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Low-Level Laser (Light) Therapy (LLLT) for Treatment of Hair Loss

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Abstract

Objective—Alopecia is a common disorder affecting more than half of the population worldwide. Androgenetic alopecia, the most common type, affects 50% of males over the age of 40 and 75% of females over 65. Only two drugs have been approved so far (minoxidil and finasteride) and hair transplant is the other treatment alternative. This review surveys the evidence for low-level laser therapy (LLLT) applied to the scalp as a treatment for hair loss and discusses possible mechanisms of actions.

Methods and Materials—Searches of PubMed and Google Scholar were carried out using keywords alopecia, hair loss, LLLT, photobiomodulation.

Results—Studies have shown that LLLT stimulated hair growth in mice subjected to chemotherapy-induced alopecia and also in alopecia areata. Controlled clinical trials demonstrated that LLLT stimulated hair growth in both men and women. Among various mechanisms, the main mechanism is hypothesized to be stimulation of epidermal stem cells in the hair follicle bulge and shifting the follicles into anagen phase.

Conclusion—LLLT for hair growth in both men and women appears to be both safe and effective. The optimum wavelength, coherence and dosimetric parameters remain to be determined.

Keywords

alopecia; androgenetic alopecia; hair loss; LLLT; low level laser (light)

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INTRODUCTION

It has long been known that red or near-infrared laser light promotes tissue repair and regeneration and low-intensity light called low-level laser therapy (LLLT) stimulates cellular activity [1]. After the discovery of lasers in the 1960s, there has been tremendous interest in using these laser devices to treat various medical conditions. The most commonly used devices have wavelengths in the range 500–1,100 nm (the so-called optical window of tissue) and they deliver fluences of 1–10 J/cm^2 with a power density of 3–90 mW/cm^2. LLLT has shown beneficial effects for a variety of medical conditions such as wound healing, nerve regeneration, joint pain relief, stroke recovery, and the prevention and treatment of mucositis [2–8]. Home-use LLLT devices that emit low power coherent monochromatic red light have been developed for various skin conditions, including hair growth [9]. In this review, we will focus on the use of LLLT as a potential treatment for several types of hair loss.

HAIR AND TYPES OF HAIR LOSS

Hair is one of the fastest growing tissues of the human body and the hair follicle, which is a unique characteristic of mammals, represents a stem cell-rich, prototypic neuroectodermal–mesodermal interaction system [10]. Hair follicles undergo repetitive regenerative cycles and each of these cycles consists of three stages: anagen (rapid growth, active stage), catagen (apoptosis-driven regression, physiological involution stage), and telogen (resting stage) (Fig. 1) [10]. Bulge stem cells are found in the region of the outer root sheath located just below the sebaceous gland, coinciding with the point of anchorage of the arrector pili muscle [11]. During the telogen to anagen transition, there is a tightly controlled activation of these epithelial bulge stem cells and within the same period, secondary hair germ cells give rise to transient amplifying (TA) progeny cells [12]. Throughout the entire anagen phase, there is a robust proliferation of the TA cells within the epithelial matrix of the hair follicle. Consequently, proliferating trichocytes terminally differentiate to form the bulk of the hair filament which is the final product of the hair cycle. The dermal papilla of the hair follicle is believed to be the key regulatory element in progenitor cell activation, hair matrix cell proliferation and terminal differentiation of trichocytes [13].

Androgenetic alopecia (AGA) is the most common form of hair loss in men affecting almost 50% of the male population [14]. AGA refers to hair loss in genetically susceptible individuals caused by effects of androgens such as testosterone and its derivative dihydrotestosterone (DHT). Testosterone is a lipophilic compound that diffuses across the cell membrane. Testosterone is converted by the cytoplasmic enzyme 5-α reductase to DHT, which is its more active form. There are two types of 5-α reductase; Type 1 is found in keratinocytes, fibroblasts, sweat glands, and sebocytes, and Type 2 is found in skin and the inner root sheath of hair follicles [15]. DHT binds the nuclear androgen receptor which regulates gene expression [15]. Disruption of epithelial progenitor cell activation and TA cell proliferation due to abnormal androgen signaling forms the essential pathophysiological component of this condition which in turn leads to continuous miniaturization of sensitive terminal hair follicles, and their conversion to vellus hair follicles [16,17]. Although the exact genes involved in hair loss are not clearly known, some of the proposed genes responsible for hair growth are desmoglein, activin, epidermal growth factor (EGF), fibroblast growth factor (FGF), lymphoid-enhancer factor-1 (LEF-1), and sonic hedgehog [15]. As of today, the most common methods used for treating AGA are topical minoxidil, finasteride (males only), and surgical hair transplantation [14]. Unfortunately, current therapies are not efficacious for all patients with AGA. Medical therapies require indefinite use and are limited by patient adherence; surgical options (hair transplants) are limited by cost, each patient's supply of donor hair, and possible scarring in donor sites [18]. Due to a

need for more efficacious therapies, LLLT has emerged as a new therapeutic approach to treat AGA. The Hairmax Lasercomb® was approved by the US Food and Drug Administration (FDA) and received 510 K clearance as a safe therapy for the treatment of male AGA in 2007 and female AGA in 2011 [19]. There has been a recent review [20] on the use of lasers and light therapies for alopecia that covered 308 nm excimer laser, fractional photothermolysis, and UV phototherapy, but did not cover LLLT mediated by red laser which is the main subject of the present review.

There are several other forms of hair loss such as alopecia areata (AA), telogen effluvium (TE), and chemotherapy-induced alopecia. AA is an autoimmune inflammatory condition, which presents with non-scarring alopecia and is characterized on histology by intra- or perifollicular lymphocytic infiltrates composed of CD4+ and CD8+ T-cells [19]. There are severe variants of AA: *alopecia totalis*, a total loss of scalp hair and *alopecia universalis*, total loss of scalp and body hair [21]. The most common treatment modality is intralesional corticosteroid injections; however, other treatments include topical and systemic corticosteroids, minoxidil, anthralin, contact sensitizers, psoralen plus ultraviolet A, cyclosporine, tacrolimus, and biologics such as alefacept, efalizumab, etanercept, infliximab, and adalimumab [15]. TE is abnormal hair cycling causing excessive loss of telogen hair [15]. Some common causes include acute severe illness, surgery, iron deficient anemia, thyroid disease, malnutrition, chronic illness, and medications such as oral contraceptives, lithium, and cimetidine. Chemotherapy works by destroying rapidly dividing cancer cells, however, at the same time, other rapidly dividing cells of the body such as hair follicles are also destroyed, and this unwanted effect leads to chemotherapy-induced alopecia starting 1–3 weeks and peaking at 1–2 months of treatment [22].

LLLT for Prevention and Reversal of Hair Loss

In the late 1960s, Endre Mester, a Hungarian physician, began a series of experiments on the carcinogenic potential of lasers by using a low-power ruby laser (694 nm) on mice. Mice were shaved as a part of the experimental protocol. To Mester's surprise, the laser did not cause cancer but instead improved hair growth around the shaved region on the animal's back [23]. This was the first demonstration of “photobiostimulation” with LLLT, and it opened a new path in the field of medicine [24].

Recently, attention has been drawn towards an uncommon but striking adverse effect of lasers being used for hair removal. It has been noticed in some cases that, increase in hair density, color or coarseness or a combination of these occurs at or around sites treated for hair removal [19,25–27]. The name given for this phenomenon is “Paradoxical Hypertrichosis” and the incidence varies from 0.6% to 10% [19]. A group of researchers also observed transformation of small vellus hairs into larger terminal hairs upon low fluence diode laser treatment and named this phenomenon “terminalization” of vellus hair follicles [28,29]. Until today, different mechanisms have been proposed to explain paradoxical hypertrichosis. In one study, this was attributed to presence of polycystic ovarian syndrome in 5 out of 49 females undergoing IPL laser treatment for facial hirsutism [27]. Another group of researchers suggested that although the heat produced by the laser is less than the temperature necessary for thermolysis of the hair follicle, this heat may be sufficient to induce follicular stem cell proliferation and differentiation by increasing the level of heat shock proteins (HSPs) such as HSP27, which plays a role in regulation of cell growth and differentiation [19]. Sub-therapeutic injury caused by the laser could also result in the release of certain factors which could potentially induce follicular angiogenesis and affect the cell cycling [29].

LLLT for Hair Regrowth, Proposed Mechanisms

As previously mentioned, in 2007 and 2011, LLLT mediated by a laser comb was approved by the FDA as a safe treatment for male and female pattern hair loss respectively [19]. Laser phototherapy is assumed to stimulate anagen re-entry in telogen hair follicles, prolong duration of anagen phase, increase rates of proliferation in active anagen hair follicles and to prevent premature catagen development [19,30]. The exact mechanism of action of LLLT in hair growth is not known; however, several mechanisms have been proposed. Evidence suggests that LLLT acts on the mitochondria and may alter cell metabolism through photodissociation of inhibitory nitric oxide (NO) from cytochrome *c* oxidase (CCO) [31] (Unit IV in the respiratory chain of mitochondria), causing increased ATP production, modulation of reactive oxygen species, and induction of transcription factors such as nuclear factor kappa B, and hypoxia-inducible factor-1 [32]. These transcription factors in return cause protein synthesis that triggers further effects down-stream, such as increased cell proliferation and migration, alteration in the levels of cytokines, growth factors and inflammatory mediators, and increased tissue oxygenation [32]. 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 [32–34]. Yamazaki and coworkers observed an upregulation of hepatocyte growth factor (HGF) and HGF activator expression following irradiation of the backs of Sprague Dawley rats with linear polarized infrared laser [35].

Some authors have drawn comparisons between the mechanism of action of LLLT and the mechanism of minoxidil. Even though the mechanism by which minoxidil promotes hair growth is not fully understood, it is known that minoxidil contains an N-oxide group which may be able to release NO, which is an important cellular signaling molecule involved in many physiological and pathological processes [36] and is also a vasodilator [37]. Furthermore, minoxidil is an ATP sensitive K^+ channel opener which in turn cause hyperpolarization of cell membranes [38]. Since ATP sensitive K^+ channels in mitochondria and increased levels of NO [39–41] may have some role to play in effects of LLLT in brain and heart [41–43], given what is known about the role of K-ATP channels and NO in hair regrowth mediated by minoxidil, a mechanistic overlap can be identified. Weiss and coworkers, by using RT-PCR and microarray analysis, demonstrated that depending on the treatment parameters, LLLT modulates 5-α reductase expression, which converts testosterone into DHT, alters vascular endothelial growth factor gene expression as wells as matrix metalloproteinase (MMP-2) which have significant roles in hair follicle growth, and in turn the group reported stimulation of hair growth on human dermal papillae cells [44–47]. Notably, similar changes have also been reported with topical minoxidil use [47]. Furthermore, LLLT has been demonstrated to modulate inflammatory processes and immunological responses, which may also have an effect in hair regrowth [32,48]. A study conducted by Wikramanayake et al. [19] on C3H/HeJ mouse model of AA supported this assumption wherein the mice treated with laser comb, increased number of hair follicles with majority in anagen phase were noted with decreased inflammatory infiltrates. Considering that inflammatory infiltrates are highly disruptive to hair follicle biology and multiple cytokines such as IFN-γ, IL-1α and β, TNF-α, MHC and Fas-antigen and macrophage migration inhibitory factor are all involved in the cyclic hair growth and have been shown to play a role in the pathogenesis of AA, modulatory effects of LLLT on inflammation might have a significant role in treatment of AA [19].

LLLT for Hair Regrowth in Animal Models

Wikramanayake et al. [19] demonstrated the hair growth effects of LLLT on C3H/HeJ mouse model of AA, using HairMax Laser Comb® (emits nine beams and attached combs help to part the hairs and improve delivery of laser light to scalp), 655 nm for 20 seconds daily three times per week for a total of 6 weeks [19]. At the end of the treatment, hair regrowth was observed in all the laser treated mice but no difference was observed in the sham-treated group (control group undergoing similar treatment procedures without administration of the key therapeutic element, such as application of light that has no therapeutic effect) [19]. On histology, while an increased number of anagen hair follicles was observed in laser-treated mice, sham-treated mice demonstrated telogen follicles with absent hair shafts [19].

Shukla et al. [49] investigated the effect of helium–neon (He–Ne) laser (632 nm, at doses of 1 and 5 J/cm^2 at 24-hour intervals for 5 days) on the hair follicle growth cycle of testosterone-treated and un-treated Swiss albino mice skin. Testosterone treatment led to the inhibition of hair growth which was characterized by a significant increase in catagen follicles [49]. The results showed that exposure of testosterone treated mice to the He–Ne laser at a dose of 1 J/cm^2 led to significant increase in the number of hair follicles in anagen phase when compared to the other groups. However, the 5 J/cm^2 treated group showed a significant decrease in the number of anagen hair and an increase in telogen hair follicles. This is consistent with the biphasic effect of LLLT wherein low irradiation doses may cause biostimulation and high irradiation doses may cause inhibition [32,49]. Since hair growth promoting effect of He–Ne laser (1 J/cm^2) was much higher for the testosterone-treated mice than the non-testosterone treated mice, it can be suggested that cells growing at slower rate or under stress conditions respond better to the stimulatory effects of LLLT. Another notable observation in this study is that in He–Ne laser (1 J/cm^2) irradiated skin, some of the anagen follicles appeared from deeper layers of the skin and possessed a different orientation which both represent the late anagen stage in the hair cycle that in turn suggests that laser irradiation prolongs the anagen phase [50,51]. Furthermore, in testosterone-treated and He–Ne (1 J/cm^2) irradiated skin, hair follicles were seen to originate from the middle of the dermis, and these follicles represent early anagen phase [49]. Based on this observation, it may be proposed that the majority of catagen and telogen follicles re-enter into anagen phase as a result of low-level laser irradiation at 1 J/cm^2.

The incidence of alopecia related to cancer treatments such as chemotherapy is close to 65% and it has severe negative psychological effects [22]. LLLT has been suggested as a treatment modality to promote hair regrowth for chemotherapy-induced alopecia. In a rat model, different regimens of chemotherapy were given to each rat in conjunction with an LLLT device which had the laser unit and switch from the HairMax LaserComb®, but without the comb or handle [52]. Hair regrowth occurred 5 days earlier in all laser treated rats when compared to control and sham-treated rats. Histology results demonstrated large anagen hair bulbs penetrating deeper into the subcutaneous adipose tissue in LLLT-treated skin. Furthermore, it did not compromise the efficacy of chemotherapy by causing localized protection of the cancer cells [52].

LLLT for Hair Growth in Clinical Trials

In order to test the effect of linear polarized infrared irradiation in treatment of AA, a study was conducted with 15 patients (6 men, 9 women) using Super Lizer™, a medical instrument emitting polarized pulsed linear light with a high output (1.8 W) of infrared radiation (600–1,600 nm) that is capable of penetrating into deep subcutaneous tissue [53]. The scalp was irradiated for 3 minutes either once every week or once every other week until vellus hair regrowth in at least 50% of the affected area was observed. Additionally,

carpronium chloride 5% was applied topically twice daily to all the lesions in combination with oral antihistamines, cepharanthin and glycyrrhizin (extracts of Chinese medicine herbs) [53]. As a result of this study, in 47% of the patients' hair growth occurred 1.6 months earlier in irradiated areas than in non-irradiated areas [53]. However, 1 year after irradiation, all the lesions disappeared; hair density, length and diameter of hair shafts were the same both in irradiated and non-irradiated lesions; suggesting that LLLT only accelerates the process of hair regrowth in AA patients. It is worth mentioning that the method for assessment of hair regrowth, density and thickness was not clearly stated, which was one of the main limitations of this study.

Using 655 nm red light and 780 nm infrared light once a day for 10 minutes, 24 male AGA patients were treated and evaluated by a group of investigators [54]. Evaluation has been performed via global photography and phototrichogram [54]. Following 14 weeks of treatment, increase in hair density on both the vertex (145.1/cm^2 vs. 137.3/cm^2 pre-treatment, $P < 0.005$) and occiput (163.3/cm^2 vs. 153.3/cm^2, $P < 0.005$) as well as anogen/telogen ratio (vertex: 84.7 vs. 79.7 pre-treatment and occiput: 91.9 vs. 89.6 pre-treatment) was observed, and 83% of the patients reported to be satisfied with the treatment [54].

Satino et al. [55] tested the efficacy of LLLT on hair growth and tensile strength on 28 male and 7 female AGA patients. Each patient was given a HairMax LaserComb® 655 nm, to use at home for 6 months for 5–10 minutes every other day [55]. Tensile strength was measured by VIP HairOSCope (Belson Imports, Hialeah, FL) through removal of three typical terminal hairs from a one square centimeter area. Hair count was performed within one centimeter square space created within a mold that was prepared around the area of greatest alopecia. A surgical hook and magnification has been used while counting the number of hair. In terms of hair tensile strength, the results revealed greater improvement in the vertex area for males and temporal area for females; however, both sexes benefited in all areas significantly [55]. In terms of hair count, both sexes and all areas had substantial improvement (for temporal area: 55% in women, 74% in men, in vertex area: 65% in women, 120% in men) with vertex area in males having the best outcome [55]. The HairMax LaserComb® device was tested by Leavitt et al. in a double-blind, sham device-controlled, multicenter, 26-week trial randomized study among 110 male AGA patients [30]. Patients used the device three times per week for 15 minutes for a total of 26 weeks [30]. Significantly greater increase in mean terminal hair density compared to subjects in the sham device group has been reported [30]. Significant improvements in overall hair regrowth, slowing of hair loss, thicker feeling hair, better scalp health and hair shine were also demonstrated in terms of patients' subjective assessment at 26 weeks over baseline [30].

Recently, a double-blind randomized controlled trial by Lanzafame et al. [56] using a helmet containing 21, 5 mW lasers and 30 LEDs (655±5 nm, 67.3 J/cm^2, 25 minutes treatment) every other day for 16 weeks reported 35% increase in hair growth among male AGA patients. Another recent study by Kim et al. [57] designed a 24 weeks randomized, double-blind, sham device-controlled multicenter trial among both male and female AGA patients in order to investigate the efficacy of a helmet type LLLT device combining 650 nm laser with 630 and 660 nm LEDs (total energy density—92.15 mW/cm^2, 47.90 J/cm^2 for 18 minutes). Even though mean hair thickness (12.6±9.4 vs. 3.9±7.3 in control group, $P = 0.01$) hair density (17.2±12.1 vs. –2.1±18.3 in control group, $P = .003$) increased significantly in the treatment group, there was no prominent difference in global appearance between the two groups [57]. Findings from a different study by Avram and Rogers [58] were in accordance with these results where LLLT increased hair count and shaft diameter, however, blinded global images did not support these observations.

Safety and Possible Side Effects

LLLT has demonstrated a remarkably low incidence of adverse effects when it has been used over 50 years for diverse medical conditions and in a variety of anatomical sites. In the specific area of LLLT for hair growth, the only adverse reports in humans, was the temporary onset of TE developing in the first 1–2 months after commencing LaserComb treatment [55], but disappearing on continued application. Some other possible considerations are presence of dysplastic or malignant lesions on the scalp which could be stimulated to grow by proliferative effects of LLLT [59].

CONCLUSION

LLLT was discovered serendipitously in the 1960s when mice irradiated with a low fluence red laser grew hair. Since that time LLLT has demonstrated promise in conditions from wound healing to stroke recovery, from treatment of musculoskeletal pain to prevention of mucositis. Animal and human data have slowly accumulated supporting LLLT for hair growth (Table 1). LLLT appears to improve a variety of non-scarring alopecias—AGA, AA, and chemotherapy-induced alopecia. Based on the studies demonstrating LLLT's effects on promoting graft survival, it may be further suggested to have a potential to be used during the immediate period of post-hair transplant surgery to facilitate the healing process and enhance viability and earlier growth of the grafts [60,61]. While mechanisms are still emerging, LLLT may increase anagen hairs through release of NO from CCO by photodissociation and LLLT may reduce inflammation in AA. However, more studies are needed to optimize treatment parameters and determine long-term efficacy as well as safety of emerging LLLT technologies. Most studies investigating effects of LLLT on hair growth have used wavelengths that range from 635 to 650 nm, but as of today no study has compared the effect of near-infrared wavelengths such as 810 nm, which have deeper penetrating capacities, to red light. Moreover, further studies are required to compare efficacy of different light sources (continuous vs. pulsed) and methods of light delivery (laser vs. LED).

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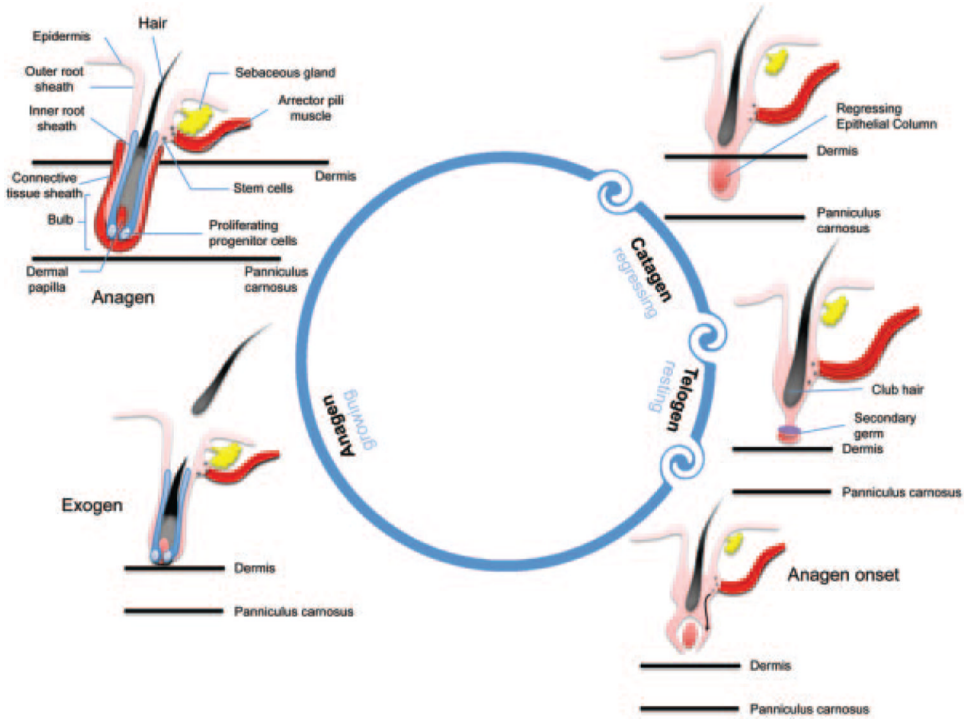

Fig. 1.

Stages of hair cycle. Anagen stage is the growth stage which may last 2–6 years. In cagaten stage, club hair transitions upwards towards the skin pore and the dermal papilla begins to separate from the follicle. This phase usually lasts from 1 to 2 weeks. In telogen stage, the dermal papilla fully separates from the follicle and it takes about 5–6 weeks. Lastly, the dermal papilla moves upward to meet hair follicle once again and the hair matrix begins to form new hair, which represents the return to anagen stage.

TABLE 1

Summary of the Studies That Investigated the Efficacy of LLLT for Hair Growth

Author, year	Subject group	Alopecia type	Device type, parameters and treatment regimen	Refs.
Wikramanayake et al., 2012	C3H/HeJ mice	Alopecia areata	HairMaxLaserComb®, 655 nm, 20 seconds daily, 3 times/week, for 6 weeks	[19]
Shukla et al., 2010	Swiss albino mice	Testosterone treated (increase in catagen follicles) vs. non-treated	632 nm, 1 and 5 J/cm^2 at 24-hour intervals for 5 days	[49]
Trueb, 2009	Rat model for chemotherapy-induced alopecia	Chemotherapy-induced alopecia	Laser unit and switch from the HairMaxLaserComb®, but without the comb or handle	[52]
Yamazaki et al., 2003	6 male and 9 female patients	Alopecia areata	Super Lizer™ emitting polarized pulsed linear light, 600–1,600 nm, 1.8 W. 3 minutes/week or every other week. Additional supplements and medications have been given. Treated until vellus hair regrowth in at least 50% of the affected area was observed.	[53]
Kim et al., 2007	24 male patients	Androgenetic alopecia	655 and 780 nm, once a day for 10 minutes, for 14 weeks	[54]
Satino et al., 2003	28 male and 7 female patients	Androgenetic alopecia	HairMaxLaserComb® 655 nm, 5–10 minutes every other day, for 6 months	[55]
Lanzafame et al., 2013	44 male patients	Androgenetic alopecia	Helmet (TOPHAT655) containing 21, 5 mW lasers and 30 LEDs, 655 ± 5 nm, 67.3 J/cm^2 25 minutes every other day, for 16 weeks	[56]
Kim et al., 2013	40 patients	Androgenetic alopecia	Helmet type LLLT device, 650 nm laser with 630 and 660 nm LEDs, 92.15 mW/cm^2, 47.90 J/cm^2, 18 minutes/day, for 24 weeks	[57]
Leavitt et al., 2009	110 male patients	Androgenetic alopecia	HairMaxLaserComb, 3 times/week for 15 minutes, for 26 weeks	[30]

Efficacy and Safety of a Low-Level Light Therapy for Androgenetic Alopecia: A 24-Week, Randomized, Double-Blind, Self-Comparison, Sham Device-Controlled Trial

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BACKGROUND Previous studies have reported the benefits of low-level/light laser therapy (LLLT) for the promotion of hair regrowth. However, the effectiveness of LLLT for the treatment of androgenetic alopecia (AGA) is still a topic of debate.

OBJECTIVE To investigate the efficacy and safety of LLLT on hair regrowth in patients with AGA.

METHODS This 24-week, randomized, double-blind, self-comparison, sham device-controlled trial enrolled 100 patients with AGA. All participants were randomly assigned to receive the investigational LLLT on one side of the head and sham light treatment on the contralateral side, 3 times weekly for 30 minutes each, over a 24-week period. Global scalp photography, phototrichogram assessment, the investigator's global assessment (IGA) of hair regrowth, and the subject's assessment of the treatment satisfaction were used for evaluation.

RESULTS After 24 weeks of treatment, the LLLT-treated scalp exhibited significantly greater hair coverage than the sham light-treated side (14.2% vs. 11.8%, $p < .001$). A significantly greater improvement from baseline in hair thickness, hair count, hair coverage, and IGA were also observed in the LLLT-treated side than in the sham light-treated side at the 12- and 24-week visits. No serious adverse events were observed.

CONCLUSION The use of LLLT might be an effective, safe, well-tolerated treatment for AGA.

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Androgenetic alopecia (AGA), a hereditary androgen-dependent progressive thinning of scalp hair with a pattern distribution, is the most common hair loss disorder affecting 60% to 70% of the adult population worldwide, with prevalence increasing with age.[1–3] Androgenetic alopecia is characterized by the androgen-mediated miniaturization of terminal hairs to vellus hairs.[4] Hair is considered to be an important feature of self-image and patients with AGA are perceived to be older, which may affect self-esteem and

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personal attractiveness, and may potentially lead to impairment of quality of life and psychosocial distress.[5] Although the prevalence of AGA is high, the treatment modalities are limited and mainly include minoxidil, 5-alpha-reductase inhibitors, and hair transplantation.[6] Hence, there is a need for adjuvant and newer modalities of treatment for AGA.

Although Andre Mester serendipitously observed hair regrowth induced by low energy lasers (694 nm) in mice as early as 1967,[7,8] low-level laser/light therapy (LLLT), or photobiomodulation or photobiostimulation, had not been promoted to prevent hair loss and to stimulate hair growth until the past decade. There is a growing body of animal and human data supporting the use of LLLT to stimulate hair growth. LLLT is speculated to exert its effects on hair growth by stimulating anagen reentry in telogen hair follicles, prolonging duration of the anagen phase, increasing rates of proliferation in active anagen hair follicles, and preventing premature catagen development.[9,10] However, most previous studies have been small-scale, uncontrolled, and open-label in nature. Well-designed controlled studies yielding convincing evidence of the efficacy of the use of these devices are scant. Therefore, this study was conducted to assess the efficacy and safety of a helmet-type LLLT device that emits red light for the treatment of AGA.

Methods

Study Design

The 24-week, randomized, double-blind, self-comparison, sham device-controlled trial was performed at 2 research centers: the National Taiwan University Hospital and the National Taiwan University Hospital Hsin-Chu branch. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by the approval given by the institutional review board of each aforementioned center (201310067DSB, 102-026-F). The trial was assigned a clinical protocol number by ClinicalTrials.gov Protocol Registration System (NCT 03331003).

Study Population

To be included in the trial, subjects were to be of 25 to 60 years of age with active AGA (Norwood–Hamilton classification of IIa–V for male subjects and Ludwig/Savin classification of I-4, II-1, II-2 for female subjects) and have Fitzpatrick skin Type I–IV. We specifically excluded any patient who used topical or systemic medications affecting hair growth within the 6 months before recruitment; or had previous hair transplantation, underwent scalp reconstruction procedure, hair braiding or scalp tattoo; used depilation agents, laser hair removal or beeswax on the scalp; or who had hair disorders other than AGA or systemic diseases that might have affected the results. We also excluded patients with insignificant contrast of scalp and hair color, such as light skin color or white hair, which would have influenced the assessment of hair growth.

Intervention

The iRestore ID-520 (WELLMIKE Technology Corp., New Taipei City, Taiwan) is a helmet-type LLLT device with a light source consisting of light-emitting diodes (LEDs) array emitting wavelengths of 660 ± 5 nm (≤22 mW/cm^2, 27 LED, AL-513UR2C) and a laser diode array emitting 650 ± 10 nm (≤4.6 mW, 27 pieces, TA520). The iRestore phototherapy system used as the light source for this study was modified such that a 650/660 nm light was emitted to half of the head and the contralateral side was exposed to non-LLLT sham light from LED bulbs, which were coated with red paint to resemble the red irradiating light of the therapeutic light source. Therefore, the participants would be exposed to LLLT (red LED and laser irradiation) on one half of the head and non-LLLT sham wavelength on the other half. All participants were randomly assigned into 2 treatment groups: one group was exposed to the investigational LLLT light on the left side and the sham light on the right, and the other group was exposed to the opposite light sources on their respective sides. In order to maintain double-blinded design, we covered the devices with exclusive masks, so that both the subjects and investigators could not distinguish the investigational group from the control group based on the light source. Participants were instructed on how to operate the device at the baseline visit and were given a schedule consisting of 10 minutes treatment for the anterior, middle, and posterior scalp (30 minutes for the global scalp) 3

times per week for 24 weeks. To assess compliance, adherence to the treatment protocol was evaluated by checking the running frequency and time of the investigated device each week. Safety of this treatment was also evaluated at each visit.

Efficacy Evaluation

Global scalp photography, phototrichogram assessment, the investigator's global assessment (IGA) of hair regrowth, and the subjects' assessment of the treatment satisfaction were performed at baseline and at the 4th, 12th, and 24th weeks from the baseline day. At the baseline visit, an anatomical symmetric area of 1 cm^2 where miniaturized hairs were prominent was selected on each side of the frontal or vertex scalp for phototrichogram assessment. The hairs in the selected site were trimmed to a maximum height of 1 mm in length and the skin was marked with a medical temporary tattoo using gardenia blue dye under aseptic technique (Figure 1). The folliscope (IBS-01 Pro Beauty Scope; Kowa Optics Corp., New Taipei City, Taiwan) was used to record the hair growth density in the tattooed area to analyze the hair count, hair thickness, and hair coverage.[11]

Several parameters have been used to assess the rate of hair growth and to determine the efficacy of treatment, including hair count, thickness, and density (number per cm^2).[12,13] Some treatments for hair loss may either stop or reverse the process of hair follicle miniaturization, others might only increase hair counts, while others may improve both. These outcomes have been observed in Phase III studies of men with AGA treated with finasteride, which showed that the increase in hair count reaches a plateau after 1 year of treatment, whereas the hair coverage increased continuously.[14] Moreover, from a clinical standpoint, both changes in hair thickness and density have an impact on the patients' perceived improvement under treatment. Hair coverage combines both the valuation

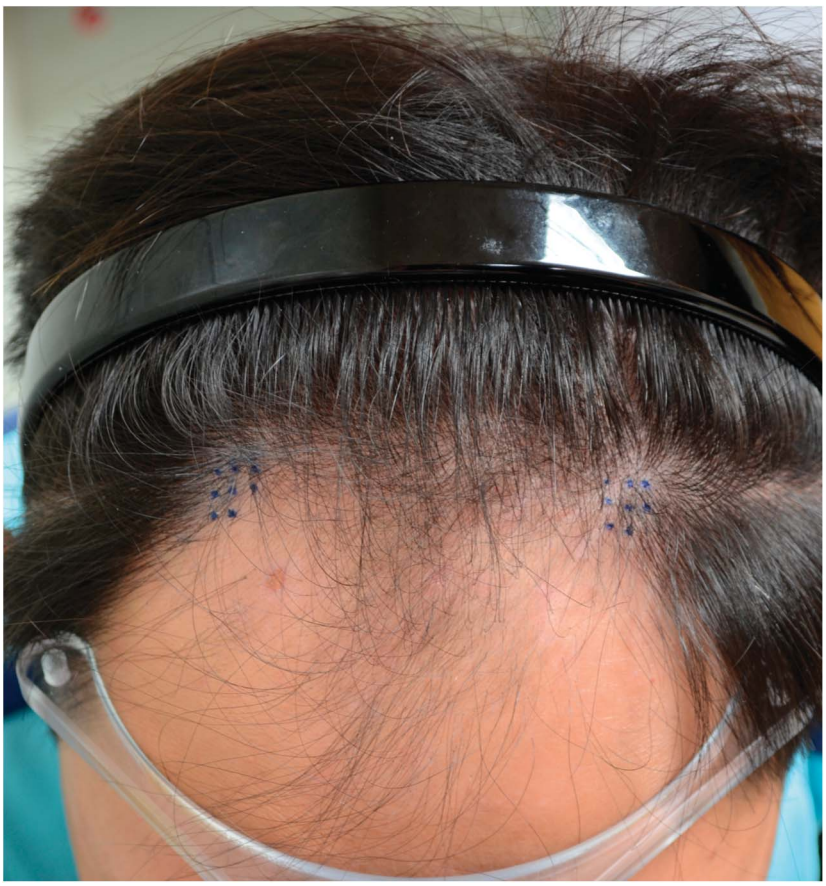

Figure 1. Global photographs of a male subject at baseline. The selected areas of the scalp on both sides of the head were marked with a medical temporary tattoo using gardenia blue dye.

of hair density and hair thickness. Thus, the primary end point in this study was hair coverage of the selected evaluation area after the 24 weeks of treatment. The hair coverage, which represents the percentage of the area covered by hairs in a unit area, was obtained using the following formula:

$$\sum_{i=1}^{n} \pi R_i^2$$

where n is the hair number in 1 cm^2 that is calculated from the selected scalp area for evaluation. R_i is the half width of hair of number i, assuming that the cross section of the hair is circular, and πR_i^2 is the cross-sectional area of a single strand of hair. Hence, $\sum_{i=1}^{n} \pi R_i^2$ is defined as the total area of all cross-sectional areas of the hair strands measured.

The investigator performed the global assessment of hair regrowth by visual inspection and by applying a 3-point evaluation scale (0 = no hair growth, 1 = thin, 2 = medium, 3 = intense). The subject's assessment of the treatment satisfaction was measured on a 4-point evaluation scale (0 = dissatisfactory, 1 = slightly satisfactory, 2 = moderately satisfactory, 3 = satisfactory, 4 = highly satisfactory). The secondary end points included hair coverage at the 4- and 24-week visits, change of hair thickness, hair number in the selected evaluation area, IGA, and subject's assessment of treatment satisfaction at the 4-, 12-, and 24-week visits.

Statistical Analysis

Our null hypothesis (H_0) was that the difference between the LLLT-treated and control scalp in the hair coverage at Week 24 was equal to zero. Hence, the alternative hypothesis (H_1) was that the difference in hair coverage between the 2 sides of the scalp at Week 24 was not equal to zero. The primary analysis was an intention-to-treat analysis (ITT) in which the results from all patients assigned to a group were taken into account. For subjects that withdraw from the trial, the missing values were calculated based on the last observation carried forward. Additionally, per-protocol (PP) analysis was also conducted. The PP analysis referred to the inclusion in the analysis of only those patients who strictly adhered to the protocol and thus provided an estimate of the true efficacy of the intervention. The safety analysis set comprised all subjects who received at least one therapy and one safety evaluation. Statistical analysis was conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). Differences between the groups were analyzed using the paired-*t*-test when normally distributed and analyzed using Wilcoxon signed-rank test otherwise. For all tests, $p < .025$ was considered significant as one-sided test, except for baseline data. $p < .05$ was considered significant for the 2-sided test.

Results

Study Population

Overall, 108 subjects were screened and of these, 100 subjects were available for ITT analysis and were randomized to receive the LLLT therapy on one side of the scalp and sham device treatment on the contralateral side. Two subjects withdrew from the study and a further 2 patients were excluded due to violation of the study protocol. Seventy-four patients completed the study per protocol and were included in the PP population (Table 1). In the PP analysis, there were no statistically significant differences in hair coverage, IGA, hair width, and hair count on the LLLT-treated side and control side at baseline.

Efficacy Analyses

For the primary end point analyzed by ITT, the hair coverage was significantly higher in the LLLT-treated side than the sham-treated side after 24 weeks of treatment (14.2% vs. 11.8%, $p < .001$), although the LLLL-treated side had lower hair coverage and hair thickness at baseline (Table 2). A significant increase in hair coverage from baseline was observed for the LLLT-treated side after a 24-week treatment ($p < .001$). In contrast, the control side showed a decrease in hair coverage from baseline at the 24-week visit ($p = .002$) (Figure 2A). Compared to the control side, the treated side also exhibited significantly increased hair coverage at the 4- and 12-week visits (Figures 2A and 3).

After 24 weeks of treatment, the LLLT-treated side showed a much higher increase in hair thickness

TABLE 1. Baseline Demographic Characteristics

Characteristic	*ITT Population (N = 100)*	*PP Population (N = 74)*
Male, n (%)	83 (83%)	61 (82.4%)
Norwood–Hamilton classification, n		
IIa	3	3
III	17	13
IIIa	2	1
IIIv	22	17
IV	11	8
IVa	0	0
V	8	19
Female, n (%)	17 (17%)	13 (17.6%)
Ludwig (Savin) classification, n		
I-4	9	5
II-1	6	6
II-4	2	2
Fitzpatrick skin type, x/n (%)		
I	0	0
II	0	0
III	31/100 (31%)	21/74 (28.4%)
IV	69/100 (69%)	53/74 (71.6%)
Age, mean ± SD	37.2 ± 8.3	37.1 ± 8.1

ITT, intention-to-treat; PP, per-protocol.

than the sham-treated side, with a mean (±SD) of 2.3 ± 4.3 μm versus −1.3 ± 3.5 μm ($p < .001$) (Figure 3). Similar improvement in hair thickness was also observed in the LLLT-treated side at the 4- and 12-week visits (Figure 2B). In terms of hair count, the difference in the hair count change at 4, 12, and 24 weeks from the baseline between the LLLT-treated and the control side was highly significant (Figure 2C). The IGA of hair growth improvement between the 2 sides was significantly different at the 12- and 24-week visits (Figure 2D), but the assessment by subjects of the treatment satisfaction between the treated and untreated sides was not significantly different (Table 2).

Moreover, the PP analysis showed similar results with the ITT analysis. A significantly higher hair count, hair width, and hair coverage were observed in the LLLT intervention side versus the control side scalp after treatment (Table 2).

Safety and Tolerability

Adverse events were reported in 29 patients (29.3%), and the events were considered to be possibly or probably associated with treatment included eczema (4%), pruritus (3.0%), and acne (1.0%). None of the subjects experienced an adverse event that resulted in the discontinued use of the study device or interruption of the study. Most adverse events resolved within 2 weeks.

Discussion

Low-level laser/light therapy devices have been used to induce a variety of biomodulatory effects associated with a diverse range of wavelengths, including anti-inflammatory activity, pain reduction, wound healing, anti-edematous effects, immunomodulatory effects, and improvement of local blood circulation.[15–17] Recently, paradoxical hair growth has been noted at or around sites treated for hair removal using most laser types and intense pulsed light sources at low fluency.[18,19] Thus, it has been proposed that such an increase in hair growth is caused by the use of sub-optimal fluencies that are too low to induce thermolysis, but high enough to stimulate follicular hair growth. Since then, attention has been drawn toward investigating whether the LLLT can indeed enhance hair growth. Treatment of hair loss with LLLT has been studied in different human and animal models using a variety of light sources, wavelengths, and treatment parameters. In 2007, LLLT was approved by the United States Food and Drug Administration as a treatment for hair loss.[20]

Although the exact mechanism of action of LLLT on hair growth is not fully understood, several theories have been proposed. LLLT is assumed to release nitric oxide from cytochrome c oxidase, a chromosphere responsible for the absorption of red/infrared light, driving the electron transport chain to generate adenosine triphosphate and reactive oxygen species, as well as the induction of transcription factors.[21–24] These effects in turn cause vasodilation, cellular proliferation, migration, modulation in the levels of growth stages of hair follicles, leading to subsequent reversal of the dormant telogen stage of growth toward the active growth anagen stage, prolonged

TABLE 2. Comparison of Changes in Hair Coverage, Hair Count, Hair Thickness, IGA, and SAS Between LLLT and Control Groups

	ITT Population (N = *100*)			*PP Population* (N = *74*)		
Parameters, Mean ± SD (p)	*Active Treatment*	*Sham*	p	*Active Treatment*	*Sham*	p
Hair coverage at baseline, %	11.8 ± 6.6	12.8 ± 7.4	.0123*	10.9 ± 5.9	11.6 ± 6.7	.106
Hair coverage at week 24, %	14.2 ± 7.6	11.8 ± 7.1	<.001***	12.9 ± 6.5	10.6 ± 6.1	<.001***
Change of hair coverage from baseline at week 4, %	1.4 ± 2.4	−0.4 ± 2.5	.0315*	1.1 ± 2.4	−0.4 ± 2.6	.026*
Change of hair coverage from baseline at week 12, %	1.6 ± 3.4	−1.0 ± 3.4	<.001***	1.4 ± 3.4	−0.7 ± 3.2	.005**
Change of hair coverage from baseline at week 24, %	2.4 ± 3.7	−1.0 ± 3.2	<.001***	2.0 ± 3.7	−1.0 ± 3.2	<.001***
Hair thickness at baseline, μm	34.3 ± 8.7	35.4 ± 9.7	.0106*	33.1 ± 8.1	33.9 ± 9.1	.079
Change of hair thickness from baseline at week 4, μm	1.2 ± 3.1	−0.6 ± 2.7	.0639	1.0 ± 3.2	−0.5 ± 2.8	.074
Change of hair thickness from baseline at week 12, μm	1.5 ± 4.0	−1.2 ± 3.8	<.001***	1.3 ± 4.1	−0.8 ± 3.9	.021*
Change of hair thickness from baseline at week 24, μm	2.3 ± 4.3	−1.3 ± 3.5	<.001***	1.9 ± 4.4	−1.2 ± 3.4	<.001***
Hair count at baseline, n	98.9 ± 23.3	100.1 ± 22.1	.651	98.5 ± 23.8	99.7 ± 22.1	.454
Change of hair count from baseline at week 4, n	4.1 ± 10.7	−0.4 ± 9.8	.0064**	2.9 ± 10.9	−1.2 ± 10.2	.035*
Change of hair count from baseline at week 12, n	4.3 ± 12.4	−0.7 ± 10.5	.0018**	3.8 ± 12.8	−1.4 ± 10.5	.004**
Change of hair count from baseline at week 24, n	6.7 ± 11.9	−1.1 ± 11.9	<.001***	6.0 ± 12.5	−2.0 ± 12.6	<.001***
IGA at week 4	1.2 ± 0.6	1.1 ± 0.6	.0672	1.2 ± 0.6	1.1 ± 0.6	.168
IGA at week 12	1.7 ± 0.6	1.5 ± 0.5	<.001***	1.7 ± 0.6	1.4 ± 0.5	<.001***
IGA at week 24	2.0 ± 0.6	1.6 ± 0.6	<.001***	2.0 ± 0.6	1.6 ± 0.6	<.001***
SAS at week 4	1.4 ± 0.9	1.4 ± 0.9	.500	1.4 ± 0.9	1.4 ± 0.9	.500
SAS at week 12	1.9 ± 0.8	1.9 ± 0.8	.375	1.8 ± 0.9	1.8 ± 0.9	.500
SAS at week 24	2.6 ± 1.0	2.6 ± 1.0	.500	2.5 ± 1.0	2.5 ± 1.0	.500

IGA, investigator's global assessment; ITT, intention-to-treat; PP, per-protocol; SAS, subjects' assessment of the treatment satisfaction.
*.01 ≤ p < .05, **.001 ≤ p < .01, ***p < .001.

duration of the anagen phase, increased rates of proliferation in active anagen hair follicles, and prevention of premature catagen development.[10,20,25,26] Another study also suggested that LLLT may induce follicular stem cell proliferation and differentiation by increasing levels of heat shock proteins (HSP), such as HSP27.[27]

Performing a literature search using the PubMed database, we found that 6 randomized controlled trials (RCTs) have investigated the application of LLLT for AGA.[11,28–32] In 2009, Leavitt and colleagues conducted the first RCT to evaluate LLLT for the management of AGA. This double-blind, sham device-controlled, multicenter trial enrolled 110 male AGA patients, who were instructed to use a LLLT comb for 15 minutes 3 times per week for 26 weeks.[28] The results showed a significantly greater increase in mean terminal hair density in the LLLT group compared to controls.[28] Kim and colleagues conducted another RCT, in which AGA patients received treatment with a helmet-type, home-use LED-based LLLT device emitting wave lengths of 630, 650, and 660 nm or a sham device for 18 minutes daily for 24 weeks. The results showed that patients receiving LLLT had a significantly greater hair density and hair diameter than the sham device group.[11] Investigator's global assessment also indicated a significant difference,

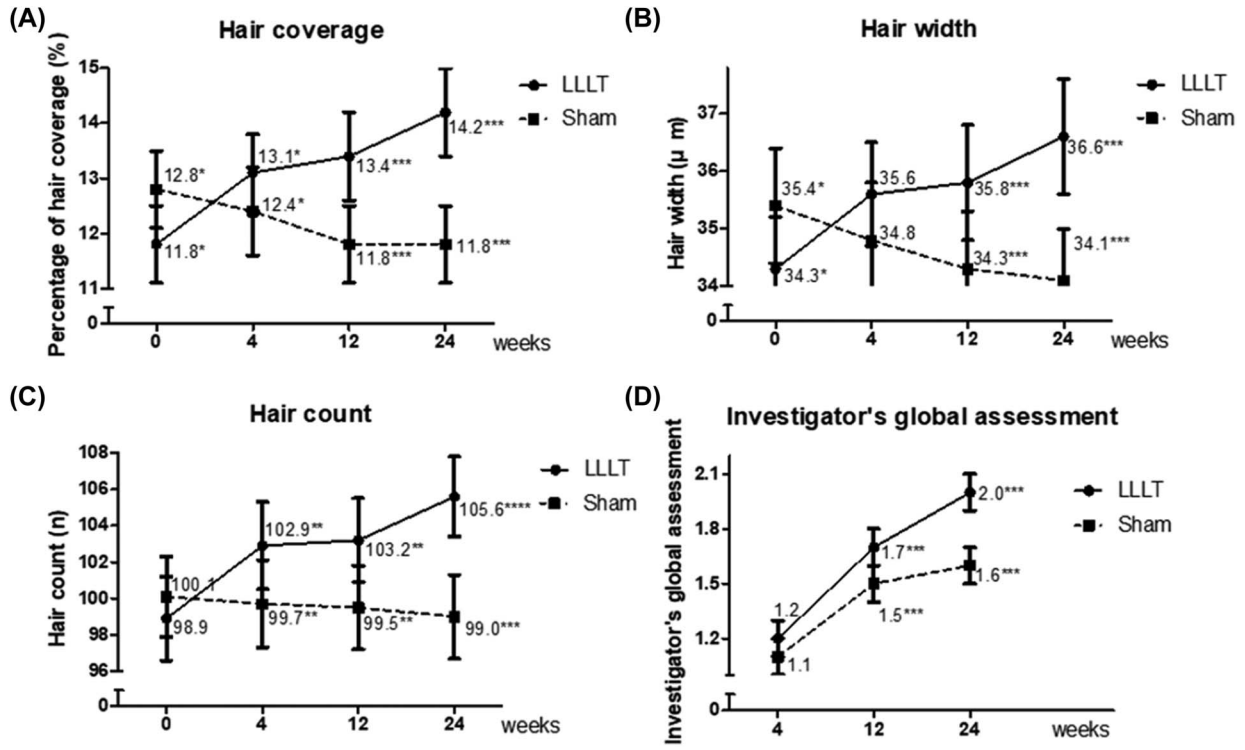

Figure 2. Evaluation of hair parameters during treatment. (A) Hair coverage, (B) hair width, (C) hair count, and (D) the investigator's global assessment from baseline to 24 weeks in subjects treated with the LLLT or sham device. Bars indicate standard error. Mean ± standard error. Statistical differences between the LLLT-treated and control side are presented: *.01 ≤ p < .05, **.001 ≤ p ≤ .01, ***p < .001. LLLT, low-level laser/light therapy.

whereas there was not a significant difference in the subjects' global assessment or subjective satisfaction between the LLLT-treated and control group.[11] More recently, Lanzafame and colleagues conducted 2 RCTs using a bicycle helmet-like apparatus containing 20, 5 mW lasers, and 31 LEDS both operating at 655 nm (655 ± 5 and 655 ± 20 nm, respectively) to determine the effectiveness of LLLT in males with AGA[29] and females with female pattern hair loss,[30] respectively. The results showed that LLLT of the scalp exposed to 655 nm wavelengths significantly improved hair counts after a 16-week treatment (25 minutes every other day).[29,30] Significant improvement in hair count and hair density was also documented in RCTs conducted by Jimenez and colleagues[31] and Blum and colleagues.[32] In agreement with previous research, our study also demonstrated significant improvements in overall hair coverage, hair thickness, hair count, and IGA on the LLLT-treated side than on the control side of the scalp. Of note is that the mean hair thickness at baseline in our study was lower than that of a previous study (mean ± SD, 34.3 ± 8.7 vs. 56.1 ± 17.7 μm).[11] However, the LLLT still showed promising effects on hair growth in our trial. Similar to that reported by Kim and colleagues,[11] the subject's assessment of the treatment satisfaction between the LLLT-treated and control side were not significantly different from this study.

Two studies have reported inconsistent results with the aforementioned studies. Avram and Rogers[33] treated 7 AGA patients with a low-level hood-type laser emitting at a wavelength of 650 nm at a fluency of 5 mW for 20 minutes twice weekly. In another study by Rushton and colleagues,[34] a laser comb was used to treat 2 AGA patients on one side of the head for 7.5 minutes for 3 days each week for 26 weeks. Both studies found an increasing trend of hair count and shaft diameter following laser therapy, but these increases were statistically insignificant.[33,34] However, the small sample size, the design of a non-blinded study without placebo-comparison might have impeded these 2 studies from

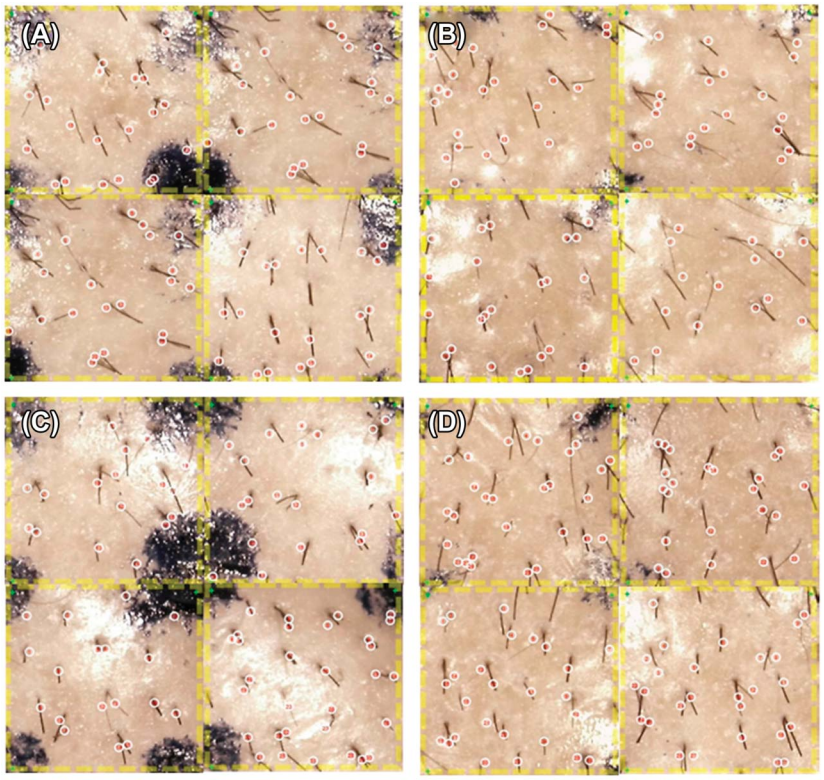

Figure 3. Phototrichogram assessment of a male participant, sham device-treated scalp at baseline (A) and after 24 weeks of treatment (B), and LLLT-treated scalp at baseline (C) and after 24 weeks of treatment (D). Blackish temporary tattoo is also shown at the center, corners, and boundary lines of the square-shaped area selected for evaluation. LLLT, low-level laser/light therapy. Original magnification ×50.

drawing statistically significant conclusions on efficacy.

The ability of LLLT to penetrate to sufficient depth to exert a biological effect on the hair follicle is a major determinant of treatment outcome. The higher hair density at baseline in the target area possibly impedes the efficiency of LLLT penetration, compromising the overall treatment effect. It is possible that LLLT may provide better efficacy in areas where hair density is less dense. However, the decreased hair density at baseline could also imply advanced stages of AGA, which could confound the effect of LLLT. Nevertheless, no studies have been designed to evaluate the impact of hair density at baseline on the efficacy of LLLT. Comparing results from previous studies,[11,31] we could not find any tendency of an inverse association between hair density at baseline and LLLT efficacy; although the indirect comparisons were limited by heterogeneity in study designs and treatment devices used. Further studies are needed to determine the optimal hair density at baseline in which LLLT could provide best treatment efficacy.

Our study provided evidence that supports LLLT for hair growth. However, there were still some limitations. First, as there are differences in light sources and treatment parameters on a variety of trials on LLLT,[11,25,28–35] additional studies are needed to determine the optimal wavelength, fluency, pulse structure, power density, frequency, and number of treatment sessions. Second, the end point of previous studies and the present study varies from 16 to 26 weeks, and there was no follow-up evaluation after treatment[11,25,28–35]; thus, it is unknown whether the improvement seen with LLLT is long lasting.[8] The nonsignificant difference in the subjects' assessment of treatment satisfaction between the LLLT-treated and control side of the head might be attributed to the limited sample size and treatment duration in this study. Third, the split head, self-comparison design in this study might raise concerns of whether the energy

from the laser was dissipated onto areas that were designated as "non-laser" treated areas. However, compared with baseline, a significant reduction of hair coverage and hair thickness in the sham device-treated side during the study period suggested the effect conferred by laser dissipation was negligible.

Conclusion

This study demonstrated a statistically significant increase in hair coverage, hair thickness, and hair count in patients with AGA (Norwood–Hamilton classification of IIa–V for male subjects and Ludwig/Savin classification of I-4, II-1, II-2) following exposure to LLLT using a helmet device 3 times per week for 24 weeks, compared with sham treatment controls. Considering the gradual progression of AGA, LLLT might be an effective, safe, and well-tolerated treatment for AGA.

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Novel Approach to Treating Androgenetic Alopecia in Females With Photobiomodulation (Low-Level Laser Therapy)

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BACKGROUND Photobiomodulation, also referred to as low-level laser therapy (LLLT), has been studied and used for (among other diseases) the promotion of hair regrowth.

OBJECTIVE/MATERIALS AND METHODS/RESULTS A clinical study was developed to define the physiologic effects that occur when the human hair follicle and surrounding tissue structures are exposed to laser light using a novel device that is fitted with an array of laser diode sources operating at 650 nm and placed inside a sports cap to promote discretion while in use. The study demonstrates that low-level laser treatment of the scalp every other day for 17 weeks using the HANDI-DOME LASER device is a safe and effective treatment for androgenetic alopecia in healthy females between the ages of 18 to 60 with Fitzpatrick skin Types I to IV and Ludwig–Savin Baldness Scale I-2 to II-2 baldness patterns. Subjects receiving LLLT at 650 nm achieved a 51% increase in hair counts as compared with sham-treated control patients in this multicenter randomized controlled trial.

CONCLUSION These results suggest that the emerging technology of low-level laser therapy may play a potentially significant role in health care providers' armamentarium for the disease androgenic alopecia.

Supported by Capillus, the manufacturer of the laser cap described. The authors have indicated no significant interest with commercial supporters. Protocol #USC650—ClinicalTrials.gov.

Photobiomodulation, also referred to as low-level laser therapy (LLLT), has been studied and used for the treatment of a variety of clinical indications,[1–21] including the promotion of hair regrowth.[22–38] Each of these applications is based on the biological effects of photobiomodulation in living organisms.[1–21]

The potential application of photobiomodulation to stimulate hair growth can be traced to Endre Mester, a physician practicing in Budapest, Hungary.[22,23] Mester discovered that mice treated with lasers regrew their shaved hair in half the time of non-radiated mice (during experiments conducted while trying to repeat McGuff's experiment to cure cancer in mice with a ruby laser). His 1967 study was the first reference to LLLT and hair growth. Other investigators noted that paradoxical hair growth sometimes occurred at the periphery of areas treated with lasers for hair removal or adjacent to lesions treated with laser sources.[24–26]

These observations led to laboratory and clinical investigations on the effects and applications of LLLT in male and female pattern hair loss.[27–36] In January, 2007, the Food and Drug Administration granted the first clearance for a device indicated for use in treating males diagnosed with androgenic alopecia (AGA) and with Fitzpatrick I to IV skin types.[32,35] In 2010, the category was expanded to treat females diagnosed with genetic hair loss based on the results of a randomized clinical trial.[37]

A clinical study was developed to define the safety and physiologic effects that occur when the human hair follicle and surrounding tissue structures are exposed to laser light using a novel device that is fitted with an

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array of laser diode sources operating at 650 nm and placed inside a sports cap to promote discretion while in use. The present report details the results obtained for the USC650 study.

Materials and Methods

A clinical study was conducted as per the institutional review board–approved USC650 protocol (Essex IRB, Lebanon, NJ). Forty-four healthy female volunteers, aged 18 to 60 years, were recruited at 2 institutional review board–approved treatment sites.

Informed consent was obtained, and patients were screened to verify that they met the inclusion and exclusion criteria for the study (Appendix 1). History and physical examinations were conducted. All 44 patients had Fitzpatrick skin Types I to IV and Ludwig–Savin Baldness Scale I to II hair loss patterns (I-2, I-3, I-4, II-1, and II-2). An area of the scalp was selected in a transition zone at the vertex of the scalp at a site determined by the investigator and based on the individual patient's hair loss pattern. The hairs in the selected site were trimmed to a maximum height of 3 mm in an area that was approximately 2.5 cm in diameter. The area was marked with a medical tattoo using green ink and aseptic technique.

The site was then photographed using a custom camera apparatus specifically configured for this purpose. (The apparatus consisted of a Canon Rebel T3i 18 Megapixel camera system equipped with a Tamron 60 mm f/2 Macro lens with 1:1 magnification. A 55-mm Lens attachment ring was used to affix a Promaster RL60 LED Ring Light.) The camera system was then mounted to a custom-made stand-off device, which was then manually positioned onto the scalp surface by the investigator each time photographs were taken. Images were taken with the tattoo positioned in the center of the frame.

These baseline images were coded and then forwarded to the photographic consultant. The photographic consultant verified that the images were of acceptable quality and processed the images for transmission to the investigator responsible for conducting the hair counts. The transmitted images were masked using a black mask to produce a 1.9-cm diameter circle centered on the tattoo, which provided a consistent 2.85 cm^2 area for hair counts.

Neither the photographic consultant nor the investigator performing the hair counts was aware of the identity of the subject or the subjects' study group assignment. One baseline photograph per participant was submitted for counting.

Patients were randomly assigned to active or placebo treatment groups. Each subject received a numbered dome laser unit which was distributed to her by the project manager, who also provided the patients with instructions for the care and use of the device.

Neither the patients, the treating physicians at the clinical sites, the photographic consultant, nor the investigator performing the hair counts was aware whether the device was a therapeutic (active) or a functioning placebo (sham) device.

The dome laser is shown in Figure 1. The investigational devices did not have any corporate logos or other identifiers with the exception of a study investigational device number (Figure 1A). An identifying number was assigned to each dome, which was then recorded in a device log that contained the code for placebo and actual test unit reference. This log was not revealed to any investigator, subject, office staff, hair counter, or sponsor employee.

The laser (active) group received a dome laser unit. This is a low-level diode laser device, operating at 650 nm, that contains 272, 5-mW diode lasers, affixed in a low-profile sport style hat. Each subject self-treated at home for 30 min/treatment every other day for 17 weeks (60 treatments [maximum] 1,360 mW total delivered energy over 582 cm^2 or 2.34 mW/cm^2). The device provided pulsed illumination on a 6.92 Hz duty cycle over the scalp covered by the device.

The placebo or sham group received a unit that was identical in appearance and function to the active treatment group devices, with the exception that the light sources were incandescent (painted) red lights that mimicked the appearance and configuration of

Figure 1. Dome laser device: (A) exterior view of device and controller; (B) interior view of an active unit; and (C) interior view of active device during operation.

the functioning device. Again, each subject in the sham group self-treated at home for 30 min/treatment, every other day for 17 weeks (60 treatments with delivered [scattered] light in the visible light range [painted incandescent bulbs] indicating a [maximum] 1,360 mW total delivered energy over 582 cm^2 or 2.34 mW/cm^2). The device provided pulsed illumination on a 6.92 Hz duty cycle over the scalp covered by the device.

The subject's head is self-positioned within the device (which is covered by a sport cap), such that a proximity sensor triggers the start of therapy. The light reaches the subject's scalp through a clear inner liner positioned inside the dome. Treatment duration is approximately 30 minutes. The lasers (lights) automatically shut off, after the treatment session is complete. User function consists of a rocker switch on the hand controller/battery pack that is actuated by the user (press on/off). The battery pack is charged using a charger plugged into a standard 120 V outlet. The user has only to press the on switch. All other functions are automatic. There is no before or after treatment care required, only that subjects' hair must be clean and not contain spray or gel fixative agents. No safety eyewear is required during the treatment session. A complete demonstration of the proper use of the dome was provided to each subject at the time the test units were distributed. Periodic subject monitoring was conducted by telephone. Subjects were queried relative to their use of the device and for any possible side effects or adverse events.

All patients who completed the study exchanged their investigational dome laser unit for a fully functional, production commercial system.

Data analysis was conducted by a consulting statistician, who was provided the raw data and who was blinded as to the identity of the subjects or their individual treatments. The primary endpoint for evaluation was the percent increase in hair counts from baseline at the end of 17 weeks of treatment. The percent increase from baseline is the obtained by the following formula:

TABLE 1. Subjects, Treatment Assignments, and Study

Site	*Sham (Placebo)*	*Active (Laser)*	*Total*
1	7	12	19
2	15	10	25
Total	22	22	44

$$x = 100 \times \frac{(\text{End Count} - \text{Baseline Count})}{\text{Baseline Count}}$$

An analysis of variance was done with site, treatment group, and site treatment group comparisons in the model. The data did not indicate a statistically significant difference in data between the sites. Therefore, the data were pooled across both sites to arrive at an estimate of the effect for the primary endpoint. Univariate tests comparing the sham and laser groups were performed by 2-sided Wilcoxon rank-sum tests, and an unequal variance *t* test was performed.

Results/Statistical Analysis

Study Site Subject Distribution

The study was a blinded multicenter study. The study subjects were allocated to active treatment or sham on a 1:1 basis at each of 2 study sites. The distribution of study subjects by random treatment assignment and study site are given in Table 1 below.

A total of 44 patients were enrolled in the study and completed baseline screening. There were 19 active treatment patients and 21 sham patients available for analysis at the end of the study after 17 weeks of treatment. There were no reported side effects or adverse events reported by any subject or site at any time during the conduct of the study.

Hair Counts and Photography

The area of treatment was the vertex of the scalp. Photographs of the area being treated were taken

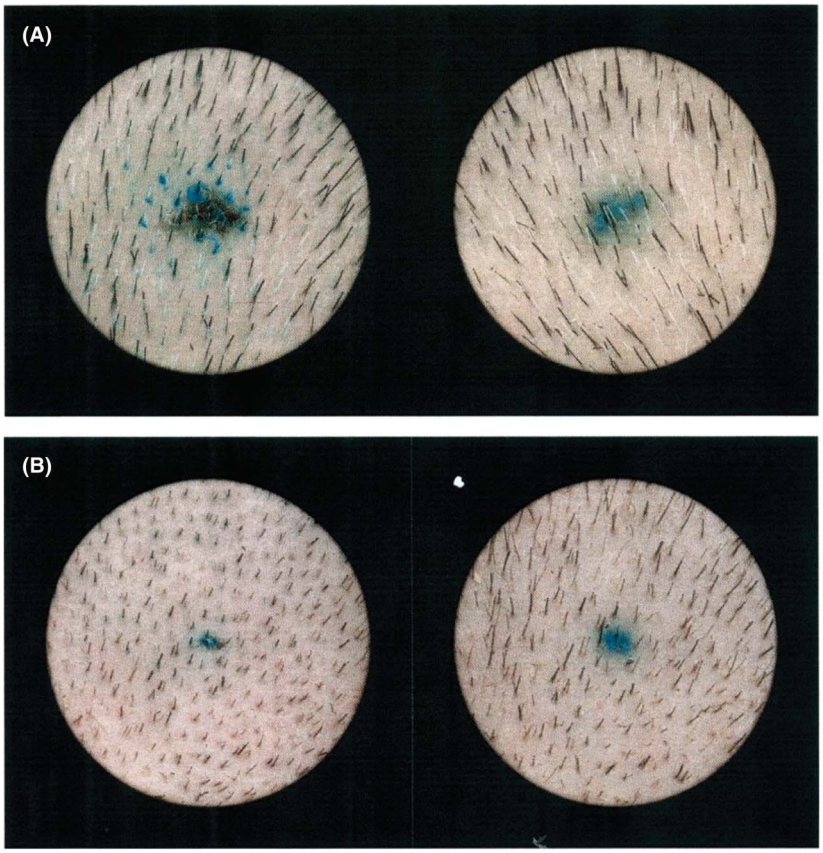

Figure 2. Sham treatment group subject before and after treatment image example: (A) before and after treatment and (B) before and after treatment.

before any therapy treatment being performed by the subject (baseline) and photographs were taken of the treated area after the final light treatment had been performed (final). There were no interim office visits during the 17-week trial. The photographic site was comprised an area on the vertex that was approximately 25 mm in diameter, and all hairs in this area were trimmed to a length not to exceed 3 mm to enhance counting by an evaluator blinded to treatment assignment.

Examples of baseline (before treatment) and final (after treatment) images are presented in Figures 2 and 3. Note that these images are provided for informational and illustrational purposes only and are not intended to be used as evaluative data. Figure 2 demonstrates examples for 2 patients in the placebo or sham group. Note that there is minimal change in the 17-week study interval. Figure 3 demonstrates examples of baseline and final images for 2 subjects in the active treatment group. Note that there is a significant increase in the number of terminal hairs present in these examples.

Hair counts for Subject A were 137 at baseline and 135 after treatment. Hair counts for Subject B were 142 at baseline and 141 after treatment.

Hair counts for Subject A were 108 at baseline and 198 after treatment. Hair counts for Subject B were 123 at baseline and 356 after treatment.

Baseline Demographic Characteristics

There was information gathered on 3 important demographic characteristics, subject age, subject Fitzpatrick skin type, and Ludwig–Savin Baldness Scale. The results of these characteristics by treatment group are presented in Table 2 below.

Note that age was not statistically significant by treatment group nor was it significant by study site ($p = .083$).

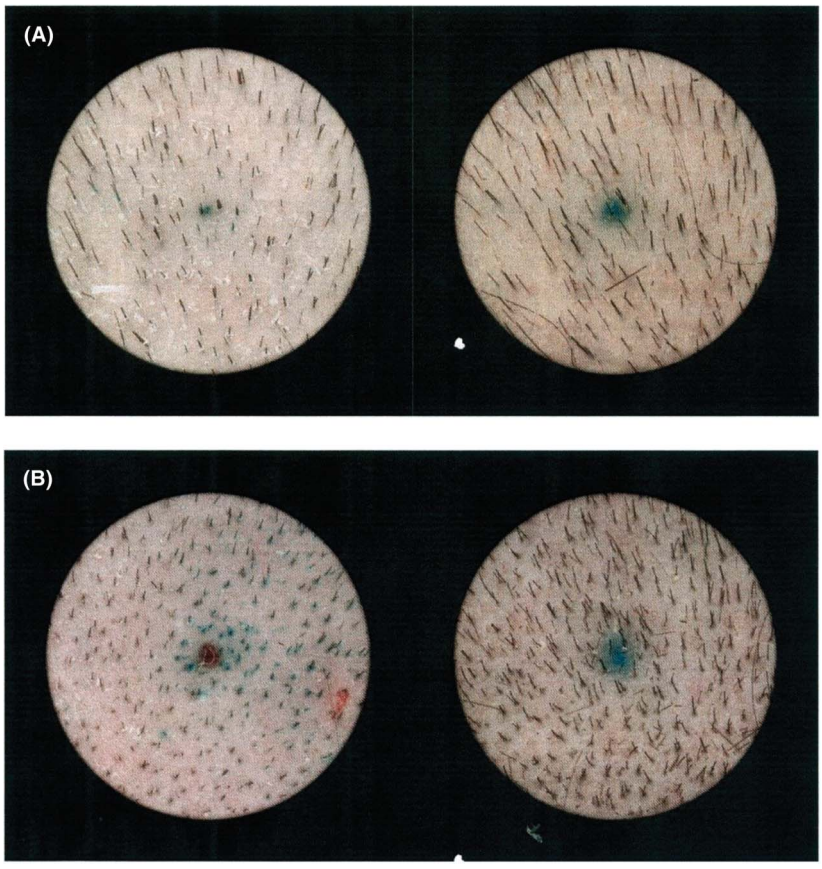

Figure 3. Active treatment group subject before and after treatment image example: before and after treatment and (B) before and after treatment.

TABLE 2. Baseline Demographic Characteristics by Treatment Group

Characteristic	*Sham*	*Active*	*p*
Age			.656
Mean (SD), *N*	47.05 (11.62), 22	48.41 (5.25), 22	
Med (min, max)	49 (28, 60)	49.5 (28, 58)	
Hair color x/*n* (%)			.058
Black	2/22 (9.09)	0/22 (0.00)	
Blonde	1/22 (4.55)	0/22 (0.00)	
Brown	13/22 (59.09)	11/22 (50.00)	
Dark brown	1/22 (4.55)	5/22 (22.73)	
Light brown	2/22 (9.09)	6/22 (27.27)	
Medium brown	1/22 (4.55)	0/22 (0.00)	
Red brown	2/22 (9.09)	0/22 (0.00)	
Fitzpatrick skin type x/*n* (%)			1.000
1	0/22 (0.00)	0/22 (16.67)	
2	4/22 (18.18)	5/22 (22.73)	
3	17/22 (77.27)	17/22 (77.27)	
4	1/22 (4.55)	0/22 (8.33)	
Ludwig–Savin Baldness Scale x/*n* (%)			.227
I	8/22 (36.36)	13/22 (59.09)	
II	14/22 (63.64)	9/22 (40.91)	

Max, maximum; Min, minimum; SD, standard deviation.

Neither Fitzpatrick skin type nor the Ludwig–Savin Baldness Scale differed by treatment group. Study sites did not differ by hair color ($p = .275$) but differed by Fitzpatrick skin type ($p < .013$) and by Ludwig–Savin Baldness Scale ($p < .001$). In pooling analysis below, study site is put into a multivariable model to see if it affects the primary endpoint.

Baseline Hair Counts

The analyses reported below were conducted in Minitab 16. The raw data for these analyses appear in Appendix 2. The baseline hair counts by treatment group and study site are presented in Table 3 below.

The study sites do not differ in baseline hair counts and the treatment groups do not differ.

Primary Analysis

The primary endpoint is the percent increase in hair counts from baseline at the end of 17 weeks of treatment. The percent increase from baseline is the obtained by the following formula.

TABLE 3. Baseline Hair Counts of Vertex Scalp Site

Site	*Sham*	*Active*	*p*
1			.373*
Mean (SD), *N*	220.0 (74.42), 7	188.5 (71.26), 12	
Med (min, max)	195 (137, 335)	200.0 (39, 305)	
2			.605*
Mean (SD), *N*	215.4 (124.38), 15	190.3 (104.78), 10	
Med (min, max)	196.0 (21, 502)	181.5 (39, 379)	
p	.929*	.962*	—

*Two-sided unequal variance *t* test.
Max, maximum; Min, minimum; SD, standard deviation.

$$x = 100 \times \frac{(\text{End Count} - \text{Baseline Count})}{\text{Baseline Count}}$$

A data pooling analysis was done to determine whether there is a site by treatment interaction in the percent increase. If the interaction between site and treatment was significant with a $p < .15$, there would be evidence of a site by treatment interaction that would require weighting the site results to obtain an estimate of the study effect. An analysis of variance was performed with only site, treatment group, and site by treatment group interaction in the model, and the interaction was not statistically significant ($p = 0.190$). Note that 3 subjects in the active arm and 1 in the sham arm were found to never have begun therapy or were not forthcoming with the monitor about the use of the device and would not return for final clipping and photography. These subjects were deleted from the analysis.

Univariate tests comparing the sham and laser groups were intended to be by Wilcoxon rank-sum tests unless the variance between the 2 groups was statistically significantly different. In that case, the comparison was conducted by an unequal variance *t* test. The relevant data for this analysis appears in Table 4 below.

These data indicate that the univariate result comparing the increase in hair counts was statistically significant ($p < .001$). Thus, the results indicate that low-level laser treatment for 17 weeks increases mean hair counts by approximately 51%.

A multivariable analysis accounting for baseline differences in study site and treatment group without interaction indicated that the study site had a significant impact on the percent change from baseline ($p = .036$) but the treatment effect was still statistically significant ($p < .001$). So, the study site differences in percent change from baseline did not modify the effect of treatment on the percent increase in hair counts after treatment.

A second supportive multivariable analysis used baseline count as a covariate and in that analysis, the baseline term was significant ($p = .003$), treatment was highly significant ($p < .001$), and study site was statistically significant ($p = .024$). Furthermore, when age, Fitzpatrick type, and Ludwig–Savin Baldness Scale were included in a third sensitivity model, none were statistically significant with *p* value of .268, .397, and .268, respectively, with site, baseline count, and treatment included in the model. Thus, the univariate result is confirmed by the multivariable analysis with laser treatment term in the model with statistical significance unchanged from the univariate analysis ($p < .001$). These data indicate that low-level laser

TABLE 4. Baseline Hair Counts, End of Study Hair Counts, and Percent Increase by Treatment Group

Variable	*Sham*	*Active (Laser)*	*p*
Baseline			.500*
Mean (SD), *N*	216.9 (109.1), 22	189.3 (85.8), 22	
Med (min, max)	195.5 (21, 502)	195.5 (39, 379)	
After treatment			.377*
Mean (SD), *N*	235.3 (105.8), 21	268.3 (117.7), 19	
Med (min, max)	225.0 (28, 499)	275.0 (87, 559)	
Difference from baseline			.001†
Mean (SD), *N*	18.5 (24.4), 21	89.9 (63.3), 19	
Med (min, max)	22.0 (−23, 62)	65.0 (28, 234)	
Percent increase			.001†
Mean (SD), *N*	12.48 (13.76), 21	63.67 (50.9), 19	
Med (min, max)	12.69 (−6.87, 37.2)	48.4 (11.2, 189.4)	

*Two-sided Wilcoxon rank-sum test.
†Two-sided unequal variance *t* test.
Max, maximum; Min, minimum; SD, standard deviation.

treatment of the scalp every other day for 30 minutes for 17 weeks improved the percent increase from baseline by 51% in females.

Adjustment for differences in baseline counts by study site and demographic variables by treatment did not change the statistical significance observed in the univariate analysis of the primary endpoint. The increase in percent hair growth in women using the active device was confirmed. No adverse events were reported by study participants. Factoring the results and the absence of reported adverse events, the device is considered safe and effective.

Results

Specifically, there was a 51% increase in terminal hair counts in the laser group as compared to the control or sham treatment group ($p < .001$) in female patients who were aged 18 to 60 years and had I-2 to II-2 Ludwig–Savin Baldness Scale baldness patterns and were of Fitzpatrick skin Types I to IV.

This study demonstrates that the use of LLLT at 650 nm as applied to the scalp every other day for 17 weeks (60 treatments) using the dome laser device resulted in a significant improvement in female patients who used the device. Representative active treatment group subject before and after treatment images are presented in Figures 4 and 5.

Primary Response (Subject A, Site 1)

The formatted photographs were submitted for terminal hair counting. In the pretreatment image, 39 terminal hairs were counted. In the post-treatment image, 87 terminal hairs were counted. This demonstrates a 123% increase in terminal hairs from baseline.

Primary Response (Subject B, Site 2)

The formatted photographs were submitted for terminal hair counting. In the pretreatment image, 97 terminal hairs were counted. In the post-treatment image, 153 terminal hairs were counted. This demonstrates a 57% increase in terminal hairs from baseline.

All the patients in this female study were able to apply and use the device as directed to self-administer their treatments at home. There were no side effects or adverse events reported by any of the study subjects at any time during the conduct of the study. This indicates that the device is safe for the unsupervised environment of home use.

This study, conducted by a neutral third party for Capillus, LLC, demonstrates that low-level laser treatment of the scalp every other day for 17 weeks using the Capillus272 Pro device is a safe and effective treatment for androgenetic alopecia. ClinicalTrials.gov Identifier: NCT01967277.

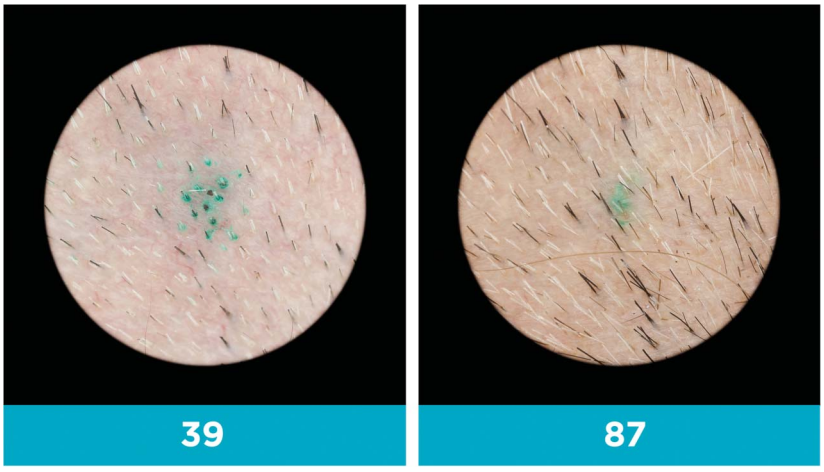

Figure 4. A 53-year-old white female, Fitzpatrick skin phototype III, Ludwig–Savin Baldness Scale 1-3, with a history of androgenetic alopecia. This subject was enrolled into the active test device group. After 17 weeks of compliant home-use treatments, she returned for her final photography and release from the trial (Subject A, Site 1).

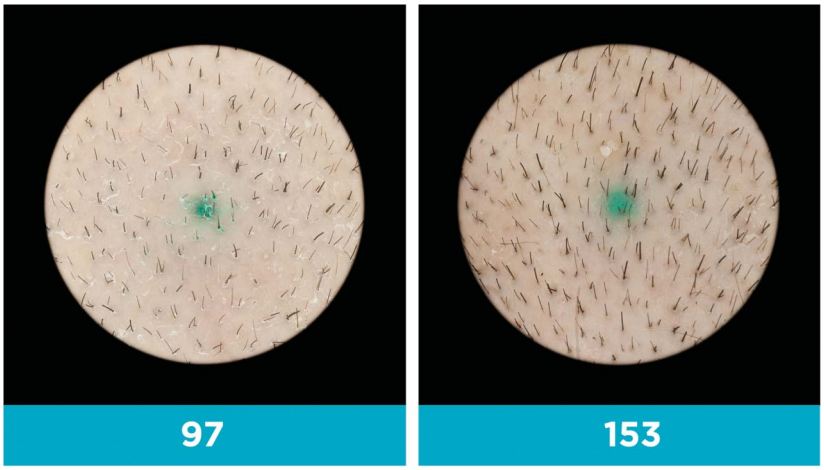

Figure 5. A 49-year-old white female, Fitzpatrick skin phototype II, Ludwig–Savin Baldness Scale 1-1, with a history of androgenetic alopecia. This subject was enrolled into the active test device group. After 17 weeks of compliant home-use treatments, she returned for her final photography and release from the trial (Subject B, Site 2).

Discussion

Various investigators have studied a variety of light sources, wavelengths, and treatment parameters for the treatment of alopecia with LLLT.[27–30,32,33,35–38] Most of these reports on the efficacy of LLLT for alopecia have been prospective, uncontrolled, open-label studies and have not been confirmed by multicenter, randomized, double-blind, controlled trials.[27–30,33,35–38]

This study used a randomized, double-blind design and used a true placebo using a device that was identical in appearance to the active device, with incandescent sources that glowed red but did not deliver coherent light to the subject's scalp. Treatments were passive and did not depend on the user for delivery, aside from the subject placing the unit on the scalp and activating the controller. This differs from the device studies that required the user to comb the scalp for a specified treatment time and used a placebo device that was readily distinguished by the fact that it was a white light source.[27–29,32,35,38]

Hair growth after exposure to LLLT alone is not sufficient to document that photobiomodulation has occurred. Increases in hair counts were also observed in the sham or placebo group in this study. These observations may represent a true placebo effect because the sham device did not deliver thermal energy or collimated light at scalp level. However, other explanations might also include seasonal variations in hair growth or other factors. This makes it important to include placebo and sham treatments in the study design and to conduct the investigation in such a manner as to minimize selection bias.

Several investigators have studied the effects of LLLT on hair growth in animal models.[22,23,32,35,38] Paradoxical hair growth after light-based hair removal and other treatments in human subjects has also been observed with various laser and intense pulsed light sources.[24–26,30]

The theory that is widely accepted is that LLLT, particularly at wavelengths in the red range as was used in this investigation, affects the functioning of the stem cells that cause hair growth. Photobiomodulation activates cytochrome c oxidase and increases mitochondrial electron transport,[11–17] which leads to an increase in adenosine triphosphate and subsequent reversal of hair follicles from the dormant telogen stage of growth, to the active growth or anagen stage.[27,28,30–32,34,35,38] However, the optimal wavelengths and treatment parameters remain indeterminate at this time. This shortcoming has been underscored in the recent review of LLLT to promote hair growth by Avci and colleagues.[38] This study was not designed to investigate alternative treatment regimens or parameters.

Are Men and Women Created Equal?

The final part of this discussion addresses sex; specifically, the question whether there is a difference between men and women with regard to the physical function of hair regrowth. This study recruited women; however, there is no published empirical evidence or reference regarding hair regrowth as a sex-specific function, other than pattern; i.e., the form in which hair is lost. (No articles or evidence was discovered during research and investigation for this article.) There is no scientific article postulating that there is a difference in the physical function of hair growth for men versus that for women. Industry opinion indicates that overall thinning is more prevalent in women, and "receding hairline" or "monk's spot" are more common in men; however, for external strategies for regrowth (i.e., LLLT), there are no published differences in industry literature. Finally, in the clinical trials for LLLT devices reviewed for this article, the treatment regimen between sexes is the same.

There is also a lack of published data specifically regarding the treatment (or difference in treatment) of androgenetic alopecia in women versus men; this very lack of such discussion gives credence to the argument that there is no difference. The discussions regarding sex are generally focused on the differences between the patterns of hair loss, and the increased likelihood that for women, hair loss is often attributable to reasons other than genetics (e.g., underlying medical cause such as thyroid disease).

References identified during research for this article regarding treatment difference between men and women were limited to the use of drugs and topicals which target specific hormones; the use of these drugs and/or topicals do present differently between the sexes. When asked, hair restoration physicians and specialists stated that with regard to LLLT, they prescribe essentially the same treatment regimen for men and women who present with androgenetic alopecia. There is no difference with regard to the physical function of hair regrowth, other than the normal differences found in individuals; that is, treatment regimen is adjusted by physician prescription based on each individual's needs, not specific to sex.

Conclusion

This study demonstrates that low-level laser treatment of the scalp every other day for 17 weeks using the dome laser device is a safe and effective treatment of androgenetic alopecia in healthy females between the ages of 18 to 60 with Fitzpatrick skin Types I to IV and Ludwig–Savin Baldness Scale I-2 to II-2 baldness patterns. Subjects receiving LLLT at 650 nm achieved a 51% increase in hair counts as compared to sham-treated control patients in this multicenter randomized controlled trial.

These results suggest that the emerging technology of low-level laser therapy may play a potentially significant role in health care providers' armamentarium for the disease AGA.

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Appendix 1. Subject Selection Criteria for USC650 Study

- Female subjects experiencing any type of hair loss, thinning hair, or androgenetic alopecia, who have a diagnosis of Ludwig–Savin Baldness Scale I or II grade of hair loss.
- Subjects having a Fitzpatrick skin phototypes of I to IV will be included.
- The total number of subjects being recruited is 44 females.
- Age range is 18 to 60 years.
- Apparent good health.
- No previous involvement in other hair studies.
- No use of any hair growth agent within the last 4 weeks.
- Subjects may continue with normal haircuts, coloring, and permanents.
- No evidence of any current viral, fungal, or bacterial infection.
- Hair must be clean and not contain spray or gel fixative agents.
- Subjects may not be pregnant or breastfeeding. No urine pregnancy test will be required.
- Must be willing to have a small section of hair cut to approximately 1/8 inch (3 mm height).

Appendix 2. Raw Hair Counts by Study Site and Treatment Group

Subject*	Site	Site ID	Trtmt	BL-Count	Pst-Count	Diff	Pct-diff	Age, yrs	Hair Color	Ftptrck Tpe	Ldwg Scl
1	1	1-1	Active	224				47	Brown	II	II
2	1	1-2	Active	179	325	146	81.56	41	Brown	III	II
3	1	1-3	Active	39	87	48	123.08	53	Med Brown	II	II
4	1	1-4	Active	96	148	52	54.17	52	Red Brown	II	II
5	1	1-5	Active	218	287	69	31.65	47	Lt Brown	II	II
6	1	1-6	Active	247				55	Brown	III	I
7	1	1-7	Active	305	358	53	17.38	47	Brown	III	I
8	1	1-8	Active	141	170	29	20.57	53	Blonde	III	I
9	1	1-9	Active	185	234	49	26.49	57	Brown	III	II
10	1	1-20	Active	174	245	71	40.80	48	Black	III	I
11	1	1-21	Active	215	275	60	27.91	58	Brown	III	I
12	1	1-22	Active	239	298	59	24.69	53	Dk Brown	III	I
13	2	2-10	Active	97	146	49	50.51	28	Brown	III	II
14	2	2-11	Active	39	104	65	166.67	58	Brown	III	I
15	2	2-12	Active	249	277	28	11.25	32	Brown	III	I
16	2	2-13	Active	123	356	233	189.43	46	Lt Brown	III	I
17	2	2-14	Active	108	198	90	83.33	45	Brown	III	I
18	2	2-15	Active	304				57	Brown	III	I
19	2	2-16	Active	206	440	234	113.59	56	Brown	III	I
20	2	2-17	Active	379	559	180	47.49	44	Brown	III	I
21	2	2-18	Active	241	358	117	48.55	37	Brown	II	II
22	2	2-19	Active	157	233	76	48.41	51	Brown	III	II
23	1	1-23	Sham	178	203	25	14.044	60	Med Brown	II	II
24	1	1-24	Sham	137	135	−2	−1.460	51	Red Brown	II	II
25	1	1-25	Sham	219				55	Lt Brown	II	II
26	1	1-26	Sham	167	192	25	14.97	51	Brown	III	I
27	1	1-27	Sham	335	312	−23	−6.87	27	Brown	III	I
28	1	1-28	Sham	195	229	34	17.44	47	Blonde	III	I
29	1	1-29	Sham	309	305	−4	−1.29	59	Brown	III	II
30	2	2-30	Sham	219	215	−4	−1.83	53	Black	III	I
31	2	2-31	Sham	187	224	37	19.79	46	Brown	III	I
32	2	2-32	Sham	164	225	61	37.20	46	Dk Brown	III	I
33	2	2-33	Sham	163	213	50	30.67	54	Brown	III	II
34	2	2-34	Sham	247	244	−3	−1.21	28	Brown	III	I
35	2	2-35	Sham	323	364	41	12.69	23	Brown	III	I
36	2	2-36	Sham	196	258	62	31.63	52	Lt Brown	III	I
37	2	2-37	Sham	34	37	3	8.82	60	Brown	III	I
38	2	2-38	Sham	21	28	7	33.33	49	Brown	III	I
39	2	2-39	Sham	221	243	22	9.95	49	Brown	III	I
40	2	2-40	Sham	142	166	24	16.90	22	Brown	III	I
41	2	2-41	Sham	273	279	6	2.20	48	Brown	II	II
42	2	2-42	Sham	392	381	−11	−2.81	46	Brown	III	II
43	2	2-47	Sham	502	499	−3	−0.60	49	Med Brown	II	II
44	2	2-44	Sham	147	189	42	28.57	60	Red Brown	II	II

Pct-diff is the percent hair increase (decrease) at 17 weeks as a percent of baseline as defined in the report. Three subjects refused to return for the 17-week assessment at Site 2. Diff = Pst-Count − BL-Count.

*Patient numbers were grouped for convenience not by the order of presentation.

BL, baseline count; Diff, difference = postcount minus baseline count; Dk, dark; ID, identification assigned; Ldwg Scl, Ludwig–Savin Baldness Scale; Lt, light; Med, medium; Pct-diff, percent hair increase (decrease); Pst-Count, hair count after 17 weeks of treatment; Trtmt, treatment.