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A. Jalili
Department of Dermatology, Bürgenstock Medical Center, Obbürgen, Switzerland

Chromophore gel-assisted phototherapy

A novel and promising photobiomodulation therapy for facial inflammatory skin diseases and skin aging

Photobiomodulation

Photobiomodulation or low-level laser (light) therapy (LLLT) refers to the use of light at a non-thermal irradiation to alter cell biological activity. This process is referred to as "low-level" because the energy or power densities employed are low compared to other forms of laser therapy such as ablation, cutting, and thermally coagulating tissue. Photobiomodulation uses either coherent light sources (lasers), non-coherent light sources consisting of filtered lamps, or light-emitting diodes (LED). Among medical applications, reducing inflammation and pain as well as augmentation of tissue repair are fields where photobiomodulation is used [10, 15].

Phototherapy employs light with wavelengths between 390 and 1100 nm, and can be continuous wave or pulsed. In normal circumstances, it uses relatively low fluences (0.04–50 J/cm^2) and power densities (<100 mW/cm^2) [1]. Wavelengths in the range of 390 to 600 nm are suited to treat superficial tissue, whereas longer wavelengths in the range of 600 to 1100 nm, which penetrate further, are used to treat deeper tissues [10, 15]. Wavelengths in the range 700 to 750 nm have been found to have limited biochemical activity and are therefore not often used [10]. A wide range of LEDs are available at wavelengths (490–620 nm) lower than gas lasers and semiconductor laser diodes (such as helium neon, ruby, argon, krypton, gallium arsenite, and gallium aluminum arsenite), whose medium contains the elements indium, phosphide, and nitride. It is rather unclear whether there is any advantage of using coherent laser light over non-coherent LED light [16]. In dermatology, the use of LEDs is becoming increasingly common due to the relatively large areas of tissue that require irradiation.

Mechanism of action of photobiomodulation

In fact, light therapy is one of the oldest therapeutic methods used by humans (historically as solar therapy by Egyptians, later as UV therapy for which Nils Finsen won the Nobel prize in 1904 [24]). In 1967, a few years after the first working laser was invented, Endre Mester in Semmelweis University, Budapest, Hungary wanted to test if laser radiation might cause cancer in mice [18]. By using a low-powered ruby laser (694 nm), the treated skin of mice did not get cancer, and to his surprise, the hair in the treated group grew back more quickly than in the untreated group. This was the first demonstration of "photobiomodulation." Since then, medical treatment with coherent light sources (lasers) or non-coherent light (LEDs) has improved, and further and enormously developed. Currently, photobiomodulation is practiced as part of medical therapy in many parts of the world.

The use of lasers and LEDs as light sources is now applied to many thousands of people worldwide every day. In photobiomodulation, the question is no longer whether light has biological effects, but rather how energy from therapeutic lasers and LEDs works at the cellular levels, and what are the optimal light parameters for different uses of these light sources. It has been found that there exists an optimal dose of light for any particular application, and doses lower than this optimum value, or more significantly, larger than the optimum value, will have a diminished therapeutic outcome, or a negative outcome may even result, respectively [26]. In general, the power densities used for photobiomodulation are lower than those needed to produce heating of tissue, i. e., less than 100 mW/cm^2, depending on wavelength and tissue type.

According to quantum mechanical theory, light energy is composed of photons or discrete packets of electromagnetic energy. The energy of an individual photon depends only on the wavelength. Therefore, the energy of a "dose" of light depends only on the number of photons and on their wavelength or color. Photons that are delivered into living tissue can either be absorbed or scattered. Scattered photons will eventually be absorbed or will escape from the tissue in the form of diffuse reflection. The photons that are absorbed interact with an organic molecule or chromophore located within the tissue. According to the first law of thermodynamics, the energy delivered to the tissue must be conserved, and several possible pathways exist to account for what happens to the

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Fig. 1 ◄ The chromophore gel-assisted light therapy procedure. **a** A thin layer of the photoconverter gel is topically applied on the targeted skin area. **b** Subsequent illumination with the blue LED light for 9 min. **c** Treatment is frequently accompanied with a mild and transient erythema

delivered light energy when low-level laser therapy is delivered into tissue.

The commonest pathway that occurs when light is absorbed by living tissue is called internal conversion. This happens when the first excited singlet state of the chromophore undergoes a transition from a higher to a lower electronic state. It is sometimes called "radiationless de-excitation," because no photons are emitted. The energy of the electronically excited state is given off to vibrational modes of the molecule; in other words, the excitation energy is transformed into heat. The next pathway that can occur is fluorescence. Fluorescence is a luminescence or re-emission of light, in which the molecular absorption of a photon triggers the emission of another photon with a longer wavelength, and this is exactly the concept of photobiomodulation by low-energy chromophore-induced fluorescent light (see below).

There are perhaps three main areas of medicine where photobiomodulation has a major role to play. These are (a) wound healing, tissue repair, and prevention of tissue death; (b) relief of inflammation in chronic diseases and injuries with its associated pain and edema; and (c) relief of neurogenic pain.

In dermatology, the clinical and biological effect of photobiomodulation is believed to originate from multiple cellular pathways, where individual wavelengths have been seen to trigger intra-cellular photobiochemical reactions. This often depends on the state of the skin, where documented effects include an anti-inflammatory response, especially beneficial for conditions such as acne, rosacea, keratosis pilaris [5, 9, 14]; post-interventional inflammation and erythema (e.g., following laser treatments); increased normalized cell growth for wound healing; photorejuvenation; and scar prevention and recovery [2, 11].

Unlike a laser, the color of light emitted from an LED is neither coherent nor monochromatic, but the spectrum is narrow with respect to human vision, and for most purposes the light from a simple diode element can be regarded as functionally monochromatic. More precisely, red and orange light has been shown to induce the dissociation of nitric oxide from the enzyme cytochrome c oxidase, and has been associated with collagen regulation. Yellow light is generally believed to alter ATP production and fibroblast activity. Blue light specifically causes disruption of the endogenous *Propionibacterium acnes* (*P. acnes*), and green and blue light are also believed to be anti-inflammatory through a shift in cytokine production [6, 12, 22]. In addition to these general effects, the various wavelengths are known to penetrate different depths of the skin, thereby gaining access to a variable selection of biological elements in the skin [6, 27].

Innovative photobiomodulation strategy using chromophore gel-assisted light therapy

Chromophore-induced generation of fluorescent light wavelengths is a novel photobiomodulation strategy. This technology induces photobiomodulation in a differential and improved fashion as compared to traditional photobiomodulation techniques, allowing the stimulation of pathways associated with cellular healing factors, possibly suggesting a reset and reboot of healing processes, especially in the context of distressed or aging skin. Chromophore gel-assisted light therapy is based on photoconverter gels, which are non-absorbing formulations containing light-absorbing molecules (mainly composed of eosin). A thin layer of the photoconverter gel is topically applied to the targeted skin area (◘ **Fig. 1a**) and subsequently illuminated with the blue light to create a biophotonic action in which fluorescence is generated (◘ **Fig. 1b**). Afterwards, the exhausted photoconverter gel is fully removed by cleaning just after the illumination period. Together, the photoconverter gel and the light source provide a unique and dynamic photonic output, both in terms of wavelength and energy delivered over a predefined treatment cycle time of 9 min. The chromophore gel-assisted light therapy is based on photophysical reactions between the photoconverter gel and the blue light, and acts on the epidermis and the dermis of the skin. As the blue light, with an optimized peak

wavelength and fluency, interacts with the photoconverter gel, it is converted into a different set of fluorescent visible wavelengths in addition to the blue light emitted by the light source (**Fig. 2**). In principle, the photoconverter gels facilitate the conversion of the non-coherent blue light wavelengths from the light source into unique dynamic hyperpulsed multiwavelengths of fluorescent energy. This shift from shorter blue wavelengths to longer wavelengths within the blue, green, yellow, orange, and red spectrum (400 to 650 nm) is caused by the phenomenon called Stoke's shift. These wavelengths have the capacity to penetrate to various depths of the skin and to stimulate the skin tissues and cells [19]. No UV light or infrared light is emitted or generated.

Chromophore gel-assisted light therapy and clinical applications in dermatology

Clinical studies with the chromophore gel-assisted light therapy have shown:

- Significant reduction of inflammation and acne lesions in both moderate and severe patients with acne vulgaris [3],
- Extended durability of the treatment in acne vulgaris up to at least 6 months [20]
- Wrinkle reduction and collagen buildup [21]

Light and laser therapies for the treatment of acne vulgaris are originally based on the observation that *P. acnes* bacteria synthesize chromophores such as porphyrins, more specifically, coproporphyrin [4, 8]. Porphyrins enable light therapy to exert a selective cytotoxic effect on *P. acnes*. The excitation of bacterial porphyrins by light absorption induces the production of singlet oxygen and reactive radicals leading to bacterial membrane damage and cell death [4, 13]. Compared to blue light, which has limited skin penetration, red light can reach deeper sebaceous glands and may have an anti-inflammatory effect through cytokine release. However, the reduced efficacy of red light on porphyrin activation has led to investigation of combination of red and blue light with or without intense pulsed light (IPL), the latter most often used for the generation of pulsed polychromatic light [9, 14, 23].

The chromophore gel-assisted light therapy, when used for acne treatment—interestingly, even in moderate and severe acne—provides a unique modality for the treatment of acne, both targeting the *P. acnes* bacteria, and also providing a significant reduction in inflammation and the overall acne severity [3]. The initiation of the unique photobiomodulation enables the results to

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Abstract

Phototherapy has been a mainstay in dermatology for many years. The field has been accompanied by tremendous developments in both the type of light used and the method of how light is delivered to the skin. Chromophore gel-assisted phototherapy is a novel type of photobiomodulation therapy using low-energy light-emitting diode (LED) blue light in combination with a chromophore gel. Upon exposure to blue LED light, chromophore gel functions as a photoconverter and starts emitting fluorescent light penetrating from epidermal to dermal layers of the skin. So far this strategy has been used successfully and shown its anti-inflammatory and bactericidal effect (against *Propionibacterium acnes*) for the treatment of moderate to severe acne and skin rejuvenation. However, the therapeutic benefit of this system is not restricted to these indications. The therapy is well tolerated and safe. Adverse events are mild and are restricted to transient erythema, and pruritus, skin hyperpigmentation, and hair color lightening, and happen in less than 5% of treated patients. Other inflammatory skin disorders such as rosacea, seborrheic dermatitis, and wound healing are potential future fields warranting more studies.

Keywords

Acne · Dermatology · Photobiomodulation · Fluorescent light · Chromophore

Chromophor-Gel-assistierte Phototherapie. Eine neuartige und vielversprechende Photobiomodulationstherapie bei entzündlichen Hauterkrankungen des Gesichts und Hautalterung

Zusammenfassung

Die Phototherapie ist seit vielen Jahren eine der wesentlichen Stützen in der dermatologischen Therapie. In diesem Bereich gab es enorme Entwicklungen sowohl bei der Art des verwendeten Lichts als auch bei den Verfahren, wie das Licht auf die Haut appliziert wird. Die Chromophor-Gel-assistierte Phototherapie stellt eine neue Art der Photobiomodulationstherapie dar, bei der niederenergetisches blaues Licht aus einer Leuchtdiode („light emitting diode", LED) in Kombination mit einem Chromophor-Gel verwendet wird. Bei Exposition gegenüber blauem LED-Licht funktioniert das Chromophor-Gel wie ein Photokonverter und beginnt, fluoreszierendes Licht zu emittieren, welches die Haut von den epidermalen bis zu den dermalen Schichten durchdringt. Diese Therapie hat sich bisher als erfolgreich herausgestellt und ihre antiinflammatorische sowie bakterizide Wirkung (gegen *Propionibacterium acnes*) bei der Behandlung von mittel- bis schwergradiger Akne und bei der Hautverjüngung erwiesen. Jedoch beschränkt sich der therapeutische Nutzen dieses Systems nicht auf die genannten Indikationen. Dabei ist die Therapie gut verträglich und sicher. Unerwünschte Nebenwirkungen sind gering und auf transientes Erythem, Pruritus, Hauthyperpigmentierung und Aufhellung der Haarfarbe begrenzt; sie treten bei weniger als 5% der behandelten Patienten auf. Andere entzündliche Hauterkrankungen wie Rosazea, seborrhoische Dermatitis und die Wundheilung sind potenzielle zukünftige Anwendungsbereiche, die weitere Studien rechtfertigen.

Schlüsselwörter

Akne · Dermatologie · Photobiomodulation · Fluoreszenzlicht · Chromophor

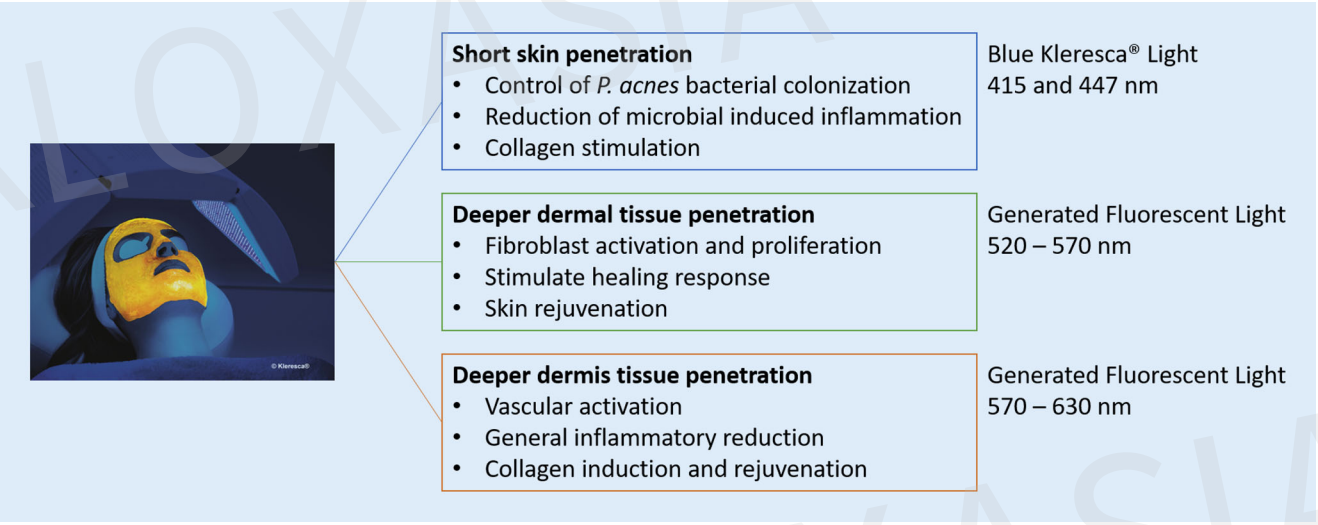

Fig. 2 ▲ Upon illumination of the photoconverter gel with the blue LED light, a biophotonic action is created in which fluorescence with different wavelengths and tissue penetration capabilities is generated. Photo: Reproduction by courtesy of Kleresca®

improve over time—even after the actual treatments have ended.

In a pilot study by Antoniou C et al. including 98 moderate to severe acne patients as defined by the Investigator's Global Assessment (IGA) scale 10 and lesion count—moderate acne defined as IGA grade 3 and 20–40 inflammatory lesions (papules or pustules) and ≤1 inflammatory nodule; severe acne defined as IGA grade 4 with more than 40 inflammatory lesions, ≤2 inflammatory nodules, and/or the presence of severe erythema and inflammatory scarring type lesions—a reduction of at least two grades in IGA scale severity was demonstrated in 51.7% of patients at week twelve. The therapy was performed twice weekly for 6 weeks and patients were followed-up for 12 weeks. Interestingly, patients with severe acne demonstrated better clinical response as compared with moderate acne. Treatment was considered as safe and well tolerated, with no serious adverse event and no patient discontinuation from the study due to any adverse event.

Treatment-emergent adverse events (TEAE; defined as those possibly, likely, or definitely causally related to treatment) were mild application site pain, erythema (as demonstrated in **Fig. 1c**), pruritus, and skin hyperpigmentation, as well as mild to moderate hair color lightening, in less than 5% of treated patients. Patient's quality of life was also improved, with a decrease in pain linked to acne after the 6-week treatment period [3, 20].

Many different treatment modalities exist to counteract the effects of cutaneous aging. Ablative methods have been the mainstay of non-surgical facial rejuvenation. In recent years, non-ablative techniques have been developed with the aim of achieving facial rejuvenation without epidermal damage [25]. Photo rejuvenation is a novel non-ablative technique that induces skin rejuvenation through photobiomodulation [7, 12]. LED photorejuvenation is a novel noninvasive procedure that is nonthermal, atraumatic, and induces collagen synthesis through biophotomodulatory pathways [17]. Subtypes of LED photomodulation include, but are not limited to, the photodynamic and the biophotonic platforms. The biophotonic platform is distinct from the photodynamic one in that both use a combination of LED light and a chromophore-rich gel, but in the biophotonic platform, chromophores act topically to enhance the effects of the LED light and are neither absorbed nor metabolized. Many clinical trials have shown the efficacy of LED therapy in skin rejuvenation [17, 26, 28, 29]. They include increased collagen deposition and decreased collagen degradation by upregulation fibroblast activity [17].

Studies with the chromophore gel-assisted light therapy have in a clinical trial been shown to stimulate the skin's own repairing mechanisms, improving complexion, encouraging the buildup of collagen wrinkle reduction, and reducing wrinkles [21]. In this study, analysis demonstrated that the chromophore gel-assisted light therapy was superior to standard of care (0.1% retinol-based cream) on subjective clinical assessment and multiple wrinkle scales, with statistically significant results obtained for brow positioning, perioral wrinkling, and total wrinkle score [21]. This was associated with significantly increased collagen production as shown by Gomori trichrome staining of skin biopsies obtained after therapy [21].

In addition, in vivo preclinical studies have shown favorable effects of the chromophore gel-assisted light therapy including stimulation of human fibroblast proliferation and increased collagen deposition in rat models. In in vitro studies a significant upregulation of 400% of collagen production has been seen by applying the chromophore gel-assisted light therapy to human fibroblasts [19], which has furthermore been confirmed by biopsies taken during a clinical trial [21].

Conclusion

The chromophore gel-assisted light therapy has so far demonstrated significant clinical efficacy in the treatment of moderate to severe acne. Treatment seems to be safe and well tolerated. It is worth mentioning that these patients are otherwise candidates for systemic antibiotics or isotretinoin therapy, which is accompanied with adverse events and is teratogenic (isotretinoin). The chromophore gel-assisted light therapy could be a potential alternative therapeutic option to conventional therapies, not just for acne but also for rosacea and probably chronic wounds. This warrants further clinical trials to prove the concept.

In contrast to ablative rejuvenation procedures, non-ablative rejuvenation procedures induce a dermal healing response without notable injury to the epidermis. Improving the appearance of the skin without injury to the epidermis is a hallmark of non-ablative skin rejuvenation. The exact mechanisms of non-ablative dermal remodeling are still under investigation; however, a subthreshold laser-induced injury to the dermis and/or the dermal vasculature theoretically results in a wound repair response, fibroblast stimulation, and collagen reformation. The chromophore gel-assisted light therapy has been shown in recent clinical trials to be a promising non-ablative rejuvenation procedure. However, further clinical trials especially comparing this strategy with ablative rejuvenation procedures would be of great interest.

Corresponding address

A. Jalili, MD, PhD
Department of Dermatology, Bürgenstock Medical Center
Bürgenstock 30, 6363 Obbürgen, Switzerland
ahmad.jalili@buergenstock.ch

Compliance with ethical guidelines

Conflict of interest. A. Jalili declares that he has no competing interests.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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