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Low-level laser therapy in immune-mediated skin disease: a narrative review

Joon Seok, Young Gue Koh, Beom Joon Kim

Department of Dermatology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea

Low-level laser therapy (LLLT) is now widely used in dermatology due to the relatively low risk of adverse events. LLLT can modulate mitochondria levels and affect various cell types, such as keratinocytes, lymphocytes, and fibroblasts, leading to its use in various treatments, such as pain reduction, tissue regeneration, and for conditions like inflammatory acne. This study explores the mechanism of action of LLLT and reviews its possible roles as a potential treatment option for common immune-mediated skin diseases, such as alopecia areata, psoriasis, and atopic dermatitis.

Key words: Alopecia areata; Atopic dermatitis; Low-level laser therapy; Phototherapy; Psoriasis

INTRODUCTION

Dermatologists have long used laser therapy for cosmetic procedures such as wrinkle reduction and skin resurfacing, and the treatment of acne and other skin diseases. Original laser technologies utilized heat-induced skin changes known as photothermolysis [1]. Low-level laser therapy (LLLT) typically has a narrow spectral width within the red or near-infrared (NIR) spectrum (600-1,000 nm) [2]. LLLT has a photochemical effect as opposed to an ablative or thermal effect like other medical laser procedures [3]. Due to its effect on stimulating tissue regeneration, reducing inflammation, and alleviating pain, LLLT is widely used in dermatologic fields such as wound healing, acne, and zoster pain [4-6]. In addition to these fields, many immunological diseases are contained in the dermatologic field, so it is necessary to consider the application of LLLT in these fields. This article covers the mechanism and application of LLLT as a potential non-invasive treatment for immune-mediated skin diseases. We describe the application of LLLT in alopecia areata (AA), psoriasis, and atopic dermatitis, which has a high frequency and large burden worldwide [7].

MECHANISM OF ACTION

The primary medical applications of LLLT are to reduce pain and inflammation, promote tissue repair, regenerate various tissues and nerves, and prevent tissue damage [8,9]. LLLT involves exposing cells or tissue to red or NIR light at low intensities [10]. This process is considered low-level because the energy or power densities employed are low in comparison with other forms of laser application, such as ablation, tissue cutting, and thermal coagulation [10].

The mechanism underlying the photobiostimulation of cells by LLLT is not yet fully understood. Absorption of red and NIR light by mitochondrial chromophores, particularly cytochrome c oxidase (CCO), which is part of the mitochondrial respiratory chain, is believed to be

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Correspondence
Beom Joon Kim
E-mail: beomjoon74@gmail.com
ORCID: https://orcid.org/0000-0003-2320-7621

the primary biological mechanism underlying the effects of LLLT [3,11]. It is believed that CCO acts as a photoacceptor for red and NIR light via Cu and Fe chromophores, thereby accelerating cellular metabolism and adenosine triphosphate (ATP) production [12,13]. In addition, LLLT promotes nitric oxide (NO) release due to the photo-dissociation of NO from CCO, thereby promoting vasodilation and increasing the rate of ATP production. NO release can modulate reactive oxygen species, which regulates growth and tissue repair-related transcription factors [14]. LLLT also reduces the inflammatory response by inhibiting cyclooxygenase-2, tumor necrosis factor-α (TNF-α), and prostaglandin E2 and modifying the affinity of transcription factors involved in cell survival, proliferation, regeneration, and tissue repair [15,16]. LLLT inhibits cell apoptosis and promotes cell proliferation in numerous cell types, including keratinocytes, lymphocytes, and fibroblasts [17-19]. Additionally, LLLT enhances cell migration and adhesion [11]. These cellular effects support the clinical application of LLLT. The suggested mechanism of LLLT is summarized in Fig. 1.

A previous study examined the changes in cytokine expression that occurred in healthy human skin following LLLT [20]. They evaluated the changes in T helper (Th)1 and Th2 activity by measuring interleukin (IL)-2 and IL-4, respectively. They demonstrated that LLLT induced endothelial cell edema and infiltration of neutrophils, monocytes, and mast cells in the extravascular dermis. They showed that LLLT increased both Th1 and Th2 activity, with greater activation of Th2 cells, as indicated by the higher levels of IL-4. This study suggests that LLLT influences immune cell infiltration, which may be a potential mechanism that LLLT influences cellular changes in immune-mediated skin diseases. Serum IL-4, IL-6, and TNF-α decreased after LLLT in the 2,4-Dinitrochlorobenzene-induced atopic dermatitis mouse model. However, there is currently no human data for the matter [21]. Further research is needed.

ALOPECIA AREATA

AA is an autoimmune disease affecting hair follicles, characterized by infiltration of inflammatory $CD8^+$ T cells predominantly around the follicular bulbs [22]. The excimer laser (308 nm) has been used as the primary light therapy for treating AA [23]. The excimer laser is a well-tolerated and effective treatment, but it is relatively expensive.

A previous study investigated the effectiveness of an infrared pulsed diode laser (904 nm) on resistant AA. Thirty-two of the thirty-four treated AA patches showed hair regrowth and no adverse side effects. However, this study did not evaluate post-treatment relapse, and only seven participants had control sites [24]. A case series demonstrated that LLLT contributed to hair regrowth in 75% of patients with scalp AA resistant to other treatments [25]. Using a medical device with a high output of infrared radiation (600-1,600 nm), 46.7% of patients with patchy AA showed hair regrowth in the treated areas 1.6 months sooner than in the untreated areas [26]. Recently, Yoo et al. [27] demonstrated that the combination therapy of LLLT and fractional laser treatment may be a promising approach to treat recalcitrant AA. Considering the excimer laser's expense and potential adverse side effects,

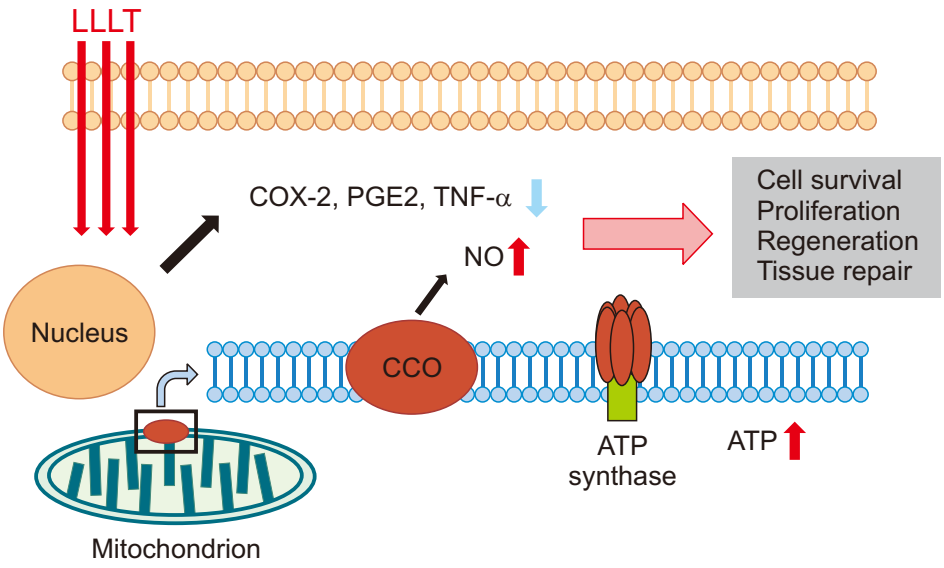

Fig. 1. Proposed model of the biological mechanism for low-level laser therapy (LLLT). COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-α; NO, nitric oxide; CCO, cytochrome c oxidase; ATP, adenosine triphosphate.

LLLT exhibits some promise in treating AA.

PSORIASIS

Psoriasis is a chronic, immune-mediated disease characterized by relapsing and remitting skin lesions

Table 1. Summary of clinical studies evaluating LLLT in alopecia areata, psoriasis vulgaris, and atopic dermatitis

Reference	Disease	Subject	Parameters	Treatment protocol	Outcomes
Waiz et al. [24]	Alopecia areata	16 Patients (34 patches) Age 4-50 yr (mean 26.6)	904 nm, 1.2 mW, 40 Hz, 0.07065 cm^2, 5 sec	1 week interval, total 4 sessions	Terminal hair regrowth (90.6%), White villous hair (9.4%) Maintained hair growth at 2 months follow-up
Yamazaki et al. [26]	Alopecia areata	15 Patients Age 18-68 yr (mean 38.4)	600-1,600 nm, 1.26 W, 4-sec pulses at 1 sec interval, 3 min	1 or 2 weeks interval With daily twice application of topical carpronium chloride 5%	7 cases (46.7%) showed regrowth in the irradiated areas earlier 1.6 months than in nonirradiated areas No effect in all atopic dermatitis patients (n = 3)
Yoo et al. [27]	Alopecia areata	20 Patients Age 29-66 yr (mean 44.84)	LLLT with fractional laser LLLT: 830 nm, 4 J/cm^2, 800 sec Fractional laser: 1,540 nm, 30 mJ, 15 ms, 1,000 MTZ/cm^2/ pass densitiy, 2 passes	2 weeks interval	The mean improvement score - 2.55 (grading scale - 4, most improvement (n = 5, 25%); 3, moderate improvement (n = 6, 30%); 2, moderate improvement (n = 5, 25%); 1, slightly improvement (n = 3, 15%); 0, no change (n = 1, 5%)
Maari et al. [32]	Psoriasis vulgaris	17 Patients Age 26-75 yr (mean 50.4)	417 nm, 8.5×10^{-3} W/cm^2, 10 J/cm^2	3 times/weeks, total 4 weeks With application of mineral oil to plaque before irradiation	The severity was similar at baseline ($p = 0.32$) Induction of complete photobleaching of protoporphyrin IX with single irradiation ($p = 0.005$)
Kleinpenning et al. [33]	Psoriasis vulgaris	20 Patients Age 28-74 yr (mean 55.7)	Blue light: 420 nm, 100 mW/cm^2 vs. Red light: 630 nm, 50 mW/cm^2, 20 min (2 plaques of one subject allocated to blue light and red light)	3 times/weeks, total 4 weeks With daily application of 10% salicylic acid in petrolatum	Significant improvement of erythema in both group (blue light: 43%, red light: 36%, control: 10%) Hyperpigmentation observed (blue light: n = 16, red light: n = 1; $p < 0.01$)
Pfaff et al. [34]	Psoriasis vulgaris	47 Patients Age 24-67 yr (mean 47.79)	453 nm, 200 or 100 mW/cm^2, 90 J/cm^2, over 30 min	5-7 times/weeks for 4 weeks, 3 times/weeks for next 4 weeks With topical calcipotriol or corticosteroids	Local Psoriasis Severity Index significantly improved compared to the control plaques (200 mW/cm^2, $p = 0.0005$; 100 mW/cm^2, $p = 0.0064$)
Morita et al. [36]	Atopic dermatitis	112 Patients Age 3-45 yr (mean 18)	830 nm, 60 mW, 120 sec	Once a week	Skin lesions improved in 69 cases (62%) Itching sensation improved in 79 cases (79%) ICAM-1 expression on epidermal cells decreased
Becker et al. [37]	Atopic dermatitis	36 Patients Age 20-57 yr (mean 36.9)	400-1,050 nm (mainly 400-500 nm), 28.9 J/cm^2, 24 min	2-5 days interval With topical corticosteroids	EASI score decreased by 29% (day 15, $p = 0.06$), 41% (3 m, $p \leq 0.005$), and 54% (6 m, $p \leq 0.002$) DLQI and clinical symptoms improved parallel to EASI score
Keemss et al. [38]	Atopic dermatitis	20 Patients Age 20-46 yr (mean 25.5)	453 nm, 50 mW/cm^2, 90 J/cm^2, 30 min	3 times/weeks, total 4 weeks	Significantly lower than control area at week 4 ($p = 0.0152$), week 6 ($p = 0.0115$)

Parmeters: wavelength (nm); power (W); power density (W/cm^2); energy (J); energy density (J/cm^2); illumination time (sec); in many cases, the parameters are partially unavailable.
LLLT, low-level laser therapy; ICAM, intercellular adhesion molecule; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index.

and joint pain. This immune response in psoriasis is characterized by an increase in Th17 cells, the source of an augmented IL-17 response. Narrowband ultraviolet B (NBUVB) therapy is one of the typical regimens for psoriasis treatment [28]. UV phototherapy offers multiple mechanisms for treating psoriasis, including apoptosis of inflammatory cells, suppression of Th17 cells, and up-regulation of regulatory T cells [29]. NBUVB has not been linked to an increased risk of skin cancer; however, UVB treatment side effects such as photosensitization make it a less desirable treatment option [30]. UVA light therapy is utilized much less often since it has been linked to an increased risk of skin cancer [31].

LLLT using UV-free light sources emitting blue (400-500 nm) or red (600-800 nm) light have been utilized recently in efforts to use UV-free devices to treat inflammatory skin diseases. However, the clinical results of using LLLT to treat psoriasis are inconsistent. Blue light treatment of psoriatic plaques did not result in clinical improvements compared with untreated plaques [32]. In contrast, a different study used higher doses of blue and red light, which improved psoriasis, and this improvement, except for erythema, was identical for both light sources [33]. However, in the clinical trial, there were no non-irradiated or sham-irradiated control plaques, and salicylic acid was permitted. The removal of scales by salicylic acid alone could have resulted in improvements of the psoriatic lesion; because of this, the interpretation of the results is limited. However, home-based UV-free blue light therapies have significantly improved psoriatic plaques compared with untreated lesions [34]. Because of the conflicting results and the observed efficacy of LLLT, additional clinical trials are required to determine whether LLLT is equivalent or inferior to the current phototherapies.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is believed to be caused by an epidermal barrier disruption and activation of epidermal inflammatory dendritic and innate lymphoid cells, which attract and interact with the invading Th2 cells [35]. The immediate cause of eczematous lesions is inflammation caused by Th2 dysregulation. Th2 cells secrete cytokines, primarily IL-4, IL-13, and IL-31, which activate Janus kinase pathways [35].

Notably, the use of LLLT in AD has not been fully evaluated and should be studied with caution because of the anecdotal reports of AD deterioration in the AA study [26]. Omi et al. [20] demonstrated that LLLT increased IL-4, a known Th2 mediator, which may influence AD pathology. Additionally, it is possible that LLLT is not beneficial for allergic skin disorders that are Th2 mediated. However, the potential efficacy of LLLT has been shown in several clinical studies of AD. 830 nm laser improved itching and skin lesions in AD patients [36]. The use of UV-free blue light to irradiate the entire patient also effectively reduced clinical symptoms. In the study, UV-free blue light was also employed as an adjunct therapy in patients that used topical steroids [37]. In a small, randomized study, locally targeted UV-free blue light treatment was found to improve clinical symptoms [38]. Additional research is needed to determine whether UV-free blue light-based LLLT effectively alleviates AD. Table 1 summarizes the clinical studies on AA, psoriasis, and AD treated with LLLT.

CONCLUSION

LLLT used in dermatologic fields is a relatively safe, non-invasive, painless, and simple to apply treatment with no reported side effects. LLLT is a relatively quick procedure, only lasting a few minutes. Unlike high-powered lasers, LLLT is compatible with all skin types. Due to its numerous benefits, LLLT is now widely utilized in dermatology to reduce pain, enhance tissue repair, promote regeneration, and treat inflammatory acne. To broaden the usage of LLLT treatment, the clinical efficacy and mechanism of action of LLLT should be clarified further to guide the future applications of laser therapies for AA, psoriasis, and AD. In addition, studies are needed to validate LLLT as an alternative treatment for other immune-mediated diseases such as vitiligo and hidradenitis suppurativa.

ORCID

Joon Seok, https://orcid.org/0000-0002-8016-8385
Young Gue Koh, https://orcid.org/0000-0002-6376-0328
Beom Joon Kim, https://orcid.org/0000-0003-2320-7621

AUTHOR CONTRIBUTIONS

Conceptualization: JS. Data curation: YGK. Formal analysis: YGK. Investigation: JS. Software: JS. Validation: BJK. Visualization: YGK. Writing–original draft: JS. Writing–review & editing: all authors.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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None.

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