

Types of Hair Loss and Treatment Options, Including the Novel Low-Level Light Therapy and Its Proposed Mechanism

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Abstract: Androgenetic alopecia (AGA) is the most common form of hair loss in men, and female pattern hair loss (FPHL) is the most common form of hair loss in women. Traditional methods of treating hair loss have included minoxidil, finasteride, and surgical transplantation. Currently there is a myriad of new and experimental treatments. In addition, low-level light therapy (LLLT) has recently been approved by the United States Food and Drug Administration (FDA) for the treatment of hair loss. There are several theories and minimal clinical evidence of the safety and efficacy of LLLT, although most experts agree that it is safe. More in vitro studies are necessary to elucidate the mechanism and effectiveness at the cellular level, and more controlled studies are necessary to assess the role of this new treatment in the general population.

Key Words: fibroblast, hair growth, hair loss, low level laser therapy, low-level light therapy

Types and Epidemiology of Hair Loss

Male pattern hair loss (MPHL), also known as androgenetic alopecia (AGA), is the most common form of hair loss in men.¹⁻³ Similarly, female pattern hair loss (FPHL) is the most common form of hair loss in women.⁴ The incidence and prevalence of MPHL is dependent on age and race. Chinese, Japanese, and African American people are affected less than Caucasians.^{2,5} Its incidence increases by age.⁵ Prevalence values have variable ranges from 16–96%, depending on the age group and whether or not mild forms of MPHL are included (Table 1).^{2,6,7} Prevalence values for FPHL are comparable to MPHL (Table 2).⁸ The severity of MPHL is based on the Norwood Hamilton Classification, which takes into account bitemporal and vertex hair loss (Fig. 1).² FPHL is

evaluated based on the Ludwig scale, which ranges from I-III (Fig. 2).⁴ These classification systems differ based on the fact that hair loss and thinning in men most commonly occurs in an orderly fashion and involves the temporal and vertex region while sparing the occipital region; diffuse thinning and loss of density with a normal distribution and maintenance of the frontal hairline is often seen in women.^{2,4,5,9,10}

The term AGA pertains to the pathophysiology of MPHL, in which there is an induction of hair loss due to the effects of androgens such as testosterone (T) and its derivative dihydrotestosterone (DHT) in genetically susceptible individuals.² Recently, authors have argued against the use of the term AGA in women, as the role of androgens in FPHL is debatable.^{4,7,11,12} Testosterone is a lipophilic compound that diffuses the cell membrane. It is converted into its more active form, DHT, by the cytoplasmic enzyme 5-alpha reductase (5-AR).^{2,4} There are two types of 5-AR. 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.^{4,13,14} Androgens play an important role in the control of hair. During puberty, due to a surge in T, there is an induction of pubic hair growth and a decrease in follicle size in the bitemporal region.⁸ Also, castrated men are not known to develop MPHL.^{2,7} However, there is no correlation between T levels and MPHL.² The role of DHT was first noticed in pseudohermaphrodites lacking this enzyme, who did not develop MPHL.^{2,7} DHT then binds the nuclear androgen receptor (AR) that regulates gene expression.^{2,7} Although the exact genes involved in hair loss are not known with certainty, some of the proposed genes responsible for hair growth (mainly studied in knockout and transgenic mice) are desmo-

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Key Points

- Low-level light therapy (LLLT) appears safe and effective for the treatment of hair loss.
- LLLT may serve as an adjunct to other treatment modalities.
- More cellular and human research is necessary to elucidate the mechanism of LLLT.

Table 1. Prevalence of male pattern hair loss

Prevalence	Participants	Author
50% by age 50 yr	Not including Type II frontal recession	Hamilton ³⁷ Norwood ³⁸
98% by age 50 yr	Including Type II frontal recession in Hamilton's data ³⁷	Haber ¹¹
67% by age 50 yr	Including Type II frontal recession in Norwoods' data ³⁸	Haber ¹¹
62% in 20–40 yr olds	Have bitemporal recession	Otberg et al ²
54% of those >30 yr old	Have androgenetic alopecia (AGA)	Otberg et al ²
53% of 40–49 yr olds	Have Type III or greater	Otberg et al ²
42% of 18–49 yr olds	Have Type III or greater	Otberg et al ²
16% of 18–29 yr olds	Have Type III or greater	Otberg et al ²
53% by age 50 yr	Moderate to severe hair loss	Rhodes ¹¹
80% by age 50 yr	Rhodes study including all types of hair loss	Haber ¹¹
30% by 30, 50% by 50, and 80% by 70	White men	Stough et al ⁵

See references for full citation.

glein, activin, epidermal growth factor (EGF), fibroblast growth factor (FGF), lymphoid-enhancer factor-1 (LEF-1), and Sonic Hedgecock.¹⁵

Besides patterned baldness, there are several other forms of hair loss, which include alopecia areata (AA), telogen effluvium (TE), and several androgen-related female alopecias. AA is an autoimmune inflammatory condition which may affect the hair of the head, face, and body.¹⁶ Although most commonly thought of as an acquired disorder, congenital cases have been described.¹⁷ It has an incidence of 0.1–0.2%, and affects 1–2% of men and women.^{16,18} Hair involvement in AA is often patchy. Two variants of AA are alopecia totalis, a total loss of scalp hair, and alopecia universalis, total loss of scalp and body hair.¹⁶ AA is linked to several human leukocyte antigen (HLA) alleles, such as HLA-AI, HLA-HLA-B26, HLA-DQ1, and HLA-DQ3.¹⁶ Although most commonly treated by an injection of intralesional corticosteroids, other treatment modalities are used.¹⁶ These include topical

Table 2. Prevalence of female pattern hair loss

Prevalence	Author
12% of those 20–29 yr old	Dinh and Sinclair ⁴
>50% in those >80 yr old	Dinh and Sinclair ⁴
86% by 50 yr old	Hamilton ³⁷
6% by 50 yr old	Birch ¹¹
10% of premenopausal women	Scheinfeld ¹⁰
50–75% of women >65 yr old	Scheinfeld ¹⁰

See References for full citation.

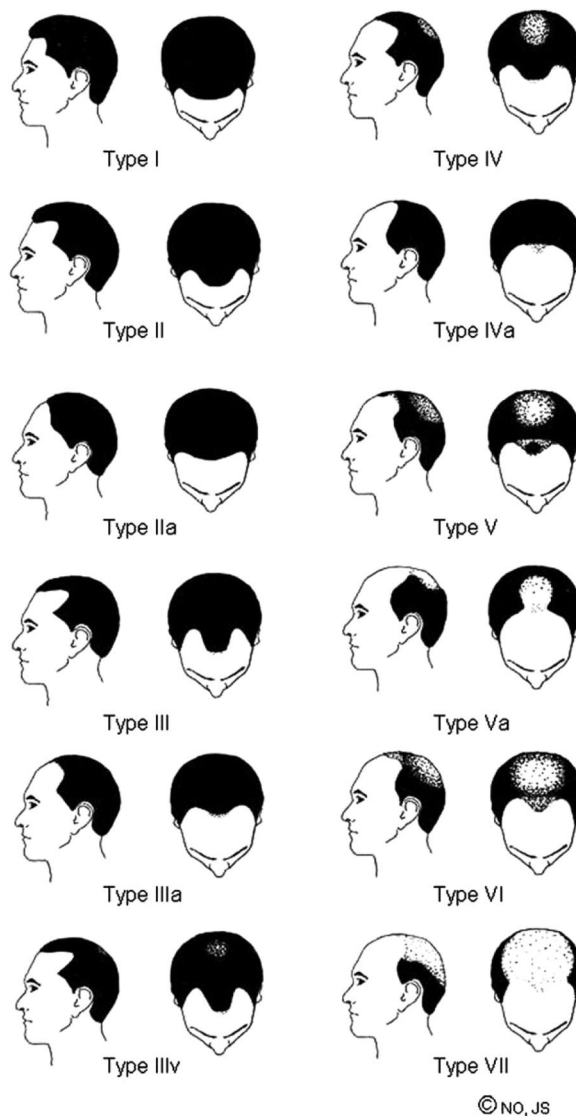


Fig. 1 Norwood Hamilton classification. Reprinted with permission from *Endocrinol Metab Clin North Am* 2007;36:381, ©2007 Elsevier Inc. All rights reserved.

and systemic corticosteroids, minoxidil for moderate cases, anthralin, contact sensitizers (when more than half the scalp is affected), psoralen plus ultraviolet A (PUVA), cyclosporine, tacrolimus, and biologics.^{16,18,19} Biologics include agents such as alefacept, efalizumab, etanercept, infliximab, and adalimumab. Of these, alefacept seems to be most promising, while adalimumab and infliximab have been reported to induce AA.²⁰

Telogen effluvium (TE) is abnormal hair cycling causing excessive loss of telogen hair.¹² It is likely the most common cause of alopecia in children.¹² Some of the common causes include acute severe illness, surgery, iron deficiency anemia, thyroid disease, malnutrition, chronic illness, and medications such as oral contraceptives, lithium, and cimetidine.^{12,19} A good illness and medication history

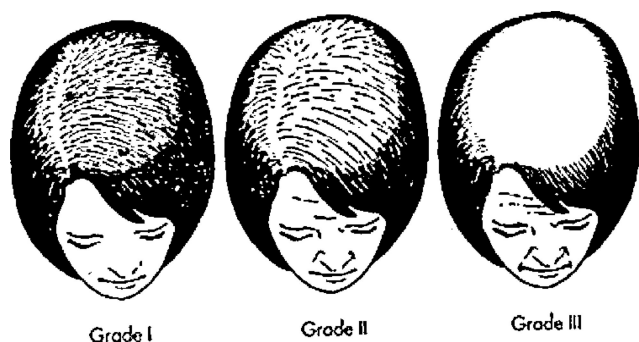


Fig. 2 Ludwig classification. Reprinted with permission from *Clin Interv Aging* 2007;2:190, ©2007 Dove Medical Press Ltd. All rights reserved.

is necessary to make the diagnosis, as well as laboratory studies such as complete blood count (CBC), thyroid function tests, and syphilis titers.^{12,19}

Androgen-related female alopecias include a variety of types of hypergonadism. Polycystic ovarian syndrome (PCOS) is a common cause of hypergonadism which could cause amenorrhea, hirsutism, and FPHL.¹⁴ Some antiandrogen medications that may be helpful for FPHL include cyproterone acetate, spironolactone, and flutamide.¹⁰ However, one study argues that 88% of FPHL will not improve with oral antiandrogens.¹⁰

Traditional Treatment Options

The two medications approved for MPHL by the United States Food and Drug Administration (FDA) are 5% minoxidil and finasteride.^{2,3,19} Two percent minoxidil is the only approved medication for FPHL.^{3,10} Minoxidil is an antihypertensive medication with peripheral vasodilator properties, and the side effect when taken systemically is hypertrichosis.^{1,11} After application, minoxidil is converted to minoxidil sulfate, a potassium channel opener which relaxes vascular smooth muscle and increases blood flow.⁶ It was first suspected that this increased blood flow is the mechanism by which minoxidil affects hair loss, but this may not be the case.¹¹ In vitro studies of hair growth have shown that hair cultures grown in the presence of minoxidil maintain morphology, whereas controls undergo kinking and necrosis.²¹ A common side effect of minoxidil is contact dermatitis, which can initially be managed by switching to a 2% solution or the foam preparation, which lacks propylene glycol (an irritating substance).² Corticosteroids may also be beneficial to improve pruritic side effects.¹¹ One drawback with minoxidil treatment is that it requires twice daily application indefinitely to maintain results.^{1,2,6} Shin et al⁶ have proposed that combination of minoxidil with tretinoin once a day makes no significant difference in efficacy or side effect profile (as opposed to minoxidil twice a day), and may improve patient compliance. Tretinoin increases the absorption of minoxidil.⁶ Two percent minoxidil is approved for women, as studies

have shown the same efficacy with the 5% solution, yet a higher rate of hypertrichosis with topical application.^{8,19} Minoxidil is effective in adolescents.¹²

Finasteride is an oral agent, which is a competitive 5-AR inhibitor with more affinity for Type II 5-AR.^{8,11,13} Thus, it inhibits the conversion of T to its more active form of DHT.^{2,4} Given its systemic nature, potential side effects of finasteride include erectile dysfunction, gynecomastia, and loss of libido.¹ Like minoxidil, this is an ongoing therapy. Finasteride is only approved for men 18 years of age or older.¹²

Whereas minoxidil and finasteride are temporizing measurements and require continuous administration, hair restoration may serve as a definitive treatment.^{2,9} This procedure is based on the fact that occipital hair follicles are not androgen dependent, and that transplanted hair maintains donor dominance.^{9,22} Follicular units are acquired from the occipital scalp and transplanted into the frontal scalp in a cosmetically acceptable manner.^{9,22} This procedure should ideally be performed on individuals who have reached a plateau in balding and have realistic expectations.^{9,22} Side effects are usually minor and include postoperative pain, delayed hair growth, and, rarely, infection.⁹ Periorbital and frontal swelling may also occur.²² Some argue that the future procedure of hair cloning may dramatically improve this process.²³

In addition, there are a variety of off-label and investigational drugs that are used or considered in the treatment of hair loss. Dutasteride is a dual Type I and II 5-AR inhibitor.^{4,7} Latanoprost is a prostaglandin mainly used for glaucoma, which was observed to stimulate eyelash and eyebrow growth.⁷ The antifungal agent ketoconazole may also promote hair growth, perhaps by inhibiting inflammation and serving as an antiandrogen.⁷ Other investigational drugs include fluridil, a topical antiandrogen; naminidil, which works through the potassium (K) channel; P-45, which may inhibit interleukin 4 (I-L4)-induced CD23 expression; PSK 3841, a topical nonsteroidal androgen antagonist; and lemuteporfin (QLT 0074), a photosensitizer to be used with photodynamic therapy.³ Other agents include antiandrogen oligonucleotides—which are deoxyribonucleic acid (DNA) that pairs with complementary ribonucleic acid (RNA)—KF19418, LGD1331, steroid sulfatase inhibitors, and thymosin beta 4, which stimulates hair growth via stem cell migration.³ Gene delivery through liposome technology has also showed some success.³

Low-Level Light Therapy

In 2007, low-level light therapy (LLLT) was approved by the FDA as a treatment for hair loss.²³ LLLT is also known as low level laser therapy, red light therapy, cold laser, soft laser, biostimulation, and photobiomodulation.^{24–26} Most experts agree that LLLT is safe for the treatment of hair loss, but more studies are needed to confirm its therapeutic effects.²⁴ LLLT was discovered in the 1960s and first used by

the National Aeronautics and Space Administration (NASA) to accelerate wound healing in space.²⁵ Since then, LLLT has been used to reduce neurogenic pain, reduce inflammation, and promote wound healing.²⁵⁻²⁷ Other uses include non-melanoma skin cancer and its precursors, acne vulgaris, photorejuvenation, hidradenitis suppurativa, and psoriasis.²⁸ It may also prove helpful in killing bacteria, fungi, and viruses.²⁸ LLLT has also been used to achieve attenuation of retinal toxicity in methanol-poisoned rats.²⁷ The role of LLLT in hair growth was discovered accidentally in 1967.²⁶ In an attempt to test if LLLT causes cancer in shaved mice, researchers discovered that these mice did not develop cancer, but instead grew hair.²⁶

Before describing the mechanisms of LLLT, a brief discourse into its terminology will be taken. The term “laser” refers to the fact that monochromatic light is used.²⁷ This is in contrast to light emitting diode (LED). The term “low level” alludes to the fact there is a specific wavelength of light that has optimal therapeutic effects, and any level higher or lower than this may not be proficient.²⁶ This therapeutic window ranges roughly from 600 to less than 1,400 nm, and is close to the absorption spectrum of hemoglobin and water, respectively.²⁶ Furthermore, respiratory chain components (mainly cytochrome c) have a similar absorption spectrum.²⁶ This low level results in a negligible change in tissue temperature.²⁵

The Mechanism of LLLT

There are several theories that explain the mechanisms of LLLT: cytochrome c oxidase-mediated increase in adenosine triphosphate (ATP) production, the singlet oxygen hypothesis, the redox properties alteration hypothesis, and nitrous oxide (NO) hypothesis.²⁶ Cytochrome c oxidase is part of the respiratory chain that ultimately results in ATP production. It is hypothesized that the light absorbed by this moiety may ultimately result in increased ATP production, which may alter cell metabolism.²⁶ This is a concept similar to photosynthesis in plants. Singlet oxygen hypothesis stems from the fact that radiation used in high doses to kill cancer cells causes a paradoxical cell proliferation in low doses.²⁶ The redox properties alteration hypothesis proposes that enzymes other than cytochrome c are induced to produce superoxide anion.²⁶ The NO hypothesis proposes that LLLT may uninhibit the effect of NO on cytochrome c.²⁶

There have been several studies to evaluate the effects of LLLT. Increase in ATP synthesis, proton electrochemical potential, and oxygen uptake have all been shown in rat liver mitochondria.^{26,29,30} LLLT has been shown to increase procollagen synthesis in fibroblasts.^{25,26} However, numerous human and animal studies have shown inconsistent results, mainly due to lack of coherence in protocols.²⁵ Some also relate the variability in results across studies to the fact that the effect of LLLT depends on the physiologic state of cells.³¹

One study reported a failure in treatment of AA.³² However, the researchers used a small dose (630 nm at 37 J/cm² for 7.5 min) only once a month.³² In addition, they reported successful treatment in beard AA after only three sessions in three patients.³² Sobanko and Alster²⁵ propose that better understanding of the mechanisms of LLLT will help resolve some of these questions. Some negative results are also attributed to poor design and use of very low doses.³³ Unresolved questions regarding the properties of light being used include: wavelength, laser vs noncoherent, dose, pulsed vs continuous wave (CW), and polarization status.²⁶ All of these conditions and cell culture condition will determine the effect of LLLT.³³ Usually wavelengths in the 600-1000 nm range and powers from 5–500 mW are used.²⁵ Evans and Abrahamse³³ studied the effect of light with wavelengths of 638.2, 830, and 1064 nm at 5, 10, and 16 J/cm² intensities to compare control vs wounded fibroblasts. They found the most stimulatory effect on wounded fibroblasts using 5 J/cm² of 632.8 nm light.³³ They also found the dose of 16 J/cm² to cause DNA damage and reversible cell damage (in most instances).³³ Similarly, in assessing free radical formation, Haywood et al³⁴ found no detectable free radicals after exposure of human skin biopsy to 694 nm light at 11–14 J/cm² in 0.9 ms pulses using electron spin resonance spectroscopy.

Conclusion

LLLT appears safe and effective for the treatment of hair loss in theory and through minimal observational studies, but more clinical and in vitro studies are needed. Proposed in vitro studies may include the effect of LLLT on fibroblast function in controlled settings. Factors such as growth rate and apoptotic rate may be assessed. Similar in vitro studies may be carried out with intact hair follicles. Finally, randomized double blind multicenter trials are needed to truly assess safety and efficacy; one such trial has found promising results thus far.³⁵ Another study of seven patients did not reveal statistical significance, and proposed that some individuals may be more responsive to this treatment.³⁶

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