. In addition, after 1 month, a decrease in the density and size of the apocrine and eccrine glands was observed (Fig. 3). The most common side effects were transient and consisted of tingling, swelling, and erythema. Two subjects experienced compensatory hyperhidrosis.

Abtahi-Naeini and Fatemi Naeini et al. also published three articles pertaining to FMR for PAH. In their 2014 study (Naeini et al. 2014), they enrolled 25 subjects with PAH who failed previous conservative therapy to undergo 3 sessions of FMR at 3-week intervals. Each subject was their own control with one axilla treated with FMR and the other with a sham device. Three months after the last treatment, significant improvement was observed in these patients with 80% reporting more than 50% satisfaction at the end of the study. Histological samples also showed a decrease in the number of sweat glands on the treated side. The most common side effects were erythema and pinpoint bleeding. In their 2015 publication (Abtahi-Naeini et al. 2015), they evaluated the quality of life in these 25 subjects and found that there was a statistically significant improvement between the before and after intervention questionnaires. In their 2016 article (Abtahi-Naeini et al. 2016), they continued to

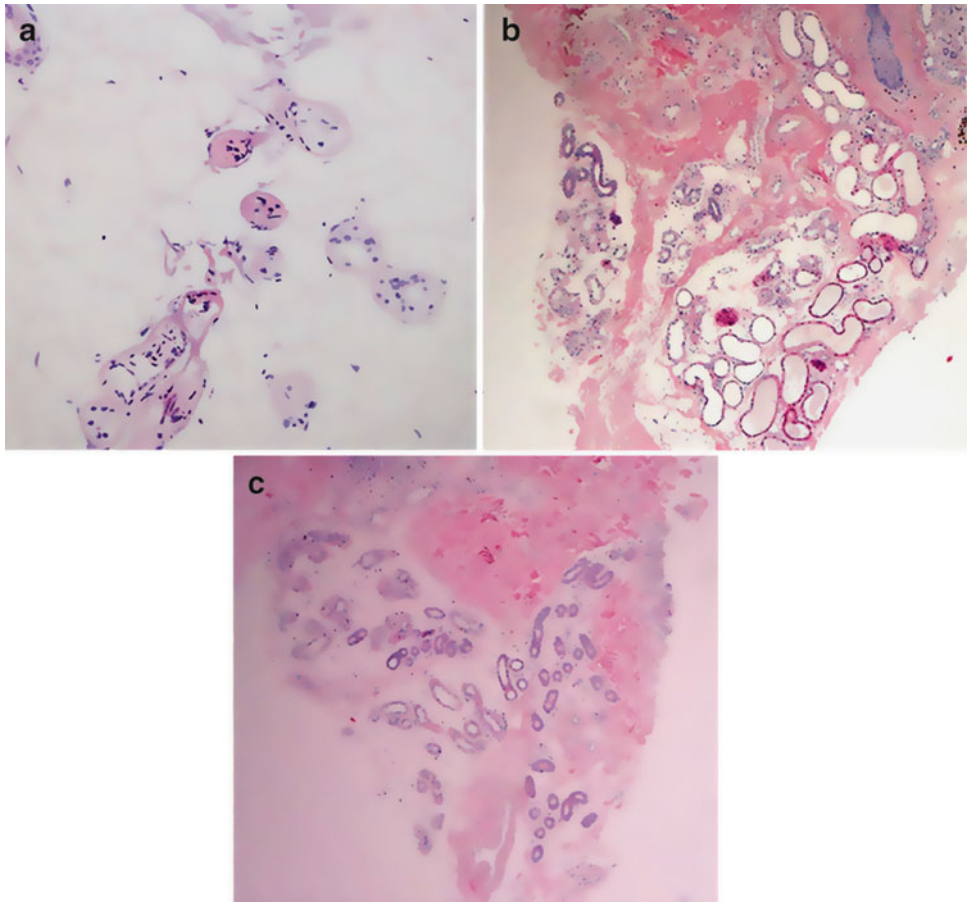

Fig. 3 Biopsy specimens before and after FMR treatment. (**a**) Skin sample obtained immediately after FMR treatment. Coagulation changes of the glands and dermis due to heat were observed at high magnification. (**b**) Skin sample from baseline. (**c**) Skin sample showing a decrease in the number and size of both apocrine and eccrine glands after treatment (Kim et al. 2013)

follow these subjects and 1 year later, they found 10 patients who did not experience any relapse of their hyperhidrosis. However, they did find a significant correlation between hyperhidrosis relapse and change in body mass index.

Most recently in 2016, Schick et al. (2016) conducted a trial for axillary hyperhidrosis. This study enrolled 30 subjects with axillary hyperhidrosis who had all previously attempted conservative treatment. They were all treated three times with radiofrequency thermotherapy at 6 week intervals, using the microneedle approach. Each treatment consisted of two consecutive rounds with a penetration depth of 3 mm. After 6 months, 27 subjects saw improvement in their sweating with an average reduction of 72% in their sweating. The average quality of life score also improved significantly. Side effects reported, starting with the most frequent, were erythema, exudation or scab, postanesthesia pain, petechial bleeding during the procedure, twitching of the arm during the procedure, and needle-puncture sites visible after 6 months.

Conclusion

In conclusion, radiofrequency therapy, especially using FMR, can offer an alternative treatment method to those with PAH who have failed

previous therapy. Further studies will need to be performed in order to see consistent results regarding radiofrequency device settings and their long-term effects.

Take Home Messages

1. Hyperhidrosis is the most common sweating disorder and can cause significant interference on quality of life.
2. Radiofrequency thermotherapy (RFTT) utilizes electromagnetic radiation to produce electric current. When this current meets resistance within the tissue, it produces heat to denature proteins and permanently destroy sweat glands.
3. Fractional radiofrequency is a newer approach that differs by allowing untreated areas to serve as a reservoir of cells to accelerate healing and maintain skin integrity.
4. When compared to other types of radiofrequency, fractional delivery causes less patient discomfort and less downtime. In addition, this delivery technique has been studied for its use in treating hyperhidrosis.
5. Studies have shown a significant decrease in the amount of sweating and improvement in quality of life.
6. Radiofrequency is a promising alternative treatment method for those with hyperhidrosis.

Cross-References

- ▶ Ablative Radiofrequency in Cosmetic Dermatology
- ▶ Non-ablative Radiofrequency for Cellulite (Gynoid Lipodystrophy) and Laxity

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Ablative Radiofrequency in Cosmetic Dermatology

Tania Meneghel and Maria Letícia Cintra

Abstract

In recent years, radiofrequency technology is being used in several medical skin care devices.

More precisely, the fractional micro-plasma radiofrequency technology was launched in 2007. It uses the radiofrequency electromagnetic radiation to get the plasma. The skin interaction with the plasma may cause heating, coagulation, vaporization, or ablation of the skin. This technology is non-chromophore dependent and can be used in high photo-types.

The fractional ablative lasers, mostly CO_2 and erbium:YAG, are excellent for treatment of unaesthetic skin defects. However, they are not used for all types of skin and the CO_2 in particular has a long downtime. The fractional micro-plasma radiofrequency is indicated for acne scars, chicken pox scars, atrophic scars, surgical scars, stretch marks (striae), fine lines and wrinkles, skin tightening, skin resurfacing, and skin rejuvenation (photo-aged skin). It is a safe, efficient treatment, with short downtime.

Keywords

Micro-plasma • Fractional • Radiofrequency • Skin resurfacing • Scars • Striae

Contents

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Introduction

The ablative fractional technologies are widely used in procedures to correct unaesthetic skin defects. Until recently CO_2 was the main available treatment option (Tanzi et al. 2008; Alexiades et al. 2008). However it is contraindicated for high photo-types (V and VI) and it has a long downtime. The other alternative ablative fractional technology was erbium:YAG. It has a shorter downtime; however, its ablation is superficial, unable to stimulate the collagen accordingly. Both CO_2 and erbium:YAG have water as their target chromophore.

Recently the population is worried with their physical appearance, perhaps because the world is more competitive. People have many activities and little time for themselves. Consequently, they are looking for efficient esthetics procedures, with short downtime. This explains the increasing trend in application of the ablative fractional technology. The fractional micro-plasma radiofrequency is independent of target chromophore (Kono et al. 2009). The erbium ablation is more superficial than CO_2 or micro-plasma radiofrequency, but micro-plasma radiofrequency ablation is very similar to CO_2, with shorter downtime (Gonzalez et al. 2008; Fitzpatrick et al. 2008).

Basic Concepts

Fractional Laser: The fractional laser emits light energy beams that turn into thermal energy and reaches the skin fractionally, causing micro-perforations (MTZ microthermal zone). It provides minimal and controlled thermal damage, allowing the adjacent undamaged tissue, not reached by laser, to promote a rapid recovery of the treated areas (Manstein et al. 2004).

Ablation Lasers: The ablation lasers promote removal of the complete epidermis and a portion of the dermis.

Plasma: Plasma occurs when the gas is partially ionized and dissociated. It is usually obtained through electrical discharges in gases. The interaction of the plasma with the skin may result from a simple heating to vaporization or ablation and coagulation of the tissue, depending on the amount of energy used and the time the plasma remains in contact with skin (Fitzpatrick et al. 2008).

Radiofrequency: It is a type of electromagnetic energy. The fractional micro-plasma uses this type of energy to produce plasma.

History

In the beginning the use of plasma in skin care devices was unpredictable (Alster and Konda 2007). Because the technology was not fractionated, it was difficult to control the thermal and ablative damage. In August 2007, the fractional micro-plasma was developed, solving this issue.

Fractional Micro-plasma Characteristics

This technology is incorporated inside a special unipolar radiofrequency handpiece. The electromagnetic energy (unipolar radio frequency) produces ionization of the air between the tip and the skin, to provoke micro-plasma electrical sparks. These sparks cause ablation and create multiple controlled micro-perforations on the skin (microthermal zone) producing the thermal and ablation damage zone, surrounded by a healthy skin (Halachmi et al. 2010). This device can be used in stationary mode (stationary tip) or in motion (roller tip) (Figs. 1 and 2).

Perforations have 100–150 μm depth and 80–120 μm diameter (depending on the pulse duration and the power used) (Halachmi et al. 2010; Xiu et al. 2013).

The parameters for the stationary mode are average power of 50 W, pulse duration from 0.1 to 0.3 s, and stack from one to five times. The tip with the smaller diameter and lower number of pins (large grate) is used for more aggressive effect. The number of stacks depends on the

Fig. 1 Stationary tips' diameters

Fig. 2 Rotative tip (roller)

desired level of penetration, i.e., the greater the number of stacked passes, the greater the penetration. The lower tip with the same energy produces most thermal damage (Halachmi et al. 2010).

The parameters for the rotative tip depend on the skin photo-type:

(i) Photo-types I–III: average power from 45 to 60 W, with pulse duration between 6 and 30 s and two to seven passes
(ii) Photo-types IV to V: average power from 40 to 50 W, with pulse duration between 6 and 30 s and two to seven passes

The number of passes depends on the desired level of penetration, i.e., the greater the number, the greater the penetration.

The treatment technique both for the stationary or the in motion application involves softly touching the surface of the skin with the tip. The applicator should not be pressed on the skin, but only touch it to obtain the ablative damage linked with the thermal damage. (If the tip is applied with too much pressure, the ablative damage is lost.) When the applicator is correctly positioned, it is possible to notice sparks on the skin, which produces the ablation effect.

Indications

This technology is indicated for the treatment of wrinkles (Halachmi et al. 2010), fine lines, atrophic scars (Kono et al. 2009), distensible and non-

distensible acne scars (Gonzalez et al. 2008; Lee et al. 2008), chicken pox scars (Halachmi et al. 2010), stretch marks, resurfacing, photo rejuvenation, skin tightening, and post-burn hyperpigmentation (Wang et al. 2015).

Pretreatment Care

The pretreatment begins 1 month before, with sunscreen every day and glycolic acid and bleaching agents during the night to avoid

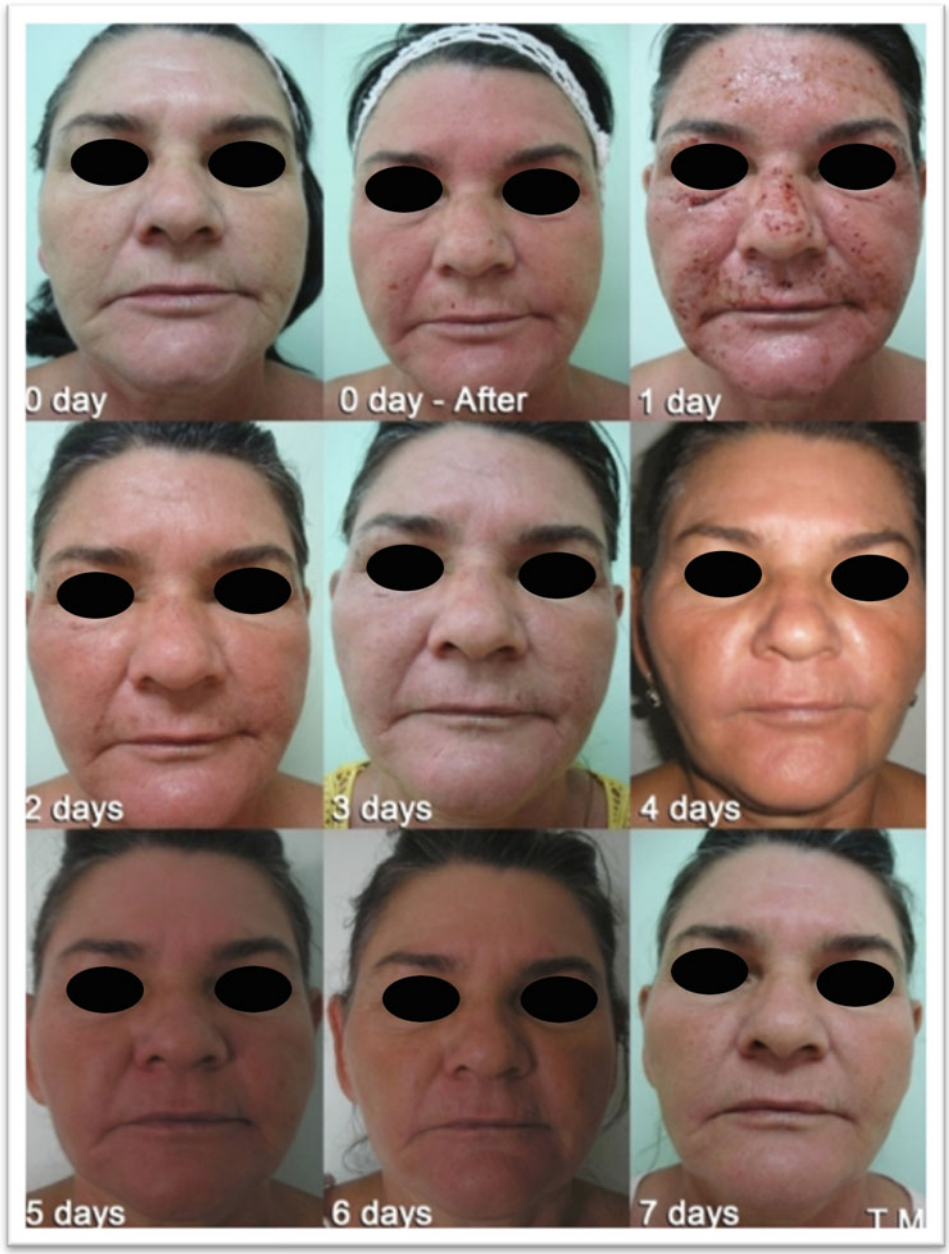

Fig. 3 Day-by-day ablative results

post-hyperpigmentation. One day before, herpes simplex virus prophylaxis is introduced, with oral antiviral agents.

Pre-procedure

After the area to be treated is washed with water and antiseptic soap, a topical anesthetic (lidocaine 7% + tetracaine 7%) is applied for 1 h. The patient should also take 1 tablet of Tylex® 7,5 mg.

Before starting the procedure, the topical anesthetic is removed, and the region to be treated is washed again with water and antiseptic soap. Then dehydrate the skin with alcohol or acetone. It is necessary to use mask and smoke evacuator for particles and virus during the procedure. The use of Zimmer helps the patient feel less pain.

Post-procedure

Immediately after the procedure, apply Vaseline and cover with plastic film. It provides a sense of comfort and avoids the nerve endings to be exposed to the environment. It is recommended that the patient does not wash the treated area for 24 h to prevent burning. After 24 h, the patient can wash the area with water and soap and apply moisturizer and sunscreen. The erythema usually lasts 24 h, with mild edema in areas where the procedure was more aggressive. The patient may feel some burning when exposed to heat (e.g., hot bath).

Contraindications

The contraindications for the procedure are photo-type VI, pacemaker, active bacterial and/or viral infection, impaired immune system (e.g., isotretinoin, cancer), unstable diabetes, pregnancy, metal implant under the treatment area, ablative procedures in the past 3 months, recent use of botulinum toxin or fillers, and collagen diseases (Halachmi et al. 2010).

Results

The ablative result can be noticed after a week (Fig. 3). The effective collagen production begins after 1 month and continues for 3 months (Figs. 4 and 5). Therefore, minimal interval between sessions is 45 days.

Application Mode for Distensible Acne Scars

For the treatment of distensible acne scars, it is applied five stacks on each scar, using the medium stationary tip, with pulse duration of 0.2 s and power of 50 W, followed by seven passes on full face, using the rotative tip in several directions, with 50 W power and pulse duration of 30 s (Fig. 6).

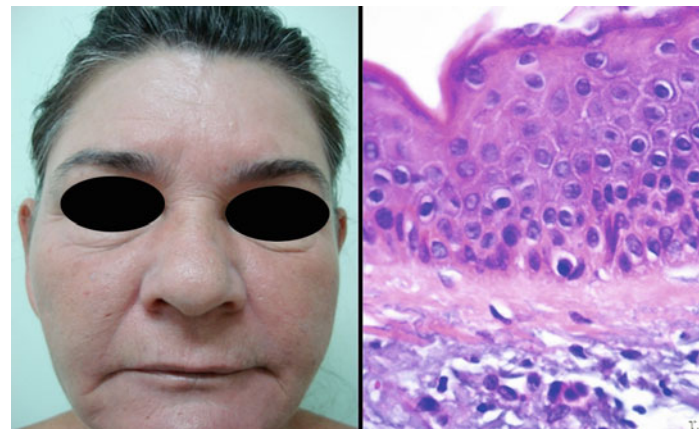

Fig. 4 Fifteen days after treatment: thin band of collagen tissue separates the epidermis from the elastotic dermis (H&E, original magnification ×100)

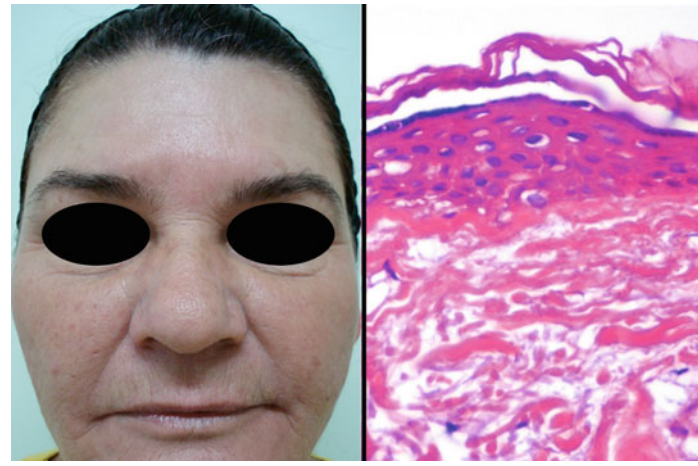

Fig. 5 Thirty days after treatment: high reticular dermis, formerly elastotic, was almost entirely replaced by dense collagen tissue (H&E, original magnification ×100)

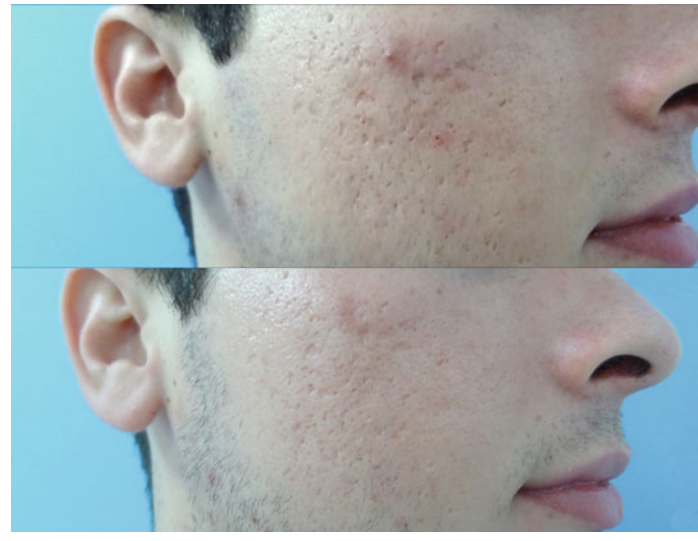

Fig. 6 Before (*left*) and after (*right*) treatment of distensible acne scars

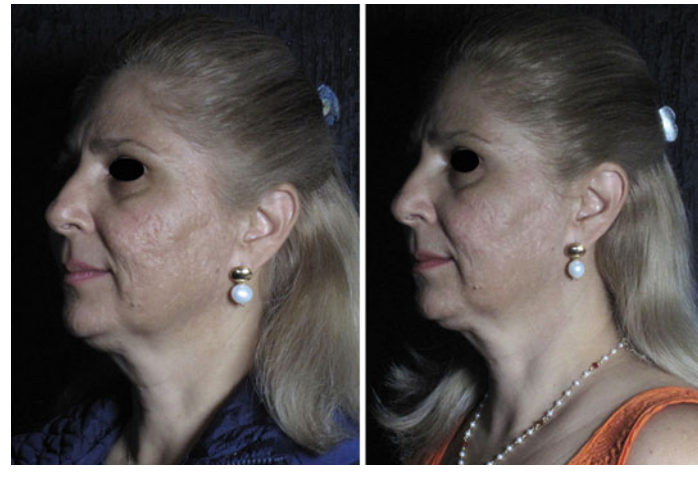

Fig. 7 Before (*up*) and after (*down*) treatment of non-distensible acne scars

Application Mode for Non-distensible Acne Scar or for Chicken Pox Scars

For the treatment of non-distensible acne scars, it is applied five stacks on each scar (specially the borders), using the medium stationary tip, with pulse duration of 0.2 s and power of 50 W, followed by seven passes on full face, using the rotative tip in several directions, with 50 W power and pulse duration of 30 s (Fig. 7).

Application Mode for Stretch Marks

For the treatment of stretch marks, make several passes (five to ten) with the rotative tip, with 50 W of power and 30 s of pulse duration, in different directions, until bleeding points are observed throughout the treatment area.

Application Mode for Wrinkles and for Fine Lines

For the treatment of wrinkles and fine lines, it is applied three stacks on fine lines and five stacks on wrinkles, using the medium stationary tip, with pulse duration of 0.2 s and power of 50 W, followed by seven passes on full face, using the rotative tip in several directions, with 30 s pulse duration and 50 W power.

Side Effects and Management

The most important side effect is post-inflammatory hyperpigmentation (Kono et al. 2009). In order to avoid it, always prepare patients 1 month before the procedure (especially higher photo-types or patients of mixed descent) with glycolic acid and bleaching agents. As soon as the complete reepithelialization is obtained, begin applying sunscreen UVA/UVB 50+. Hyperpigmentation usually begins in the second or third week after the procedure; thus, after 10 days start using topic corticosteroids in the morning under sunscreen associated with bleaching agents at night for a month. Additionally, the use of oral antioxidants is recommended (pycnogenol, resveratrol, and *Polypodium leucotomos*).

Take Home Messages

- The fractional micro-plasma RF is a kind of fractional laser.
- It is indicated for several aesthetic procedures, e.g., acne scars, striae, and skin rejuvenation.
- Results are similar to the ones obtained with fractional CO2 but with a smaller downtime.

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Part IV

Ultrasound and Cryolipolysis

Ultrasound for Lipolysis

Shirlei Schnaider Borelli, Maria Fernanda Longo Borsato, and Bruna Backsmann Braga

Abstract

Body sculpting refers to the use of either surgical or noninvasive techniques to modify the appearance of the body. Throughout the years noninvasive procedures for body sculpting gained interest of patients because of the reduced risks and complications. Technologies aiming aesthetic body sculpting include cryolipolysis, radiofrequency, light energy, low-intensity nonthermal focused ultrasound, or the combination of low-energy sources with mechanical manipulation. In this following chapter, we are going to discuss a new noninvasive technology using high-intensity focused ultrasound (HIFU) for ablation of the unwanted adipose tissue, evidencing its mechanisms and possible results for body sculpting.

Keywords

Body sculpting • Adipose tissue • Ultrasound • High-intensity focused ultrasound • Noninvasive techniques

Contents

Introduction

Body sculpting procedures are becoming increasingly popular in all over the world. Body sculpting refers to the use of either surgical or noninvasive techniques to modify the appearance of the body (Jewell et al. 2011a). Body sculpting is indicated for focal adiposity (abdomen, thighs, or hips); skin laxity (neck, arms); or both. Patients who have both focal adiposity and skin laxity usually require combined treatment (Jewell et al. 2011a; Kennedy et al. 2015). For many years a wide range of invasive procedures including liposuction

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were available for body sculpting (Jewell et al. 2011a; Mordon and Plot 2009). Although liposuction is extremely effective at removing large amounts of excess fat, it is accompanied by significant risk of complications and severe adverse effects. These may include postprocedural pain, infection, prolonged recovery, scarring, hematoma, ecchymosis, or edema (Kennedy et al. 2015; Mordon and Plot 2009).

Recently there is a tendency to achieve body fat reduction without substantial risks and financial costs, without long recovery time and with less postprocedure complications. The number of patients seeking cosmetic minimally invasive procedures had increased 110% from 2000 to 2010. Technologies aiming aesthetic body sculpting include cryolipolysis, radiofrequency, light energy, low-intensity no thermal focused ultrasound, or the combination of low-energy sources with mechanical manipulation. A new noninvasive technology using high-intensity focused ultrasound (HIFU) for ablation of unwanted adipose tissue has shown positive results (Jewell et al. 2011a, b).

Basic Concepts

Adipocytes, commonly known as fat cells, are connective-tissue cells specialized to synthesize and contain large globules of fat. Ultrasound can lyse adipocytes through mechanical and thermal mechanisms (Jewell et al. 2011a). Ultrasound is an oscillating pressure wave that propagates at the speed of sound. Ultrasonic waves are characterized by intensity, expressed in W/cm^2, and frequency, expressed as kilohertz (kHz) or megahertz (MHz). When ultrasonic waves penetrate and travel through tissue, they lose energy as they are reflected, scattered, or absorbed by the tissues. Sufficient quantities of absorbed energy create molecular vibrations in body tissues, generating heat (Haar and Coussios 2007).

There are two categories of ultrasound used for body sculpting: a low-intensity/low-frequency nonthermal ultrasound and HIFU. The nonthermal ultrasound disrupts adipose tissue through mechanical stress generated from inertial cavitation. In general, cavitation is less predictable than HIFU thermal effects (Jewell et al. 2011a).

HIFU Device

The ultrasonic energy used in HIFU device is generated by an internally focused transducer, which focuses the waves so that they converge at a specified depth and location. LipoSonix system (Medicis Technologies Corporation, Scottsdale, AZ, USA) uses this technology.

Mechanism of Action

Sound is a mechanical compression wave that travels through a medium. They are not electromagnetic waves like RF, Laser or IPL. High-intensity focused ultrasound (HIFU) is a noninvasive technology which mechanisms involve thermal ablation of the adipose tissue. It has intensity 1000 times greater than diagnostic ultrasound. HIFU crosses skin and superficial tissue without causing injury. This energy quickly deposited in a small area, creating heat. High intensities in the HIFU focal zone result in nonlinear effects in the ultrasonic beam that multiply the heating rate severalfold (Jewell et al. 2011a). By raising local temperature above 56 °C at a focal point within subcutaneous tissue, HIFU results in a coagulative necrosis and subsequently rapid cell death within the targeted area, but it doesn't affect the tissue in the ultrasound propagation path (Fatemi and Kane 2010). Irreversible cell death of fat cells occurs after 1 s at temperature >56 °C.

For body sculpting, thermal HIFU focuses energy adequate for ablation of targeted adipose tissue using ultrasonic waves at a frequency of 2 MHz and an intensity exceeding 1000 W/cm^2. At 2 MHz, a tightly focused HIFU beam creates a lesion in adipose tissue about 1 mm in diameter and 10 mm in length (Haar and Coussios 2007). This frequency has been proven capable of disrupting adipocytes and contracting collagen fibers present in the

subcutaneous layer to tighten skin (Ferraro et al. 2008). Lesions do not affect the overlying dermis or underlying fascia. There are no injuries to major vascular and nervous tissue outside the targeted treatment areas (Gadsden et al. 2010).

The disrupted adipocytes and the released triglyceride content are subsequently resorbed through a normal physiological pathway via inflammatory cells. The adipose tissue removal does not induce any clinical significant acute or chronic changes in lipid metabolism, free fatty acids, glucose metabolism, and liver function (Murray et al. 2005a).

Pathophysiological changes, induced by HIFU, occur from several hours until 8 weeks. Histological findings during the peri-acute (hours) and acute (7 days) phase revealed a well-demarcated zone of adipocyte disruption with minimal inflammatory response consisting predominantly of macrophages. Scavenger macrophages with abundant foamy cytoplasm are found within the treatment zones at the fourth week. After 8 weeks, 75% of resolution of the treated adipose tissue occurs with collapse of the surrounding fibrovascular stroma (Murray et al. 2005b).

Indications and Contraindications

The indication of the treatment areas may vary depending on the locality:

In USA: Indicated for noninvasive circumference reduction (i.e., abdomen and flanks)
In Europe: Indicated for trunk and lower extremities, excluding inner leg (i.e., abdomen, flanks, thighs, buttocks)
In Canada: Indicated for abdomen, flanks, thighs, buttocks.

The procedure is indicated for patients with body mass index lower than 30, an overall healthy life style, an average skin tightness, and lack of skin folds in the treated area. There needs to be a minimal quantity (1.0 cm) of subcutaneous tissue below the focal area, which can be detected by an impingement test. Impinge test must measure at least 2.5 cm of fat to indicate the treatment.

Patients with body mass index higher than 30, scars and/or wounds in the focal areas, severe skin flaccidity, or redundant folds in the skin are considered inappropriate candidates for the procedure.

Contraindications include the presence of hernia in the treated area, pregnancy or the suspicion of pregnancy. Additional contraindications include implants or foreign bodies of any kind in the treatment area; the use of medicaments to prevent blood coagulation or platelets aggregation (low daily dose aspirin are allowed); the use of steroid or chronic immunosuppressive therapy; systemic or localized skin disease; past of liposuction, lipolysis injection, abdominoplasty; surgeries, laser, RF, cryolipolysis within the last 90 days.

Efficacy and Fat Reduction

In literature, studies about HIFU efficacy for abdomen area or waist treatment report circumferential reduction greater than 2 cm (Jewell et al. 2011a, b). Three HIFU studies reported reductions of 4.1–4.7 cm (Fatemi and Kane 2010; Fatemi 2009; Teitelbaum et al. 2007) and four showed reductions of 2.1–2.5 cm (Shek et al. 2014; Solish et al. 2012; Hotta 2010; Gadsden et al. 2011). One HIFU study showed a 1.6 cm reduction in the thighs (Teitelbaum et al. 2007). In our experience, it is possible to achieve reductions of approximately 10% of the initial measurement of the area treated after one single session.

Side Effects and Their Managements

Patients should be advised about all the stages of HIFU treatment. Possible sensations during treatment include discomfort, cold, heat, tingling, and stinging. HIFU studies reported procedural pain (90.2%), postprocedural pain (56.6%), ecchymosis (66.4%), edema (9–72%), dysesthesia (59%), and erythema on treatment sites (45%) (Solish et al. 2012;

Hotta 2010). Most of these adverse events resolved spontaneously within 4 weeks, but they can last 12 weeks. Hard lumps, prolonged tenderness, discomfort, burning sensation, mild blisters, and purpura had also been reported (Fatemi 2009; Teitelbaum et al. 2007; Hotta 2010).

The pain is handled with oral analgesic, which can be offered just after the procedure and sustained until necessary.

Ecchymosis can last 2–3 weeks and it is solved by itself, but if patients ask for treatment some creams containing cumarin and heparin or vitamin K can be applied until complete resolution.

If nodules occur, therapeutic massages are indicated after 3 weeks.

Procedure

- Evaluate, measure, and photograph the patient.
- Shave (if the area is very hairy) and clean the treatment area.
- Marking the circle of treatment(s) while the patient is standing. Reassess the area of treatment, with patient in dorsal decubitus.
- Mark the treatment area with the numbered grid.
- Remove excess paint.
- Select the treatment model and fluency.
- Align the treatment head on the treatment site and activate the device.
- Execute three or more shots at the same location (site) until reaching the appropriate total fluence 140–180 J/cm^2.
- Clear the area after completion of all treatment points.

After Treatment

The way to handle the expectations of the patient is very important. The patient should be advised that the reduction of the measure is gradual. The maximum effect of treatment with HIFU will usually be seen approximately 8–12 weeks after treatment (Figs. 1, 2, and 3).

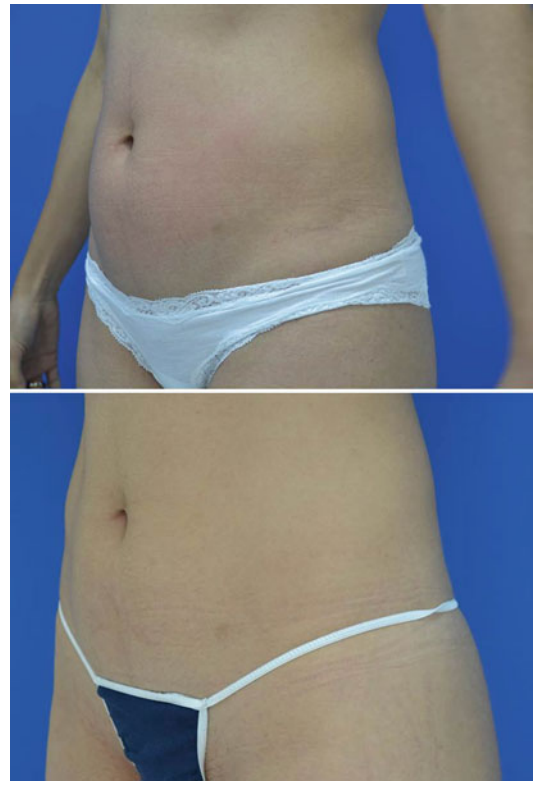

Fig. 1 Before and after 12 weeks (diagonal view)

Some studies have reported satisfaction rates ranging from 47.5% to 85% (Fatemi and Kane 2010; Fatemi 2009; Hotta 2010). However, as other aesthetic procedures, up to 20% of patients may not have satisfactory results.

Measures and good photography are essential for patient satisfaction. Follow-up visits should be scheduled with the patient for measurements and photos. The same person should perform the patient's measurements at each visit to decrease variability.

Take Home Messages

- With the aim of reaching best results the appropriate patient selection is essential.
- Adjusting realistic expectation is always a concern when approaching body-sculpting techniques.

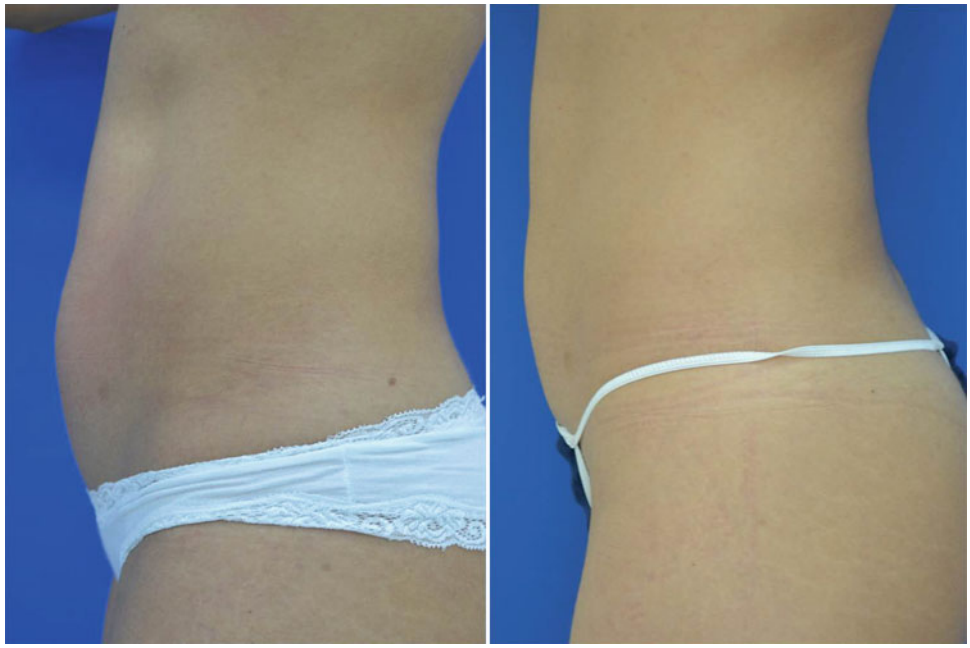

Fig. 2 Before and after 12 weeks (lateral view)

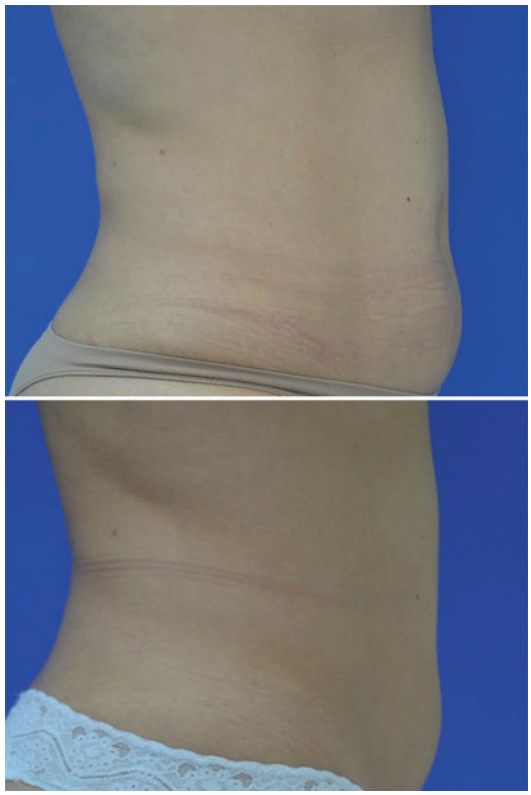

Fig. 3 Before and after 8 weeks (lateral view)

- Results are usually seen between 8 and 12 weeks after the treatment.
- Individual results may vary. It is possible to achieve reductions of approximately 10% of the initial measurement.

Cross-References

► Cryolipolysis for Body Sculpting

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Ultrasound for Tightening

Guilherme Bueno de Oliveira and Carlos Roberto Antonio

Abstract

Ultrasound is a well-known method used for medical imaging. However, microfocused ultrasound differs for emitting a convergent beam of energy at a specific point. For this, the different types of devices that use ultrasound energy are used for a small focal point, where high temperatures are adequate to cause tissue coagulation. The technology exclusively depends on heat for its effects on the tissue. The objective is to raise the local temperature to at least 65 °C, which is a temperature suitable for collagen contraction. By directing the focused energy wave into deep areas, it causes thermal coagulation points sparing adjacent nontarget tissues. The result obtained when treating this structure is of tissue contraction with effective noninvasive lifting of the skin of the neck and face, in addition to the improvement of fine lines and wrinkles. This chapter is going to describe basic concepts of this new technology and explain the procedure and its indications.

Keywords

Ultrasound • Tightening • Flaccid skin • SMAS • Collagen

Contents

Introduction

The Dermatology participates in the revolution of development of noninvasive technologies for tissue contraction and consequent lifting effect. Among the numerous devices and variety of energy technologies that have been recently developed for this purpose, microfocused ultrasound is also included. For this, according to Alam et al. (2010) the different types of devices that use ultrasound energy are used for a small focal point, where high temperatures are adequate to cause tissue coagulation.

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Similar to the traditional ultrasound used for medical imaging, the focused beam of energy can pass inoffensively through the epidermis, allowing the focal point to reach deeper tissues, such as the deep dermis, subcutaneous and superficial aponeurotic muscular system (SMAS),where a temperature reaches approximately 65 °C and causes protein denaturation within milliseconds.

According to Kim et al. (2008), one distinction must be made between the two main types of focused ultrasound used in medicine. High-intensity focused ultrasound (HIFU) uses high-energy waves and is primarily used for deep tissue medical applications between 1.1 cm and 1.8 cm, such as for ablating adipose tissue to the contour of the body. In contrast, microfused ultrasound (MFU) uses much lower energy waves to treat the more superficial layers of the skin, between 1.5 mm and 4.5 mm. Despite its lower energy, the MFU is able to stimulate tissue heating above 60 °C, producing small coagulation points (less than 1 mm^3) to a depth of up to 5 mm, reaching the deep dermis and SMAS, sparing the overlying epidermis.

According to Baumann and Zelickson (2016), the MFU only depends on heat to achieve its effects on the tissue. The goal is to raise the local temperature to at least 65 °C, which is the temperature at which collagen contraction begins. By directing the focused energy wave into deep areas, the MFU causes thermal coagulation points sparing adjacent nontarget tissues. In addition to local coagulation, the application of heat causes the collagen fibers in the SMAS and subcutaneous fat layer to become denatured and contract. This occurs by breaking intramolecular hydrogen bonds, determining the fold of the collagen chains and consequent configuration more stable and with thicker fiber. In addition, neo-collagen formation occurs within the areas of thermal tissue coagulation and new forms of viscoelastic collagen are produced, resulting in tissue contraction of flaccid skin. The MFU aims to treat facial SMAS, a fan-shaped structure that covers the face and connects the facial muscles with the dermis. The result obtained when treating this structure is of tissue contraction with a noninvasive lifting effect of all the skin of the neck and face, in addition to the improvement of fine lines and wrinkles.

The treatment with MFU can be customized to meet the unique physical characteristics of each patient, adjusting the energy and focal depth of the emitted ultrasound wave. These options differ in their focus and wavelength, wherein the depth and amount of energy delivered during the treatment may be varied to achieve a desired effect within the target tissue layer. Currently available transducers emit 10.0 MHz, 7.0 MHz, and 4.0 MHz frequencies with focal depths of 1.5 mm, 3.0 mm, and 4.5 mm, respectively. Two 10 MHz/1.5 mm and 7.0 MHz/3.0 mm transducers are also available to allow the release of energy into smaller anatomical regions that are harder to reach with larger transducers. Together, these transducers can be used in combination to achieve superficial dermis (1.5 mm), deep dermis (3.0 mm), or subcutaneous tissues and SMAS (4.5 mm).

According to Dayan et al. (2014), there are commercially available MFU devices that are also capable of generating high-resolution ultrasound imaging, allowing the tissue plane to be viewed at a depth of 8 mm and making the user see where the energy will be applied. According to Hitchcock and Dobke (2014), each handpiece uses high-resolution ultrasound that is capable of clearly generating the image of the target facial anatomy, including skin, subcutaneous fat, SMAS, facial muscles, and underlying bone. This ensures a treatment at the appropriate depth and allows avoiding inadvertent treatment of nontarget tissue, such as bone and larger blood vessels. The image also allows the operator to be certain of the appropriate acoustic coupling between the transducer and the skin prior to applying power from the MFU.

Patient Selection: Indications and Contraindications

According to Oni et al. (2014), there are relatively few absolute contraindications to the use of MFU. These include infections and open cutaneous lesions in the treatment area, severe acne or active cystic, presence of active metal implants such as pacemakers or defibrillators in the treatment area. Precautions include treatment directly on keloids,

permanent dermal fillers, and the presence of factors that could alter or impair wound healing, such as smoking.

Although not all people achieve a full aesthetic benefit with the MFU, patient satisfaction will be enhanced by appropriate patient selection and realistic expectations. MFU is best suited for patients with mild to moderate muscle and skin according to MacGregor and Tanzi (2013), flaccidity. An ideal patient is younger with normal healing, since the clinical response to treatment with MFU depends in part on the synthesis of new collagen and the so-called wound healing. Patients older or heavily damaged by light, sagging skin, marked looseness of the platysmal bands may require a higher energy density during a single treatment or more than one treatment to achieve the maximum benefits of the technology. In this way, older patients with extensive photodamage, severe skin sagging, and very marked platysma bands are not good candidates for treatment with MFU, and surgical treatment or other adjuvant technologies should be recommended.

Application Technique

Pretreatment

In the author's practice, patients typically receive the topical application of lidocaine 12% and ingested paracetamol 500 mg + codeine 30 mg 45 mins before the procedure, diazepam 5–10 mg is administered only if there is much anxiety.

Demarcation of the Area to Be Treated

The MFU devices have standardized protocol of shots according to the type of transducer to be used and to the region. According to Brobst et al. (2012, 2014), these protocols have standard demarcation and predeterrminated number of shots in each region. It is important to respect the demarcation to avoid side effects, as MFU should not be applied in area where there are superficial nerves.

The demarcation recommended by the industry is followed by a marking ruler that accompanies the apparatus. This has the correct size because it is the appropriate space between the lines of application of the transducer. In this way, there is greater security for not overcoming shots of the MFU in the region to be treated. According to Fabi (2015), the marking should be done with white pencil, and it must obey the following steps: (1) draw a line on the entire mandibular contour and mental region; (2) draw a line over the arc line of the zygomatic bone, bypassing the orbital region, until it reaches the nasal region; (3) demarcate the regions of danger for application of the MFU on the face – draw a line in the nasogenian sulcus, extending to the jaw line. In the encounter of these lines, mark 2 cm for lateral and 1 cm for top to make a square of protection of the branch of the marginal nerve of the mandible. To mark the infraorbital nerve region as a danger area follow these steps: (4) on the upper third of the face, draw a line between the lateral epicanto and the capillary implant line and, with the size of a ruler above this line, draw a second line, thus creating an application space; draw a line between the eyebrow tail and the capillary implant line and, as long as an application ruler is on the medial side, draw a second line, thereby creating an application space in the frontal region. (5) In the region of the neck palpate the eminence of the thyroid cartilage, mark 1 cm up and 1 cm on each side of it and draw a safety area running down the entire region of the trachea, draw a second line over the clavicular line. (6) After these defined lines, we must make markings on the face and neck, all with the size of one marking ruler, vertically, totaling two to three areas of application on the face by side and two to three areas of application in the neck per side, added of one central area. Each area has the total number of shots defined by manufacturers and varies according to the machine the user owns.

In the author's practice, the marking is performed after the identification of the sagging vectors. The flaccidity vectors of the face and neck obey a diagonal fall in the median direction. This angulation of the vector is determined by palpation in clinical examination, since this sagging SMAS is variable among patients. The evaluation technique consists of clamping the fingers on a

part of the skin and its traction to a point where there is better lifting effect response. Thus, we demarcate the necessary angulation to draw the lines of application of the MFU. We respect all the safety lines, changing only the direction of the marking lines, following the order: (1) Draw a line on the entire mandibular contour and mental region; (2) Draw a line over the arc line of the zygomatic bone, bypassing the orbital region, until it reaches the nasal region; (3) Demarcate the regions of danger for application of the MFU on the face – draw a line in the nasogenian sulcus, extending to the jaw line. In the encounter of these lines, mark 2 cm for lateral and 1 cm for top to make a square of protection of the branch of the marginal nerve of the mandible. To mark the infraorbital nerve region as a danger area follow these steps: (4) on the upper third of the face, draw a line between the lateral epicanto and the capillary implant line and, with the size of a ruler above this line, draw a second line, thus creating an application space; draw a line between the eyebrow tail and the capillary implant line and, as long as an application ruler is on the medial side, draw a second line, thereby creating an application space in the frontal region. (5) In the region of the neck palpate the eminence of the thyroid cartilage, mark 1 cm up and 1 cm on each side of it and draw a safety area running down the entire region of the trachea, draw a second line over the clavicular line. (6) After these defined lines, we must make markings on the face and neck, all with the size of one marking ruler, diagonally opposite the sagging vectors identified by the technique described above, totaling three to five areas of application on the face by side and four to six application areas in the neck for side, added of one central area. The total number of shots per area is defined by immediate clinical response at the time of the procedure. The total number of shots in the area never exceeds the total released by the company, but the total per space of application is not equal between them. They depend on the immediate response of the patient's skin. (Figs. 1 and 2).

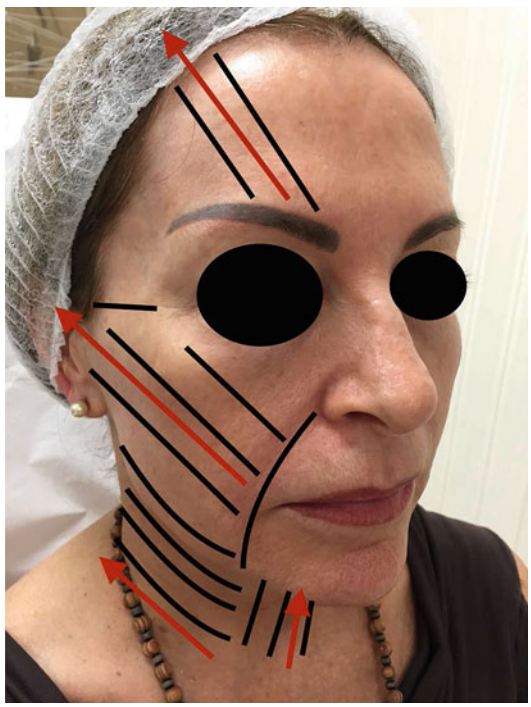

Fig. 1 Diagonal marking, right side

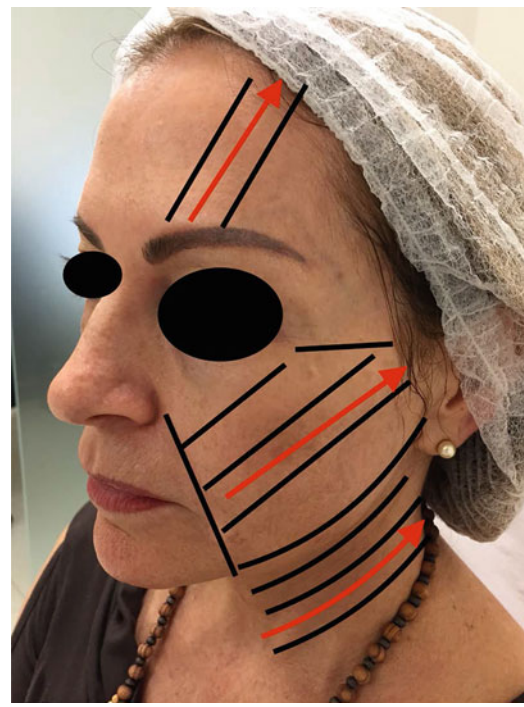

Fig. 2 Diagonal marking, left side

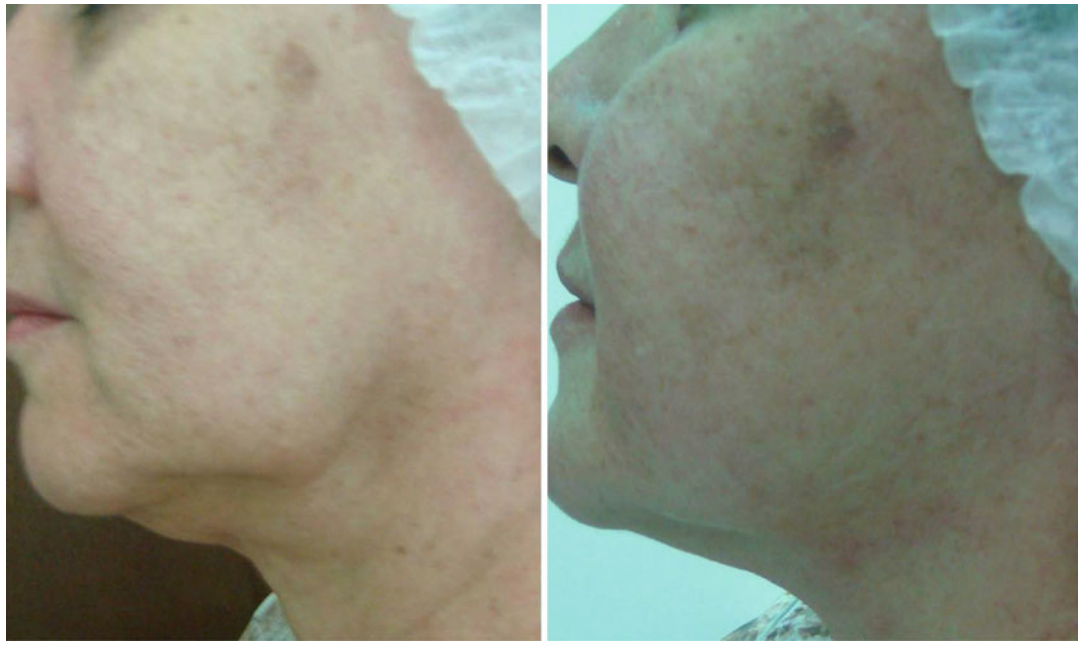

Fig. 3 Improvement of the mandibular contour after treatment

Application

The number of shots with each transducer has been previously determined between minimum and maximum numbers of shots by the company for each region. Preference is given to the maximum energy of the device, which is decreased if the patient's pain sensitivity is low. It should always be started with transducers that reach a greater depth and come superficial with the other transducers.

In the author's technique, the number of shots is respected between the minimum and maximum predetermined by the company. However, the final number is determined clinically by the immediate treatment outcome.

Results

The effectiveness of MFU treatment is superior when multiple transducers are used. The beneficial effects of double depth treatment are evaluated by the lifting effect of the middle third of the face, mandibular definition, and reduction of sagging of the submental skin. The final result occurs at 90 days post treatment. New session can only be held after this time period. Usually the maintenance is carried out between 10 and 18 months.

See results with Ulthera® (Ultherapy®; Ulthera Inc.) in Figs. 3, 4, and 5 and with AccuTyte® (Vydence®) in Fig. 6.

Side Effects and Their Managements

Pain

According to Pak et al. (2014), the most commonly reported side effect associated with MFU is painful discomfort during the treatment session. In the literature, studies do not report significant pain. According to Kakar et al. (2014), suggestions for minimizing discomfort during treatment include pretreatment with oral paracetamol, nonsteroidal anti-inflammatory drug or narcotic analgesic, topical anesthetics with lidocaine when using the 1.5 mm transducer, and applying the most energy possible according to the tolerance.

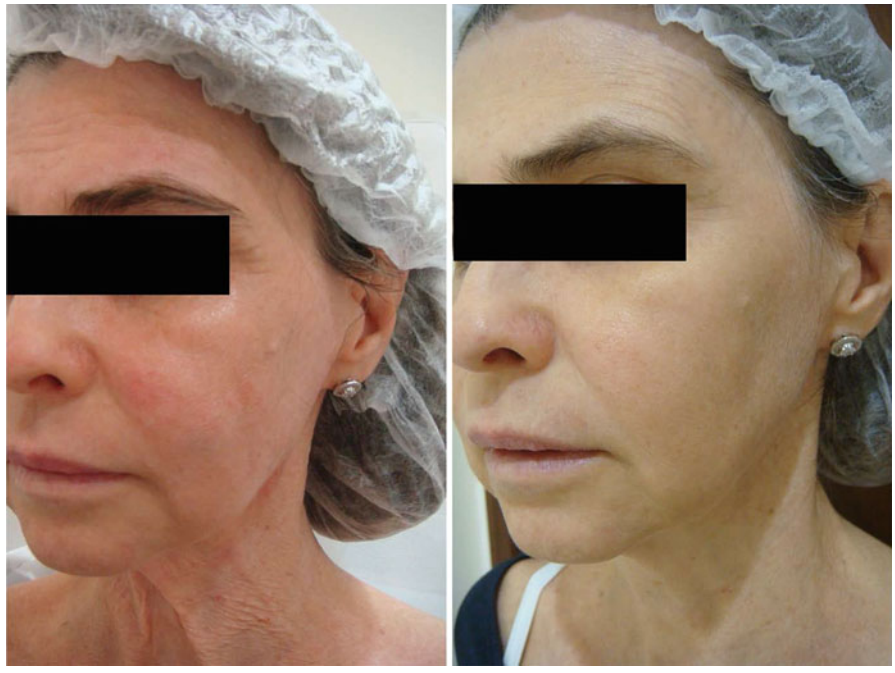

Fig. 4 Improvement of the mandibular contour with facial tightening

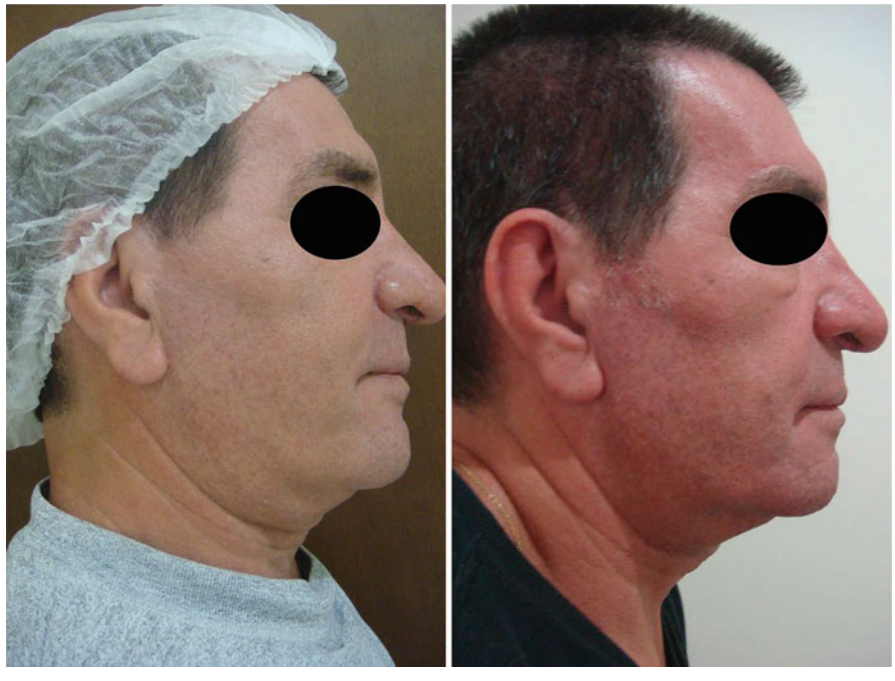

Fig. 5 Improvement of the mandibular contour after treatment

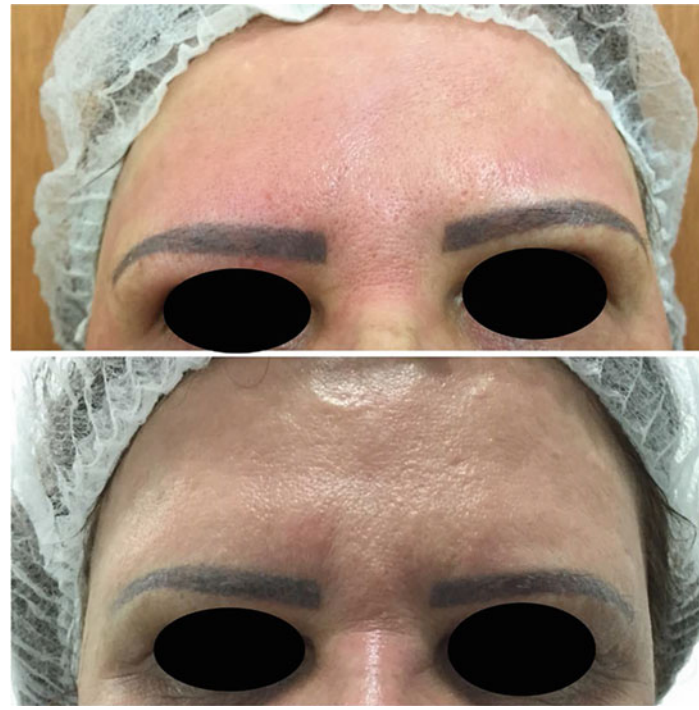

Fig. 6 Frontal treatment for right eyebrow correction

In the author's practice, patients typically receive the topical application of lidocaine 12% and ingested paracetamol 500 mg + codeine 30 mg 45 mins before the procedure. Diazepam 5–10 mg is administered only in cases of great anxiety.

Transient Erythema

The second most commonly reported side effect is the combination of transient erythema and edema (Fig. 7a–c). This is usually transient, giving in most cases within 3 h after the session. It is due to regional warming with stimulation of the inflammatory reaction and vasodilation. Patients do not usually complain it; however, cold compresses can be made at most to speed up the improvement of these symptoms.

Less Common Side Effects

Occasional side effects include postinflammatory hyperpigmentation after 1 month of treatment, muscle weakness and transient local numbness, striated linear skin excoriations, or papule formation. The papules appear to be due to nonideal technique and are more likely to be associated with the use of 3 mm and 1.5 mm transducers.

The most serious effects reported in the literature are facial paralysis. The reported cases had a modification of the facial anatomy by previous surgical facelift or by application in areas known to be not safe.

Take Home Messages

- Microfocused ultrasound (MFU) aims to treat facial SMAS, a fan-like structure that covers the face and connects the facial muscles to the dermis.
- The MFU uses special acoustic transducers that direct the energy of the ultrasound to a small focal point, where the high temperatures are able to cause tissue clotting.
- Treatment with MFU should be customized to meet the unique physical characteristics of each patient, adjusting the energy and focal

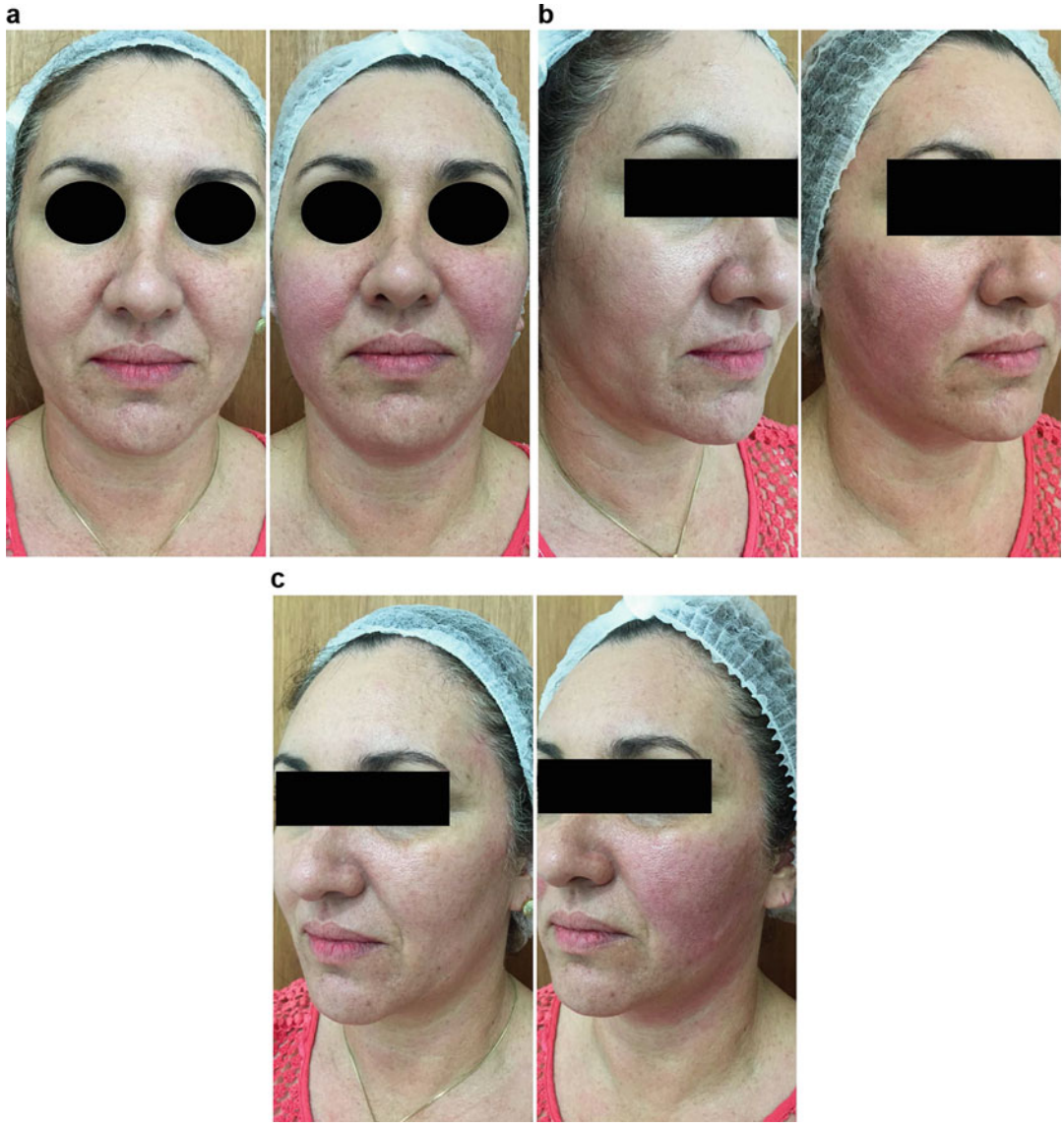

Fig. 7 (**a**) Immediate effect face, frontal view. (**b**) Immediate effect face, right view. (**c**) Immediate effect face, left view

depth of the emitted ultrasound wave. These options differ in their focus and wavelength, in that the depth and amount of energy supplied during the treatment.

- MFU is best suited for patients with mild to moderate muscle and skin flaccidity. Patient satisfaction will be enhanced by appropriate patient selection and realistic expectations.
- Older patients with extensive photodamage, severe sagging skin, and very marked platysma bands are not good candidates for treatment with MFU, and surgical treatment or other adjuvant technologies should be recommended.

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Cryolipolysis for Body Sculpting

Roberta Bibas, Alexandra Cariello Mesquita,
Diego Cerqueira Alexandre, and Maria Claudia Almeida Issa

Abstract

Cryolipolysis is a nonsurgical technique for localized fat reduction and it is a promising procedure for nonsurgical fat reduction and body contouring. It presents a compelling alternative to liposuction or any other invasive methods. This procedure appears to be safe in the short term, with limited adverse effects, and results in significant fat reduction when used for localized adiposities.

Keywords

Cryolipolysis • Nonsurgical fat reduction • Body contouring • Lipolysis • Liposuction

Contents

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Introduction

Body contouring is the most common cosmetic surgical procedure performed in the United States. Data from the American Society of Aesthetic Plastic Surgery indicate that breast augmentation is no longer the most popular surgical procedure. Liposuction has replaced breast augmentation in 2013, with 363,912 procedures (Ingargiola et al. 2015).

Although liposuction constitutes an effective therapy for the removal of excess fat tissue, it remains an invasive procedure and carries the inherent risks associated with surgery. Nowadays, novel modalities have been described to address body contouring from a less-invasive perspective. These modalities selective destruct adipose cells, targeting the physical properties of them, which differentiate from the overlying epidermis and dermis cells. Devices using high frequency ultrasound, radiofrequency energy, and laser light have the potential to improve efficiency, minimize adverse consequences, and shorten postoperative recovery time. Thermal destruction, cavitational destruction, or creation of a temporary adipocyte cell membrane pore induce a reduction of the

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number of adipocytes, which results in a measurable reduction of fat (Ingargiola et al. 2015; Manstein et al. 2008; Zelickson et al. 2009; Ferraro et al. 2012; Sasaki et al. 2014).

Cryolipolysis is the noninvasive, selective destruction of adipose tissue by controlled cooling. The methodology was based on the observation that lipid-rich cells are more susceptible to cryoinjury than the surrounding water-rich counterparts, such as in the overlying dermis and epidermis. The device consists in a cup-shaped applicator that draws a roll of skin and subcutaneous adipose tissue between two cooling plates. The temperature of the tissue roll must decrease to about 0 °C, which normally takes 1 hour. Crystallization of cytoplasmic adipocytes lipids initiates a cascade of events, characterized by adipocyte apoptosis, panniculitis, and eventual loss of adipocytes. Clinically, this is expressed by an effective decrease in fat layer thickness. In 2008, the United States Food and Drug Administration (FDA) initially approved cryolipolysis for the noninvasive reduction in focal adiposity of the flanks and later for the abdomen in 2011. Common side effects of the treatment can occur, for example, temporary erythema, edema, and mild pain. Occasionally, posttreatment pain may last for days after treatment (Jalian et al. 2014).

Localized Fat

Obesity is commonly defined as the high accumulation of body fat due to imbalance between received and burnt calories. Over the past 20 years, obesity has been raised as a highly common nutritional disorder and the main risk factor for chronic noninfectious diseases worldwide. The prevention and management of obesity are highly complicated because there is no clear and easy solution. A large proportion of obese individuals need help with their weight management. To prevent and treat obesity, there are currently different types of slimming and beauty systems of noninvasive intervention such as radiofrequency, cryolipolysis, and surgical interventions such as liposuction, and laser lipolysis. (chapter ▶ "Ultrasound for Lipolysis," this volume). There are also preventive methods such as change of lifestyle and diet. The effectiveness, safety, and cost-effectiveness of noninvasive and invasive interventions to treat obesity are still unclear.

Recently, novel technologies involving noninvasive, energy-based techniques have been developed, signaling a potential paradigm shift in fat reduction and body contouring practices. The major goal of these modern therapies includes reduction of tissue mass, with a possible end point of noninvasive body contouring (Manstein et al. 2008; Ferraro et al. 2012).

Cryolipolysis' Mechanism of Action

In 1970, Epstein and Oren conceived the term popsicle panniculitis after describing the presence of an erythematous indurated nodule followed by short-term fat necrosis in the cheek of an infant who had been sucking a popsicle. Although cold-induced panniculitis was first described in infants, it has also been observed in adult patients. These observations led to the concept that lipid-rich cells are more susceptible to cold injury than the surrounding water-rich cells (Ingargiola et al. 2015; Manstein et al. 2008; Beacham et al. 1980; Epstein and Oren 1970).

In 2007, Manstein introduced a new noninvasive method, termed cryolipolysis, for fat reduction with freezing technique. This technique is performed by using an applicator on the targeted area, set at a specific cooling temperature, for a preset period of time. This targets adipocytes while sparing the skin, nerves, vessels, and muscles (Manstein et al. 2008).

Cryolipolysis damages exclusively fat cells through a programmed cooling of the skin. The treatment received FDA approval for fat reduction of the flanks in 2010, of the abdomen in 2012, and of the thighs in 2014. Studies have also demonstrated safety and effectiveness for treatment of undesirable fat in the back, arms, and chest (Zelickson et al. 2009; Stevens et al. 2013; Munavalli 2013).

This technique is based on the concept that fat cells are more sensitive to low temperatures than the surrounding tissue. Cold exposure can induce

selective damage to the subcutaneous tissue via induction of panniculitis, resulting in reduction of the superficial fat layer. This damage triggers the death of adipocytes, which are subsequently engulfed and digested by macrophages. Adipocytes undergo apoptosis and necrosis following exposure to cold temperatures (Manstein et al. 2008; Zelickson et al. 2009; Ferraro et al. 2012; Beacham et al. 1980; Nelson et al. 2009; Boey and Wasilenchuk 2014).

Initial adipocyte damage is noted histologically at day 2 and increases throughout the next month. By 14–30 days of treatment, macrophages and other phagocytes surround, envelope, and digest the lipid cells as part of the body's natural response to injury. Four weeks after the treatment, the inflammation lessens and the adipocyte volume are decreased. Two to 3 months after the procedure, the interlobular septa are distinctly thickened and the inflammatory process further decreases. By this time, the fat volume in the treated area is apparently reduced and the septa represents the majority of tissue volume (Nelson et al. 2009).

Although its mechanism is not completely understood, it is believed that the vacuum suction with regulated heat extraction cuts off the blood flow and induces lipid crystallization of the targeted cells. In addition, this cold ischemic injury might promote cellular damage in adipose tissue via cellular edema, reduced Na-K-ATPase activity, reduced adenosine triphosphate, elevated lactic acid levels, and mitochondrial free radical release. Another mechanism described proposes that the initial lipid crystallization and cold ischemic injury is further compounded by ischemia reperfusion injury, causing generation of reactive oxygen species, elevation of cytosolic calcium levels, and activation of apoptotic pathways. Finally, lipid crystallization and cold ischemic injury of the targeted fat cells induce apoptosis of them and a pronounced inflammatory response, resulting in their eventual removal from the treatment site within the following weeks (Ingargiola et al. 2015; Manstein et al. 2008; Zelickson et al. 2009; Sasaki et al. 2014; Pinto et al. 2012; Pinto et al. 2013).

Histological studies show that macrophages are mostly responsible for clearing the damaged cells and debris. Cryolipolysis may raise blood lipid and liver enzymes levels due to the removal of adipocytes internally, which might bring additional risk to the patient, particularly for cardiovascular parameters. However, multiple studies have demonstrated that cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, aspartate/alanine transaminase, total bilirubin, albumin, and glucose blood levels remained unaltered during and after this procedure. (Ingargiola et al. 2015; Ferraro et al. 2012; Riopelle and Kovach 2009; Coleman et al. 2009; Klein et al. 2009)

As cryolipolysis is a relatively recent technology, some points still need to be considered and investigated, including what type of patient would benefit most from this procedure. Studies suggested that the results were most visible in patients with discrete localized adipose tissue and cellulite (Ingargiola et al. 2015; Ferraro et al. 2012).

Common treatment areas include abdomen, brassiere rolls, lumbar rolls, hip rolls/flanks, inner thighs, medial knee, peritrochanteric areas, arms, and ankle. Follow-up length generally ranges from 2 to 6 months. One study presented two patients at 2 and 5 years after treatment, emphasizing the persistent reduction of fat tissue at these time points, when comparing pretreatment and posttreatment photographs (Bernstein 2013) (Figs. 1, 2, 3, 4, 5).

Although a fat reduction in every area examined was observed, it is still unknown which areas are the most susceptible to cryolipolysis. Various factors may contribute to the fat reduction observed after this procedure, for instance the vascularity, local cytoarchitecture, and metabolic activity of the specific fat depots (Ingargiola et al. 2015).

A subsequent treatment leads to further fat reduction; nevertheless, the extent of improvement was not as expressive as the first session. However, one study demonstrated that a second treatment enhanced fat layer reduction in the abdomen area, but not the love handles. The diminished effect of the second session might be explained by the fat exposed to the second heat extraction that is closer to the muscle layer. The vascular supply to the muscle layer may contribute to the inefficiency of heat extraction, not reaching the preset optimal temperature of 4 °C.

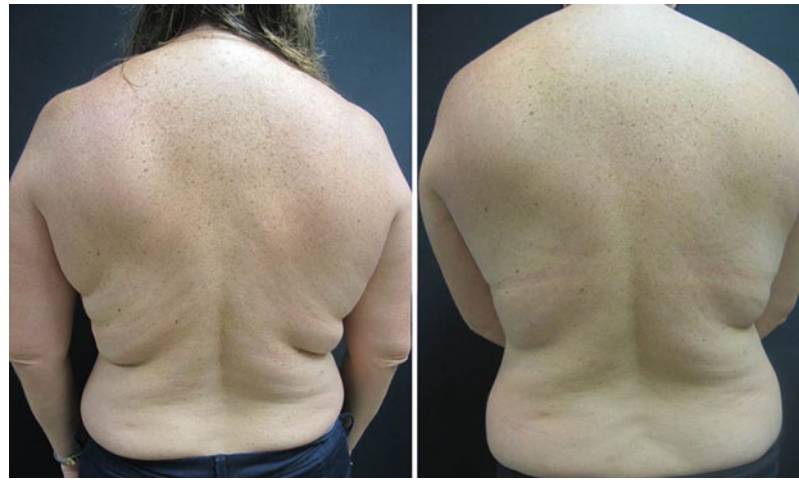

Fig. 1 Before and 2 months after one session on the dorsal region

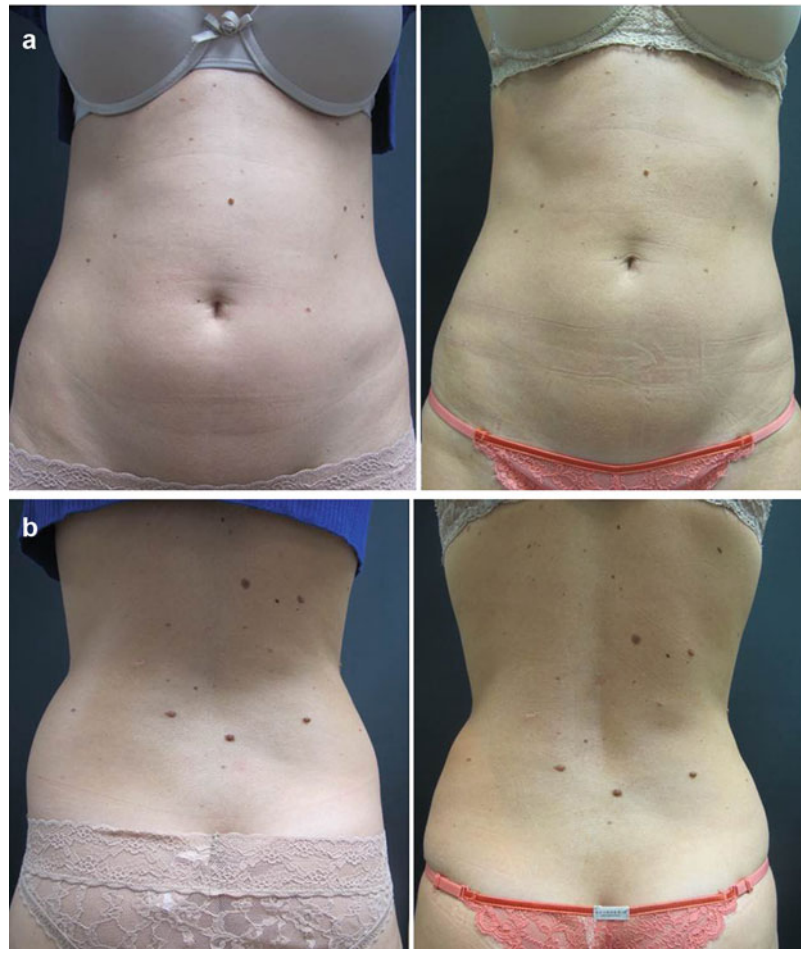

Fig. 2 Before and two months after one session for localized fat on the abdomen. (**a**)frontal view, (**b**) posterior view

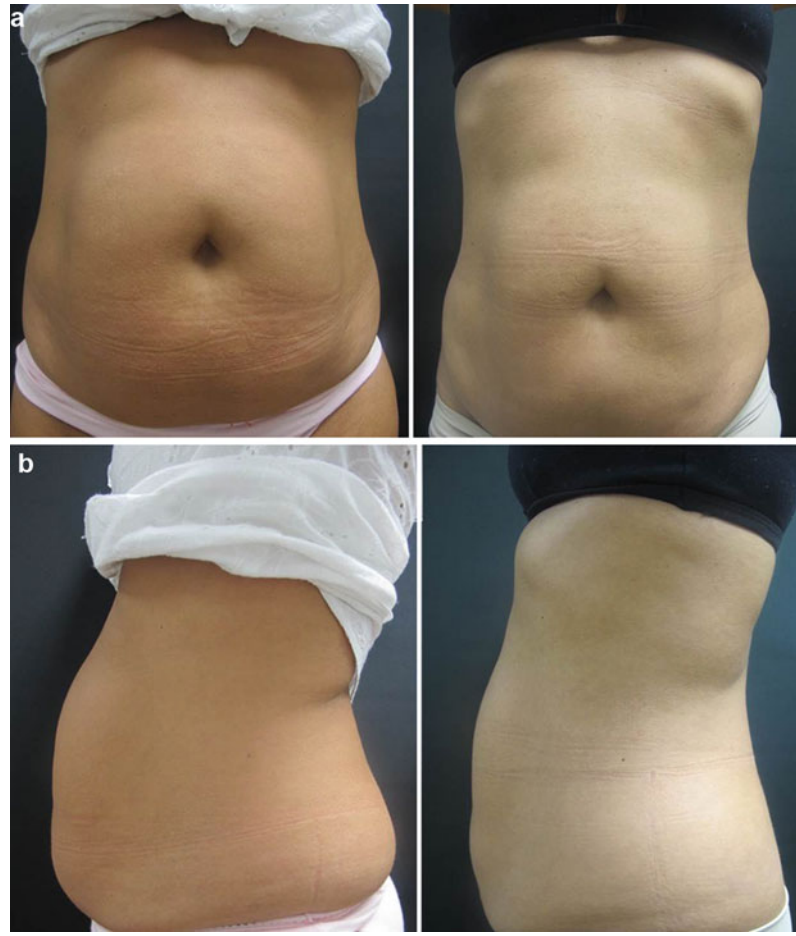

Fig. 3 Before and 2 months after one sessions on the flanks (**a**) anterior view, (**b**) left lateral view

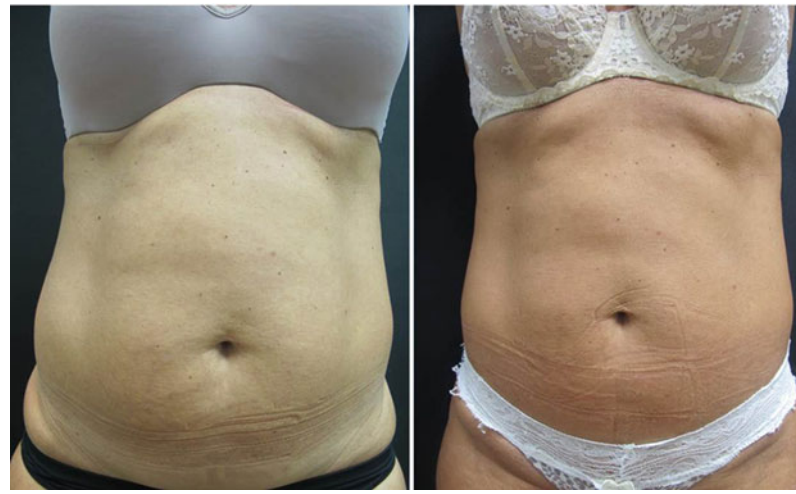

Fig. 4 Before and 2 months after one session on the abdomen

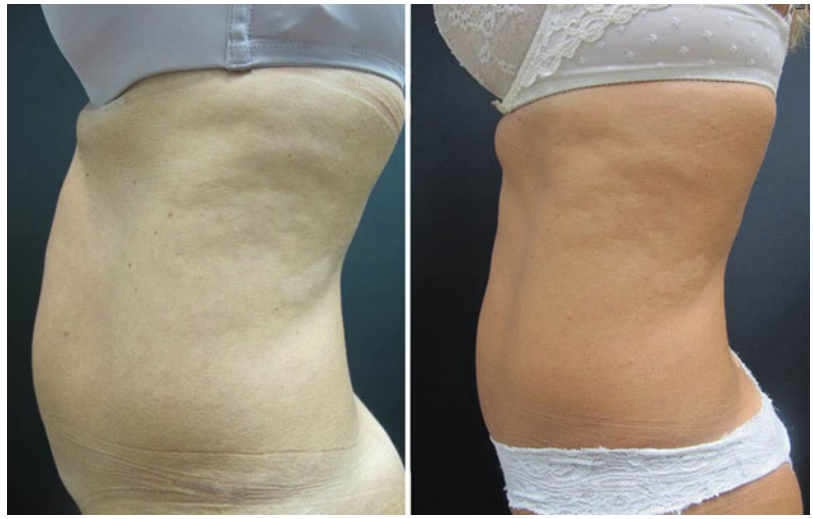

Fig. 5 Before and 2 months after one session on the abdomen

Another hypothesis is that adipocytes that survived the first treatment have a higher tolerance to cold (Ingargiola et al. 2015; Munavalli 2013; Boey and Wasilenchuk 2014; Pinto et al. 2012).

Besides subsequent treatment, posttreatment massage was also evaluated to explain why this technique enhances the efficacy of a single cryolipolysis treatment. One hypothesis for the potentially improved efficacy with posttreatment manual massage is an additional mechanism of damage to the targeted adipose tissue immediately after cooling, perhaps from tissue-reperfusion injury. Histological analysis revealed no evidence of necrosis or fibrosis resulting from the massage, thus showing that posttreatment manual massage is a safe and effective method to further reduce the fat layer after cryolipolysis, with excellent outcomes (Ingargiola et al. 2015; Sasaki et al. 2014; Boey and Wasilenchuk 2014).

Adverse Effects

One of the main advantages of cryolipolysis is the low profile of adverse effects, especially when compared with more invasive procedures. Only mild, short-term side effects, such as erythema, bruising, changes in sensation, hypersensitivity and hyposensitivity, and pain, were reported in the literature. These effects can be mostly explained by the strength of the vacuum and the temperature at which the tissue is kept for extended durations and poses no threat to the patients (Ingargiola et al. 2015; Ferraro et al. 2012; Avram and Harry 2009).

Patients usually observe a red color in the treated site, which disappear in a few hours. In some cases, bruises may appear, which could last for a week. A feeling of dumbness may occur in some of the treated areas. The decreased nerve sensation takes 1–6 weeks (mean 3.6 weeks), but it completely disappears after 2 months. This case of reduced sensation is self-limited and it does not need any intervention. No persistent ulcerations, scarring, paresthesias, hematomas, blistering, bleeding, hyperpigmentation or hypopigmentation, or infections have been described. Swelling and bruising of the area were shown to a slightly lesser extent than erythema, but are believed to be because of the same processes. These complications also subsided shortly after (Ferraro et al. 2012; Nelson et al. 2009).

In one study, pain during the procedure was generally nonexistent to tolerable 96% of the time. Some studies showed no long-term changes to nerve fibers through nerve biopsy taken after normally at 3 months of treatment, concluding that temperature and duration of cryolipolysis have no permanent effect on peripheral nervous tissue. Rare side effects that have been described include vasovagal reaction and paradoxical adipose hyperplasia. Jalian et al. estimated an incidence

of 0.0051 percent, or approximately one in 20,000, for paradoxical adipose hyperplasia (Ingargiola et al. 2015; Jalian et al. 2014).

Histologic outcomes were evaluated in a handful of studies. No evidence of fibrosis was noted. Most studies demonstrate an inflammatory response at different stages after cryolipolysis, with inflammatory cell infiltrates peaking at 30 days (Coleman et al. 2009).

Contraindications to cryolipolysis include cold-induced conditions, such as cryoglobulinemia, cold urticaria, and paroxysmal cold hemoglobinuria. Cryolipolysis should not be performed in treatment areas with severe varicose veins, dermatitis, or other cutaneous lesions (Ingargiola et al. 2015; Avram and Harry 2009).

Procedure and Authors' Experience

In our experience, the cryolipolysis treatment does not require a preparation or restriction preprocedure. The patient should not be fasting and there is no need to discontinue medications of regular use. We advise the patient to bring a bikini or trunks to use during the cryolipolysis session.

Firstly, we perform a corporal evaluation of the area to be treated, which includes photographic documentation, measure of the treated area, and fat percentage obtained with an adipometer.

The consent term, given to all patients, clarifies the mechanism of action, expected outcome, contraindications, and adverse effects.

In agreement with the treatment, we mark the area to be treated, in the proper positions for better esthetic results (e.g., diamond technique in the abdomen).

When patient's position is suitable for the coupling and comfortable to remain during the treatment time, we apply the protective blanket with gel, specific to the device and then, we couple the tip to begin the suction.

During the first 10 minutes, there is a painful discomfort, which ceases due to the analgesia obtained by freezing the area. The process of freezing a tip takes about 1 hour, varying with tip type and/or manufacturer.

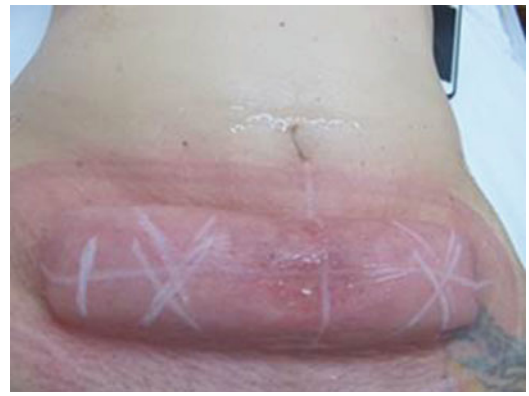

Fig. 6 Frozen "mass" with the shape of the tip with Erythema and edema immediately after cryolipolysis on the abdomen

After finishing the treatment cycle, decouple the tip and notice the formation of a frozen "mass" with the shape of the tip (Fig. 6). The skin of the treated area should be red, slightly swollen, but intact. Erosions, blisters, or other injuries are not expected after the procedure. We should then start the manual massage with gentle movements aiming to warm the treated area.

Regarding the adverse effects, we commonly observe transitory pain, erythema, and edema. Ecchymosis and nodules can occur. In our experience, the greatest discomfort is during the treatment of the abdomen. The pain is handled with oral gabapentin, which can be offered just after the procedure and sustained for 2 weeks if necessary. The edema should not be drained. Ecchymosis can last 2–3 weeks and it is solved by itself, but if patients ask for treatment some creams containing cumarin and heparin or vitamin K can be applied until complete resolution.

There is no restriction of physical activity in the posttreatment. Also, we do not usually indicate massages as part of the treatment program. The patient is evaluated in 2 months and if necessary, we repeat the treatment aiming at greater loss of local fat.

Conclusion

Cryolipolysis is becoming one of the most popular alternatives to liposuction for local reduction of adipose tissue. Due to its ease of use and limited

adverse effects, this procedure is becoming the leading technology of noninvasive techniques as well. As cryolipolysis is a considerably novel procedure, treatment protocols still have to be ameliorated to maximize results.

Compared with traditional cosmetic surgical procedures side effects, cryolipolysis possesses a minor threat to patients, with a very low incidence of complications. Some studies have compared caliper, ultrasound, three-dimensional imaging, and manual tape measurements with cryolipolysis. Although no single study has compared all of these modalities, the available data suggest that these techniques have a good correlation with each other.

Cryolipolysis was first described in 2007, and although its popularity has increased dramatically, the available literature remains limited. Tremendous variability exists in study design, machinery used, and outcome measures. Due to this lack of uniformity, comparing size effect becomes challenging, and the value of a meta-analysis of the available data is limited.

Take Home Messages

Body contouring remains among the most common cosmetic surgical procedure performed in the United States.

Cryolipolysis is a promising nonsurgical technique for localized fat reduction and body contouring.

Cryolipolysis is becoming one of the most popular alternatives to liposuction for spot reduction of adipose tissue.

Cryolipolysis consists of selected damaging of fat cells induced by a programmed cooling of the skin.

Rare side effects that have been described.

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Ultrasound-Assisted Drug Delivery in Fractional Cutaneous Applications

Joseph Lepselter, Alex Britva, Ziv Karni, and Maria Claudia Almeida Issa

Abstract

Cutaneous biodistribution and bioavailability of most topically applied drugs are quite low. For a topical agent to be active, it must first traverse the rate-limiting barrier of the stratum corneum. Many medications are too large (size >500 Da in molecular weight) to penetrate this barrier which require either an injectable or systemic delivery. Fractional ablative skin therapy became a common modality in procedural dermatology with the ability to create ablative microscopic channels of varying depths in the stratum corneum and other epidermal layers in a predictable manner, thus creating new opportunities in drug delivery. Pairing fractional ablation skin perforation with physical-assisted modality for the enhancement of drug delivery would seem attractive option for various skin indications. That said, the extent of collateral damage created by the ablative fractional technology on the microchannels and the unavoidable exudates created by the natural wound healing process would prove problematic for passive drug delivery. Recently, a novel ultrasound-assisted drug delivery device (IMPACT™) was introduced and clinically used in pairing with fractional ablation technology for pushing and enhancing the delivery of substances immediately after the skin perforation for the purpose of increasing biodistribution and bioavailability through the microchannels for variety of cutaneous indications such as scars, striae distensae, actinic keratosis, or dysplastic skin lesions in photodynamic therapy. This ultrasound-assisted drug delivery device should be used by a qualified practitioner that must possess an understanding in cutaneous anatomy in relation to the local target (indication), appropriate training, and comfort level and familiarity with the properties and appropriate selection of the topical agent.

Keywords

Transepidermal drug delivery • Transdermal drug delivery • Transcutaneous administration • Transdermal administration • Laser • Ultrasound

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Contents

Introduction

The skin is one of the most readily accessible organs of the human body, covering a surface area of approximately 2 m^2 and receiving about one third of the body's blood circulation The skin is a complex system consisting of the epidermis, the dermis, and skin appendages, such as hairs, interwoven within the two layers. The outermost layer of the skin, the epidermis, is avascular, receiving nutrients from the underlying dermal capillaries by diffusion through a basement membrane. The outermost layer of the epidermis is called the stratum corneum, the protective covering that serves as a barrier to prevent desiccation of the underlying tissues and to exclude the entry of noxious substances from the environment, including agents applied to the skin. This layer consists of corneocytes embedded in lipid regions (Michael et al. 2002).

Transdermal (or transcutaneous) drug delivery offers advantages over traditional drug delivery methods, such as injections and oral delivery. In particular, transdermal drug delivery avoids gastrointestinal drug metabolism, reduces side effects, and can provide sustained release of therapeutic compounds. The term "transdermal" is used generically because, in reality, transport of compounds by passive diffusion occurs only across the epidermis where absorption into the blood via capillaries occurs (Elias and Menon 1991).

However, the diffusion rate of topically applied compounds will vary because of both internal (physiological) and external (environmental) factors. The diffusion rate is also dependent upon physical and chemical properties of the compounds being delivered. The patient's skin needs to be carefully evaluated to minimize the natural, internal barriers to transdermal drug delivery (e.g., dry skin, thick skin, dehydration, poor circulation, poor metabolism) and to maximize the natural enhancers (e.g., ensuring the patient is well hydrated and selecting an area of skin that is thin, warm, moist, and well perfused). The stratum corneum is considered to be the rate-limiting barrier for transdermal delivery, and so diffusion is often enhanced. Various methods include preheating the skin to increase kinetic energy and dilate hair follicles and covering the area with an occlusive dressing after the drug application to maintain moisture and activate the reservoir capacity of the skin (Scheuplein and Blank 1971; Prausnitz et al. 2012; Kurihara-Bergstrom and Good 1987).

Enhancers of transcutaneous drugs are usually used to alter the nature of the stratum corneum to ease diffusion. This alteration may result from denaturing the structural keratin proteins in the stratum corneum, stripping or delaminating the cornified layers of the stratum corneum, changing cell permeability, or altering the lipid-enriched intercellular structure between corneocytes. Enhancers are incorporated into transdermal-controlled drug delivery systems, or they are used prior to, during, or after the topical application of a drug. Preferred enhancers allow drugs to diffuse actively and quickly, but do not inactivate the drug molecules, damage healthy epidermis, cause pain, or have toxicological side effects (Haftek et al. 1998; Menon and Elias 1997; Akomeah 2010).

Even though ultrasound has been used extensively for medical diagnostics and physical therapy, it has only recently become popular as an enhancer of drug delivery. Numerous studies have demonstrated that ultrasound is generally safe, with no negative long-term or short-term side effects, but the mechanisms by which ultrasound works for the purpose of transepidermal drug delivery as an enhancer are less clearly understood (Nino et al. 2010; Prausnitz and Langer 2008; Smith 2007).

Ultrasound-Skin Interaction in Cutaneous Application

Ultrasound is defined as an acoustic wave at frequency of between 20 kHz and 10 MHz. The properties defining the ultrasound are the amplitude and the frequency of the acoustic waves. Similar to audible sound, ultrasound waves undergo reflection and refraction, when they encounter another medium with dissimilar properties. If the properties of the encountered medium are different from those of the transmitting medium, the acoustic energy of the transmitted ultrasound beam is attenuated by being reflected from this medium. Attenuation of ultrasound by its absorption and scattering in tissue also limits its depth of penetration (Anselmo and Mitragotri 2014; Byl 1995; Mitragotri 2004a).

Ultrasound may bring various reactions when propagated in biological tissue. The resulting effects include thermal, mechanical, chemical, and optical reactions. Mechanical effects, more specifically, may consist of acoustic cavitation, radiation force, shear stress, and acoustic streaming/microstreaming (David and Gary 2010).

The use of ultrasound to enhance the transport of a substance through a liquid medium is referred to as sonophoresis or phonophoresis. It may be used alone or in combination with other enhancers, such as chemical enhancers, iontophoresis, electroporation, magnetic force fields, electromagnetic forces, mechanical pressure fields or electrical fields (Mitragotri 2004b).

Both the thermal and non-thermal characteristics of high-frequency sound waves can enhance the diffusion of topically applied drugs. Heating from ultrasound increases the kinetic energy of the molecules (mobility) in the drug and in the cell membrane, dilates points of entry such as the hair follicles and the sweat glands, and increases the circulation to the treated area. These physiological changes enhance the opportunity for drug molecules to diffuse through the stratum corneum and be collected by the capillary network in the dermis. Both the thermal and non-thermal effects of ultrasound increase cell permeability. The mechanical characteristics of the sound wave also enhance drug diffusion by oscillating the cells at high speed, changing the resting potential of the cell membrane and potentially disrupting the cell membrane of some of the cells in the area (David and Gary 2010; Mitragotri 2004b). One of the theories of ultrasound phoresis postulates that the main factor is increasing the permeability of a skin by creating lipid bridges between keratin layers in stratum corneum (Mason 2011; Guy 2010; Pitt et al. 2004).

Another important factor that may affect drug diffusion is related to the shear forces (or shock waves) that occur when adjacent portions of the same membranous structures vibrate with different displacement amplitudes. The acoustic waves cause streaming and/or cavitation in the drug medium and the skin layers, which helps the drug molecules to diffuse into and through the skin. “Streaming” is essentially oscillation in a liquid that forces the liquid away from the source of the energy, while “cavitation” is the formation of bubbles in a liquid that is subjected to intense vibration. Cavitation is the result of rarefaction areas during propagation of longitudinal acoustic waves in the liquid when the waves have an amplitude above a certain threshold (Mitragotri 2005; Pua and Pei 2009).

When these bubbles occur in specific cells of the skin, fatigue or rupture of the cells can occur as the bubbles reach an unstable size. Destruction of cells in the transmission path of the ultrasound may facilitate intercellular diffusion of drug molecules. Cavitation may also destruct the organization of lipids in the stratum corneum, resulting in an increase in the distance between the lipid layers. As a result, the amount of water phase in the stratum corneum increases thereby enhancing the diffusion of water-soluble components through the intercellular space (Sivakumari et al. 2005). As the permeation pathway for topically applied products is mainly along the tortuous intercellular route, the lipids in the stratum corneum play a crucial role in proper skin barrier function.

Ultrasound (sonophoresis, phonophoresis, and ultraphonophoresis) is a technique for increasing the skin permeation of drugs using ultrasound

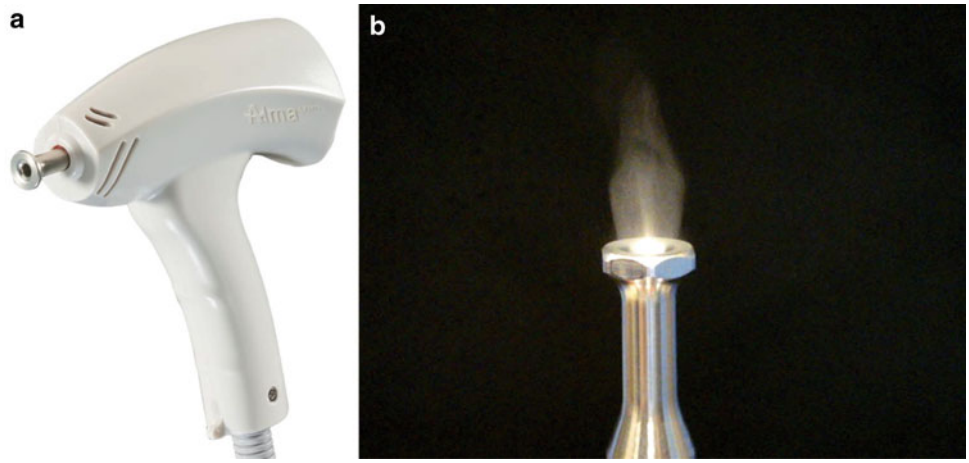

Fig. 1 A low-frequency (kHz) ultrasound-assisted drug delivery technology (IMPACT™). The ultrasound applicator (**a**) handpiece and its sonotrode (**b**)

(20–16 MHZ) as a physical force. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel, but sometimes a cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent (Lee and Zhou 2015). Application of low-frequency ultrasound (20–100 KHZ) enhances skin permeability more effectively than high-frequency ultrasound (1–16 MHZ). The mechanism of transdermal skin permeation involves disruption of the stratum corneum lipids, thus allowing the drug to pass through the skin. A corresponding reduction in skin resistance was observed due to cavitation, microstreaming, and heat generation (Park et al. 2014; Mormito et al. 2005; Mitragotri and Kost 2001).

With this in mind, burning and abrasion of the epidermis are a serious consideration when using ultrasound. Ultrasound should act as a mechanical acoustic pressure agent without destructing the epidermis of the skin. However, cavitation in the liquid coupling the sonotrode to the skin may produce cavitation erosion of the epidermis and the dermis. While this cavitation assists with active penetration of the substance being delivered, such cavitation may also destruct the epidermis. A further challenge when using ultrasound is that it is low in efficiency due to cavitation in the buffer suspension and the low acoustic pressure and ultrasonic energy that is required to prevent burning and other injury (Tang et al. 2002; Terahara et al. 2002; Mitragotri and Kost 2000; Mitragotri et al. 1995).

There is an ongoing need for improved devices and methods to enhance transdermal medical and cosmetic compound delivery. In particular, there is an ongoing need for ultrasound-based devices and techniques for transdermal drug or cosmetic delivery. A low-frequency (kHz) ultrasound-assisted drug delivery technology was developed for the purpose of transepidermal delivery of topical ingredients, i.e., drugs or cosmeceuticals, used in pairing with fractional laser or radiofrequency-assisted technology (Fig. 1a, b).

Laser-Assisted Skin Permeation in Transepidermal Drug Delivery

Fractional ablation of the skin is a special laser-skin interaction event of photo-thermolysis first described in 2004. Fractional ablative lasers (erbium:YAG and CO_2) or other fractional ablative modalities such as radiofrequency ablate the skin in fractions, splitting the laser beam into microbeams. These microbeams create microscopic vertical channels of ablation in the skin.

The creation of these channels may provide access pathways for topically applied drug molecules that would otherwise be too large to traverse the epidermal layer. The location, diameter, depth, and other characteristics of these channels can be controlled or manipulated by the settings of the laser or radiofrequency technology (Manstein et al. 2004; Alexiades-Armenakas et al. 2008; Haak et al. 2011; Lin et al. 2014; Carniol et al. 2015; Forster et al. 2010).

Investigation into the in vitro/in vivo effectiveness of fractional laser devices for facilitating drug permeation in animals is abundant. However, few studies have examined clinical studies of the laser-assisted drug delivery in humans.

Oni et al. (2012) demonstrated in vivo lidocaine absorption by the fractional Er:YAG laser using pig as the animal model. The drug level in the serum was detected after topical application of 4% lidocaine. The serum concentration was undetectable in the nontreated group. The serum level was detectable following laser treatment. Peak levels of lidocaine were significantly greater at 250-μm pore depth (0.62 mg/l), compared to 500 μm (0.45 mg/l), 50 μm (0.48 mg/l), and 25 μm (0.3 mg/l). The greater depth of the microchannels did not guarantee greater enhancement.

Haersdal et al. (2010) evaluated skin delivery assisted by the fractional CO_2 laser by using methyl aminolevulinic (MAL) as the model permeant. MAL is an ester prodrug of aminolevulinic acid (ALA). Yorkshire swine were treated with the fractional CO_2 laser and were subsequently applied with MAL. Fluorescence derived from protoporphyrin IX (PpIX) was measured by fluorescence microscopy at a skin depth of 1800 μm. The fractional laser created cone-shaped channels of 300 μm in diameter and 1850 μm in depth. This ablation enhanced drug delivery with higher fluorescence in the hair follicles and dermis as compared to intact skin. The fractional laser irradiation facilitates topical delivery of porphyrin precursor deep into the skin. Haedersdal et al. (2011) also investigated the MLA permeation enhanced by fractional CO_2 laser quantifying PpIX skin distribution and photodynamic therapy (PDT)-induced photobleaching from the skin surface to the depth of 1800 μm in Yorkshire swine. The red light for creating photobleaching was light-emitting diode arrays delivered at fluencies of 37 and 200 J/cm^2. The fraction of porphyrin fluorescence lost by photobleaching was less after 37 J/cm^2 than after 200 J/cm^2. The fractional laser greatly facilitated the skin PpIX, and the fraction of photobleached porphyrins was similar for the superficial and deep skin layers. Distribution of PpIX into laser-treated skin may depend on the microchannel depth and the drug incubation period. Haak et al. (2012a) further evaluated whether the depth of the fractional laser and the incubation time affect methyl ALA permeation. Yorkshire swine were treated with the fractional CO_2 laser at 37, 190 and 380 mJ to create microchannel depths of 300 (superficial), 1400 (mid) and 2100 μm (deep dermis/subcutaneous), respectively. The incubation times for methyl ALA cream were 30, 60, 120, and 180 min. Similar fluorescence of PpIX was induced throughout the skin layers independent of the laser channel depth by a 180-min incubation. Laser irradiation and the following methyl ALA incubation for 60 min increased fluorescence in the skin surface compared to intact skin. Laser exposure and the subsequent methyl ALA incubation for 120 min increased fluorescence in the follicles and the dermis compared to intact skin.

Treatment of scars, including hypertrophic scars and keloids, intrinsically poses a delivery challenge given their variable and fibrotic nature, especially when considering penetration into the mid-to-deep dermis. Corticosteroids, 5- fluorouracil (5-FU), imiquimod, methotrexate, and other immunomodulators have been used as adjuvant scar therapies for years. However, when used topically, these agents demonstrate only mild efficacy and may carry risks such as corticosteroid-related epidermal atrophy. Intralesional use may prove more efficacious but may also be associated with significant pain, atrophy, pigmentary changes, and a high recurrence rate (Haak et al. 2012a; Brauer et al. 2014). Furthermore, the extent of collateral damage created by fractional ablative lasers or non-laser fractional technology and the post-trauma exudate (interstitial fluid or fibrin) within the microchannels would prove

problematic for drug delivery. This is because, the hydrostatic forces pushing the exudative fluid out of the tissue into the channels would directly compete with the diffusion of the substance applied topically. This, therefore, reduces any potential for passive transdermal diffusion and emphasizes the need for pressure-assisted technology that will immediately push the substance into the viable microchannels space (Haedersdal et al. 2011; Haak et al. 2012a, b; Erlendsson et al. 2014a).

Ultrasound-Assisted Drug Delivery in Fractional Cutaneous Applications

In the past two decades, numerous studies have described the usefulness of that low-frequency ultrasound to improve skin permeability. Only recently, application of fractional ablative methods using lasers and radiofrequency has been described for potential therapeutic purposes in investigational and procedural dermatology, aiming at creating microchannels in the epidermis to increase permeability of tropically applied drugs in indications such as hypertrophic and atrophic scars and other skin imperfections (Bloom et al. 2013; Sklar et al. 2014; Gauglitz 2013; Arno et al. 2014; Waibel and Rudnick 2015; Rkein et al. 2014; Waibel et al. 2013; Togsverd-Bo et al. 2012, 2015; Taudorf et al. 2014; Erlendsson et al. 2014b). Table 1 depicts assisted-drug delivery compounds currently tested and used with fractional ablative applications.

A novel ultrasound-assisted drug delivery device (IMPACT™) is displayed in Fig. 1. The ultrasound applicator is an acoustic wave proprietary technology (Britva et al.) that operates at low frequency (kHz). The ultrasound applicator has a sonotrode that emits acoustic waves and creates mechanical air pressure which helps to advance topical cosmetic products/substances into the top layers of the skin, creating cycles of negative/positive pressure – "push and pull" effect (Fig. 2a, b) – within the preliminary organized channels to release the buildup of intracellular fluid and help the cosmetic product more rapidly advance into the skin to the targeted tissue depth.

Table 1 Assisted drug delivery of compounds in fractional ablative applications

ALA and MAL (PDT)
Topical anesthetics
NSAIDS
Opioids
Chemotherapeutic drugs
Corticosteroids
Vaccinations
Topical ascorbic acid (vitamin C)
Imiquimod
Allogenic mesenchymal stem cells
Botulinum toxin
Antioxidants
Beta-blockers
Antifungals
Bone marrow transplantation
5-Fluorouracil (5-FU)
Interferons
Filler agents

Sklar et al. (2014) and Brauer et al. (2014)

The sonotrode serves various functions such as conversion of the acoustic waves, by increasing the amplitude of the oscillations, modifying the distribution, and matching acoustic impedance to that of the substrate. Resonance of the sonotrode, which increases the amplitude of the acoustic wave, occurs at a frequency determined by the characteristics of modulus elasticity and density of the material from which the sonotrode is made, the speed of sound through the material, and the ultrasonic frequency. The size and shape (round, square, profiled) of a sonotrode will depend on the quantity of vibratory energy and a physical requirements for each specific application. Sonotrodes connected to ultrasound transducers, especially those employed for transdermal delivery of drugs, typically have a length L, expressed by the equation $L = n(\lambda/2)$, where λ is the wavelength of the ultrasound in the sonotrode and n is a positive integer. In this case, the maximum amplitudes of the acoustic wave are found at the proximal end of the sonotrode and at the $\lambda/2$ length beyond the foot of the sonotrode. The vibrating column of air within the bore in the distal end of the sonotrode, together with the vibration of the annular end surface of the foot portion, has the effect of cyclically reducing and increasing the

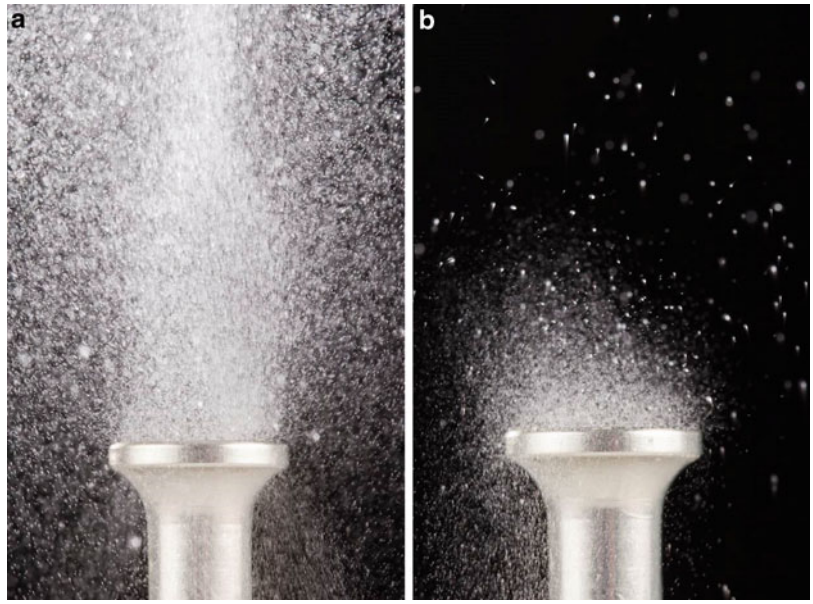

Fig. 2 The sonotrode that emits acoustic waves and creates mechanical upstream/positive (**a**) and downstream/negative (**b**) cyclic-vibrational air pressure

pressure at the skin interface, and this sucking and blowing action facilitates the transport of the compound to be delivered through the microchannel perforations created by ablative fractional laser or radiofrequency across the stratum corneum (Britva et al.).

The mode of operation is based on mechanical (acoustic) pressure and torques by propagation of US wave via the sonotrode to the distal horn and the creation hammering-like effect ("push and pull") in the thin layer between the cosmetic products and the distal surface of sonotrode. The sonotrode is applied normally to the surface of the skin contacting continuously with the skin surface. The vibrational cycles (push-pull) enhance its delivery via the skin microchannels. Thus, this ultrasound-assisted technology emits acoustic waves producing ultrasonic pressure and creating a "push and pull" effect within the channels to release the buildup of intracellular fluid and enhances the cosmetic ingredients or the drugs to the tissue depth.

Ultrasound is applied via a sonotrode, also termed an acoustic horn. The sonotrode serves various functions such as conversion of the acoustic waves, by increasing the amplitude of the oscillations, modifying the distribution, and matching acoustic impedance to that of the substrate. Resonance of the sonotrode, which increases the amplitude of the acoustic wave, occurs at a frequency determined by the characteristics of modulus elasticity and density of the material from which the sonotrode is made, the speed of sound through the material, and the ultrasonic frequency. The size and shape (round, square, profiled) of a sonotrode will depend on the quantity of vibratory energy and a physical requirements for each specific application. The ultrasonic acoustic waves emitted by the flared foot (Figs. 1 and 2) of the sonotrode are believed to assist in spreading through the dermis the compound that has been transported through the perforated stratum corneum, and the flaring of the foot serves to spread the ultrasonic waves over a greater area to assist in diffusion of the compound.

The shape of the sonotrode is believed to achieve two effects. First, the hollow neck creates a vibrating air column that blows and sucks alternately, serving to transfer the medicament through the stratum corneum. Second, the setting of the length of the sonotrode to $\lambda/6$ allows the acoustic energy to be focused to a point that is between approximately 0.3 and 2 mm beneath the surface of the skin. This positioning of the maximum acoustic wave amplitude at a point deeper in the tissue magnifies the sonophoresis effect of

cavitation, lipid destruction, etc. and increases absorption of the drug or cosmetic.

The pairing of fractional ablative technology and ultrasound-assisted technology in procedural dermatology has gained attention for the purpose of skin permeation to facilitate transepidermal drug delivery. In the past 5 years, clinical efficacy and safety of the IMPACT technology has been tested and validated in various preclinical and clinical ex vivo and in vivo models.

Lepselter et al. (2013) analyze transepidermal enhancement following fractional ablative skin permeation in a rat model. Rats (Sprague Dawley, either sex) were anesthetized with a mixture of ketamine (60 mg/kg) and xylazine (10 mg/kg) injected ip or im. Rats were shaved and prepped on their dorsal and lateral sides. Skin perforation (SP) followed by low-frequency ultrasound-assisted device (IMPACT) was studied in five different conditions: normal skin (control), topical Evans blue (EB), topical EB + US, topical SP + EB, and topical SP + EB + US. Frozen sections from skin biopsies were taken at 0 and 15 min incubation time for histological examination using a high-resolution digital microscope. Penetration area (penetration depth + width) and coloration between distances of penetration were analyzed by advanced imaging software. Reflectance intensity by spectroscopy was measured under two wavelength conditions: 665 nm (EB sensitive) and 772 nm (EB insensitive). The 665/772-nm ratio was used as a penetration indicator – low ratio denoted to higher EB penetration and high ratio to low EB penetration. Biopsies were taken and frozen for histological examination, using digital microscope (Olympus, Japan) and data analysis using image processing ImageJ software (Burger and Burg, Hagenberg, Austria). Penetration area was defined as the colored area divided by the crater area and expressed in %. Penetration width was defined as width line divided by crater width, expressed in %. Penetration depth was defined as depth line divided by crater depth, expressed in %. To visualize and analyze the ultrasound-assisted device effect, a polarization imaging system was used. A CCD camera (Olympus, Japan) was located above the prepared skin sample slide for image acquisition. EB color intensity versus distance (depth and width) was significantly higher for the SP + EB + US (99.66 ± 23.67 pixels) versus SP + EB (52.33 ± 25.34 pixels) and SP + EB + US (80.83 ± 15.41 pixels) versus SP + EB (66.83 ± 28.56 pixels), respectively ($p < 0.05$–0.01). Similarly, topical EB (2.1 ± 0.4) and topical EB + US (1.8 ± 0.3) spectrometry reflectance intensity ratios were high, indicating low EB penetration. In contrast, SP + EB + US (0.4 ± 0.02) versus SP + EB (1.4 ± 0.08) ratios were low, indicating significant higher EB penetration for the former ($p < 0.01$). Histology frozen sections of high-resolution digital photographs were in agreement with the objective measurements. At 0-min incubation time, EB penetration was significantly higher at 70 versus 40 W ($p < 0.01$). At 15 min, EB penetration was significantly higher when compared to 0 min for 70 versus 40 W, respectively. EB color intensity versus distance (depth and width) was significantly higher for the RF + EB + US (99.66 ± 23.67 pixels) versus RF + EB (52.33 ± 25.34 pixels) and RF + EB + US (80.83 ± 15.41 pixels) versus RF + EB (66.83 ± 28.56 pixels), respectively ($p < 0.05$–0.01). Similarly, topical EB (2.1 ± 0.4) and topical EB + US (1.8 ± 0.3) spectrometry reflectance intensity ratios were high, indicating low EB penetration. In contrast, RF + EB + US (0.4 ± 0.02) versus RF + EB (1.4 ± 0.08) ratios were low, indicating significant higher EB penetration for the former ($p < 0.01$). Histology frozen sections of high-resolution digital photographs were in agreement with the objective measurements. It was concluded that the ultrasound-assisted device following ablative RF permeation significantly enhances the amount of EB penetration as evidenced by depth, width, and color intensity (Fig. 3a–d).

The assisted-ultrasound drug delivery device first clinical experience was reported in 2011 by Kassuga and colleagues (2011). This case study described two female patients with multiple actinic keratosis (AK). The study evaluated the effectiveness of the transepidermal (TED) application of methyl aminolevulinate (MAL)

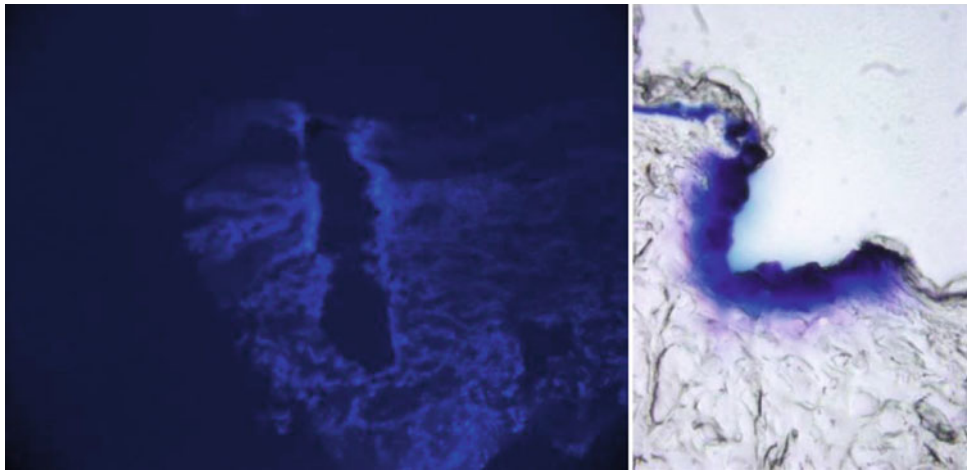

Fig. 3 Histology frozen sections of high-resolution digital photographs without Evans blue (*EB*) (**a**) and with EB ultrasound-assisted device (**b**) following ablative RF permeation significantly enhance the amount of EB. Fluorescent microscopy of high-resolution digital photos without aminolevulinic acid (*ALA*) (**c**) and with ALA ultrasound-assisted device (**d**) following ablative fractional CO_2 laser permeation significantly enhances the amount of ALA

prodrugs in PDT combined with the ultrasound-assisted drug delivery device. Clinical efficacy evaluation was based on reducing the AK number and improving skin texture and color. The two patients were simultaneously treated with the standard MAL-PDT (left forearm) and modified protocols – fractional radiofrequency (RF) combined with MAL and the ultrasound device in the opposite forearm (MAL-GT). Improvements in the texture and pigmentation of the skin were observed after a single treatment on both sides and were more evident on the side previously treated in the MAL-GT modality (in 6-month follow-up visit). Patient 1 had 34 lesions on right forearm (MAL-GT protocol) and 54 lesions on the contralateral forearm (standard MAL-PDT protocol). After 6 months of protocol implementation, there were 8 AK injuries on the MAL-GT condition treated side and 34 on the MAL-PDT condition treated side. These results demonstrated a 76.4% and a 37% decrease in right and left treated forearms respectively. Patient 2, initially with 24 and 21 lesions on the right and left forearms, respectively, had presented after PDT, two and six lesions, respectively, which represents a 91.6% and a 71.4% decrease, respectively. Overall, it was concluded that for these cases, the PDT associated with TED of the MAL with an incubation time of 1 h not only is effective in the AK treatment but also shows better results than the standard protocol.

Issa et al. (2013a) evaluated efficacy, safety, and patient's satisfaction in using ablative fractional RF technology (Pixel RF) associated with retinoic acid 0.05% cream and an acoustic pressure wave ultrasound (US) in patients with alba-type striae distensae (SD) on the breast. Eight patients were treated with a three-step procedure (Michael et al. 2002): fractional ablative RF for skin perforation (Elias and Menon 1991), topical application of retinoic acid 0.05% on the perforated skin, and (Scheuplein and Blank 1971) US applied to enhance penetration. Additional eight patients with abdominal alba-type SD were submitted to RF treatment isolated without retinoic acid or US. Three patients with SD on the breast area improved from "severe" to "moderate," two patients from "severe" to "mild," two patients from "moderate" to "mild," and one patient from "marked" to "mild." Clinical assessment demonstrated significant improvement in appearance of SD in all patients within this ($P = 0.008$), with low incidence of side effects and high level of patient's satisfaction. Among the patients treated

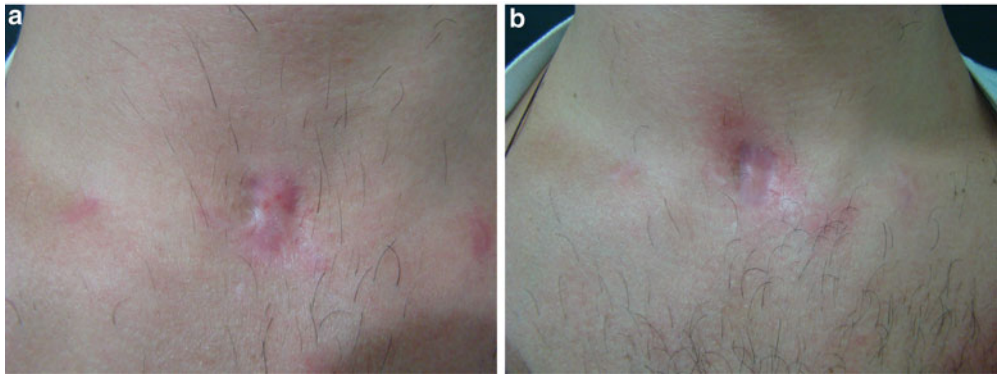

Fig. 4 Tracheostomy scar (**a**) on the neck showed complete resolution after four sessions (**b**) with ablative fractional RF for skin perforation, topical application of triamcinolone on the perforated skin, and acoustic pressure wave US applied to enhance penetration

only with RF, two patients improved from "severe" to "marked," one patient from "marked" to "moderate," and one patient from "marked" to "mild." Four patients did not show any sort of improvement.

Clinical assessment demonstrated no significant improvement in the appearance of SD treated with RF isolated with low incidence of side effects, but low level of patient's satisfaction. It was concluded that ablative fractional RF and acoustic pressure US associated with retinoic acid 0.05% cream is safe and effective for albatype SD treatment.

The aim of the study conducted by Issa et al. (2013b) was to evaluate clinical response and side effects of transepidermal drug delivery (TED) technology in hypertrophic scars in body and face using ablative fractional radiofrequency (RF) associated with low-frequency acoustic pressure ultrasound (US). Four patients with hypertrophic scars were treated with triamcinolone using fractional ablative RF and US. The treatment procedure comprised three steps: (i) ablative fractional RF for skin perforation, (ii) topical application of triamcinolone acetonide 20 mg/ml on the perforated skin, and (iii) acoustic pressure wave US applied to enhance penetration. Study resulted in complete resolution after one session in patients with scars on the nose and mandibular area. The scar on the neck (tracheostomy) showed complete resolution after four sessions (Fig.4a, b). The scar on the knee showed a marked improvement after four sessions. Mild and homogeneous atrophy was observed in hypertrophic scars on the neck.

The method used in this study was shown to improve efficacy of steroids in hypertrophic scar treatment, minimizing risks of localized atrophy and irregular appearance of the treated lesion. The same method, with the three-step procedure (Fig. 5), can be used to improve the quality of non-hypertrophic scar in which retinoic acid and vitamin C, instead of triamcinolone, are better indicated (Fig. 6a, b).

In a recent study, Trelles et al. (Trelles and Martínez-Carpio 2014) aimed to evaluate efficacy and safety of transepidermal delivery (TED) method for treating acne scarring. A total of 19 patients with moderate to severe scarring were treated using unipolar fractional ablative RF technology (Pixel RF) to create dermal microchannels followed by acoustic pressure ultrasound. All patients underwent four treatment sessions at 3-week intervals. The study illustrated significant improvement in scarring on the face, back, and shoulders ($P < 0.0001$). In a 2-month follow-up, fading on total scarring was 57% on the face and 49% on the back and shoulders. After 6 months, percentage increased to 62% and 58% on the face and on the back/shoulders, respectively. Patients reported to be somewhat satisfied (16%), satisfied (53%), and very satisfied (31%). No unexpected side effects to the ablation and no hypersensitive were observed. It was concluded

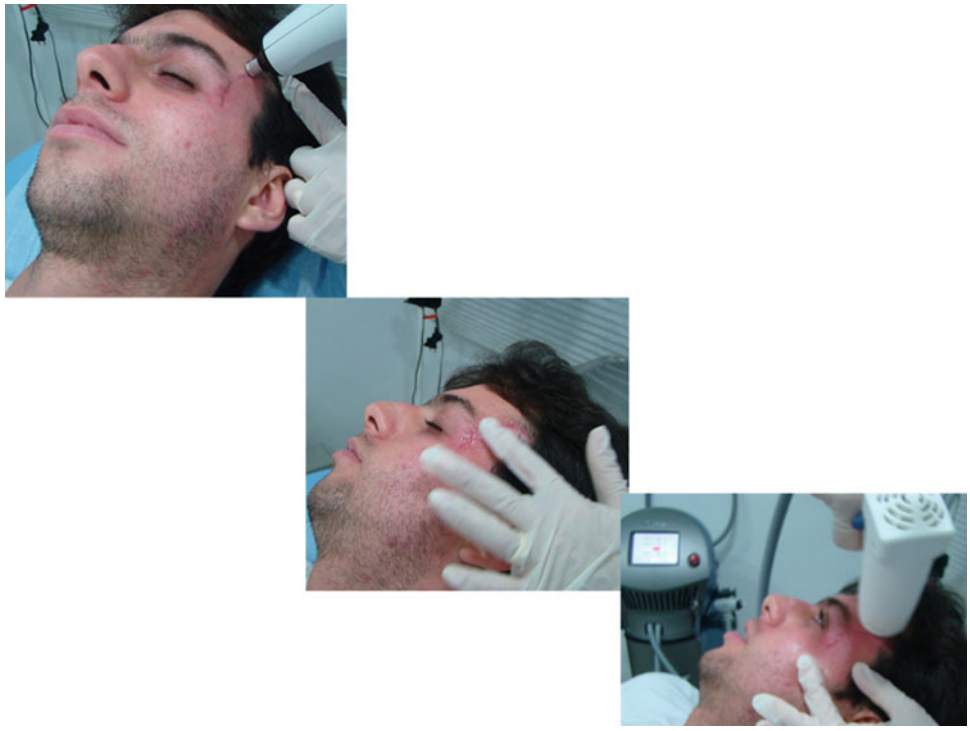

Fig. 5 The treatment procedure comprised three steps: (i) ablative fractional RF for skin perforation, (ii) topical application of drug on the perforated skin, and (iii) acoustic pressure wave US applied to enhance penetration

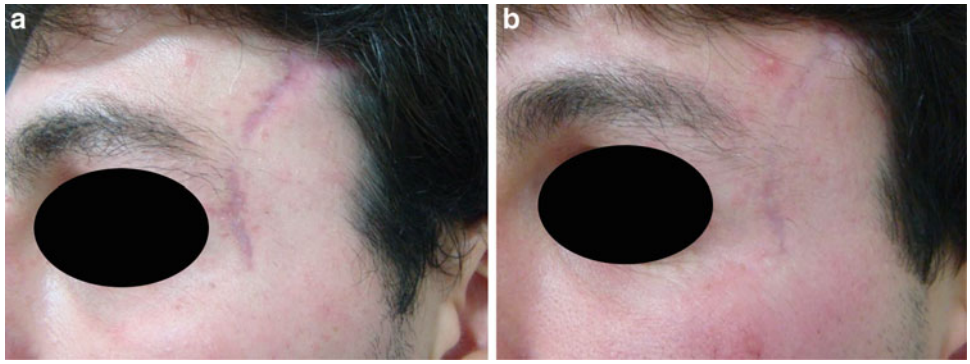

Fig. 6 Before (**a**) and after treatment (**b**) with ablative fractional RF + retinoic acid and vitamin C + acoustic pressure wave US; improvement of the traumatic non-hypertrophic scar on the face (temporal area)

that the bimodal procedure is safe and effective in reducing acne scarring.

Earlier, Trelles et al. (2013) aimed to determine efficacy and safety of facial rejuvenation using fractional carbon dioxide (CO_2) laser (iPixel CO_2), an ultrasound emitter (IMPACT), and a cosmeceutical preparation to be applied intraoperatively. Fourteen patients were enrolled to this split-face, double-blind randomized prospective study; for each patient, one half of the face was treated with a fractional CO_2 laser alone while the other half receiving the same laser followed by acoustic pressure ultrasound of cosmeceuticals. Both treatments achieved

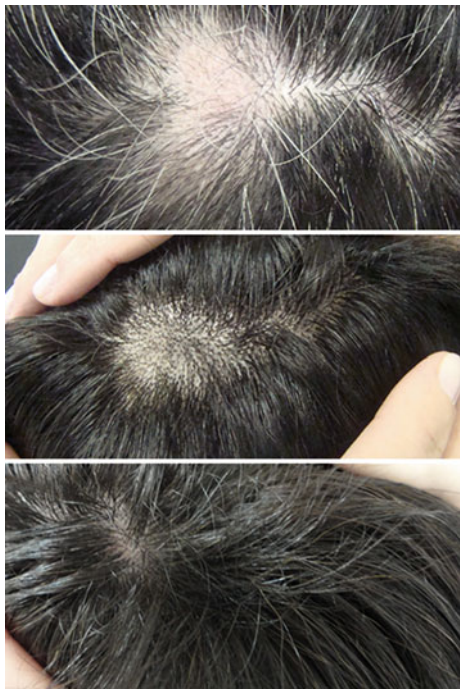

Fig. 7 Complete response of the alopecia areata patch after one session treatment with ablative fractional CO_2 + triamcinolone + acoustic pressure US (before, after 1 month, and after 3 months; from *top* to *bottom*)

significant improvements in all parameters evaluated, yet combined US and cosmeceutical treatment had better scores for reduced fine lines and wrinkles as well as 80% overall improvement of facial aging in 6-month follow-up. Treatment was well tolerated and no adverse effects were observed. Eighty-six percent of patients stated that they were satisfied or very satisfied with their results. The conclusion was that one session of fractional ablative CO_2 laser and acoustic pressure ultrasound technology for TED of cosmeceuticals is an effective method for facial rejuvenation.

Recently, Issa and her colleagues (2015) studied the clinical efficacy and side effects of TED in areata alopecia (AA) using ablative fractional methods and acoustic pressure ultrasound (US) to deliver triamcinolone solution into the skin. Treatment comprised three steps, ablative fractioned RF or CO_2 laser followed by topical application of *triamcinolone* and inserting it using acoustic pressure wave US. Number of sessions varied according to clinical response (range 1–6). Treatment resulted in complete recovery of the area treated in all patients; four of them had even presented results in a 12-month follow-up. Two of the patients were treated with ablative fractional RF + *triamcinolone* + US and had complete response after three and six sessions. The other two treated with ablative fractional CO_2 + triamcinolone + US had a complete response after one session (Fig. 7). Researchers concluded that fractioned ablative resurfacing associated with acoustic pressure wave US is a new option to AA treatment with good clinical result and low incidence of side effects.

In a recent study Waibel et al. (2015) evaluated in vivo if there is increased efficacy of fractional ablative laser with immediate transdermal acoustic waves (IMPACT) to enhance drug delivery via histologic immunofluorescent evaluation. Aminolevulinic acid (ALA) has been chosen to evaluate if the combination of fractional ablative laser with immediate transdermal ultrasound will enhance drug delivery. Six patients were treated with four treatment sites – one area treated with topically applied ALA, one area with fractional ablative laser (iPixel CO_2) and ALA topically applied, one area with fractional ablative laser and transdermal delivery system, and a final area of ALA topically applied with transdermal delivery system. Comparison of the difference of magnitude of diffusion both lateral spread of ALA and depth diffusion of ALA was measured by fluorescence microscopy. With laser + ALA + acoustic device, the protoporphyrin IX lateral fluorescence was 0.024 mm on average versus fractional laser, and ALA was only 0.0084. The diffusion with the acoustic air device was an order of magnitude greater. The authors concluded that the combined approach of fractional CO_2 laser and the IMPACT device demonstrated the best results of the increased depth of penetration of the ALA (Fig. 3).

Suh et al. (2012) had conducted a study to evaluate effectiveness and safety of enhanced penetration of platelet-rich plasma (PRP) with ultrasound after plasma fractional radiofrequency for the treatment of striae distensae. Participants

were treated with the ultrasound-assisted drug delivery device in pairing with fractional radiofrequency technology (Pixel RF) for three sessions in 3 weeks interval. In order to enhance platelet-rich plasma penetration, ultrasound is applied. Two months after last treatment, average width of the widest striae had decreased from 0.75 to 0.27 mm; from a total of 18 participants, 13 were evaluated by two blinded reviewers as "excellent" or "very good" overall improvement. 72.2% of the participants reported "very satisfied" or "extremely satisfied" with overall improvement. Only side effect reported was post-inflammatory hyperpigmentation (11.1%). The researchers concluded that fractional radiofrequency and transepidermal delivery of PRP using ultrasound are effective and safe in the treatment of striae distensae.

In a recent prospective, controlled study, Trelles et al. (2015) used florescent technique (fluorescein) to qualitatively and quantitatively determine the transepidermal penetration of a cosmeceutical after permeabilizing the skin using the ultrasound-assisted drug delivery device and fractional ablative radiofrequency technology (Pixel RF) techniques. The treatments were performed in the retroauricular area in 16 patients, and biopsies were taken at 10 min and at 15 h after the procedure. The intensity of dermal fluorescence in the treated samples was compared to that of autofluorescence controls (AC) and technical controls (TC). The results have demonstrated that the samples treated with the Pixel RF+ US displayed a greater intensity of fluorescence than the AC and TC, both at 10 min and 15 h after the treatment. The increases in fluorescence were graded as moderate or intense, but in no case as nil or slight. The results at 10 min were Pixel RF + US (55.4 ± 10.1), AC (8.6 ± 2.8), and TC (8.2 ± 3.6). At 15 h, the results were Pixel RF + US (54.2 ± 7.2), AC (8.9 ± 1.7), and TC (8.3 ± 2.4). The differences between the samples and the controls were significant, both at 10 min and at 15 h ($p < 0.0008$). The authors concluded that the transepidermal delivery procedure carried out facilitated a prolonged and effective dermal penetration of the topically applied products.

Summary

This reviewed novel ultrasound-assisted drug delivery device creates mechanical air pressure, which helps to advance topical cosmetic products/substances into the top layers of the skin and, more importantly, to create cycles of negative/positive pressure ("push and pull") effect within the perforated microchannels that may release the buildup of intracellular fluid and help the cosmetic product, thus enhancing the substance into the skin to the targeted tissue depth.

The idea of ablative fractionation treatment prior to application of topical agents in an attempt to enhance drug delivery is one that continues to garner increasing attention and interest in procedural dermatology (Brauer et al. 2014; Loesch et al. 2014).

In view to mitigating the drawbacks and limitations of topically applied compounds, this novel ultrasound-assisted drug delivery device provides new possibilities for assisted-drug delivery. The use of this ultrasound-assisted drug delivery device in pairing with fractional energy delivery technology has been tested and validated clinically in the past 5 years and is a promising method that can pave future opportunities in transepidermal delivery in challenging cutaneous indications such as photodynamic therapy or skin cancer or aesthetic indications such as scars, acne, or alopecia in procedural dermatology.

Take Home Messages

- Many medications are too large (size >500 Da in molecular weight) to penetrate the barrier of the stratum corneum, which require either an injectable or systemic delivery.
- Fractional ablative skin therapy became a common modality in procedural dermatology with the ability to create ablative microscopic channels of varying depths in the stratum corneum and

other epidermal layers in a predictable manner, thus creating new opportunities in drug delivery.

The novel ultrasound-assisted drug delivery device creates mechanical air pressure, creating cycles of negative/positive pressure effect within the perforated microchannels, preformed by ablative methods.

This push and pull effect may release the buildup of intracellular fluid inside the microchannels, increasing the cosmetic/drug penetration into the skin.

The use of this ultrasound-assisted drug delivery device in pairing with fractional energy delivery technology has been reported as an effective method to improve drug permeation into the skin in many different dermatoses (Bloom et al. 2013).

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Part V

Transepidermal Drug Delivery

Transepidermal Drug Delivery: Overview, Concept, and Applications

Andrés Már Erlendsson, Emily Wenande, and Merete Haedersdal

Abstract

Laser-assisted drug delivery (LADD) is currently being implemented in the dermatological clinic as a new method to enhance skin uptake of topical therapeutics. Compared to conventional topical use, clinical evidence shows benefit for neoplastic lesions, photodamaged skin, scars, onychomycosis, and topical anesthetic procedures. Particularly compelling evidence is available for photodynamic therapy (PDT), where improved and longer-lasting remission using laser-assisted methyl aminolevulinate (MAL) treatment for actinic keratosis is established compared to conventional PDT. Still, safety concerns related to increased risks of local and systemic side effects remain, especially when performing LADD over large skin areas. Provided responsible development, however, LADD holds promise as a new delivery modality with the potential to improve treatment of numerous dermatological conditions.

Keywords

Ablative fractional laser • Non-ablative fractional laser • Cutaneous • Drug delivery • Laser • Laser-assisted drug delivery • Topical administration • Transepidermal • Transepidermal drug delivery

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Introduction

The Skin Barrier

Topical drug therapy is a basic principle in dermatology. The therapeutic efficacy of topical drugs relates to both their inherent potency and ability to penetrate different skin layers. The major rate-limiting step of drug permeation is passage through stratum corneum (SC). Composed of densely packed corneocytes embedded in a hydrophobic nonpolar extracellular lipid matrix organized in a "brick and mortar" architecture, this outermost epidermal skin layer is an efficient barrier to cutaneous drug delivery (Elias and Menon 1991). Transport across the SC is primarily by passive diffusion in accordance with Fick's law. Thus, topically applied drugs pass along concentration gradients and penetrate into skin via intercellular and follicular diffusion pathways before reaching target cells in specific skin compartments. In general, topical therapeutics demonstrate poor total absorption and cutaneous bioavailability, with only 1–5% being absorbed into the skin (Surber and Davis 2002).

Overcoming the Skin Barrier

Intact SC is permeable for small, lipophilic, uncharged molecules up to approximately 500 Daltons (Da). In contrast, hydrophilic, charged, and lipophilic compounds with molecular weights over 500 Da do not readily penetrate the skin barrier (Morrow et al. 2007; Govil 1988). Accordingly, many topical drugs are limited in their ability to reach target cells at deeper skin layers. There has therefore been considerable interest in developing novel drug delivery methods.

Currently available drug delivery strategies include chemical biomodulation as well as physical energy-based techniques to disrupt the skin barrier (Benson 2005). Chemical biomodulation of topical medications increases skin permeability and drug diffusion due to optimized drug-vehicle composition, achieved through penetration enhancers, supersaturated systems, prodrugs, liposomes, nanoparticles, and other carrier systems (Benson 2005; Pathan and Setty 2009; Brown et al. 2006). However, limitations to overall drug delivery persist, as the cutaneous barrier is not fundamentally changed. Chemical biomodulation has therefore traditionally been used to deliver small compounds and compared to physical enhancement techniques shows only limited success in enhancing cutaneous penetration of macromolecules (Paudel et al. 2010).

Physical Enhancement Techniques

Physical enhancement techniques involve the use of external energy to disrupt the skin barrier, aiding uptake of topically applied drugs. Several concepts have been developed, involving the use of electroporation, iontophoresis, lasers, microdermabrasion, microneedles, pressure, radiofrequency, and sonophoresis (Table 1). This armamentarium of techniques has demonstrated improved cutaneous and transcutaneous delivery of various therapeutics, ranging from small topical and systemic drugs (e.g., aminolevulinic acid (ALA) (Fang et al. 2004; Mikolajewska et al. 2010; Krishnan et al. 2013) and methotrexate (MTX) (Lee et al. 2008; Alvarez-Figueroa and Blanco-Méndez 2001)) to larger macromolecules exceeding 20,000 Da [e.g., human growth hormone (Fukushima et al. 2011; Ameri et al. 2014) and erythropoietin (Mitragotri et al. 1995)]. The literature however largely relies on in vitro experiments, and the majority of techniques have yet to gain substantial clinical impact due to various practical impediments. Still, many strategies including microneedling, radio frequency, and fractional lasers show promise and are increasingly gaining precedence in the dermatological clinic. In the following chapter, we focus on fractional laser-assisted drug delivery.

Fractional Laser-Assisted Drug Delivery

History

Laser-assisted drug delivery (LADD) was first described in 1988, initially practiced with fully ablative lasers that removed the stratum corneum

Table 1 Different types of physical enhancement techniques to enhance skin permeability, their proposed mechanism of action (MoA), and examples of delivered compounds

Type	Technique External driving energy force	Proposed MoA	Examples of delivered compound
Electroporation	High-voltage (≥100 V) electric pulses	Formation of transient transmembrane pores and disruption of cell membranes	ALA (177 Da) (Fang et al. 2004) Methotrexate (455 Da) (Lee et al. 2008) Bleomycin (1500 Da) (Gothelf et al. 2003) Vaccines (Sardesai and Weiner 2011)
Iontophoresis	Low-level electric current (max 0.5 mA cm^2)	Active ion flow driven by an applied electric field	ALA (177 Da) (Fang et al. 2004) Lidocaine (234 Da) (Marro et al. 2001) Methotrexate (455 Da) (Alvarez-Figueroa and Blanco-Méndez 2001) Botulinum toxin (150 kDa) (Pacini et al. 2007)
Laser techniques	(1) Tissue ablation (2) Photomechanical waves (3) Fractional tissue ablation	(1) Thermal removal of stratum corneum and cutis (2) Light energy converted to mechanical energy (3) Fractional ablative and non-ablative resurfacing	5-Fluorouracil (130 Da) (Lee et al. 2002; Wenande et al. 2016) ALA/MAL (177–182 Da) (Fang et al. 2004; Doukas and Kollias 2004) Lidocaine (234 Da) (Baron et al. 2014) Methotrexate (455 Da) (Lee et al. 2008)
Microdermabrasion	Mechanical abrasion	Exfoliative crystals or sandpaper, mechanically removing stratum corneum	5-Fluorouracil (130 Da) (Lee et al. 2006) Ascorbic acid (176 Da) (Lee et al. 2003) ALA (177 Da) (Fang et al. 2004) Insulin (5.8 kDa) (Andrews et al. 2011)
Microneedles	Mechanical introduction of an array of needles	Physical disruption of skin barrier with vertical microchannels through the skin	Ascorbic acid (176 Da) (You et al. 2010) ALA/MAL (177–182 Da) (Mikolajewska et al. 2010) Tretinoin (300 Da) (Kim et al. 2013)

(*continued*)

Table 1 (continued)

Type	Technique External driving energy force	Proposed MoA	Examples of delivered compound
			hGH (22.1 kDa) (Fukushima et al. 2011)
Pressure	Mechanical pressure force	External pressure	Caffeine (194 Da) (Treffel et al. 1993) Polyethylene glycol (400 Da)
Radiofrequency	High-frequency alternating current (~100 kHz)	Ionic vibrations within cells, causing localized heating and ablation	ALA (177 Da) (Park et al. 2016b) hGH (22.1 kDa) (Levin et al. 2005)
Sonophoresis	Ultrasound. Most often low-frequency waves are used in the range of 20–100 kHz. High-frequency sonophoresis may also be used (> 3 MHz)	Primary mechanism is considered transient cavitation in intercellular lipids. Also thermal effects, induction of convective transport, and mechanical effects due to pressure variation	ALA (177 Da) (Krishnan et al. 2013) Diclofenac (296 Da) (Rosim et al. 2005) Hydrocortisone (363 Da) (Griffin et al. 1967) EPO (48.0 kDa) (Mitragotri et al. 1995)

ALA aminolevulinic acid, *EPO* erythropoietin, *hGH* human growth hormone, *MAL* methyl aminolevulinate

in its entirety (Jacques et al. 1987). The concept of fractional photothermolysis was developed in 2004, using focused laser beams to create arrays of microscopic injuries in the skin while leaving intermediate skin intact (Manstein et al. 2004). The first devices operated at non-ablative wavelengths, generating localized tissue coagulation while preserving the SC layer (Laubach et al. 2006). In 2007, ablative fractional lasers (AFXL) were introduced. By generating small ablation channels in the skin, AFXL provided a seemingly straightforward and useful means of drug delivery to, and through, the skin (Hantash et al. 2007a; Haedersdal et al. 2010).

Fractional Laser Systems

Fractional laser systems comprise both non-ablative (NAFL) and ablative devices. The systems in most widespread use include erbium-doped yttrium aluminum garnet (Er:YAG: AFXL; $\lambda = 2940$ nm), carbon dioxide (CO_2; AFXL; $\lambda = 10{,}600$ nm), and erbium-doped glass (NAFL; $\lambda = 1530$–1560 nm) lasers, all operating in the absorption spectra of water (>1000 nm). Wavelength-dependent variations in water absorption result in vastly different tissue responses between devices. By operating in the near-infrared spectra where water absorption is fair, NAFLs result in localized tissue denaturation with heat deposition. Emitting in the mid-infrared spectra where water absorption is enhanced, AFXLs on the other hand generate greater energy depositions and localized tissue evaporation. The histological response to NAFL and AFXL treatments are depicted in Fig. 1.

AFXL

AFXL is an advantageous drug delivery technique as it provides predictable, controlled tissue responses and enables fast, sterile, and concurrent treatment of large skin areas (Hantash et al. 2007b; Taudorf et al. 2014). In AFXL-assisted drug delivery, there are two main parameters that can be adjusted for a given laser: laser channel

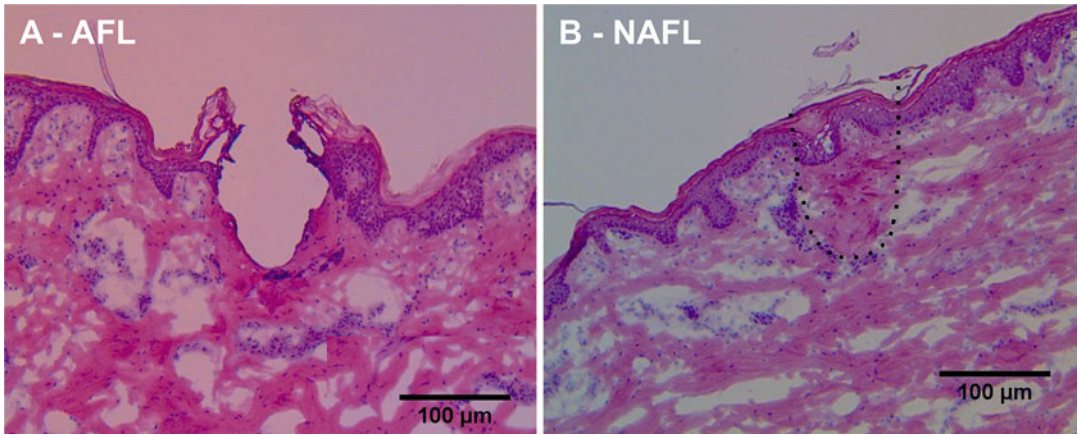

Fig. 1 Histological tissue responses in skin following AFXL and NAFL exposure. **A** Hematoxylin and eosin (H&E)-stained skin section illustrating a microscopic ablation zone (MAZ) following fractional ablative exposure using a 10,600 nm CO_2 laser (GME DotScan 10,600) at 30 mJ/microbeam, 1 millisecond pulse duration. **B** Hematoxylin and eosin (H&E)-stained skin section illustrating a microthermal zone (MTZ) following fractional non-ablative exposure using a 1540 nm erbium/glass laser (StarLux-500TM superficial Extra-Fast handpiece) at 26 mJ/microbeam, 15 millisecond pulse duration

density and depth. *Density* represents the ablated skin surface area, which is regulated by spot size and number of applied channels per unit skin area. *Channel depth* represents how deep laser channels extend into the skin and is mainly controlled by pulse energy. By calibrating laser density and depth, it is possible to (1) increase the accumulated drug amount in the skin to improve clinical efficacy and (2) adjust drug delivery rate, which can be used to reduce incubation time. Depending on the applied pulse energy and wavelength, residual thermal damage may vary; CO_2 lasers induce greater coagulation zones than Er:YAG lasers, due to lower water absorbance at 10,600 nm (800 cm^{-1}) (Marini and Krunic 2015) compared to 2940 nm (12,800 cm^{-1}) (Walsh & Deutsch 1989). Although the importance of the residual thermal damage is currently unknown, bleeding is less common after treatment with CO_2 lasers, a factor that may prove advantageous for AFXL-assisted drug delivery.

AFXL: Theoretical Concepts

The basic concept of AFXL-assisted cutaneous drug delivery can be illustrated by Fick's law of diffusion, which describes passive diffusion through a medium (flux) as $J = -D \times K \frac{\delta c}{\delta l}$. The simplest way to describe how AFXL impacts drug delivery is to assume steady-state conditions with a constant drug concentration in the vehicle and a negligible drug concentration at the bottom of the dermal layer. Flux is then constant and can be described as $J = D \times K \frac{\Delta C}{L}$. Under these assumptions, delivery of a particular drug depends on four conditions: (1) concentration gradient (ΔC), (2) partition coefficient between vehicle and skin (K), (3) diffusivity in skin (D), and (4) diffusion distance (L) (Franz 1983). By removing fractions of the SC, drug diffusion is facilitated by creating direct access to cellular epidermis and dermis. Over the laser channels, partition (K) thus occurs between vehicle and aqueous viable skin, enabling improved delivery of *hydrophilic* compounds. Upon leaving the vehicle, the drug enters directly into cellular skin where diffusivity (D) is higher than in SC, which results in a wide and rapid distribution of both small and large molecules around the channel. For therapeutic targets located in deeper dermis, the depth of the laser channels can be increased to minimize diffusion distance (L), in theory aiding delivery to deeper skin layers.

AFXL: Drug Delivery

AFXL has successfully enhanced delivery of the vast majority of drugs investigated thus far, including both lipophilic and hydrophilic molecules with molecular weights ranging from 177 to 13,300 Da. In preclinical trials, examined compounds include ALA, MAL (Haedersdal et al. 2010, 2011, 2014; Haak et al. 2012a, 2016; Forster et al. 2010; Huth et al. 2016), imiquimod (Lee et al. 2011a), ingenol mebutate (Erlendsson et al. 2015), diclofenac (Bachhav et al. 2011), methotrexate (Taudorf et al. 2015, 2016), 5-fluorouracil (Wenande et al. 2016), prednisolone (Yu et al. 2010), tranexamic acid (Hsiao et al. 2015), tretinoin (Chen et al. 2013), tetracycline (Chen et al. 2013), ascorbic acid (Hsiao et al. 2012), lidocaine (Bachhav et al. 2010a; Oni and Brown 2012), minoxidil (Lee et al. 2014a), diphencyprone (Lee et al. 2014a), small interfering RNA (siRNA) (Lee et al. 2014b), and polymeric microparticles containing triamcinolone acetonide (Singhal et al. 2016).

Drug delivery can be adjusted with laser density, and cutaneous drug accumulation increases with density to a point of saturation after which enhancement ceases. The specific relationship between laser density and skin deposition is best established for MAL, where laser density up to 5% coverage results in increased uptake, while no further enhancement is obtained from use of higher laser densities (Haak et al. 2016). MAL distributes horizontally up to 1.5 mm away from single laser holes, providing the rationale for why low laser densities may suffice (Haedersdal et al. 2010). Analogous results have been confirmed for other small-size drugs such as ingenol mebutate (431 Da) (Erlendsson et al. 2015), diclofenac (296 Da) (Bachhav et al. 2011), and tretinoin (300 Da) (Chen et al. 2012). At present, densities beyond 5% seem unwarranted for use in AFXL-assisted drug delivery, although more information concerning the parameter's effect on cutaneous diffusion pattern and biodistribution is currently needed (Haak et al. 2012b; Bachhav et al. 2010b).

Laser channel depth could in theory be regulated to target delivery to a specific, predetermined skin layer. However, studies have failed to agree on the relation between channel depth and drug deposition. While depth-dependent uptake has been described for hydrophilic compounds, e.g., methotrexate, (logP −1.85), and slightly lipophilic compounds, e.g., prednisone (logP 1.46) and diclofenac (logP 1.90), more hydrophobic drugs, such as lidocaine (logP 2.44), ingenol mebutate (logP 2.51), and imiquimod (logP 2.7), demonstrate no such relationship. Interstitial fluid and fibrin plugs have been reported to occupy the channels shortly after laser treatment, possibly inhibiting drugs and vehicles from filling deeper channel portions. Taking advantage of channel depth may thus depend on the individual drug's ability to partition and diffuse in the medium filling channels, and various methods to actively fill the channels are currently under investigation (Erlendsson et al. 2016; Waibel et al. 2016; Alexiades 2015). At present, however, the specific relationship between laser channel depth and drug accumulation remains to be clarified for individual drugs.

Clinical Applications of AFXL Drug Delivery

AFXL-assisted delivery has been shown to enhance topical treatment efficacy for different dermatological conditions, including actinic keratoses (AKs), non-melanoma skin cancer (NMSC), actinic cheilitis, topical anesthetic treatment, rythids, scars, wound healing, hemangiomas, vitiligo, and cutaneous infections such as onychomycosis, warts, and leishmaniasis (Vachiramon et al. 2016; Haedersdal et al. 2016; Park et al. 2016a; Gupta and Studholme 2016; Basnett et al. 2015; Ma et al. n.d.; Waibel et al. 2015). Principal findings for the most common of these indications are summarized below.

Neoplastic Lesions The bulk of evidence on dysplastic lesions centers on PDT with methyl aminolevulinate (MAL) for AKs, demonstrating *superior efficacy* with AFXL compared to PDT alone. Thus, randomized controlled clinical trials report AK clearance rates of 87–92% for AFXL-assisted PDT versus 61–67% PDT alone

3 months posttreatment (Choi et al. 2015a; Ko et al. 2014a; Togsverd-Bo et al. 2012). The long-term benefit of AFXL-assisted PDT versus conventional PDT is similarly supported for actinic cheilitis (85% vs. 29%) (Choi et al. 2015b) and Bowen's disease (79% vs. 45%) (Ko et al. 2014b). *Prolonged remission* after AFXL-assisted PDT has also been described with recurrence rates of 8–10% at 12 months follow-up compared to 22–27% with conventional PDT (Haedersdal et al. 2016). In addition to improved efficacy, AFXL may *reduce PDT incubation time*, and AK clearance rates after AFXL-assisted PDT with 2- (77%) (Choi et al. 2015a) and 1.5 h (71.4%) (Song et al. 2015) incubation are similar to conventional 3-h PDT (64.7–66%). Although *side effects occur more frequently* following AFXL-assisted versus PDT alone, treatments appear safe and side effects tolerable (Choi et al. 2015a, b; Ko et al. 2014a, b; Togsverd-Bo et al. 2012, 2015; Haak et al. 2015). For individuals taking immunosuppressants or with fields of severe actinic damage, AFXL-assisted PDT may further provide a *more potent therapy requiring fewer treatment courses* than conventional PDT (Togsverd-Bo et al. 2015; Helsing et al. 2013).

In contrast to AK treatment, there is not sufficient evidence supporting a beneficial effect of AFXL-assisted PDT for nodular basal cell carcinoma (BCC), although AFXL-assisted topical 5% 5-fluorouracil (5-FU) for Bowens disease and superficial BCC has shown initial promise (Hsu et al. 2016). Still, both AFXL-assisted 5-FU and PDT require further improvement to warrant recommendation for NMSC (Haak et al. 2015; Lippert et al. 2013). Figures 2 and 3 offer a practical, stepwise illustration of AFXL-assisted PDT using MAL (Fig. 2) and 5-FU (Fig. 3) for the treatment of multiple AKs.

Anesthetics AFXL prior to application of topical anesthetics has been shown to offer significant, subject-reported *pain reduction* compared to sham laser pretreatment in few clinical trials (Meesters et al. 2016; Tian et al. 2016). As an indication of the importance of vehicle formulation, greater benefit of AFXL has also been noted using articaine hydrochloride + epinephrine liquid solution (AHES) compared to topical lidocaine + prilocaine in cream (Meesters et al. 2016).

Aesthetics In addition to providing a new administration strategy, fractional laser-assisted delivery offers the potential for improved treatment outcomes with aesthetic and antiaging agents (Alexiades 2015; Mahmoud et al. 2015; Shin et al. 2012a). Of note, AFXL-assisted topical botulinum toxin A delivery has offered superior clinical efficacy for rhytides compared to AFXL-delivery of normal saline (Mahmoud et al. 2015). Superior outcomes following AFXL-delivery of cosmeceuticals are further reported for treatment of photoaging, dyschromia, and acne scarring (Alexiades 2015). AFXL-delivery of aesthetic agents remains new, however, and future studies are needed to reveal both its full potential and safety for this indication.

Scars Initial evidence on topical AFXL-assisted drug delivery in the treatment of scars appears promising (Ali and Al-Niaimi 2016). AFXL-assisted betamethasone is reported to offer a 50% clinical improvement average for treatment-resistant keloids (Cavalié et al. 2015), and enhanced appearance consisting of improved scar texture, reduced hypertrophy, and dyschromia are noted for hypertrophic scars following AFXL-delivery of triamcinolone acetonide (average improvement 2.73 on a 0–3 scale) (Waibel et al. 2013). For atrophic scars, combined AFXL + poly-L-lactic acid (PLLA) treatment has offered a reported average clinical enhancement of 2.18 (scale 0–3) (Rkein et al. 2014), and improvement following AFXL + autologous platelet-rich plasma is shown to be comparable to intradermal injection (Gawdat et al. 2014). Though a multitude of scar types may benefit form AFXL-assisted treatments, randomized controlled clinical trials are in the future nonetheless needed before recommendations can be made.

Onychomycosis Indicating increased efficacy with LADD, AFXL-assisted topical amorolfine treatment for *Trichophyton (T) rubrum*-, *T. mentagrophytes*-, and *Epidermophyton floccosum*-infected nail plates has demonstrated

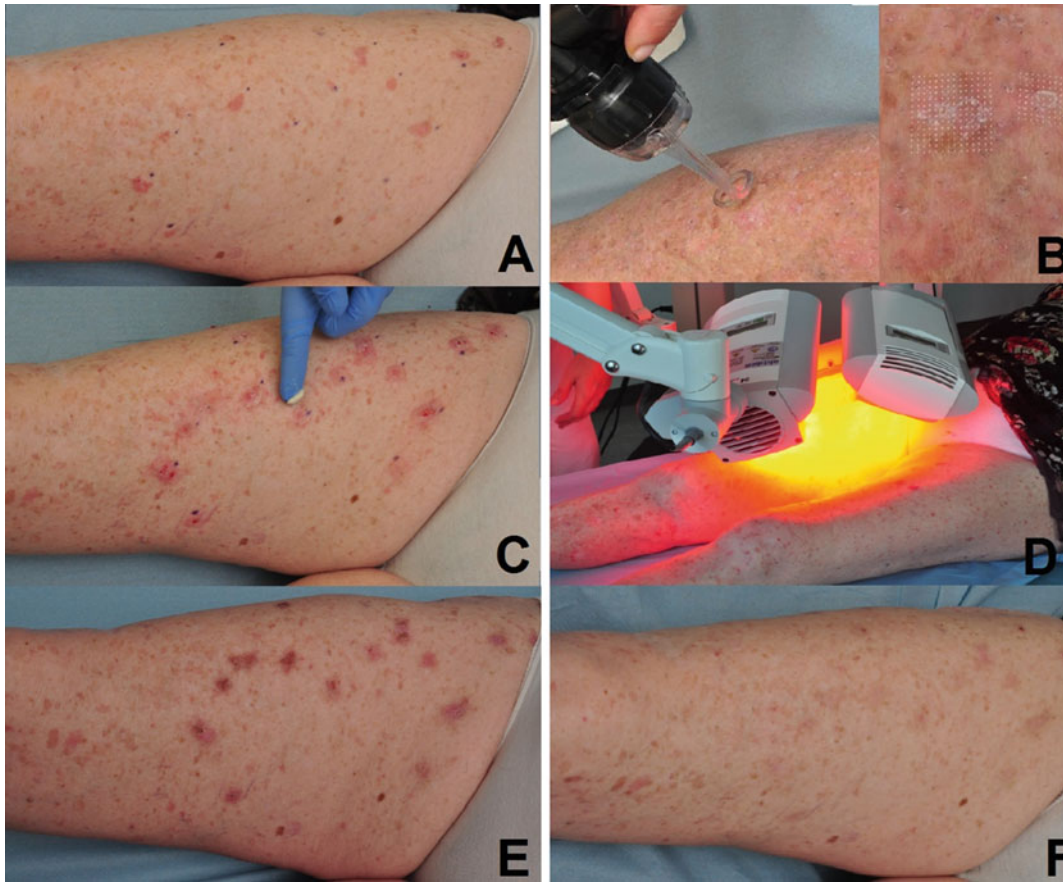

Fig. 2 A course of fractional CO_2 laser-assisted MAL-PDT for actinic keratosis (AK) (*Note:* Figs. 2 and 3 *illustrate two treatments performed concurrently on separate legs in a single patient*). A 72-year-old woman with multiple actinic keratoses (AKs) on her thigh receives targeted AFXL-assisted photodynamic therapy (PDT) using topical methyl aminolevulinate (MAL) cream. (**a**) Prior to PDT treatment. (**b**) During fractional CO_2 laser exposure of AKs at 20–40 mJ/microbeam depending on degree of hyperkeratosis. Close-up illustration of laser grid at 5% density (Deep FX, Lumenis® UltraPulse). (**c**) Topical application of MAL cream on AK lesions, left under occlusion for 3 h. (**d**) Illumination of treatment area using a red light source (630 nm, 37 J/cm (Surber and Davis 2002), 8 min, Aktilite®). (**e**) Local skin reactions demonstrated 14 days posttreatment. (**f**) Treatment effect demonstrated 10 weeks posttreatment

a 50% clinical and mycological cure rate 12 weeks after three treatment sessions (Lim et al. 2014a). More recently, fractional CO_2 laser-assisted delivery of terbinafine resulted in a 92% negative culture rate at 3 months and 80% rate 6 months after three treatment sessions (Bhatta et al. 2016). As with scar treatment, future randomized controlled trials are needed to substantiate the benefits of AFXL-delivery of antimycotic drugs.

NAFXL

Due to the weaker absorption by water, NAFLs do not establish direct access by microporation, but rather induce cylindrical zones of thermal damage, also known as microthermal zones (MTZs; Fig. 1). MTZs extend into underlying epidermis and dermis, leaving the SC with its low water content relatively intact (Laubach et al. 2006; Alexiades-Armenakas

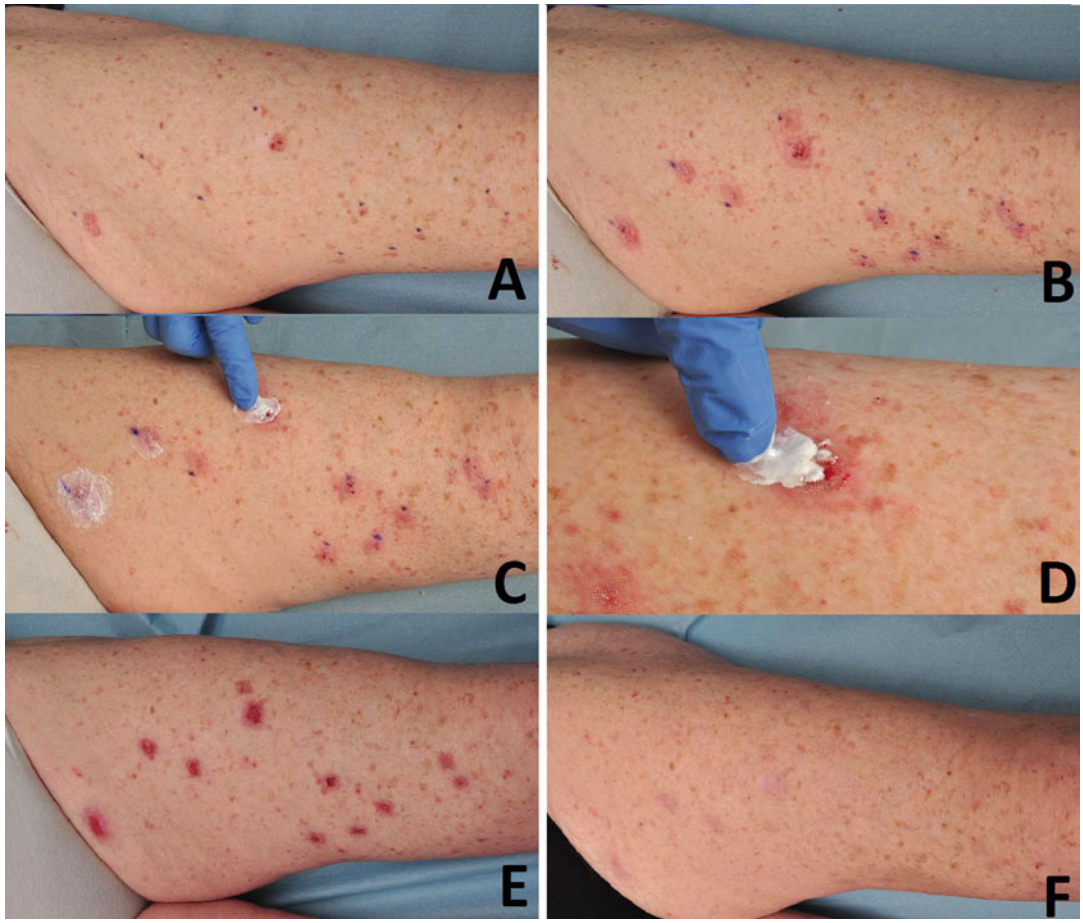

Fig. 3 A course of AFXL-assisted 5% 5-FU treatment for actinic keratosis (AK) (*Note:* Figs. 2 and 3 *illustrate two treatments performed concurrently on separate legs in a single patient*). A 72-year-old woman with multiple actinic keratoses (AKs) on her thigh receives targeted AFXL-assisted treatment with 5% 5-fluorouracil (5-FU) cream. (**a**) Prior to treatment. (**b**) After fractional CO_2 laser exposure of AKs at 5% density (Deep FX, Lumenis® UltraPulse). (**c** and **d**) Topical application of 5-FU cream on AK lesions, left under occlusion for 5 days. (**e**) Local skin reactions demonstrated 14 days posttreatment. (**f**) Treatment effect demonstrated 10 weeks posttreatment

et al. 2008; Ganti and Banga 2016). Similar to AFXL, depth and density of MTZs represent adjustable parameters during NAFL treatment (Kim et al. 2016) and may be proven valuable to regulate LADD. However, investigation of the relation between laser settings and drug uptake remains in its initial phase for NAFL.

Increased TEWL values after NAFL give indication of temporary disruption of the skin's barrier function (Ganti and Banga 2016; Lim et al. 2014b; Kim et al. 2016). However, the mechanisms by which NAFLs increase topical drug delivery remain unclear. Beyond generation of MTZs via NAFL's direct photothermal effect, possible theories include temporary expansion of cutaneous intercellular spaces by photomechanical wave (PW) with formation of epidermal vacuoles and dermal-epidermal junction disruption (Laubach et al. 2006; Ganti and Banga 2016; Lim et al. 2014b; Lee et al. 2002; Ruiz-Rodriguez et al.

2007). At this time, however, additional studies are needed before a mechanism of action for NAFL-assisted drug delivery can be definitively established.

NAFL Drug Delivery

Compared to AFXL, fewer studies to date examine the applicability of NAFL as a drug delivery strategy. In preclinical settings, NAFLs have been shown to enhance topical drug uptake of diclofenac, sumatriptan succinate, ALA, imiquimod, tretinoin, and peptides (Ganti and Banga 2016; Lee et al. 2016). In addition, clinical trials have indicated benefit of NAFL in combination with the following drugs: topical tretinoin (Prens et al. 2013), bimatoprost (Massaki et al. 2012), MAL (Ruiz-Rodriguez et al. 2007), ALA (Lim et al. 2014b), platelet-rich plasma (Shin et al. 2012b), tacrolimus (Chitvanich et al. 2016; Wolfshohl et al. 2016), and botulinum toxin A (Fan et al. 2016). Going forward, it is conceivable that NAFL's combined drug delivery capabilities and favorable safety profile will provide new avenues for fractional LADD. However, whether NAFL is as effective as AFXL in enhancing cutaneous topical drug penetration has yet to be seen.

Safety Aspects

AFXL-assisted delivery breaks the natural skin barrier and provides access to the viable skin and papillary plexus (Oni and Brown 2012). Local skin responses are often aggravated by the combined effects of laser and topical drugs, and proximate access to the vascular system may result in systemic toxicity and introduction of virulent pathogens from the cutaneous flora or from nonsterile formulations (Oni and Brown 2012; Togsverd-Bo et al. 2012). Topical preparations designed for intact skin often include ingredients not intended for intradermal or systemic entry. Though these risks are reported to be significantly lower compared to fully ablative procedures (Oni et al. 2013a; Zaleski-Larsen and Fabi 2016), introduction of such agents may cause unwanted toxicity and potential immunological sensitization, resulting in hypersensitivity or anaphylaxis.

The reduced impact on the SC by NAFL significantly decreases the severity and duration of treatment-related side effects (Hantash and Mahmood 2007). While NAFL- and AFXL-assisted drug delivery safety profiles have yet to be adequately examined in direct comparison, potential advantages of NAFL include lower downtime and reduced post-inflammatory hyperpigmentation, erythema, crusting, and pain (Fan et al. 2016; Yang and Lee 2011). NAFL further carries a lower risk of infection, and in contrast to AFXL, skin permeation of bacteria following NAFL is reported comparable to that of intact skin (Lim et al. 2014b). When determining which laser technique to apply during LADD, the improved safety profile of NAFL should however be balanced against the prospect of reduced efficacy as compared to AFXL (Laubach et al. 2006; Prens et al. 2013).

In sum, LADD should be exercised with caution, and it seems appropriate to consider the technique only in well-controlled settings, using formulations and doses suitable for local injection. When performing fractional LADD, providers must be observant of known, laser-related side effects, signs of infection, hypersensitivity reactions, the risk of systemic uptake and potential for adverse events not previously described. Growth factors and platelet-rich plasma are increasingly applied to reduce downtime after AFXL treatments, and whether they promote proliferation of aberrant cells has yet to be investigated; the long-term consequences of AFXL-assisted delivery are thus currently unknown, and clinical studies are needed to fully evaluate the safety profile of combination with individual topical drugs (Lee et al. 2011b; Ai et al. 2013).

Perspectives

The full potential of fractional LADD has yet to be realized. To date, a number of emerging studies demonstrate that AFXL not only enhances cutaneous and transdermal delivery of topical drugs but also therapeutic antibodies, macromolecules, nucleic acids, allergens, scaffold materials, cells,

as well as assist in delivery of light (Lee et al. 2013, 2014b; Yu et al. 2011; Oni et al. 2013b; Bachhav et al. 2013; Bach et al. 2012). Successful immunization with AFXL-assisted delivery of ovalbumin vaccines has been conducted, and the combination of AFXL with other drug delivery techniques such as iontophoresis, electroporation, and acoustic pressure wave is forthcoming. Topical application of systemic drugs not previously delivered through the skin is further made possible by AFXL and NAFL, providing new pharmaceutical treatment options and administration routes in the management of a multitude of diseases. Though still in its infant phase, fractional LADD thus holds promise as a useful, minimally invasive drug delivery system – both in dermatology and beyond.

Take Home Messages

1. Fractional ablative and non-ablative laser-assisted drug delivery (LADD) is increasingly used to enhance cutaneous uptake and intensify clinical efficacy of topical drugs.
2. In particular, current preclinical and clinical evidence substantiates the use of ablative fractional laser (AFXL) in photodynamic therapy for actinic keratosis.
3. Fractional LADD potentially offers increased potency of currently approved, topical treatment regimes.
4. When performing fractional LADD, providers must be observant of enhanced local skin reactions, potential for systemic uptake, signs of infection, hypersensitivity to drug formulation ingredients, as well as new adverse events not previously described.

Cross-References

- Biophotonics
- Laser Safety
- Transepidermal Drug Delivery with Ablative Methods (Lasers and Radiofrequency)
- Transepidermal Drug Delivery and Photodynamic Therapy

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Transepidermal Drug Delivery with Ablative Methods (Lasers and Radiofrequency)

Maria Claudia Almeida Issa and Paulo Santos Torreão

Abstract

The skin is almost impermeable for most hydrophilic and charged molecules. A molecular weight (MW) of 500 Da is generally accepted as the upper limit for passive diffusion of lipophilic molecules. Several strategies have been used to improve many drug penetrations into the skin: microneedle, ultrasound, and more recently transepidermal drug delivery (TED). TED is a technique based on applying a medication following an ablative method (CO_2 laser, erbium lasers, ablative radiofrequency). So far, there have been many reports about ablative fractional lasers, which create vertical channels to assist the delivery of topically applied drugs into the skin. In this chapter, ablative methods such as radiofrequency, lasers, and microneedling are going to be discussed. See also chapters ▶ "Transepidermal Drug Delivery: Overview, Concept, and Applications," ▶ "Transepidermal Drug Delivery and Photodynamic Therapy," and ▶ "Microneedling for Transepidermal Drug Delivery on Stretch Marks," this volume.

Keywords

Ablation • Transepidermal drug delivery • Transdermal drug delivery laser • Radiofrequency, resurfacing, and ablative methods

Contents

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Introduction

Fractional ablation of the skin is a special laser-skin interaction of photo-thermolysis first described in 2004. Fractional ablative lasers (erbium:YAG and CO_2) or other fractional ablative modalities such as radiofrequency ablate the skin in fractions. Microscopic vertical channels are created providing access pathways for large drug molecules topically applied that would not otherwise traverse the epidermal layer. The penetration of small molecules is also enhanced. The location, diameter, depth, and other characteristics of these channels can be controlled or manipulated by the settings and type of the laser or radiofrequency technology (Mitragotri et al. 1995; Manstein et al. 2004; Alexiades-Armenakas et al. 2008; Haak et al. 2011; Lin et al. 2014; Carniol et al. 2015; Forster et al. 2010).

The use of fractional ablative lasers for TED purpose, such as erbium:YAG and CO_2 lasers, has been reported in many different studies (Haerdersdal et al. 2010; Gómez et al. 2008; Stumpp et al. 2005; Wang et al. 2004; Lee et al. 2003; Baron et al. 2003). To form the micro-channels in epidermis, lasers produce vaporization, coagulation, other thermal effects in different proportions depending on the wavelength, and laser settings (Haerdersdal et al. 2010). Apart from lasers, RF device does not use light but another source of electromagnetic energy which is then transformed into thermal energy. To cause ablation with RF, it is necessary to ionize the oxygen, producing microplasma (sparks) on the skin surface. It is possible when there is thin layer (space) between the RF handpiece and the skin; therefore, micro-sparks are formed on the surface, producing micro-channels in the epidermis.

Different drugs can be used for TED and should be chosen accordingly to the disease to be treated, as will be described.

In 2010 a low-frequency and high-pressure US, called impact US, was created in order to enhance the penetration of substances with TED technique. These US waves act by propelling molecules through preformed channels. It depends on the previous use of an ablative method to perform its function, frequently named as ITED (impact US + TED) (Fig. 1a–c) (see chapter ▶ "Microneedling for Transepidermal Drug Delivery on Stretch Marks").

Histopathological Studies

In laser-treated tissues, through hematoxylin and eosin (H&E) staining, it is possible to observe vertical channels created by columns of vaporization. This is true for ablative fractional lasers that create a grid of microscopic treatment zones (MTZ) (Skovbølling Haak et al. 2011). Each MTZ is composed of the ablated channels, the microscopic ablation zones (MAZ), and a border of carbonization surrounded by coagulated tissue, the microscopic thermal zone (Sklar et al. 2014), that result from thermal damage by the light source (Taudorf et al. 2014).

The ideal parameters needed to create the skin channels absolutely vary on the laser type, device model, and settings. Also, the available data involving the best energies and channel depth for skin drug delivery is a bit contradictory. Nevertheless, there is some evidence showing that for hydrophilic and slightly lipophilic molecules, the drug uptake was channel depth-dependent, while lipophilic drugs have shown a channel depth independent uptake (Haedersdal et al. 2016; Wenande et al. 2017).

Haak et al. described the impact of laser treatment density (% of skin occupied by channels) and molecular weight (MW) for fractional CO_2 laser-assisted drug delivery. Ablative fractional treatment substantially increased intra- and transcutaneous delivery of polyethylene glycols (PEGs) in a MW that ranged from 240 to 4,300 Da. Increasing laser density from 1% to 20% resulted in augmented intra- and transdermal delivery, but densities higher than 1% resulted in reduced delivery per channel. Mass spectrometry indicated that larger molecules have greater intracutaneous retention than transcutaneous penetration (Haak et al. 2012; Haedersdal et al. 2014).

Skovbølling et al. conduced a histopathological study on an ex vivo animal skin model with a fractioned CO_2 laser (Medart, Hvidovre, Denmark), with the aim to establish a standard model to document the histological tissue damage

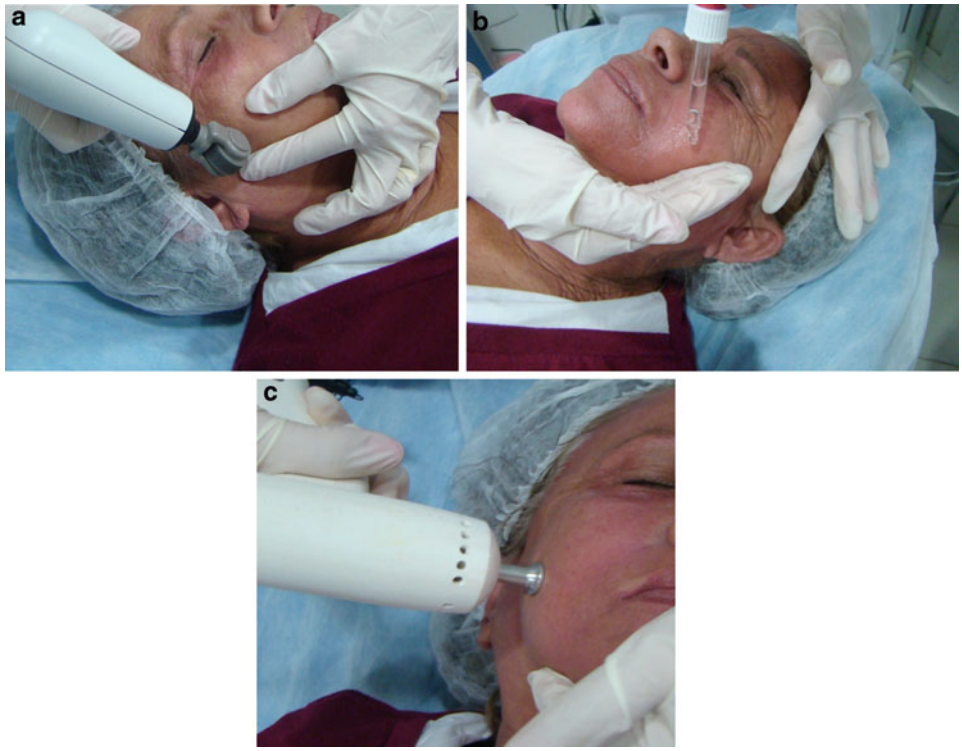


Fig. 1 (**a**–**c**) TED procedure in three steps: ablative RF, topical drug application, and impact US

profiles after ablative fractional laser treatment. It was shown that the studied laser produced a cone-shaped lesion with the base being the circular epidermal surface lesion and the apex pointing toward the dermis, and a proposed mathematical formula was able to predict cone volume. It was also demonstrated that ablation depth increased in a linear relation with increased laser energies, dermal ablation width increased slightly with increasing energies, and thickness of coagulation zone reached a plateau at a certain energy level (Skovbølling Haak et al. 2011).

Taudorf et al. conducted an animal ex vivo study with a 2,940 nm laser with the aim of establishing the impact of laser parameters, staked pulses and the tissue effects. It was shown that low pulse energy and high repetition rate required many stacked pulses at the same spot to induce ablation, whereas high pulse energy delivered by decreased pulse repetition rate and fewer stacked pulses led to ablation by less applied total energy. Ablation depth was likewise affected not only by total energy delivered by pulse stacking but also by variations in pulse energy, pulse repetition rate, and pulse duration. Low pulse repetition rate (Hz) and reduced number of stacked pulses are important to avoid progressive accumulation of residual heat by allowing the exposed tissue to cool and ablation plume to be evacuated between pulses, otherwise leading to shallow-wide craters instead of increasing ablation depth. It was also discussed that the advantage of using Er:YAG (2,940) laser instead of CO_2 laser is the possibility of creating purely ablated tissue with virtual no coagulation zone. Although the importance of the coagulation zone is not completely established, a thick coagulation zone may pose a significant induced barrier for molecules delivery (Taudorf et al. 2014). Brauer et al. demonstrated that fractional treatment results in untreated areas between the MTZs allowing a more rapid healing response (Brauer et al. 2014).

Banzhaf et al. have published that 100% of the channels created by a fractional ablative CO2

laser were kept opened for the first 30 minutes after the intervention. From this point on, there was a gradual decrease in the percentage of channels opened, with substantial decreased from 6 hours on (Banzhaf et al. 2017). Olesen et al. have shown that liquid based vehicles were better for transepidermal drug delivery purposes than cream or gel (Olesen et al. 2017).

It not possible to establish the parameters needed to perform the ideal drug delivery. Nevertheless when doing this treatment, it is important to take in account the laser type, the device model, the laser settings, and the desired effect. CO_2 lasers may create thicker coagulation zones, when compared to Er:YAG lasers. Treatment with high energy, very short pulse width, and low density may facilitate the penetration of drugs, specially for hydrophilic and slightly lipophilic molecules.

Indications

TED for Photodynamic Therapy

It has already been reported the use of ablative lasers (erbium:YAG or CO_2 lasers) prior to the application of methyl aminolevulinate (MAL) for PDT treatment (Haerdersdal et al. 2010; Shen et al. 2006). Some studies also describe the use of microneedling technique applied before the application of the photosensitizer (Donelly et al. 2008; Mikolajewska et al. 2010). See chapter ▶ "Transepidermal Drug Delivery and Photodynamic Therapy".

A recent study was conducted to evaluate and compare clinical effects induced by PDT (MAL-PDT with red light) alone versus PDT (MAL-PDT with red light) associated with TED using fractional ablative RF. The results showed that even reducing the incubation time of the photosensitizing agent (MAL) from 3 to 1 h, improvement of actinic keratosis and skin texture could be observed. TED + PDT was more effective in reducing the number of actinic keratosis lesions in the forearms compared to PDT alone. Moreover, an improvement in the texture and pigmentation was better observed on the side treated with the TED + PDT side (Kassuga et al. 2012).

Scars

Hypertrophic scars and keloids are disorders of the healing process in predisposed individuals in response to different types of injuries to the dermis, such as trauma, inflammation, surgery, burns, and even insect bites (Wolfram et al. 2009). Despite the increasing knowledge in the field of wound repair and collagen metabolism, its treatment remains a challenge for dermatologists and plastic surgeons. Clinically, hypertrophic scars are limited to the original site of injury, while the keloid exceeds this threshold and reaches the adjacent skin. Hypertrophic scars appear after 4 weeks of the triggering event, grow intensely for a few months, and then regress. In keloids, collagen production is 20 times greater than the normal healing (Wolfram et al. 2009) and rarely disappears spontaneously. It can be difficult to distinguish them in the initial growth phase.

Intralesional steroids are the first-line therapy (Al-Attar et al. 2006). The most widely used steroid is triamcinolone acetonide, a synthetic corticosteroid derived from hydrocortisone with potent anti-inflammatory action (Chrousos and Margioris 2003), whose mechanism of action is the inhibition of fibroblast proliferation and collagen synthesis, increase in collagenase production, and reduction of collagenase inhibitors (Al-Attar et al. 2006). It should be applied every 2–6 weeks until clinical improvement of the lesion or the appearance of local side effects that prohibits their use. The use of intralesional corticosteroid is painful and its distribution is not homogeneous.

Garg et al. (2011) demonstrated that the use of CO_2 ablative laser alone was not sufficient to permanently treat keloids, requiring intralesional application of triamcinolone every 3–4 weeks for a period of 6 months after ablation.

The use of steroid injections in keloid treatment is the most popular therapy modality for such problem because it is technically easy and less costly for the patient, not to mention the most satisfactory result compared with other proposed methods. On the other hand, injections are painful and sometimes intolerable, and it is also difficult to apply it evenly causing localized areas of atrophic lesion.

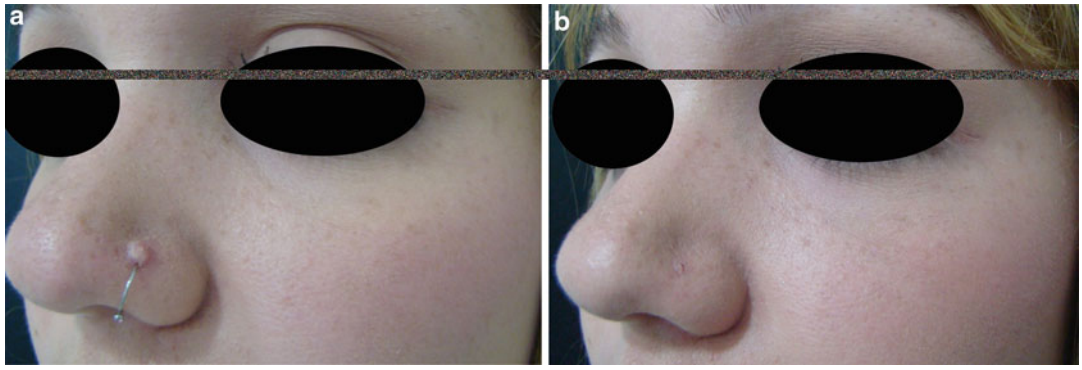


Fig. 2 (**a**, **b**) Hypertrophic scar on the nose: before and after one session (RF 45 W + triamcinolone 20 mg/ml + impact US, $50H_Z$, 80%)

Issa et al. (2012) conducted a study about transepidermal application of triamcinolone assisted by fractional RF associated with the impact US in the treatment of hypertrophic scars. The results showed improvement or complete resolution of the hypertrophic scars with an excellent aesthetic result. This technique was also considered less painful than regular injections (Fig. 2a, b). It is noteworthy that in another study, not published, using the same technique for the treatment of keloids, the same effectiveness was not observed.

Atrophic Striae

Striae are a common and easily recognized amendment, which rarely cause significant medical problems, but often are a source of stress for their carriers. The origin of striae is not well known. There are a number of therapeutic modalities, but none of them is considered effective, and no single therapy is considered essential to this problem. With high incidence and poor treatment results, there is a tendency in targeting the research for consensus and optimal treatment. Therapeutic strategies are numerous, and no single therapy has been more consistent than the others. The treatment of the striae remains a problem to dermatologists. Recent striae may be treated with topical medication, such as tretinoin, and show better results after various surgical procedures such as subcisions. Striae with longstanding course do not show the same result. The future of treatment strategies is encouraging, with advances in laser therapy. Many sources reported the use of lasers to diminish the appearance of striae (Elsaie et al. 2009; Bak et al. 2009).

A recent study about TED using 0.05% tretinoin cream after fractional ablative method (RF) (Issa 2013) has shown the efficacy in the treatment of atrophic white striae. When comparing the treatment of stretch marks located in the abdomen with ablative fractional RF alone or TED (RF + 0.05% tretinoin cream + US impact), the latter was more effective. Authors concluded that TED using ablative RF to permeate the tretinoin cream + impact US to increase this permeation is a new interesting method for white old striae, mainly on the breast (Fig. 3a, b).

Alopecia Areata

Alopecia areata (AA) is the most common cause of non-scarring alopecia. It is suspected to be an autoimmune disease with a genetic predisposition. Environmental and ethnic factors seem to be involved. It presents commonly as oval or circular plates of non-scarring hair loss. Steroids are widely used to treat AA, and intralesional triamcinolone is a very effective and painful method. Issa et al. (2012) reported five cases of AA treated with TED using ablative fractional resurfacing (CO_2 laser or RF) + triamcinolone + acoustic pressure wave US. Triamcinolone solution was dropped above the ablated area, and the impact US was applied just after the medication to push the drug into the skin. In all cases, patients exhibited an excellent improvement, and only one patient did not sustain the result after

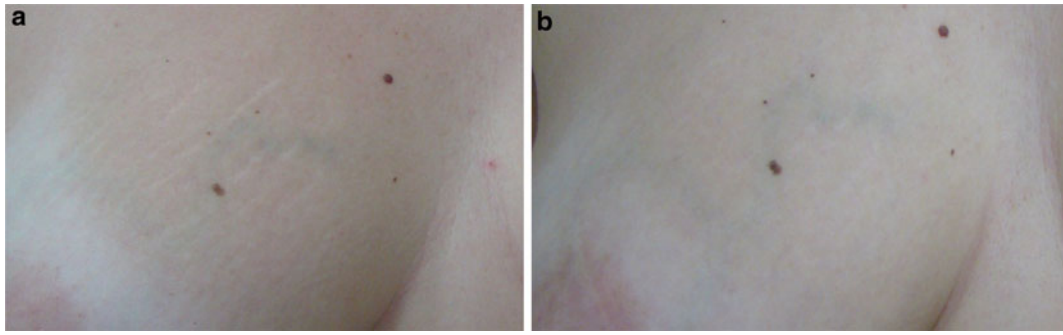


Fig. 3 (**a**, **b**) Atrophic white striae: before and after treatment (three sessions) with RF 45 W + topical tretinoin 0,05% cream + impact US, $50H_Z$, 80%

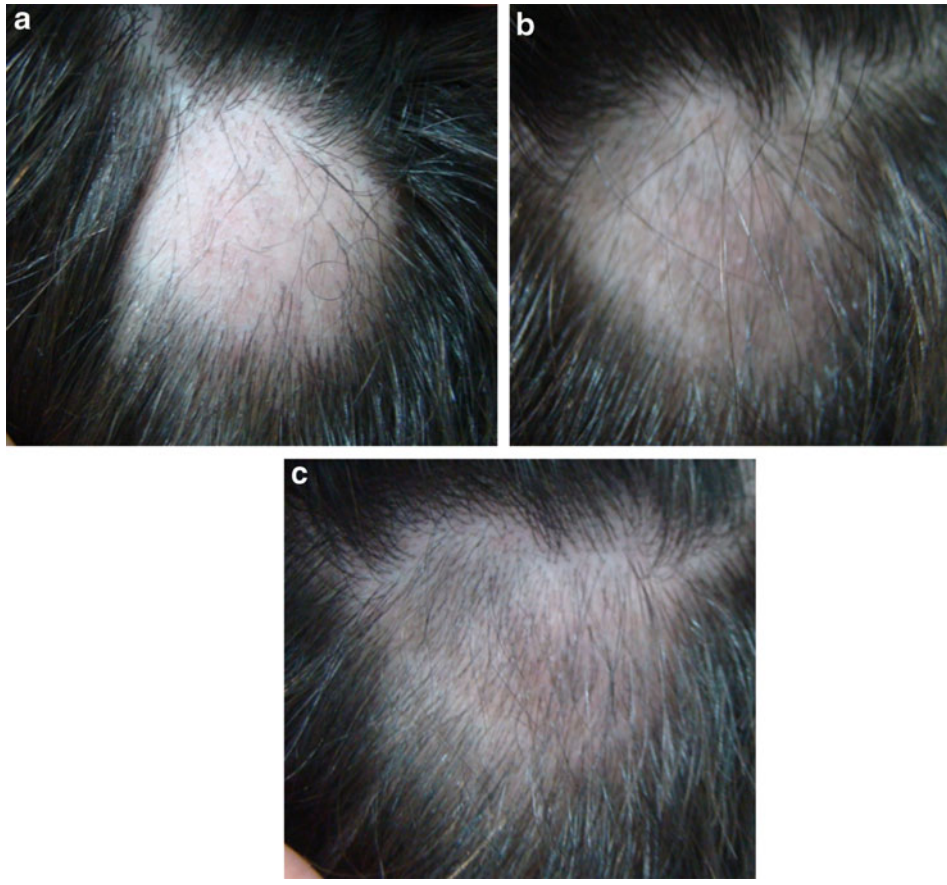


Fig. 4 (**a**–**c**) Areata alopecia: before, after one session, and after three sessions (RF 45 W + triamcinolone 20 mg/ml + US 60 HZ, 80%)

12 months of follow-up. In the cases of alopecia areata treated with CO_2 laser + triamcinolone + US, excellent results were reached with only one session (Fig. 4a–c). When using ablative RF + triamcinolone + US for AA treatment, good results were also reached, but more than one session was necessary. Authors observed a minimal clinical improvement in the patch treated with fractional

ablation CO_2 laser + triamcinolone without US, but any clinical improvement was observed on the patch treated with fractional ablation CO_2 laser isolated without applying triamcinolone or US.

TED for Photoaging and Melasma

The drugs used for photoaging and melasma treatment include tretinoin 0.05% cream, vitamin C (Farris 2005; Hsiao et al. 2012) 5–10% cream or serum alone or combined with other components such as ferulic acid (Waibel and Wulkan 2013), hyaluronic acid 5% for rejuvenation (Fig. 5a, b), and hydroquinone 4% associated or not with glycolic acid 10% cream for melasma.

In the case of melasma, CO_2 laser should be used at very low energy, only with the aim to produce micro-channels on the skin surface; good results with hydroquinone 4% cream were obtained without post-inflammatory hyperpigmentation (Fig. 6a, b) (study conducted by the author, not published yet).

In a split-face comparison study for photodamaged skin, CE ferulic acid formula (L'oreal-SkinCeuticals) was evaluated after fractional laser ablation showing decrease in postoperative recovery time and increase in neocollagenesis in the treated side (Waibel and Wulkan 2013). Topical vitamin C after laser fractional ablation was also assessed for this purpose, but further investigation is needed (Hsiao et al. 2012).

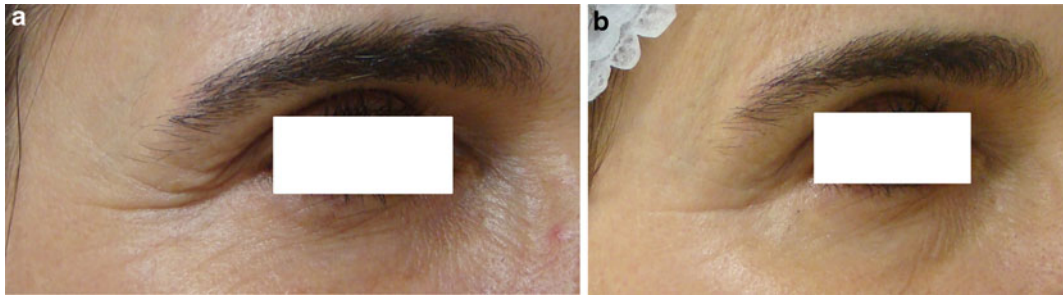
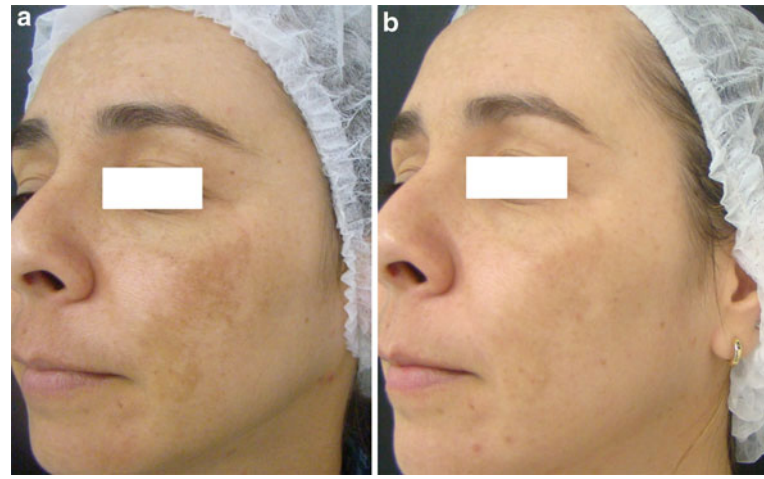


Fig. 5 (**a**, **b**) Photodamaged skin: before and after four sessions (RF 45 W + tretinoin 0,0 5% + vitamin C + US 50 Hz, 80%)

Fig. 6 (**a**, **b**) Melasma: before and after three sessions with CO_2 laser (10 mJ/pixel roller handpiece) + hydroquinone 5% cream + US 50 Hz, 80%



TED for Other Indications

There are some investigations about the use of growth factors for wound healing and the use of antifungal agents and antimicrobials to target infections (Brauer et al. 2014).

Axillary and palmar-plantar hyperhidrosis is another possible indication. It has been evaluated in some patients in a clinical trial in which botulinum toxin was applied through TED one side and through the standard injectable application on the other for comparison. In the first cases, reduction of sweating was observed in the iodine-starch test with both techniques (study about to be published).

Protocol of Application and Directions

The first step is to clean the skin using a cleanser without soap and chlorhexedine solution. The fractional ablative method is applied imediatly before the topcial medication, which is chosen according to the disease to be treaed. These can have its vehicle as cream, solution, or serum, with the same concentrations as the products used topically at home, with no need for high concentrations as in the case of solutions for peelings. If possible the impact US can be used. This is the last step with the aim to push the drug into the dermis through the channels preformed by the ablative methods, as a "hammering effect."

Post-procedure directions include proper hygiene with antiseptic soap, which starts after 8 h of the intervention. Avoid friction in the treated area, not wearing tight clothes. The use of healing moisturizer is advised, three to five times a day, avoiding crust formation. Patients are advised not to remove crusts, these should flake off spontaneously, and to avoid sun exposure throughout the healing time (7–14 days depending on the area). Topical photoprotection should be started at the third day. Oral photoprotection can also be indicated, and it is very important in cases of melasma.

Antiviral prophylaxis is advised with the usual treatment dose, starting 3 days before the procedure when treating the facial region, no matter the herpes simplex history.

Residual hyperpigmentation prevention can be done with the use of despigmentant substances for 3 weeks before the first session and restarting immediately after the skin recovery in each session, maintaining throughout the treatment period.

Side Effects

For all indications, side effects are usually less intense than those after fractioned ablative lasers isolated, as less density are used for TED. On the other hand, side effects can be related to the lasers and to the drugs applied. Moreover systemic side effect is a possibility. Adverse effects include redness, swelling, pain, crusting, and transient residual hyperpigmentation. Usually the topically applied medications, even retinoic acid, do not change the intensity of discomfort caused by the laser or RF previously used. Infections can also occur.

Conclusions

When using fractioned ablative methods for TED, it is possible to achieve a more homogeneous and convenient application of intralesional drugs, as well as more effective treatment comparing to the use of topical drugs or laser isolated.

According to the literature, TED with both RF and lasers (CO_2 and erbium) can promote good results in many different treatments. It seems that each method has its advantages and disadvantages. RF can be used in all phototypes as it does not cause dyschromia; on the other hand, CO_2 laser can bring better results with fewer sessions.

TED can be considered effective for many diseases and also for cosmetic indications.

Take Home Messages

1. TED through ablation methods produces micro-perforations in the epidermis, allowing the permeation of drugs topically applied into the skin through these micro-channels.

2. The ideal parameters needed to create the skin channels will absolutely vary on the laser type and device model. It has been shown, although, that the best results in drug permeation consist of an ablation of low density,
3. Many substances, cosmeceuticals or medicaments, can be used for TED purpose and are chosen according to the disease to be treated.
4. TED with ablative methods can be indicated for PDT, scars, striae distensae, areata alopecia, melasma, and photorejuvenation treatment, among others.
5. Better clinical results can be reached with TED comparing to laser isolated

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Transepidermal Drug Delivery and Photodynamic Therapy

Marianna Tavares Fernandes Pires, Livia Roale Nogueira, and Maria Claudia Almeida Issa

Abstract

Transepidermal drug delivery (TED) has been used with the aim to increase drug penetration into the skin, and its association with photodynamic therapy (PDT) is described for nonmelanoma skin cancer, porokeratosis, and photorejuvenation treatment. TED with PDT has been reported with fractional ablative methods (ablative laser and ablative radiofrequency), as well as with non-ablative lasers and with microneedles. TED with PDT is considered an effective method for actinic keratosis (field of cancerization) and for photorejuvenation.

Keywords

Photodynamic therapy • Photoaging • Rejuvenation • Skin drug administration • Drug delivery • Transepidermal drug delivery • Actinic keratosis • Field of cancerization

Contents

Introduction

Topical photodynamic therapy (PDT) is approved for nonmelanoma skin cancer, actinic keratosis (AK), basal cell carcinoma (BCC), and Bowen's disease (BD). However, conventional PDT can fail to treat thick lesions of NMSC, due to the limited penetration of the photosensitizer, which causes limited local bioavailability.

The stratum corneum is a significant barrier to percutaneous drug and particle absorption. The association of several modalities, such as ablative methods (fractional ablative lasers and

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fractional ablative radiofrequency), non-ablative lasers, and microneedling with PDT, has been studied, in the last years, with the aim to enhance photosensitizer penetration into the skin. This new concept of treatment is called transepidermal drug delivery (TED). TED and methyl aminolevulinate (MAL)-PDT has been studied, showing efficacy in AK and field cancerization treatment in immunocompetent and immunosuppressed patients.

It is also reported that there are benefits of skin rejuvenation during the field of cancerization treatment, such as improving skin texture, pigmentation, wrinkles, and laxity, after TED and conventional PDT, even when photosensitizer's incubation time is reduced. Some new protocols using TED and daylight PDT has been evaluated with good results.

Photodynamic Therapy

History

Oscar Raab, a German medical student, described the first photodynamic reaction in 1900. He reported that neither acridine orange, a dye, nor light alone was toxic to paramecia; however, when both were combined, they could induce cell death in less than 2 h. He realized this while using acridine orange in paramecia during a coincidental thunderstorm (Raab 1900). Later, von Tappeiner and Jesionek used eosin and light together to treat skin cancer, lupus vulgaris, and condyloma lata. At this time, they speculated that eosin, like acridine, after being incorporated into the cell, would produce a cytotoxic reaction when exposed to an adequate light source in the presence of oxygen (von Tappeiner and Jesionek 1903). In 1990s, Kennedy et al. described the use of aminolevulinic acid (ALA), a protoporphyrin IX (PpIX) precursor, to be topically applied avoiding systemic photosensitivity (Kennedy et al. 1990).

Since 1999, the US Food and Drug Administration (FDA) have approved photodynamic therapy (PDT) with topical ALA in dermatology for the treatment of actinic keratosis (AK). In Europe, methyl aminolevulinate (MAL), an esterified form of ALA with lipophilic properties, has been approved for the treatment of AK and basal cell carcinoma (BCC) since 2001 (Sandberg et al. 2008a). In 2004, MAL was approved for the treatment of AK in the United States. In 2006, MAL was approved in Brazil for AK and for superficial and nodular BCC. MAL is currently approved in many countries of Europe, Asia, and the Americas for the treatment of AK, BCC, and Bowen's disease. In 2009, MAL was also approved in Brazil for Bowen's disease.

Concept

PDT is defined as a photochemical reaction used to selectively destroy target tissue. Photodynamic action requires three components: light, oxygen, and a photosensitizer agent. When these components are combined, they become toxic to the target cell. It is a two-stage therapeutic technique that employs light activation of localized photosensitized tissue in an oxygen-dependent process, which initiates oxidative stress, inflammation, and cell death.

Photosensitizers

There are two main prodrugs used for topical PDT: ALA and MAL. Both are precursors of an endogenous photosensitizer, PpIX (Kalka et al. 2000). After topical application, photosensitizers are mainly absorbed into abnormal cells and converted, via the heme cycle, to PpIX. Abnormal tumor cells have low ferrochelatase activity and lower ferric ion concentrations, limiting the last step in the heme cycle, promoting the accumulation of PpIX (Ericson et al. 2008).

Porphyrin-based photosensitizer agents are selectively concentrated in human cancerous tissue and are activated by light in the presence of oxygen to initiate cytotoxic chemical reactions. Based on the comparison of fluorescence intensities on a same individual from normal and tumor tissues of the

same pigmentation, ratios of up to 15:1 for PpIX fluorescence between nonmelanoma skin cancer and normal skin have been reported with ALA sensitizer (Svanberg et al. 1994).

Source of Light

Light must be absorbed by PpIX, which has a peak of excitation in the blue-violet light part of the spectrum (Soret band) with maximum at 410 nm. This part of the spectrum has very poor tissue penetration (1 mm). For this reason, red light (630–635 nm), which is also absorbed by PpIX and has deeper penetration (up to 6 mm), is usually used.

PDT is based on the chemical reaction in which PpIX is photoactivated by different sources of light, including incoherent, continuous-wave red or blue light, intense pulsed light (IPL), as well as pulsed dye laser (PDL) (Friedmann et al. 2014). The light-emitting diode (LED) is the main source of light for topical PDT treatment (Moseley et al. 2006) with easier maintenance and lower costs when compared with lasers (Brancaleon and Moseley 2012).

Recent studies have shown that natural daylight can be successfully used for topical PDT. Daylight PDT (DLPDT) is a new modality for actinic keratoses (AKs) and field of cancerization treatment. DLPDT is considered as effective as conventional PDT with the advantage of being almost painless (Rubel et al. 2014) (see chapter ▶ "Daylight Photodynamic Therapy and Its Relation to Photodamaged Skin" – author Beni Grinblat).

Indications

Topical PDT is approved for nonmelanoma skin cancer, actinic keratosis (AK), basal cell carcinoma (BCC), and Bowen's disease (BD). Regarding squamous cell carcinoma, although occasionally resulting in initial encouraging results, it is associated with unacceptable recurrence rates, and PDT would not be recommended (Ericson et al. 2008).

There are many randomized, controlled, and open studies in which the role of topical PDT in AK, BD, and BCC has been examined, and both British and European guidelines for the use of PDT are available (Morton et al. 2013a, b). PDT is a very important and effective treatment for field of cancerization, and many authors reported not only cure of AKs but also skin rejuvenation with texture, wrinkle, and pigmentation improvement on the area treated. For this reason, PDT has been also studied and indicated for skin rejuvenation (see chapter ▶ "Photodynamic Therapy for Photodamaged Skin" – Issa e Ferola).

1. Actinic keratosis

AKs are common epidermal lesions associated with chronic exposure to ultraviolet (UV) radiation, which have the potential of progressing to squamous cell carcinoma (SCC), with the highest incidence in the aged and fair-skinned population (Traianou et al. 2012). AK is the second most common diagnosis by dermatologists in the United States, with direct cost of therapy estimated at more than US$ 1 billion per year and indirect cost nearing US$ 300 million (Neidecker et al. 2009).

The early identification and treatment of AKs are necessary because it is very difficult or even impossible to predict which lesions may become invasive and develop into metastatic SCC. The fact that 65–97% of squamous cell carcinomas develop from AKs or areas of field cancerization highlights the need for effective treatment of these lesions (Rosen and Lebwohl 2013).

The aim of photodynamic therapy is not only to treat clinical or visible AKs but also to treat subclinical lesions. PDT may also have the potential to decrease expression of early markers of cutaneous neoplasia Ki-67 and p53, as demonstrated in multiple studies following methyl aminolevulinate-PDT (MAL-PDT) using incoherent red light (Bagazgoitia et al. 2011). In comparative studies between PDT and cryotherapy for AK treatment, clinical results were equal or even better, with superior

cosmetic outcome, in the cases reported in PDT groups (Tarstedt et al. 2005). Some authors reported better results and cosmetic outcome with MAL-PDT compared with trichloroacetic acid (TCA 50%) for AK treatment (Di Nuzzo et al. 2015).

2. Bowen's disease

Bowen's disease (BD) is an in situ carcinoma, clinically presented as an erythematous-squamous plaque with sharply demarcated, irregular borders. Sometimes, it can be a verrucous, hypo- or hyperpigmented, and, eventually, exulcerated lesion. Its evolution is slow and progressive, generally asymptomatic. However, local pain, irritation, pruritus, and bleeding can occur (Moraes 2002).

Treatments include surgery, radiotherapy, 5-FU, curettage, cryotherapy, and PDT. To choose the best option, dermatologists should take into account the patient's age and frailty, comorbidities, and lesion's body site. PDT is well recommended to treat lesions located in areas that are difficult to heal, such as lower limbs (Cox et al. 2007).

In comparative studies, ALA-PDT has been shown to be more effective and cause less adverse effects than cryotherapy or 5-FU for the treatment of BD (Morton et al. 1996). A large randomized controlled trial comparing topical MAL-PDT with either cryotherapy or 5-FU reported that a sustained response after 12 months following treatment was 80% for PDT, 67% for cryotherapy, and 69% for 5-FU with a superior cosmetic outcome in the PDT group (Morton et al. 2006).

3. Organ transplant recipients

The relative risk of SCC is estimated to be 65- to 250-fold in organ transplant recipients (OTRs) compared with the rest of the population, increasing with time after transplantation and depending on the type of organ transplant (Hartevelt et al. 1990).

Topical PDT may potentially be used in the treatment of organ transplant recipients who are at markedly increased risk of developing dysplastic skin changes and nonmelanoma skin cancers. Initial cure rates of topical PDT for AK and BD in immunosuppressed patients were equivalent to those in immunocompetent subjects, but with longer-term follow-up, higher relapse rates were reported (Dragieva et al. 2004). The PDT protocol for immunosuppressed patients are the same used for immunocompetent patients, but the number of sessions in one treatment and the interval between treatments may vary for better results..

4. Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common skin cancer. It is derived from non-keratinizing cells that originate in the basal layer of the epidermis. There are more skin cancers in the population of the United States than there are all other cancers combined, and it is estimated that one in five Americans will develop skin cancer during their lifetime (over 95% will be non-melanoma skin cancers) (Rigel et al. 1996).

BCC should not be considered the first treatment option in some conditions, due to the high risk for complications (Morton et al. 1998; Kaviani et al. 2005; Lien and Sondak 2011). These conditions include patient's age (24 years old or younger), immunocompromised patient, genetically predisposed patients (e.g., Gorlin's syndrome), recurrent or incompletely treated BCC, lesions on nose and lips (including nasofacial sulci and nasolabial folds) or around the eyes (periorbital) or ears, flat lesion, hard thickened skin (appearance of morphoeic BCC), poorly defined margins, some histological subtypes (morphoeic, micronodular, infiltrative, and basosquamous), and lesions greater than 2 cm in diameter below the clavicle or greater than 1 cm above the clavicle (Table 1). Furthermore, very heavily pigmented BCCs are not recommended for PDT because pigment might cause difficult light absorption into tumoral cells. Likewise, morphoeic, infiltrative BCCs are aggressive tumors and do not selectively accumulate PpIX following ALA or MAL application. They do not respond well to topical PDT and should be avoided (Lien and Sondak 2011).

PDT is a minimally invasive procedure, which achieves acceptable short-term cure rates for BCC. Topical MAL-PDT is considered effective

Table 1 Risk factors for basal cell carcinoma

Clinical risk factor	Low risk	High risk
Location and size	Low-risk area < 20 mm[a] Middle-risk area < 10 mm[b] High-risk area < 6 mm[c]	Low-risk area $> = 20$ mm[a] Middle-risk area $> = 10$ mm[b] High-risk area $> = 6$ mm[c]
Primary and recurrent	Primary lesion	Recurrent lesion
Tumor subtype	Nodular, superficial	Aggressive growth pattern

Legend: [a]**Low-risk area**: Trunk and extremities, excluding pretibial surface, hands, feet, nail, and ankles
[b]**Middle-risk area**: Cheeks, forehead, neck, jawline, scalp, and pretibial surface
[c]**High-risk area**: Central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible preauricular and postauricular skin, temple, ear, genitalia, feet, nail unit, ankles, nipples, and areola

to treat superficial BCC and thin nodular BCC due to its deeper tissue penetration, comparing to ALA. However, nodular BCC greater than 2 mm in histological thickness are unlikely to respond well to topical PDT (Morton et al. 1998).

A randomized multicenter open non-inferiority study compared MAL-PDT with standard excision surgery for superficial BCC (8–20 mm diameter). Similar high efficacy rates were seen at 12 months for the two treatment arms with 9.3% recurrence for PDT and no recurrences in the surgery group. However, superior cosmetic outcome was reported with PDT (Szeimies et al. 2008). PDT has equivalent efficacy and superior cosmetic outcome when compared with cryotherapy for both superficial and thin nodular BCC (Wang et al. 2001).

5. Photodamaged skin

Aging is a complex and multifactorial process that occurs in all individuals, influenced by environmental, hormonal, and genetic factors. The photoaging, or extrinsic aging, is due to exposure to many different environmental factors, mainly the ultraviolet (UV) light. The clinical signs associated with photoaging include laxity, wrinkles, dyspigmentation, a yellow hue, a leathery appearance, telangiectasia, and cutaneous malignancies in the sun-exposed area such as the face, neck, and dorsum of hands (Chung et al. 2003).

The main constituent of dermal extracellular matrix (ECM) is collagen, particularly collagen types I and III, which provides skin's strength and resilience. However, in photoaged skin, the production of procollagen, the precursor of collagen, is reduced. Transforming growth factor-b (TGF-b) is the major regulator of ECM synthesis in human skin. It stimulates fibroblast proliferation in the dermis to enhance collagen synthesis. An impaired TGF-b/Smad pathway, caused by UV irradiation, might play a role in the pathology. UV radiation is also responsible to induce the expression of matrix metalloproteinases (MMPs), mainly MMP-1, promoting collagen degradation (Chung et al. 2003).

Many significant histological changes in photodamaged skin are reported after PDT treatment, photodynamic rejuvenation. Epidermis modifications include reduction of the epidermis thickness (stratum corneum) and atypical keratinocytes. The expression of p53, an early marker of epidermal carcinogenesis, not expressed in normal skin, is also reduced after PDT. Dermis modifications include reduction in elastotic material, increase of procollagen and collagen types I and III, and decrease of collagen and elastin degrading metalloproteinases (MMP-1, MMP-3, and MMP-12) expression. All these histological changes in epidermis and dermis can explain the clinical effects observed after PDT treatment (Sjerobabski Masnec and Situm 2014; Hai-yan Zhang et al. 2014; Orringer et al. 2008; Park et al. 2009).

Disadvantages of topical PDT are largely related to minor and expected adverse events following the procedure. Pain and erythema occur during and after procedure. Mild crusting and edema also occur in variable degree. High ALA concentration and photosensitizer's long incubation time often results in an increased severity of side effects, such as severe pain, erythema, and edema (Hai-yan Zhang et al. 2014).

Procedure and Follow-up in Conventional PDT (MAL-LED)

The area to be treated is prepared with a superficial curettage. Topical anesthesia with lidocaine, prilocaine, or tetracaine has been found to provide insufficient pain relief and may also interfere with PDT efficacy because of pH changes (Borelli et al. 2007). MAL should be applied on the skin on the area to be treated, with 1 mm thick layer on top and 5 mm around AK, BCC, or Bowen's disease. The area should be occluded with plastic film and laminated paper for 3 h before illumination with red light with a dose of 37 J/cm^2. One session is recommended for AK and two sessions 1 week apart for BCC and Bowen's disease. Assessment is recommended at 3 months, and re-treatment is carried out with a second treatment cycle if indicated based on clinic and histological grounds. Patients treated for Bowen or BCC are followed up up to 5 years.

Transepidermal Drug Delivery

The skin is the largest organ of the human body occupying an area of 2 m^2 and 15% of an adult body mass, receiving approximately 1/3 of the blood circulating through the body. The stratum corneum is a significant barrier to percutaneous drug and particles absorption. Several modalities, such as ablative methods (fractional ablative lasers and fractional ablative radiofrequency), non-ablative lasers, and microneedling, have been studied to reduce this barrier to enhance drug penetration through the skin (Zhang et al. 2015; Sklar et al. 2014).

1. Ablative and non-ablative methods

Fractional ablative laser produces microchannels in epidermis, increasing topical drug permeation into skin (Sklar et al. 2014). There are two main types of ablative fractioned lasers that are used to assist drug delivery: erbium/yttrium-aluminum-garnet (Er:YAG) laser and the carbon dioxide (CO_2) laser. These fractioned lasers create microscopic vertical channels of ablation surrounded by coagulated tissue. A normal healthy tissue is preserved between channels (Sklar et al. 2014; Manstein et al. 2004). These channels are preformed in the skin immediately before applying the medication chosen for the treatment. The depth and diameter of these channels vary according to the type of laser and to the laser's parameters, which are directly related to laser-tissue interaction.

Many different substances have been used for TED in the last years. Topical anesthesia (lidocaine) had been reported after Er:YAG laser treatment with the aim to decrease needle prick pain (Baron et al. 2003). This method has been used for actinic keratosis treatment using 5-FU (Lee et al. 2002), imiquimod (Lee et al. 2011), and PDT (Kassuga et al. 2011). Lee et al. (2011) reported increased transdermal delivery of 5-FU following pretreatment with Er:YAG and CO_2 laser for actinic keratosis (AK). Kassuga and Issa (Kassuga et al. 2011) described better results associating MAL with ablative RF for AK treatment.

The use of triamcinolone solution topically applied just after fractional ablative methods has demonstrated very good results for hypertrophic scars and areata alopecia (Issa et al. 2013a, 2015). Issa et al. (2013b) reported that topical delivery of retinoic acid 0.05% cream after fractional ablative RF was effective and safe for stretch marks treatment. Other substances such as vitamin C and diclofenac have also been evaluated (Hsiao et al. 2012; Bachhav et al. 2011). Issa et al. are investigating the use of botulinum toxin for palmar hyperhidrosis after CO_2 laser (not published yet).

Non-ablative fractional lasers promote a controlled dermal heating without significant structural damage of the epidermis. They have been described as an option for TED with a different mechanism of action. It involves lost of cohesion between cells in the epidermis, facilitating drug penetration (Lim et al. 2014a). Some authors described the pretreatment with a 1550 nm fractional erbium glass laser for AK treatment and concluded that incubation time could be reduced due to the greater ALA uptake (Lim et al. 2014b).

2. Microneedling

Microneedling is a recent therapy in dermatology. They are micrometer-scale needles, which cause a minimal skin trauma, promoting the release of growth factors and stimulating the formation of new collagen and elastin in the papillary dermis (Aust et al. 2008). They disrupt the skin barrier in a minimally invasive and painless way with minimal or no bleeding and therefore can be considered a new technique for TED (Gill and Prausnitz 2007; Wermeling et al. 2008; Mikolajewska et al. 2010). During TED treatment, the needles perforate the stratum corneum and create microconduits (holes). It has been shown that rolling with a dermaroller (192 needles, 200 μm length, and 70 μm diameter) over an area, for 15 times, will result in approximately 250 holes/cm^2. The microneedles are usually designed in arrays in order to improve the surface contact with the skin. Due to microscopic projections on microneedle arrays, compounds can be delivered either precisely into or just beyond the epidermis. Delivery using microneedles is almost pain-free in comparison with hypodermic needles.

For PDT treatment, microneedles create microperforations in the stratum corneum, modifying the intercellular lipids, increasing the photosensitizer diffusion, and therefore increasing PpIX production. It is reported that microneedle associated with PDT improves skin quality, promoting skin rejuvenation (Torezan et al. 2013; Clementoni et al. 2010). Torezan et al. used 1.5-mm long microneedles to create virtual holes and facilitate MAL penetration. The MAL cream was applied before microneedling to mechanically promote its penetration. It was demonstrated that microneedles-assisted PDT resulted in greater improvement of the photoaging. The procedure was a safe and effective method and had a better cosmetic result comparing to conventional MAL-PDT. They reported better improvement in the quality of the skin (pigmentation and fine lines), but the reduction in the number was similar to the isolated PDT (Torezan et al. 2013). Clementoni et al. (2010) reported the association of microneedling with PDT (red light) and intense pulsed light for photodynamic rejuvenation.

Transepidermal Drug Delivery and Photodynamic Therapy

Conventional PDT can fail to treat thick lesions of NMSC. It occurs due to the limited penetration of the photosensitizer, which causes limited local bioavailability, resulting in insufficient PDT response in deep tissue layers. For this reason, some new studies evaluated the effectiveness of associating TED and PDT with the aim to improve photosensitizer's penetration into the skin (Haak et al. 2012; Sandberg et al. 2008b).

Procedure in TED Associated with Topical Conventional PDT

When associating ablative methods and PDT, the protocol is the following: The lesion is prepared with a superficial curettage, and the ablative laser or ablative RF is applied on the area to be treated, with low density. MAL is applied immediately after laser or RF, and it occluded with plastic film and laminated paper. The incubation time can be reduced for 1–2 h (Issa et al. 2013a). Illumination with red light, dose of 37 J/cm^2, is performed, as in the standard conventional PDT protocol (Fig. 1).

Literature Review and Author's Experience

Some studies have been published about PDT associated with an ablative method for nonmelanoma skin cancer, extramammary Paget's disease, and porokeratosis treatment with good results (Haak et al. 2012; Fukui et al. 2009). AFXL-assisted MAL-PDT has been studied in clinical practice, showing benefit to immunocompetent patients and immunosuppressed patients with AK and field cancerization (Paasch and Haedersdal 2011; Haedersdal et al. 2011; Togsverd-Bo et al. 2012).

Kassuga and Issa et al. (Kassuga et al. 2011) reported that the incubation time could be reduced for 1 h when associating ablative RF before topical PDT for AK treatment, maintaining the AK

Fig. 1 *Step 1*: Lesion is prepared with a superficial curettage; *Step 2*: Fractional ablation; *Step 3*: MAL is applied in the region to be treated; *Step 4*: Occlusion with plastic film and laminated paper; *Step 5*: Red light illumination

cure rate and with better skin rejuvenation (Fig. 2.) The authors also have good experience with CO_2 laser before PDT for AK field of cancerization treatment (Figs. 3 and 4).

Three groups of AFXLs was described for TED x PDT: CO_2-laser (10,600 nm), Er:YAG (erbium/yttrium-aluminum-garnet, 2,940 nm) laser and Er:YSSG (yttrium-scandium-gallium-garnet, 2,790 nm) laser. These lasers create vertical channels that facilitate the penetration of topically applied MAL into superficial and deep skin layers and promote an intensified PDT response (Haak et al. 2012; Paasch and Haedersdal 2011; Haedersdal et al. 2011).

It is reported that once the stratum corneum is disrupted by ablative fractional laser treatment, there will be no further benefit from drilling deeper laser channels for the delivery of topical photosensitizer. For this reason, some authors reported good results with erbium laser, which is not able to promote deep channels as CO_2 laser does (Haak et al. 2012). The benefit of deeper channels produced by CO_2 laser comparing with erbium lasers is still questioned.

Pretreatment with fractional laser resurfacing may be a new alternative technique to improve the efficacy of PDT for actinic cheilitis by increasing the bioavailability of MAL within the skin and enhancing the PDT response (Choi et al. 2015).

Very recently, daylight photodynamic therapy (DLPDT) was approved for AK treatment and field of cancerization with similar efficacy and less side effects, with few or no pain, comparing to conventional PDT (Morton et al. 2015). Clinical improvement in texture and pigmentation can also be observed after DLPDT treatment and for this reason can be indicated for skin rejuvenation. DLPDT is contraindicated for skin tumors.

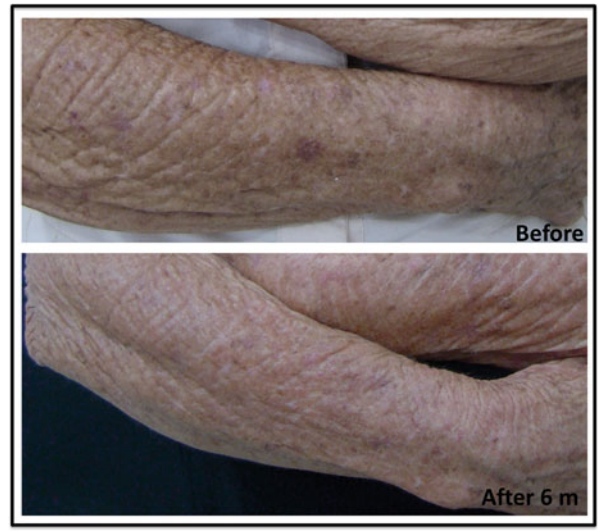

Fig. 2 Before and after 6 months: TED + PDT using ablative RF + PDT for AK (field of cancerization) on forearms

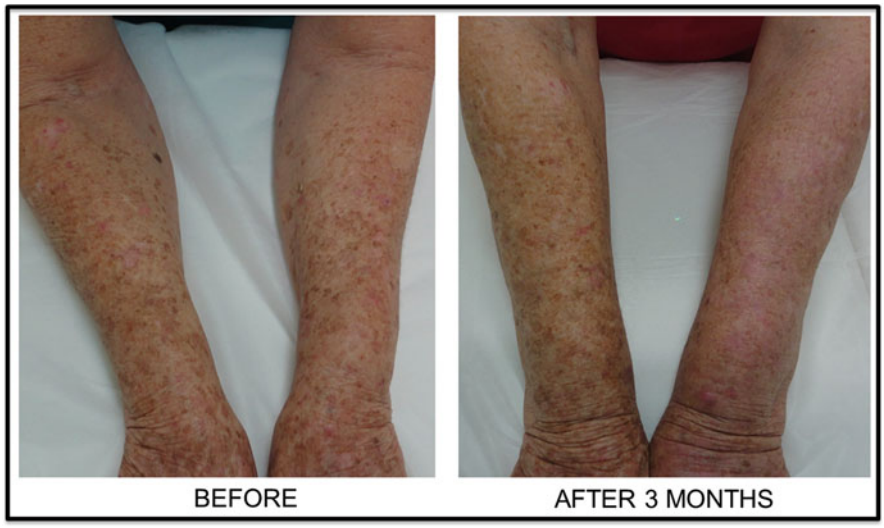

Fig. 3 Before and after 3 months: comparison of the standard PDT (3 h) on right arm to the CO_2 laser + PDT with reduced incubation time (1 h) on left arm

The protocol for DLPDT isolated is already established, and a superficial curettage is done similar to the conventional PDT. However, a chemical sunscreen should be applied on the skin 15 min before applying MAL (not covered). Patient should be indoor for maximum 30 min before daylight exposure for 2 h. DLPDT with TED is a very new modality of treatment, and very few data are reported. DLPDT associated with TED seems to have better results for photorejuvenation, comparing with DLPDT isolated.

According to authors, experience to both microneedling and laser is safe to be used associated with DLPDT, but it seems that CO_2 laser before DLPDT has better results comparing to microneedling associated with DLPDT for field of cancerization treatment (Fig. 5).

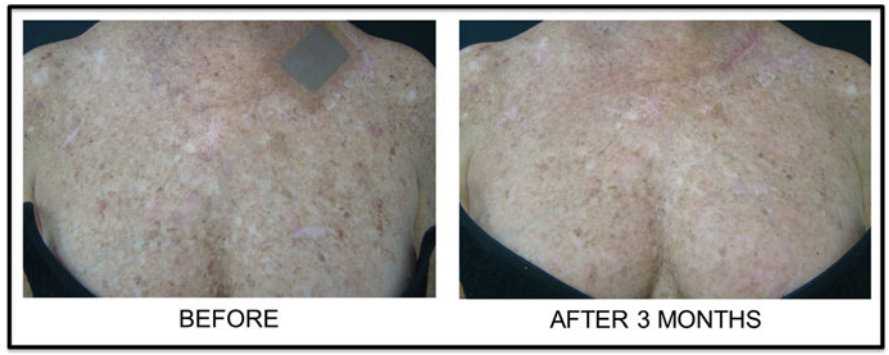

Fig. 4 CO_2 laser associated with red light PDT (1 h incubation time) for field of cancerization treatment in an immunosuppressed patient

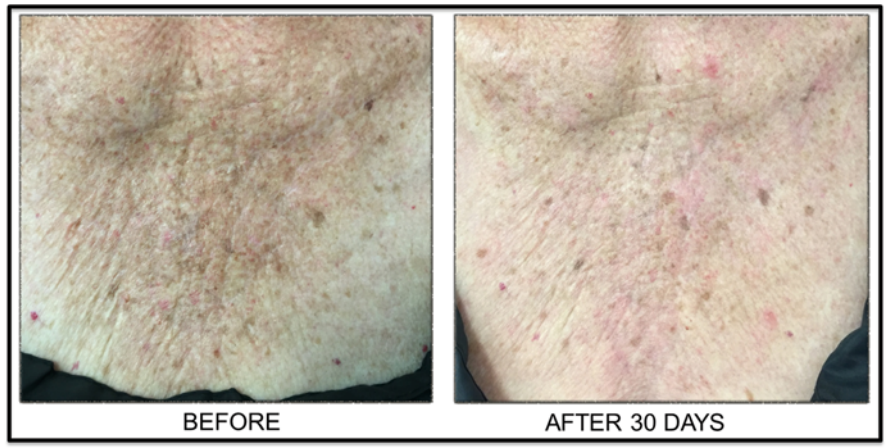

Fig. 5 Before and 30 days after CO_2 laser associated with daylight PDT (MAL-DLPDT) for field of cancerization treatment in an immunocompetent patient

Take Home Messages

1. PDT allows simple and effective treatment of multiple lesions simultaneously, avoiding numerous surgeries and unaesthetic scars.
2. When treating NMSC with conventional PDT, it is supposed that inferior treatment outcomes can occur in thick lesions due to the limited penetration of the photosensitizer.
3. Many studies evaluated the effectiveness of associating TED with PDT with the aim to improve photosensitizers delivery through the skin.
4. AFXL-assisted MAL-PDT has been studied in clinical practice, showing benefit to immunocompetent patients and immunosuppressed organ transplant recipients with AK and field cancerization.
5. TED is also new option to enhance the delivery of ALA or MAL through the skin when using PDT for skin rejuvenation. For this purpose, TED and PDT have been described using microneedling technique and fractional ablative laser.
6. Authors have good experience with ablative RF and CO_2 laser before conventional PDT using MAL and red light.

7. The association of DLPDT with laser and microneedling is a promising new modality for skin rejuvenation.

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Microneedling for Transepidermal Drug Delivery on Stretch Marks

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Abstract

Stretch marks (SMs) are a well-recognized, common skin condition that rarely cause any significant medical problems but are often a significant source of distress to those affected. The origins of SM are poorly understood, and a number of treatment modalities (Elsaie et al. 2009) are available for their treatment, yet none of them is consistently effective, and no single therapy is considered to be consensus for this problem. Multiple sittings of treatments such as chemical peelings, microdermabrasion, nonablative and ablative laser techniques, and light and radiofrequency devices are performed to improve the SM appearance. Microneedling and transepidermal drug delivery together are a new modality of treatment for SM. It is based on stimulation of collagen production and enhancement of the penetration of certain active substances across the skin with which it is possible to achieve satisfactory results.

Keywords

Microneedling • Transdermal drug delivery • Transepidermal drug delivery • Stretch marks • Collagen

Contents

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Introduction

Stretch marks (SMs) are an undesirable cutaneous disorder, which causes significant cosmetic problems with an evident psychological impact. There is loss of the normal random collagen distribution to the level of the mid-dermis or deeper (Singh and Kumar 2005). A single treatment modality that is consistently effective with minimal adverse effects does not exist to date. There are several modalities of treatment such as topical tretinoin 0.1% cream, topical 20% glycolic acid, microdermabrasion, lasers, and light and radiofrequency devices. Microneedling therapy is a new addition to the treatment techniques for SM. It is a simple, inexpensive office procedure, with small downtime that allows collagen stimulation and transepidermal drug delivery (TDD). Percutaneous collagen induction goal is to stimulate collagen production by using the chemical cascade that happens after any trauma. Approximately 5 days after the skin injury, a fibronectin matrix forms with an alignment of the fibroblasts that determines the deposition of collagen (Widgeron 2012). Treatment with skin needling should be able to promote the removal of old damaged collagen and induce more collagen growth beneath the epidermis. The microneedling devices have micron-sized needles that can perforate the skin in a minimally invasive and low pain level manner (Kaushik et al. 2001), thereby creating aqueous transport pathways within the skin referred to as microchannels. Many active substances can be delivered into the skin by microneedling. In this chapter, we will focus on the delivery of three components, which are effective on treating stretch marks. They are vitamin A, vitamin C, and platelet-rich plasma (PRP). The development of microneedling associated with drug delivery seems to be a good option in SM treatment. Combined, they are able to effectively change the collagen organization, transforming the SM skin into a more healthy skin.

Stretch Marks

Stretch marks (SMs) are an undesirable cutaneous disorder, which causes significant cosmetic problems with an evident psychological impact. It occurs mainly in adolescence, pregnancy, and obesity (Satish 2009).

Causes of SM are not clear, and a number of theories were proposed. Infection leading to the release of striatoxin that damages the tissues in a microbial toxic way, mechanical effect of stretching, which is proposed to lead to rupture of the connective tissue framework (e.g., pregnancy, obesity, weight lifting), normal growth as seen in adolescence and the pubertal spurt that leads to increase in sizes of particular body regions, increase in the levels of adrenocorticotropic hormone and cortisol which are thought to promote fibroblast activity leading to increased protein catabolism and thus alterations to collagen and elastin fibers (Cushing's syndrome, local or systemic steroid therapy), genetic factors (absence of striae in pregnancy in people with Ehlers-Danlos syndrome and their presence as one of the minor diagnostic criteria for Marfan syndrome suggest an important genetic element).

SM can be divided into striae rubrae (Fig. 1a) and striae albae (Fig. 1b). They are distinct, evolutionary linked forms of SM and their distinction has therapeutic implications. The color of the SM is related to the stage of evolution and to melanocyte mechanobiological influences.

Striae rubra is an erythematous striae; as it matures, it becomes white and more atrophic in the end; it is an atrophic dermal scar with overlying epidermal atrophy. Initially, striae appear as flattened areas of thinned skin with a pink-red hue that may be pruritic. They usually increase in length and width and acquire a darker reddish-purple appearance over time. The typical white, depressed appearance of older striae develops with time along the long axis aligned parallel with the normal lines of skin tension.

Histologically, striae display an atrophic, thinned epidermis with a flattening of the rete pegs. There is loss of the normal random collagen distribution to the level of the mid-dermis or deeper. Elastin stains reveal scarce or absent elastin fibers and reduced fibrillin in the papillary and reticular dermis within affected areas; the elastin fibers present appear tangled and frayed. The pathogenesis and those predisposed to developing SM may have an underlying deficiency of fibrillin 54. This histologic appearance

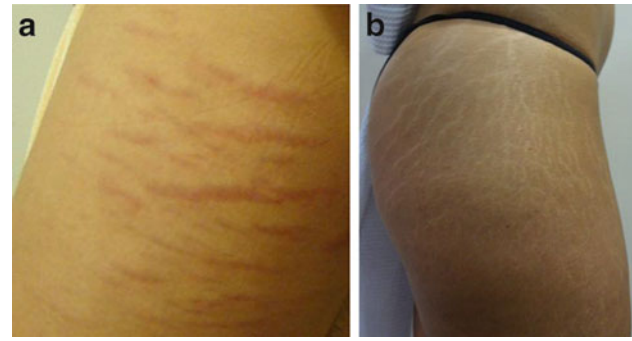

Fig. 1 (**a**) Striae rubrae, (**b**) striae albae

probably likely results from mast cell degranulation and macrophage activation (McDaniel 2002) with resultant destruction of both collagen and elastin fibers (Budamakuntla 2013).

A universal approach to evaluating the severity of SM and a treatment modality that is consistently effective with minimal adverse effects do not exist to date.

There are several modalities of treatment:

(a) Topical treatments
- Tretinoin 0.1% cream is thought to work through its affinity for fibroblasts and induction of collagen synthesis (Bernard 2002). It has maximal efficacy in striae rubrae and poor, unpredictable responses in striae albae. It seems to decrease in mean length and width of the SM after months of daily use. Studies have demonstrated that improvement in the clinical appearance of striae after treatment with retinoic acid correlates with new fibrillin production (Fisher 1995).
- Creams and lotions that contain actives such as *Centella asiatica* extract, vitamin E, vitamin A, collagen-elastin hydrolysates, panthenol, and menthol are widely used, mainly by women during pregnancy. Scientific data available are not sufficient to conclude that such creams are effective, and larger studies are needed to determine the efficacy and safety of such products. There is no statistically significant evidence to support their use in the prevention of SM.
- Topical 20% glycolic acid (GA) pure or mixed with other substances such as 0.05% tretinoin or 10% L-ascorbic acid improves the appearance of striae alba, but the precise mechanism of action of GA is still unknown. It is reported that GA stimulates collagen production by fibroblasts and increase their proliferation, but further investigations and studies are required to prove such theory.

(b) Lasers and light devices: intense pulsed light (515–1.200 nm), 585 nm flashlamp-pumped pulsed dye laser (PDL), 308 nm xenon chloride (excimer laser), 577 nm copper bromide laser, 1.450 nm diode laser, 1.064 nm Nd:YAG laser, carbon dioxide (CO2) laser, fractionated 1550 nm erbium-doped fiber laser and fractional photothermolysis are some examples of technologies that can be used in SM treatment (Alster and Handrick 2000, 2005). Prior to selecting one device, one must perform the correct analysis of the SM and of the patients' Fitzpatrick skin type to diminish the risk of injuries and pigmentary alterations.

(c) Radiofrequency (RF) devices: the effects of dermal heating are well recognized and include immediate effects on collagen structure with stimulation of dermal fibroblasts inducing a synthesis of new collagen fibers (neocollagenesis) and elastic fibers (neoelastogenesis) (Al-Himdani et al. 2014; Gold 2015), improving the appearance and histological findings in SM (Suh et al. 2007).

(d) Microdermabrasion is a skin resurfacing technique using aluminum oxide. It has been reported to increase type I collagen and has a greater effect on stretch marks. This technique can be used in combination with intradermal platelet-rich plasma (PRP); in a study, patients were treated with a combination of intradermal

Fig. 2 Dermaroller® device

Fig. 3 Dermapen® device

PRP and microdermabrasion in the same session. There was significant clinical improvement of SM in patients treated with a combination of PRP and microdermabrasion when compared with patients treated with just microdermabrasion. A combination of PRP and microdermabrasion in the same session showed better results in short duration (Ibrahim et al. 2015).

(e) Microneedling therapy is a new addition to the treatment techniques for SM. It is a simple, inexpensive office procedure, with small downtime that allows collagen stimulation and transepidermal drug delivery (TDD). Substances such as vitamin A (retinyl palmitate and retinyl acetate), vitamin C, and platelet-rich plasma (PRP) can be used for TDD. In this chapter, we are going to describe the use of the microneedling technique as a way of stimulating collagen and facilitating the delivery of active ingredients to the skin affected by stretch marks.

Microneedling

History

In 1995 Orentreich described collagen percutaneous stimulation with dermal needling for scars. Then, in 1997, Camirand and Doucet described needle dermabrasion using a "tattoo pistol" to treat scars. And only in 2006 a doctor from South Africa, Dr Desmond Fernandes, developed percutaneous collagen induction therapy with the dermaroller (Dermaroller®) (Henry et al. 1998) (Fig. 2). In 2010 a new electronic pen-shaped device (Dermapen®) (Fig. 3) was developed in Australia for a more cost-effective procedure. Using the pen you can choose different needle lengths and speed vibration providing not only microneedling but also a certain level of dermabrasion depending in the used technique.

Since then, the use of the microneedling devices is growing along with the number of indications. The addition of transepidermal drug delivery to the microneedling technique made it even more interesting to treat certain conditions, such as stretch marks and melasma.

The Devices

Since 2006, when the first dermaroller was used by Dr Fernandes, the device suffered numerous changes to get more ergonomic and resistant. The standard dermaroller used for acne scars is a drum-shaped roller studded with 192 fine microneedles in 8 rows, 0.5–1.5 mm in length and 0.1 mm in diameter. The microneedles are synthesized by reactive ion etching techniques on silicon or medical-grade stainless steel. The

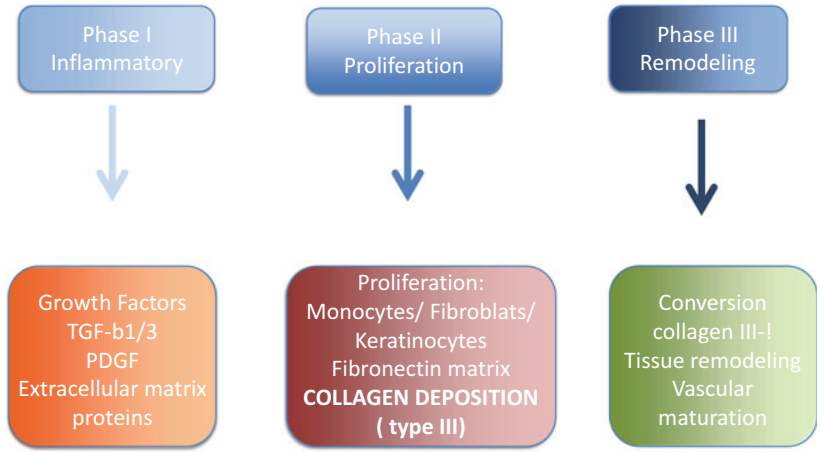

Fig. 4 Cascade of healing after trauma injury and collagen deposition

instrument is sterilized by gamma irradiation. Now you can find thinner versions and larger versions, and the length of the needles can come up to 2.5 mm.

As it is supposed to be disposable, if you have more than one needle length indication, the doctor would have to use more than one roller, which is not cost-effective to the patient. For example, if you want to treat the patient under the eyes and for a scar in the malar area, we would have to use both 1.0 mm- and 1.5–2.0 mm-long needles.

Other electronic pen-shaped microneedle devices were developed with disposable needles. The length and the speed vibration of the exposed needle, in and out, can be controlled. In the end, with these devices, we can not only create microtunnels but also achieve a certain level of dermabrasion of the epidermis, if that is the goal.

Mechanisms of Action

The microneedle devices create microtunnels that vary from 0.5 to 2.5 mm in depth (Cho 2010). Percutaneous collagen induction goal is to stimulate collagen production by using the chemical cascade that happens after any trauma. There are three phases in the body's wound healing process (Tejero-Trujeque 2001), which follow each other in a predictable fashion. This has been well described in *The Biology of the Skin* by Falabella and Falanga (Falabella et al. 2000). Platelets and eventually neutrophils release growth factors such as the connective tissue growth factor, TGF-B1, TGF-B3, platelet-derived growth factor, connective tissue activating protein III, and others that work together to increase the production of intercellular matrix (Lynch 1989; Tran 2004; Faler 2006) (Fig. 4). Only then, monocytes also produce growth factors to increase the production of collagen III, elastin, glycosaminoglycans, and so on (Johnstone 2005).

Approximately 5 days after the skin injury, a fibronectin matrix forms with an alignment of the fibroblasts that determines the deposition of collagen. Eventually, collagen III is converted into collagen I, which remains for 5–7 years. Due to this conversion, the collagen tightens naturally over a few months (Martin 2005).

Normally, during the usual conditions of wound healing, scar tissue is formed with minimal regeneration of normal tissue (Fenske 1986). Percutaneous collagen induction causes even further tightening of lax skin and smoothening of scars and wrinkles several weeks or even months after the injury (Fernandes 2002). In addition, percutaneous collagen induction has proven to be very effective in minimizing acne and burn scars, by promoting the replacement of scar collagen with normal collagen and the reduction of depressed and contracted scars (Ruszczak 2003).

Treatment with skin needling should be able to promote the removal of old damaged collagen and induce more collagen growth beneath the epidermis. Puncturing the skin multiple times in acne scars increases the amount of collagen and elastin deposition. Thus, it was hypothesized that skin needling would also be useful in SM because these seem to be dermal scars with epidermal atrophy (Majid 2009).

Microneedling and SM

A study made in South Korea in 2012 enrolled 16 volunteers with SM, who received three treatments with a microneedling device at 4-week intervals. Clinical response to treatment was assessed by comparing pre- and posttreatment clinical photographs, skin biopsies, and patient satisfaction scores. The general histopathologic features of the lesional specimens collected before treatment showed epidermal thinning with fine dermal collagen bundles arranged in straight lines. After treatment, the epidermis was thickened, and the amounts of dermal collagen and elastic fibers were increased (McCrudden et al. 2015). This study proved that microneedling can be effectively and safely used for SM treatment.

In addition to this technique, the transepidermal drug delivery can be associated in order to increase the collagen production.

Microneedling and Transepidermal Drug Delivery

The dispersion and effectiveness of active ingredients into the skin, without prior perforation, are severely limited by the inability of the large majority of drugs to cross the skin at therapeutic rates due to the great barrier imposed by the skin's outer stratum corneum layer (Menon et al. 2012).

In 2004, Prausnitz (Prausnitz 2004), described the use of microneedles for transdermal drug delivery. The outstanding motivation for microneedles is that they can provide a minimally invasive means to transport molecules into the skin (Oh et al. 2015).

As with lasers, the microneedling technique started being used as a way to trespass the stratum corneum to deliver active ingredients to the skin in a more efficient way (Brauer et al. 2014).

The stratum corneum (SC), the skin's outermost layer, is a barrier that prevents molecular transport across the skin. Therapeutic agents, such as peptides, proteins, and oligonucleotides, are difficult to reach deeper layers of the skin by conventional methods or topical delivery (Petchsangsai et al. 2014).

The microneedling technique (MT), as shown, uses micron-sized needles that can perforate the skin in a minimally invasive and low pain level manner, thereby creating aqueous transport pathways within the skin referred to as microchannels (Park et al. 2012).

Moreover, these microchannels present no limitation regarding the size of molecules that can pass through their tunnels (Kumar and Banga 2012). While, in terms of size, the microchannels are in the range of microns, the macromolecules delivered are typically nanometers in size.

The only question that remains is if, after the microneedling, blood and fibrin will invade the microchannels creating a new barrier for this penetration (Milewski et al. 2010). Consequently, we recommend, as the biopsies presented in Fig. 5, to proceed in an inverse technique, where the drug is applied prior to the microneedling technique and prior to each step to guarantee more efficient delivery of the active ingredient.

In the past, local microinjections, the so-called mesotherapy, were introduced in France by Pistor (Pistor 1979). Mesotherapy is a widely used technique in medicine. This technique consists of intradermal or subcutaneous microinjections of 0.05–0.1 mL of highly diluted drug mixtures or a single drug, on body parts affected with medical or aesthetic problems. Nevertheless, recent studies show that the drug delivery with microneedling is more effective than mesotherapy because it not only allows the penetration of active ingredients into the skin but also induces the chemical cascade that takes place after a trauma which will stimulate collagen production.

Many active substances can be delivered into the skin by microneedling. Depending on the

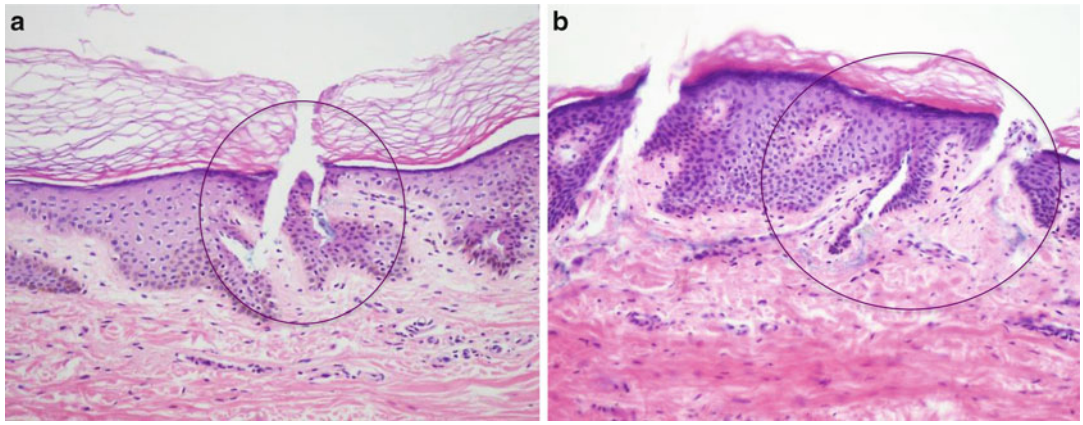

Fig. 5 Histopathology of the skin after methylene blue ink diluted in the same vitamin C vehicle used to do the drug delivery. Applied prior every dermroller pass, 20 passes (**a**) After 0,5 dermaroller, (**b**) after 1 mm dermaroller. Both showed penetration of the ink in different levels according to the needle length

disease you wish to treat, there are a number of substances that can be chosen, for example, steroids (triamcinolone acetonide) for hypertrophic scars and areata alopecia, tranexamic acid for melasma, minoxidil for androgenetic alopecia, and aminolevulinic acid for actinic keratosis.

In this chapter, we will focus on the delivery of three components, which are effective on treating stretch marks. They are vitamin A, vitamin C, and platelet-rich plasma (PRP).

Vitamin A

The possibility of using vitamins A and C for percutaneous collagen induction has been described by Aust in (2008). Vitamin A, a retinoic acid, is an essential vitamin also considered a hormone for the skin. It expresses its influence on many genes that control proliferation and differentiation of all the major cells in the epidermis and dermis (Rosdahl 1997). Percutaneous collagen induction and vitamin A switch on the fibroblasts to produce collagen and therefore increase the need for vitamin C. Vitamin A may control the release of TGF-B3 in preference to TGF-B1 and TGF-B2 because, in general, retinoic acid seems to favor the development of a regenerative lattice-patterned collagen network rather than the parallel deposition of scar collagen found with cicatrization (Oliveira Marcela et al. 2016).

Retinyl palmitate (RP) is an ester of retinol and is the major form of vitamin A found in the epidermis. It has a high molecular weight and a stable formulation. To be active, RP has to be enzymatically converted in the skin to retinol by cleavage of the ester linkage and then be converted to tretinoin via oxidative processes. It has been established that the topical administration of RP for 14 days in rats resulted in increased protein and collagen and an epidermal thickening (Ro et al. 2015).

Ascorbic Acid (Vitamin C)

Ascorbic acid (AA) or vitamin C is also essential for the production of normal collagen. Percutaneous collagen induction and vitamin A stimulate the fibroblasts to produce collagen and therefore increase the need for vitamin C. Topical vitamins A and C both maximize initial release of growth factors and stimulate collagen production (Palma 2006).

Apart from its role as a potent antioxidant, it has also been demonstrated that AA functions as an essential cofactor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for the posttranslational processing of types I and III collagen (Nusgens 2001).

AA stimulates collagen production in the dermis and can cause a dramatic increase in fibroblast

proliferation potentially resulting in greater collagen production; it might be presumed that AA also possesses the potential to increase collagen production for SM appearance reduction. AA even plays a role in collagen synthesis at the level of gene expression. It has been shown to upregulate collagen synthesis and increase the synthesis of the inhibitor of metalloproteinase-1 which decreases UV-induced collagen degradation.

Platelet-Rich Plasma (PRP)

PRP is a source of numerous growth factors which facilitate repair and healing. It is a potential reservoir of essential growth factors, including platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor-beta 1, and insulin-like growth factor which play an important role on the recovery of the skin (Sonker et al. 2015).

It has been found to accelerate endothelial, epithelial, and epidermal regeneration, stimulate angiogenesis, enhance collagen synthesis, promote soft tissue healing, decrease dermal scarring, enhance the hemostatic response to injury, and reverse the inhibition of wound healing caused by glucocorticoids.

There are different preparation protocols to obtain PRP, and physicians should select proper PRP preparations after considering their biomolecular characteristics and patient indications.

A split-face comparative study published in 2014 of microneedling with PRP versus microneedling with vitamin C in treating atrophic post-acne scars revealed better results with microneedling and PRP. Thirty patients with post-acne atrophic facial scars were offered four sittings of microneedling with PRP on one side and microneedling with vitamin C on the other side of the face at an interval of 1 month. Overall results were better with microneedling and PRP (Chawla 2014).

PRP along with microneedling would intensify the natural wound healing cascade because of the high concentration of patients own growth factors. It acts synergistically with growth factors induced by skin needling in order to enhance the wound healing response. As stretch marks are atrophic scars, we can hypothesize that microneedling and PRP would have good results for them.

Uses and Doses

It is very important to assure that the substances that are going to be applied on the skin surface prior microneedling are substances that could be used intradermally or intravenously.

For stretch marks' treatment, we indicate the use of:

- Fifteen to 20% vitamin C (L-ascorbic acid 0,15 g/ml or L-ascorbic acid 0,2 g/ml) ampoules.
- Retinyl palmitate (an ester of retinol) ampoules for endovenous administration can be safely applied topically.
- MTS® ampoules: a combination of palmitoyl tripeptide-28 3% and growth factors 10%.
- PRP preparations (follow proper protocols).

Procedure

During treatment, the needles pierce the stratum corneum and create microconduits (holes) without damaging the epidermis. It has been shown that rolling with a dermaroller (192 needles, 200 mm length and 70 mm diameter) over an area for 15 times will result in approximately 250 holes/cm^2.

Microneedling is a mild pain drug delivery. Because the skin's stratum corneum barrier has no nerves, skin anatomy provides the opportunity to pierce needles across the stratum corneum without stimulating nerves. Although, the microneedles are inserted only deep enough to reach the superficial dermis, which is not much painful, probably because their small size reduces the odds of encountering a nerve or of stimulating it to produce a strong painful sensation (Figs. 6a, b and 7a, b).

1. Take photographs of the area you are going to treat using a consistent background, position, and lighting, and they will be compared with the posttreatment images.

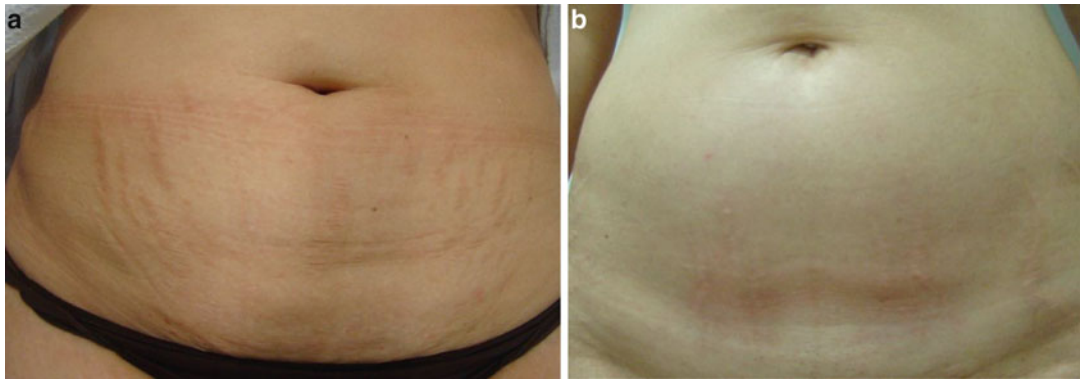

Fig. 6 (**a**) 1 day before treatment; (**b**) 30 days after one session of microneedling with TDD of vitamin C and non-cross-linked hyaluronic acid

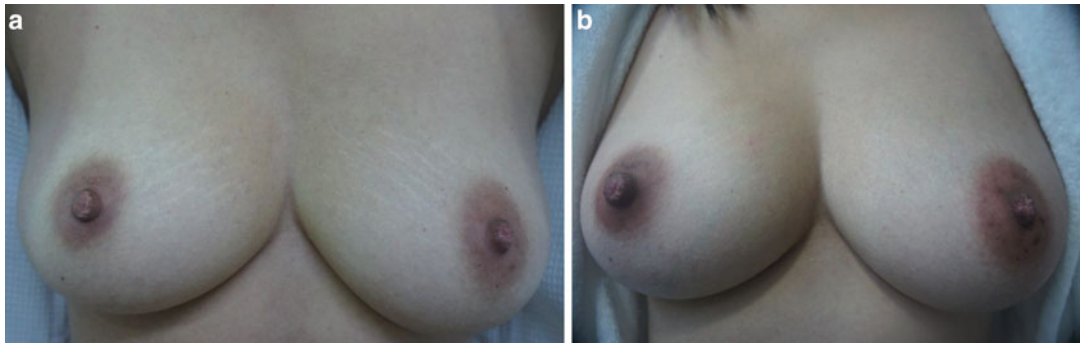

Fig. 7 Before (**a**) and after 30 days (**b**): one session Dermapen® TDD with sterile vitamin C + AH non-cross-linked

2. Anesthetize using a thick application of topical anesthetic cream for about 60 min. Remove it completely before starting the procedure to prevent topical anesthetic intoxication.
3. Clean the area with alcoholic chlorhexidine.
4. Choose a device: roller or pen.
5. Choose depth of the needle and speed of the pen (quicker vibrations lead to less abrasion).
6. Choose the active ingredient to use (the use of sterile and injectable products is important to avoid the risk of infection and also diminish the risk of contact dermatitis).
7. Apply a thin layer of the liquid with a disposable brush.
8. Pass the device and repeat the process over and over. Roll at least 20 passes in the same area in different ways, and pen pass at least ten times in each area making circular movements.
9. Clean just the excess of liquid and blood (leave a thin layer of blood for at least 4 h to function as a natural PRP dress that helps to heal).
10. Cover the skin with a sterile active ingredient in an oleous vehicle such as glycosaminoglycans (Antiage Flash® Mesoestetic) to prevent water loss through the skin.
11. Cover with a thin plastic drape.
12. Instruct the patient to follow strict photoprotective measures. Schedule sittings are at intervals of 4 weeks.

Other Indications

- Androgenetic alopecia, areata alopecia, acne scars, hypertrophic scars, melasma, skin regeneration, and preparation of skin prior to fat graft

Contraindications

- History of contact dermatitis especially to metal and to the active ingredients that are going to be used
- Chronic Urticaria
- Immunosuppression
- Diabetes
- Pustular or nodular rosacea or acne
- Anticoagulant medications
- Pregnancy
- Moles (always verify moles prior to treat the area and try to avoid using microneedling on top of them)
- Keloids
- Skin infection
- Psoriasis (Koebner phenomenon)

Advantages

– Nonablative.
– Healing process is fast (1–5 days depending on needle length and number of passes) and has less chance for complications if compared to ablative techniques.
– The immediate effects are a thicker and more resistant skin.
– Can be used in every skin type even off face.
– Low cost if compared to lasers.

Disadvantages

– Training required.
– If a very high density or coverage is used, then the healing time and erythema can last longer.
– Does not promote immediate tightening of the collagen fibers.
– Requires more than one session to achieve good results.

Side Effects and Their Management

The microneedling treatment is well tolerated. Minor side effects reported are mild pain at the treating area, erythema, spotty bleeding, and pruritus for 2 or 3 days after the procedure, which are solved without any specific treatment. Moisturizing creams can be applied to keep the area hydrated, which diminishes the discomfort.

Infection at the treating area is very unlikely to happen. As the microholes close almost immediately, postoperative infections are rare. If they occur, oral or topic antibiotics can be used for treatment.

Irritant or allergic contact dermatitis can occur depending on the characteristics of the substance applied on the skin surface and the immunological characteristics of the patient. Oral antihistamines and topical steroids can be used if necessary (Soltani-Arabshahi et al. 2014).

Hyperpigmentation is uncommon, but if it happens, topical Kligman formula can be applied. For long-lasting erythema, micropulsed YAG laser, pulsed dye laser (PDL), and intense pulsed light (IPL) devices can be used. The emergence of papules and pustules on the treating area must be treated with topical or oral antibiotics used in acne and rosacea treatment.

A case report study published in 2014 reports three patients who developed facial allergic granulomatous reaction and systemic hypersensitivity after microneedling drug delivery therapy. Microneedles are powerful means of transdermal delivery of drugs. Thus, only chemicals approved for intradermal injection are safe to be used in conjunction with microneedling. Application of various nonapproved topical products before a microneedling procedure can introduce immunogenic particles into the dermis and potentiate local or systemic hypersensitivity reactions (Lima et al. 2013). For facial allergic granulomatous reaction and systemic hypersensitivity, oral steroids and minocycline can be used, but the treatment is not always effective.

Microneedling and Vitamin C Drug Delivery Plus Calcium Hydroxylapatite Fillers: A Pilot retrospective Study for Stretch Marks

Calcium hydroxyapatite (CH) is a white substance made of microspheres (45 mm) of CH in a

carboxymethyl cellulose gel and is a filler and biostimulator because it is supposed to induce neocollagenesis during the first 6 months after injection. CH can be used either in the subcutaneous layers to volumize a region or in the dermis to correct dermal atrophy. It is made to be applied in more deep planes such as subcutaneously, and when it is injected more superficially, it can give a yellowish look. The CH injection into SM in all depths intends to improve atrophy (Casabona e Michalany 2014) through the stimulation of the production of endogenous collagen and also to promote a yellowish look to the striae promoting a more natural appearance matching the color of the normal skin (Berlin et al. 2008; Parvicic 2015).

Table 1 Drugs and vitamins with scientific evidence to be used prior to microneedling and its effects

Substance	Effect
Vitamin A	Growth factor release, regulates differentiation and proliferation of the epidermis and dermis, skin regeneration, increased protein and collagen, epidermal thickening
Vitamin C	Stimulates collagen production in the dermis, increases fibroblast proliferation resulting in greater collagen production
Platelet-rich plasma	Enhances collagen synthesis

Table 2 Side effects: how to manage

Side effect	Management
Infection	Oral or topical antibiotic[a]
Contact dermatitis	Oral antihistamine and topical can be steroids
Hyperpigmentation	Topical Kligman formula
Long-lasting erythema	Micropulsed YAG laser, pdl or ipl
Acne and rosacea	Oral antibiotic[a] and topical acne treatment
Facial allergic granulomatous reaction and systemic hypersensitivity	Oral steroids, minocycline

[a]*Lymecycline*, *minocycline*, *tetracycline*)

Authors' Experience

A Retrospective study conducted at private office in São Paulo, Brazil (publishing process), during a 3-year period (January 2012 to July 2015), enrolled 35 patients with stretch marks in different regions of the body (gluteus, thighs, knees, abdomen, and breasts) and evaluated the efficacy of a new combined treatment for SM; the dermal injection of calcium hydroxyapatite and microneedling with vitamin C drug delivery were put together to enhance the appearance of SM.

Among 35 patients, there was one male (2.85%) and 34 females (97.14%). Twenty five (71.42%) had red SM and ten (28.57%) had white SM. Ages ranged between 21 and 34 years, and they were submitted to the same treatment for SM (Table 1).

Patients had their SM evaluated by a physician observer and scores were assigned in accordance to a visual analogue scale, the Manchester Scar Scale (Table 2). This evaluation was performed at the beginning and after the end of treatment sessions. Both scores were compared in order to identify if there was an improvement in the appearance of stretch marks.

Patients were submitted to four treatment sessions with a 4-week interval between them. The first session included the dermal injection of calcium hydroxyapatite (Radiesse®) followed by microneedling (Dermapen®) and topical application of 20% vitamin C onto the affected areas. The three remaining sessions included microneedling with vitamin C drug delivery, with no dermal injections.

All the 35 patients had better scores according to the Manchester Scar Scale evaluation at the end of the study. Thirty patients were asked about their level of satisfaction with the treatment: 8 patients (27%) were very satisfied, 15 patients (50%) were satisfied, 5 patients (7%) were neither satisfied nor dissatisfied, 2 patients (6%) were unsatisfied, and none answered very unsatisfied.

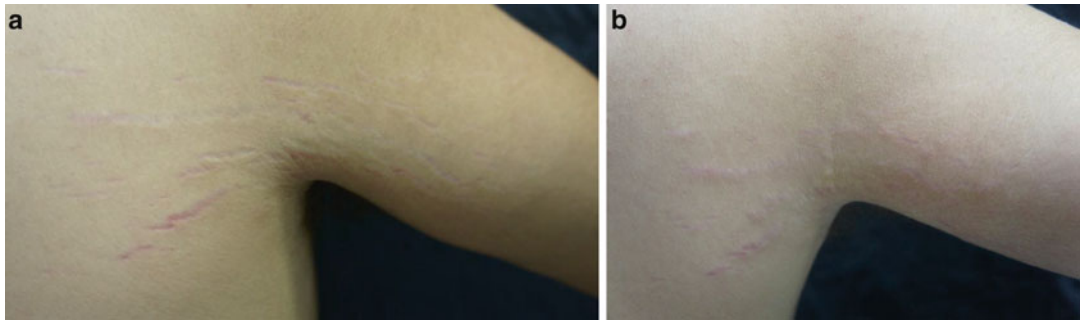

Fig. 8 Before (**a**) and after (**b**) two sessions of Dermapen® TDD with sterile vitamin C. In this case one session of CaHa injection was also done before TDD

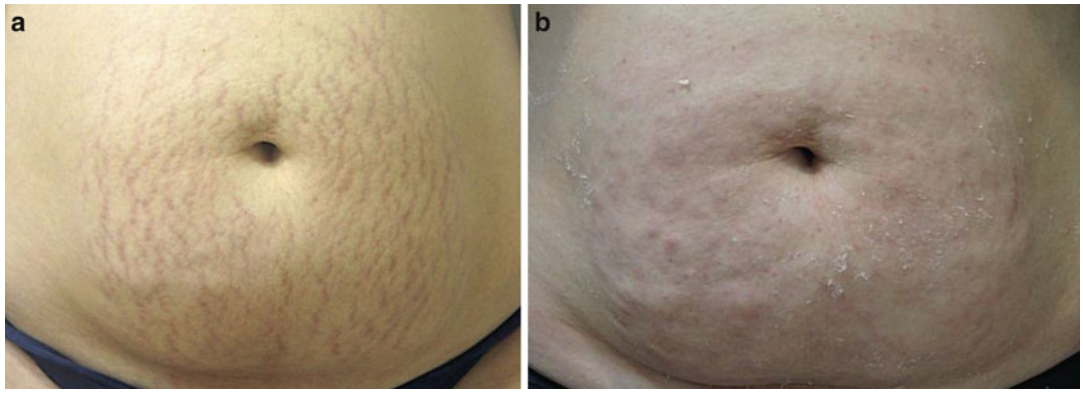

Fig. 9 Before (**a**) and after (**b**) two sessions of Dermapen® TDD with sterile vitamin C. In this case one session of CaHa injection was also done before TDD

Results are encouraging. With the injection calcium hydroxyapatite and microneedling with vitamin C topical application, it is possible to stimulate collagen production in three different pathways at the same time. This combined technique may have better results than those obtained when each technique is performed alone (Figs. 8a, b, 9a, b, 10a–f, and 11a–d).

Conclusions

The improvement in the appearance of SM, rather than its complete removal, is a more realistic clinical goal. Complete disappearance of SM may be occasionally observed; nevertheless, this occurrence is uncommon and should not be presented to patients as a realistic goal.

Using combination of treatments over a prolonged period of time can improve the appearance of striae. Unless a revolutionary monotherapy becomes available that dramatically improves striae treatment results, the use of multimodal treatments tends to increase (Goldberg et al. 2005) consistently.

The development of microneedling associated with drug delivery seems to be a good option in SM treatment. Combined, they are able to effectively change the collagen organization, transforming the SM skin into a more healthy skin.

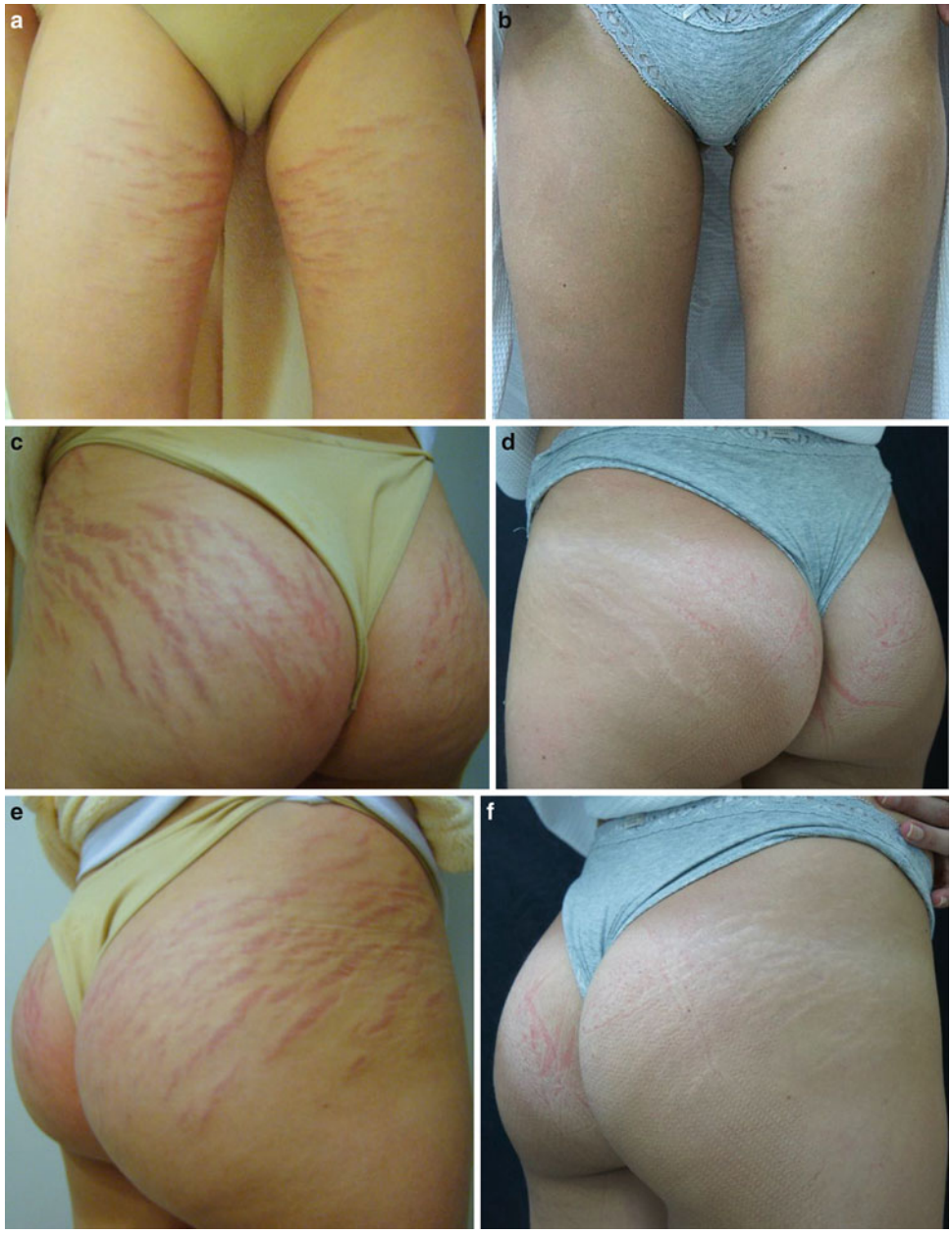

Fig. 10 Before and after two sessions of Dermapen® RTDD with sterile vitamin C. In this case two sessions of CaHa injection were also done before TDD. Inner thigh before (**a**) and after (**b**). Gluteus left side before (**c**) and after (**d**); gluteus right side before (**e**) and after (**f**)

Take Home Messages

- Stretch marks are often a significant source of distress to those affected, and no single therapy is considered to be a consensus for this problem.
- Microneedling and transepidermal drug delivery together are an option of treatment, with which it is possible to achieve satisfactory results.
- Skin needling promotes the removal of old damaged collagen, induces more collagen

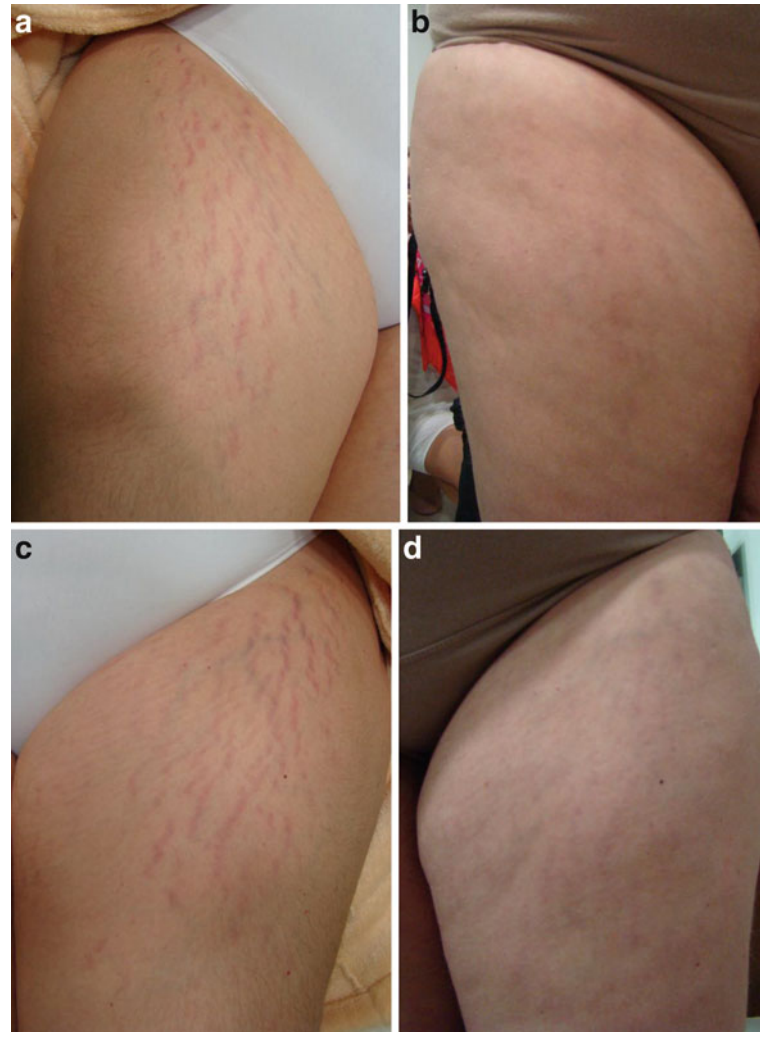

Fig. 11 Before and after two sessions of Dermapen® TDD with sterile vitamin C. In this case one session of CaHa injection was also done before TDD. Right thigh before (**a**) and after (**b**), left thigh before (**c**) and after (**d**)

growth beneath the epidermis, and creates aqueous transport pathways within the skin for drug delivery.

- Vitamin A, vitamin C, and platelet-rich plasma are substances that can be used for drug delivery.
- Microneedling with drug delivery is a cost-effective office procedure, well tolerated, and with few minor side effects and short down-time that can be safely used for SM treatment.
- The injection of calcium hydroxyapatite into SM prior the microneedling with vitamin C topical application is an innovative combined technique that may have even better results.
- The improvement in the appearance of SM, rather than its complete removal, is a more realistic goal.

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