Utilizing Electromagnetic Radiation for Hair Growth: A Critical Review of Phototrichogenesis

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INTRODUCTION
Although hair loss is a common medical problem with significant psychological consequences, satisfactory and effective treatment options are somewhat limited. MPHL/FPHL and AA represent the most prevalent disorders for which patients seek medical treatment of hair loss.1–3 Because conventional medical treatment has proved inadequate in many cases, a variety of novel treatment options have been investigated. Low-level laser therapy (LLLT) has recently been approved by the US Food and Drug Administration (FDA) for the treatment of MPHL/FPHL, and it is currently being studied for AA.4,5 In this article, the evidence for using LLLT and other forms of light-based treatment for inducing hair growth (ie, phototrichogenesis) is critically reviewed and compared with conventional treatments.

PATTERN HAIR LOSS AND ITS DEPENDENCY ON ANDROGENS
MPHL/FPHL and AA represent the most common hair conditions for which patients consult dermatologists. The specific incidences of MPHL/FPHL vary according to the diagnostic criteria used, with clear trends toward higher prevalences with advancing age.6 The white population tends to manifest MPHL/FPHL more commonly than Chinese, Japanese, or African American descendants.7,8 Depending on the age group studied, prevalence estimates have ranged from 16% to 100%.1,6,9,10 MPHL tends to affect the temporal and vertex areas and has been categorized into different stages with the Norwood-Hamilton classification,1 whereas FPHL tends to have preservation of the frontal hair region and vertex and is evaluated using the Ludwig scale.11

KEYWORDS
- Laser
- Ultraviolet radiation
- Hair stimulation
- Photobiology
- Alopecia areata
- Male and female pattern hair loss

KEY POINTS
- Although hair loss is a common medical problem with significant psychological consequences, satisfactory and effective treatment options are somewhat limited.
- Male pattern hair loss (MPHL), female pattern hair loss (FPHL), and alopecia areata (AA) represent the most prevalent disorders for which patients seek medical treatment of hair loss.
- MPHL/FPHL and AA represent the most common hair conditions for which patients consult dermatologists.

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MPHL has been linked to the downstream effects of testosterone and develops in individuals who are genetically susceptible to the hair miniaturizing effects of androgens on hair follicles. Because men with a genetic deficiency of the enzyme steroid 5α-reductase (5αR) type II do not develop MPHL, this enzyme was hypothesized as playing a pivotal role in the development of MPHL. The enzyme, 5αR, converts testosterone to dihydrotestosterone, and this latter hormone binds 5 times more potently to androgen receptors. Two isoforms are present for 5αR. Hair follicles on the scalp and the prostate gland contain mostly 5αR type II. The role of androgens in FPHL is less clear. The duration of the anagen active growth phase is shortened in FPHL, but the detailed mechanism for this is poorly understood. Growth factors have been proposed to play a role and their effects have been demonstrated in mice models, but consistent studies in humans are lacking.

ALOPECIA AND THE IMMUNE SYSTEM

The prevalence of AA seems similar across different population groups, with a lifetime risk of approximately 1.5% to 2% in the general population. In the United States, the incidence has been estimated at 0.1% to 0.2% per year and affects male and female patients equally. Although AA most commonly presents with focal nonscarring isolated patches, patients may develop diffuse or refractory cases. Both MPHL/FPHL and AA are linked to severe psychosocial distress and social impairment, and, therefore, individuals with these conditions often seek therapy.

The pathogenesis of AA is currently hypothesized to be an autoimmune-mediated hair loss disorder because it is strongly associated with several other autoimmune-based disorders. Furthermore, its relationship with autoimmunity is supported by its response to immunosuppressive agents. At the molecular level, HLA class II antigens are highly expressed in AA hair follicles and are responsible for up-regulating CD4+ T lymphocytes. In addition, antigen-presenting cells, such as macrophages and Langerhans cells, are increased. The hair cycle is also believed altered in AA, and the disruption depends on the stage of AA. In patients with early AA, the anagen phase predominates; however, increased numbers of dystrophic hair follicles are found. With further progression of AA, there is increased follicular conversion to telogen, such that with chronic AA, hair follicles remain suspended in the telogen phase.

CONVENTIONAL MANAGEMENT OF MPHL/FPHL AND AA

Because androgenetic alopecia and extensive, refractory AA represent progressive and chronic conditions, patients seek therapy that is effective but with minimal long-term side effects. Available medical treatment options used to treat MPHL include minoxidil, finasteride, and dutasteride (although dutasteride is not currently FDA approved). FPHL is more difficult to manage, because androgen effects do not seem to play as significant a role. Androgen receptor inhibitors are often not as effective and may be contraindicated, particularly in men. Spironolactone is a viable option in some patients with FPHL. Patients who do not obtain satisfactory response from medical treatments may need to consider hair transplant surgery.

AA is routinely managed with topical and intraleisional corticosteroids. Topical minoxidil or anthratin may be used in cases with inadequate response with corticosteroids. Refractory or severe cases may require additional treatment, such as contact therapy with diphenylcyclopropenone, dinitrochlorobenzene, or squaric acid dibutyl ester. Short courses of systemic cyclosporine and corticosteroids are occasionally prescribed in widespread diseases of AA. Hairpieces, wigs, and toupees are other options for patients who find medical or surgical therapy unsatisfactory for extensive hair loss caused by MPHL/FPHL or AA. Despite all these readily available treatment options, there remains a need for more effective management options.

THE CLINICAL PHENOMENON OF LIGHT-INDUCED HAIR GROWTH

The putative effects of light, which is a form of electromagnetic radiation, on hair growth stimulation have been observed empirically by dermatologists, but there has been minimal insight into the responsible mechanisms. Hypertrichosis occurs on light-exposed skin sites in several types of porphyrias, including porphyria cutanea tarda, hepatoerythropoietic porphyria, variegate porphyria, and congenital erythropoietic porphyria. Photoactivated porphyrins produce reactive single oxygen and free radicals that result in subsequent lipid peroxidation and protein cross-linking yielding alteration of cellular and tissue structures. Although it is well understood that porphyrins tend to accumulate with the pilosebaceous unit, the link between the photochemical activation of porphyrins and the induction of hair growth is essentially unknown.
Hypertrichosis has also been reported to occur during psoralen–UV-A (PUVA) therapy. This phenomenon is also poorly understood, but it may be accounted for by the light-induced production growth factors and prostaglandins. There is one documented study where 15 of 23 female patients (65%) receiving systemic PUVA therapy developed moderate-severe hypertrichosis, compared with only 2 of 14 patients on UV-A therapy alone.\textsuperscript{33,34} These observations led the author to evaluate 7 male patients receiving 8-methoxypsoralen with UV-A twice weekly. Hair lengthening was noted post-PUVA in all 7 patients after 8 weeks of therapy (range 17%–71%). Other studies, however, that evaluated PUVA patients retrospectively have shown hypertrichosis an uncommon occurrence at only in 4.4\% of patients.\textsuperscript{33}

Several reports have focused on the seemingly paradoxical development of hypertrichosis after laser epilation. In one retrospective study of 489 patients who were treated with long-pulsed alexandrite laser (755 nm), 3 patients (0.6\%) reported increased hair growth after laser hair epilation.\textsuperscript{35} This phenomenon tended to occur in darker skin phototypes (Fitzpatrick skin type >IV) and with black hair. The fluence settings used in these patients were 15 J/cm\textsuperscript{2} to 40 J/cm\textsuperscript{2} at pulse durations between 10 milliseconds and 40 milliseconds. Similar findings of paradoxical hair growth have been reported with the use of intense pulse light.\textsuperscript{36} The mechanism for why hair growth is actually stimulated during the course of its attempted removal has not been studied in any detail, but one hypothesis is that the appearance of increased hair may simply reflect that laser treatments may serve to synchronize the hair growth cycles of all the follicles within the laser-exposed sites.\textsuperscript{36} Once the hair follicles in a treatment site are synchronized they presumably enter anagen at the same time, such that the overall hair density seems to be increased relative to untreated areas where the hair cycling is typically asynchronous.

These unequivocal observations of increased hair growth in porphyria patients and those who have received PUVA or laser epilation have demonstrated that in principle the energy of electromagnetic radiation can be harnessed to treat hair loss.

LOW-LEVEL LASER THERAPY

LLLT has also been referred to red light therapy, cold laser, soft laser, biostimulation, and photobiomodulation. The characteristics of LLLT that distinguish it from other laser-based therapies, include the use of very low power densities and the requirement for continual maintenance treatment.\textsuperscript{37} Most LLLT devices are within the red to near-infrared wavelength range (600–1000 nm) and use power densities much less than that required to heat tissue (10 mW/cm\textsuperscript{2}–5 W/cm\textsuperscript{2}).\textsuperscript{38} The use of LLLT evolved after its first reported use in humans in the 1960s by the National Aeronautics and Space Administration to promote wound healing. Since then, LLLT devices have been used and promoted to treat patients with strokes, myocardial infarctions, major depression and anxiety, oral mucositis, arthritis, lateral epicondylitis, and carpal tunnel syndrome.\textsuperscript{39–42} The hard clinical evidence, however, that LLLT is effective in these conditions is controversial because several studies have shown a lack of improvement.

PROPOSED MECHANISM OF ACTION OF LOW-LEVEL LASER THERAPY

The mechanism of action of LLLT continues to remain poorly understood. Several molecular theories regarding the biostimulatory effect with LLLT have been proposed. Studies have shown that the cellular respiratory chain of mitochondria absorbs LLLT energy. In particular, cytochrome C oxidase, a complex of the integral membrane protein of the inner mitochondria membrane, has an action spectrum ranging from 600 nm to 900 nm. Absorption of photons from LLLT oxidizes cytochrome C oxidase and increases electron transport, leading to increased ATP production. Both calcium ions and cAMP are upregulated via ATP, thus promoting cellular signaling and purportedly allowing for possible hair regrowth. Increased circulation caused by release of nitrogen oxide, promoting vasodilation, also allows for a metabolic boost. Endogenous growth factors, such as basic fibroblast growth factor and insulin-like growth factor, are also upregulated, allowing for cellular proliferation.\textsuperscript{43}

A narrow-band red light-emitting diode, 638 nm (Mignon Belle LT-1, Crystalline, Mignon Belle, Osaka, Japan), studied mice in vivo and human dermal papilla in vitro at 1.0 J/cm\textsuperscript{2} and 1.5 J/cm\textsuperscript{2} respectively.\textsuperscript{44} Six shaved BL-6 mice were irradiated with narrow-band red light-emitting diode and compared with placebo; statistically significant increased hair regrowth was detected. Evaluation of dermal papillae revealed agreement with previous observations, demonstrating (1) hair growth acceleration via human growth factor regulation and decreased number of hair follicles entering the catagen phase, (2) induction of anagen phase due to leptin expression, and (3) perifollicular angiogenesis due to vascular endothelial
growth factor-A, resulting in increased hair follicle diameter size and accelerated hair regrowth.44,45

These theories need to be studied further, because confirmatory studies directly done on hair growth in vivo on humans are lacking. The majority of mechanistic studies are based on extrapolations on wound healing.

**RECONCILING LOW-LEVEL LASER THERAPY WITH PHOTOBIOLOGIC PRINCIPLES**

If LLLT leads to hair growth, then the mechanisms for this should be in accordance with other known photobiologic principles and reactions that are used therapeutically in dermatology. For all known uses of light in dermatology, the first law of photobiology requires the absorption of a photon by a putative chromophore to a higher energy state. The subsequent release of energy from this excited chromophore then results in either (1) the production of heat to drive photothermal effects or (2) the alteration of biomolecules through photochemical reactions. Because LLLT power densities are not expected to generate much tissue heat, any therapeutic effect on hair growth stimulation presumably arises from photochemistry. All of these photobiologic steps, including the role chromophores and the chemical/biomolecular mediators, are specific. Using the generic term, biostimulation, to describe how LLLT works implies a precision of understanding that has actually not yet been achieved.

Photobiologic effects should be predictable and relevant therapeutic parameters, such as wavelength, fluence, and exposure time, should thus be of critical importance to a large degree. The systematic evaluation of such parameters for LLLT hair growth is not well demonstrated in the literature, including the appropriate action spectrum and detailed dose-ranging studies.

**CLINICAL STUDIES EVALUATING LOW-LEVEL LASER THERAPY USED TO TREAT HAIR LOSS**

Notwithstanding the lack of a firmly established and well-understood mechanism of action for light-induced hair growth, the key clinical issue is whether LLLT can lead to visibly appreciable hair growth in controlled studies.

**Male/Female Pattern Hair Loss**

Different laser and light-emitting diodes have been studied to evaluate hair regrowth, including excimer (XeCl, 308 nm), helium-neon laser (HeNe, 632.8 nm), and fractional erbium-glass (1550 nm). The device that has been most thoroughly studied is the HairMax LaserComb (Lexington International, Boca Raton, Florida), a handheld class 3R lower-level laser therapy device, which contains a single laser module that emulates 9 beams (total maximal output at 45 mW) at a wavelength of 655 nm.46 Each of the teeth on the combs is aligned with a laser beam. The device is used by parting the user’s hair with the comb that is attached to the device, which enhances delivery of the laser light. The study that led to this device’s FDA approval was conducted at 4 sites and was a double-blinded, sham device–controlled, multicenter, 26-week trial.110 men completed the study and were aged 30 to 60 years with MPHL classified as Norwood-Hamilton classes IIa-V and Fitzpatrick skin types I to IV. Subjects were instructed to use the device 3 times per week for 15 minutes, on nonconsecutive days, for a total of 26 weeks. Sites were marked with a tattoo, and a circular area with a diameter of 2.96 cm was evaluated after hair clipping. Through computer-aided counts assessed by scalp macroimaging, the 655-nm laser comb demonstrated a hair density of 19.8 hairs per cm² compared with 7.6 hairs per cm² for the sham device treatment (\(P<.0001\)). No statistical improvement was noted on global investigator assessment. Independent prospective investigator studies have not been published to date, and case studies have shown a lack of effect for this particular device.

To date, LLLT has not been compared in a clinical trial against current standard therapies for pattern hair loss, such as minoxidil and finasteride. Both of these treatments have been shown to stabilize pattern alopecia by preventing further hair loss in the long term (ie, at least 1 year). There have been no published studies on the use of LLLT for long-term hair stabilization. Thus, patients who use the laser comb should not necessarily expect that it will result in hair growth that is clinically or visibly apparent nor should they anticipate that it will reliably prevent their pattern hair loss from worsening with time.

**Alopecia Areata**

The use of the Lexington LaserComb has been studied for AA. Twelve C3H/HeJ mice induced with AA were randomized into 2 groups; 1 received the laser comb treatment (wavelength 655 nm, beam diameter <5 mm, divergence 57 mrad, 9 lasers) whereas the other group received sham-treatment.48 The laser was given for 20 seconds for each session, 3 times per week for a total of 6 weeks. Hair regrowth was observed in all the mice in the treatment arm after 6 weeks, whereas no mice had regrowth in the sham-treatment group. Histologic evaluation demonstrated increased
anagen hair follicles in those treated with the laser comb, whereas the control mice had hair follicles still present only in the telogen phase. Longer-term studies and evaluation need to be conducted in humans for this indication.

Currently, there are insufficient randomized, multicenter controlled trials to prove the efficacy of LLLT. Parameters, such as wavelength, fluence, pulse structure, power density, time, and number of treatment sessions, have not been fully defined for LLLT. Proponents of LLLT claim that studies that demonstrate a lack of efficacy with LLLT are faulted due to inadequate parameter settings, yet there is a significant paucity of rigorous studies evaluating the optimal parameters for hair regrowth.

**CLINICAL STUDIES EVALUATING OTHER FORMS OF RADIATION FOR HAIR LOSS**

Ultraviolet phototherapy has also been studied for AA. For PUVA the published experience has yielded mixed results. The formation of monoaducts with pyrimidine bases and cross-links with opposite DNA strands inhibits DNA synthesis and culminates in the depletion of infiltrating T lymphocytes. Furthermore, PUVA causes T-cell apoptosis. Studies of topical and oral PUVA differ widely in their results with 15% to 70% of patients experiencing improvement of AA lesions. Two large retrospective studies showed no difference in the improvement of AA lesions treated with PUVA compared with control lesions. Another device, the 308-nm excimer lamp, induces T-cell apoptosis and might, therefore, be capable of improving AA. With this treatment device, the exposure field is more selective and targeted, which means that higher fluences can be more readily and safely used compared with fluorescent UV lamps. In a study evaluating 3 patients with AA, lesions were treated twice weekly (irradiance 150 mW/cm², spot size 18.9 cm²). Lesions were initially treated with a fluence of 150 mJ/cm² and irradiation doses were increased by 50 mJ/cm² until erythema was observed. After 10 treatment sessions, all 3 patients were noted to have hair regrowth. Also promising is 1 case report showing improvement with fractional erbium:glass photothermolysis therapy in a 35-year-old men who was refractory to conventional treatment. Controlled trials are needed to properly assess the effectiveness of the 308-nm excimer lamp and fractional photothermolysis therapy for AA patients.

Topical photodynamic therapy with 5-aminolevulinic acid (ALA) has not been shown to induce hair growth in patients with extensive AA. Six patients with extensive AA had different scalp areas exposed to topical ALA lotion at 5%, 10%, and 20% as well as vehicle lotion alone, followed 3 hours later by red light exposure at each treatment session. After 20 twice-weekly treatment sessions, no significant hair growth was seen between the vehicle and the 3 ALA-treated sites.

**FUTURE STUDIES CONDUCTED EVALUATING RADIATION DEVICES FOR HAIR LOSS**

Different radiation devices using LLLT are currently being evaluated for MPHL/FPHL, including the Hairmax LaserComb, LaserCap, TopHat 655 Rejuvenation System, and Erchonia ML Scanner devices. Similar to the trial done for MPHL, has been under way at multiple sites evaluating the Hairmax LaserComb in FPHL patients and is now reported as completed, although the results have not yet been disseminated. This phase II study will also be a double-blind, sham-controlled trial evaluating changes in terminal hair count and global assessments and has enrolled 72 patients. The LaserCap (Transdermal Cap, Gates Mills, Ohio) contains 224 laser diodes (total maximum output of 1120 mW) affixed to a mesh framework under a cap. The LaserCap is currently being investigated in multicenter trial to gain FDA approval. A study sponsored by Apira Science is currently evaluating patients aged 18 to 48 years, with hair loss classified as Norwood-Hamilton Ila to V for men and Ludvig I or II for women. This randomized, double-blinded study will evaluate the TopHat 655 Rejuvenation System (Apira Science, Newport Beach, California) in comparison with a sham device that will only contain red incandescent bulbs rather than laser beams at 655 nm. The study is expected to enroll 88 patients. The TopHat 655 system will be worn every other day for 16 weeks for a preprogrammed time period. Erchonia Corporation is currently evaluating their Erchonia ML Scanner (Erchonia Cooperation, McKinney, Texas), in 70 patients with FPHL. Subjects will be randomly assigned to receive the scanner device or a sham device. The exact details of this device, including the laser beam, have not yet been released.

LLLT is also being evaluated for patients with telogen effluvium secondary to chemotherapy. A nonrandomized, open-label, safety/efficacy study is currently evaluating hair preservation with patients receiving chemotherapy for breast cancer. A 670-nm LLLT device with laser beams affixed in a rotating helmet apparatus will be used by 15 subjects twice a week before receiving chemotherapy and once a week until 1 week after the last chemotherapy.
**SUMMARY**

Hair loss secondary to either MPHL/FPHL or AA is a common problem in the general population. Conventional management for MPHL/FPHL includes the use of minoxidil, finasteride, dutasteride, spironolactone, hair fillers, hairpieces, and wigs. Most AA cases can be managed with intralesional steroids injections, but resistant cases can be treated with anthralin or diphenylcyclopropenone. Despite these available treatment options, LLLT and other forms of radiation have been investigated for both MPHL/FPHL and AA. Consistent results, however, showing beneficial improvement in clinical trials are lacking. Furthermore, LLLT has been criticized for several reasons, including (1) lack of independent peer-reviewed randomized trials showing efficacy, (2) inadequate explanation of LLLT’s mechanism of action relating to the pathophysiology of MPHL/FPHL and AA, (3) failure to incorporate the fundamental laws of photochemistry in the mechanism of action for LLLT, and (4) lack of success with anecdotal experience of patients receiving treatment with LLLT. Further studies are being conducted to test the efficacy of LLLT for hair loss using different modes of light delivery.

**REFERENCES**

25. Tang L, Cao L, Bernardo O, et al. Topical mechloromenone restores autoimmune-arrested follicular...


