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# Androgenetic Alopecia: A Comprehensive Review of Pathogenesis, Diagnosis, and Treatment Options

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# Abstract

**Background:** The most prevalent kind of male pattern baldness, androgenetic alopecia (AGA), has major emotional and social effects on affected individuals. The progressive miniaturisation of hair follicles is the outcome of a complex interaction between genetic predisposition and androgenic stimuli. **Objectives:** The purpose of this review is to provide a thorough overview of AGA, including all aspects such as its clinical features, pathogenesis, diagnostic methods, and current treatment choices. **Conclusions:** AGA has several causes and progresses over time. Multiple diagnostic tests may corroborate a patient's symptoms and signs that point to a diagnosis. A variety of treatment methods were available, including surgical interventions, oral and topical therapies, and combination therapies, the latter of which showed encouraging results. The key to the best results is prompt intervention and ongoing treatment. New management avenues are opened up by emerging therapies such cell-based treatments and low-level laser therapy, although their long-term efficacy and safety need further research.

**Keywords:** Androgenetic alopecia, hair loss, dihydrotestosterone, 5-alpha reductase inhibitors, minoxidil, hair transplantation, platelet-rich plasma, stem cell therapy.

# 1. Introduction

As a hereditary condition, androgen etic alopecia (AGA), often known as male pattern hair loss, affects more men than any other kind of alopecia. Genetic susceptibility and endocrine variables combine to cause AGA to develop and manifest. Humans use hair as a means of sexual and social expression. Men with thinning hair are stereotyped as being less attractive, both physically and socially (1).

Men with hair loss often have low self-esteem, a sense of ageing, and a lack of self-assurance, in addition to being irritated by the realisation that they have the disease. Millions of dollars are spent annually on hair restoration treatments, even though AGA may be considered as a physiological process (2).

Ancient Egyptian papyruses detail the psychological and social significance of hair and include recipes for various hair loss treatments. Baldness does not happen among eunuchs or before sexual maturity, according to Aristotle (384–322 BC), who also linked desire to the extent of hair loss. Seborrhoea, pityriasis capitis, and AGA were thought to be related by dermatologists in Vienna in the 1800s (3).

Another theory put AGA on the back burner, suggesting that seborrhoeic dermatitis caused by Pityrosporum ovale, occlusion, or cerebral congestion was the underlying cause. Last but not least, a poison in the air or careless hair care were brought up. Modern knowledge of AGA began with research conducted by Hamilton in 1942. He proved that androgens cause genetically predisposed hair follicles to undergo a physiological process known as male pattern hair loss. Individuals are genetically predisposed to AGA, which may present at normal androgen levels in males (4). The purpose of this review is to provide a thorough overview of AGA, including all aspects such as its clinical features, pathogenesis, diagnostic methods, and current treatment choices.

#### **Clinical features and classification**

There are predictable patterns in the pattern of hair loss seen by adult males with AGA, as thin vellus-like hair gradually replaces robust, thick, pigmented terminal hair on the scalp. Hamilton created the first grading system for Caucasian males and females, spanning type I to type VIII, in 1951. Type I is indicative of a prepubescent scalp with widespread and terminal hair development, while types VII and VIII reveal a merging of balding regions and the remaining hair is limited to the sides and back of the head (5).

A more noticeable gradual receding of the middle portion of the frontal hair line is observed in IIIa, IVa, and Va, according to Norwood's revised classification. Type III vertex, on the other hand, is defined by hair loss primarily in the tonsure area and a frontotemporal recession, but it never surpasses that of type III. Using a five-point alopecia severity scale, another research detailed varying forms of hair loss across racial and gender lines (6). Classes A, B, C, and D represent different variants of AGA. Class A is the Caucasian variant, which eventually develops a central lock; class B is Asian, with a denuded frontal hair line and diffuse thinning in the frontoparietal area; class C is Mediterranean or Latin, with the Hamilton scale corresponding to this pattern; and class D is the female pattern, with diffuse thinning and typically a persistent frontal hair line (3).

# **Rate of incidence**

Prevalence estimates of AGA are very subjective. More than 96% of Caucasian males, according to some writers. In males between the ages of 20 and 40, bitemporal recession affects 62% of Caucasian men, whereas in those over the age of 30, AGA affects 54% (7).

Age is a major factor in the occurrence of male pattern baldness; although 16% of men between the ages of 18 and 29 have moderate to severe hair loss (Norwood/Hamilton type III or more), 53% of men between the ages of 40 and 49 do. In males between the ages of 18 and 49, 42% have hair loss that is classed as type III or higher. A positive family history in either the mother, the father, or the maternal grandparents increases the likelihood of having AGA (2).

# Diagnostics

In most cases, a man's AGA may be easily diagnosed. In AGA, the follicular ostia is preserved and the hair loss does not leave scars. The unique pattern, variations in hair shaft diameter, and the presence of tiny, vellus-like hairs that may sometimes be seen only under a microscope or dermatoscope are the hallmarks of this condition. During a hair consultation, simple qualitative tests like dermoscopy, the hair pull test, and contrast paper may be used with ease. In most cases, a hair pull test, which is often used to rapidly evaluate the severity of hair loss, yields negative results (8).

When AGA is progressing and there is an elevated telogen count in the affected region, the pull test may come out positive. Approximately fifty to sixty hairs are held near the skin's surface by the investigator using their thumb, index, and middle fingers in a hair pull test. From the beginning to the conclusion, the hairs are tugged forcefully yet softly. It is said that the test is affirmative if three hairs or more can be taken out (9).

By placing a piece of contrast paper in a section of the scalp that is separated, you may see the existence of miniaturised hair and variations in the diameter of the hair shaft. This background allows for a careful examination of the hair. The existence of miniaturised hair and follicular ostia may be detected by dermoscopy of the scalp (10).

As a qualitative evaluation of the development of hair loss and as a therapeutic control, standardised overview images are useful for monitoring AGA in males. A scalp biopsy is often unnecessary for routine diagnosis. The histologic characteristics, area-specific counts of terminal and vellus hairs, and anagen and telogen hair counts may all be determined with the use of a scalp biopsy, which ultimately leads to a conclusive diagnosis. Patients will have a little scar on their scalps as a result of the invasive scalp biopsy procedure. It is appropriate to utilise quantitative testing, including trichoscan and trichogram, for reliable therapeutic monitoring (11).

The trichogram, also known as the traditional hair-root examination, is a method that uses light microscopy and is semi-invasive. Roughly fifty hairs will be plucked. Using light microscopy, the morphologic characteristics of each root are evaluated after placing the hairs on a glass plate. Using this method, one can precisely determine the proportion of active (anagen), dormant (telogen), and regression (catagen) hair (12).

Identifying toxically damaged hair, also known as dystrophic hair, is possible. The latter occurs when the hair development phase is interrupted, which may happen as a result of infections, organic disorders, or certain medications. The hairs are often plucked in close proximity to one another. Consequently, the region of the scalp that is plucked is almost invisible, and the process is much more comfortable. The inability to get a hair count is the technique's main drawback. Only by epilating the hairs in a certain circular pattern can their terminal hair counts be determined. The patient will have greater discomfort and temporary hair loss for a few of weeks with this method. The trichogram method cannot be used to determine the number of vellus hairs (6).

A hybrid of the traditional trichogram and the phototrichogram, the trichoscan has many photographic useful applications. The technique allows for the evaluation of the patient's scalp hair growth rate, density of terminal and vellus hair, and the ratio of growing to non-growing hair, all without intrusive procedures. Hair in a circular region of 1.8 cm in diameter is trimmed to a certain length and then dyed black for the trichoscan. A software tool determines the density of terminal and vellus hair from digital photographs (12).

This method can only be used on people with light skin types (I - III). If generalised hair loss

is not present at the same time, a laboratory evaluation is often unnecessary. The use of anabolic steroids should be enquired about by every patient diagnosed with AGA. Springer and colleagues provide a great synopsis of alopecia's differential diagnosis and other possible causes (10).

# Mechanism of Injury

# Androgenetic alopecia: alterations to the hair cycle

Patterned baldness in males develops when dense, pigmented hair on the scalp (terminal hair) gradually changes into fine, colourless, almost undetectable vellus-like hair follicles. The typical hair cycle for scalp hair consists of an anagen phase that lasts about 2–6 years, a catagen phase that lasts about 2–3 weeks, and a telogen phase that lasts around 12 weeks. Although there might be seasonal changes, a typical anagen/telogen ratio for scalp hair is 9:1.

As the hair cycle progresses, the anagen phase becomes shorter in AGA. The maximal length of newly grown anagen hair is less than that of its predecessor due to the fact that the duration of the anagen phase is the primary factor determining hair length. As the percentage of telogen hair grows, the hair becomes progressively thinner and finer with each cycle. There is less hair on the scalp because the duration between hair shedding and anagen regeneration is becoming longer (6).

#### Androgens' function

According to Hamilton's findings, baldness did not appear in ten eunuchoids, ten men who had castration during puberty, and thirty-four men who underwent castration during adolescence. Baldness occurred in those who were already susceptible after receiving testosterone. The baldness halted, but did not reverse, once testosterone was removed. The formation of a beard was inhibited by castration conducted before to puberty, somewhat prevented by castration performed between the ages of 16 and 20, and had no influence on beard development when castrated beyond the age of 20. No evidence has been found to suggest a relationship between testosterone levels and either libido or baldness (2).

#### **Molecular Biology**

A considerable genetic component is involved in the development of AGA. Having a positive family history greatly raises the risk of MPHL. Genetics have a significant role in male pattern baldness, as is shown by the presence of ethnic differences. It is still not obvious what inheritance is. There is evidence that variations in the CYP17 gene on chromosome 10q24.3 may be associated with polycystic ovarian syndrome and with autosomal dominant inheritance (13).

A polygenic inheritance of the feature is, according to some experts, the much more probable explanation. It seems that the genes SRD5A1 on chromosome 5 and SRD5A2 on chromosome 2 are involved, as individuals with pseudo hermaphroditism caused by 5a-reductase-2 deficiency do not have male pattern hair loss. There is no evidence that the 5a-reductase isoenzymes are related to male pattern baldness (2).

Some researchers believe that IGF-1 expression in the dermal papilla is crucial to the onset of patterned baldness. Plasma IGF-1 levels are greater and circulating IGF binding protein 3 levels are lower in older males with vertex baldness. The tissue of balding scalps showed reduced expression of IGF-1 (14).

Male pattern baldness does not include the hairless gene on chromosome 8. A polymorphism in the ornithine decarboxylase gene has been linked to a probable relationship in a research. This gene is known to regulate the hair cycle and is involved in polyamine production. Two different alleles of ornithine decarboxylase are present in humans, and they each perform different functions. Balding males often have both the main and lesser alleles, which the authors hypothesised may be linked to AGA (15).

# The function of the SRD5A enzyme in steroid metabolism

Enzyme SRD5A is a family of five members that all reside in the cell membrane: SRD5A types 1–3, GSPN2, and GSPN2-like. The activity of SRD5A1 as a neurosteroids metaboliser is primarily regulated in the scalp, skin, and liver. SRD5A2 is highly selective for steroids with the  $\Delta$ 4,3-keto structure, such as testosterone (16), and it is expressed in hair follicles, the prostate, and the genitourinary tract.

The capacity of SRD5A2 to transform  $\Delta 4,3$ keto steroids into metabolites with specific functions was used to define it, and it is the one linked to AGA. SRD5A3 is expressed in breast cancer, prostate cancer, and malignant human prostate tissues; it acts in protein Nlinked glycosylation (17).

Bile acid biosynthesis, androgen metabolism, and oestrogen metabolism are the three metabolic pathways mediated by SRD5A. For instance, SRD5A1 causes BPH by converting testosterone to DHT, while SRD5A2 is implicated in AGA; in androgen metabolism, SRD5A uses NADPH to decrease  $\Delta$ 4,5 bonds in substrates. The 5- $\alpha$ -stereoisomer DHT is formed when these two iso-enzymes break

down the  $\Delta 4$  group (double bond) of C-19 and C-21 steroids (1).

#### Disease risk factors and their connections

One possible indicator of early-onset coronary heart disease is vertex baldness, which is more common in young men with hypertension or dyslipidaemia. Hyperinsulinemia and insulin resistance-related diseases, including obesity, hypertension, and dyslipidaemia, are more common in men between the ages of 19 and 50 who have early AGA (beginning before the age of 35). Male pattern baldness, especially vertex baldness, is associated with an increased risk of prostate cancer in males. These discoveries' pathogenesis remains a mystery. The common androgen pathways in prostate cancer, insulin resistance, and coronary heart disease need further research (18).

# Androgenetic Alopecia Treatment Options

Paraphysiological as AGA may be, it has profound societal consequences due to the drastic changes it brings to patients' physical appearance, especially in younger males (2).

Because AGA progresses over time, it is important to begin treatment as soon as possible and keep it up forever so that the patient may continue to reap the benefits. There are a number of therapy options for AGA, which is reasonable given the complexity of the pathogenic pathways that cause it. Several considerations, including as AGA grade, effectiveness, practicability, costs, and dangers, determine the decision of topical and systemic medications, either alone or in combination (19).

#### Aesthetic treatments

As an alternative to or in addition to oral drugs, topical treatments may be useful as a first line of defence against AGA in individuals with mild to moderate hair loss who are concerned about the possibility of systemic adverse effects (20).

# Minivascular tretinoin

There are only three therapies for alopecia that have been authorised by the FDA, and topical minoxidil is one of them. In 1988, it was given the green light to treat mild to moderate AGA in males, making it the first-line therapy for this condition. The first application of the oral formulation for the treatment of hypertension was as a vasodilator in the 1960s. The discovery of hypertrichosis as a side effect of long-term oral minoxidil usage led to the creation of a topical formulation to stimulate hair growth. Minoxidil is easily accessible in a variety of foam and liquid solutions, with varied strengths and efficacies, including 2% and 5% (21).

# Intramuscular finasteride

Topical versions of finasteride are available from compounding pharmacies; research has shown that some of these formulations effectively lower DHT levels in the blood and on the scalp. Initial testing was a 52-person placebo-controlled experiment that showed encouraging outcomes for hair regeneration and baldness reduction with no adverse effects observed (22).

# Vitamin A valproate

This anticonvulsant medication was first investigated in 2012 for its potential to promote hair development when applied topically to male murine mice. Several epidermal indicators, including loricrin and filaggrin, and the dermal papilla-resident alkaline phosphatase were shown to be increased by VPA, according to the scientists' observations. They are all connected to inducing the anagen phase by upregulating the Wnt/b-catenin pathway (23).

#### Treatments administered by mouth

Although topical treatments have fewer possible side effects than oral medications, the former are often the most convenient for individuals with moderate or advanced AGA (19).

# Buy finasteride online

Since its approval in 1997, finasteride has been used to treat male pattern baldness. Inhibiting the enzyme Type II 5-alphareductase is how the medicine prevents testosterone from being converted to dihydrotestosterone (1).

The 1 mg pill is recommended for men with male pattern baldness, while the 5 mg tablet is offered for other uses. The potential for ambiguous genitalia in a male foetus is the reason it is classified as pregnancy category X and is not meant for usage by pregnant women. According to research, finasteride is helpful for AGA patients, and studies have shown that using the medication for up to five years may result in noticeable hair growth and the permanent stabilisation of hair loss (2).

The medicine works better on the vertex scalp than on the frontal, and finasteride should be taken forever to keep the hair that was saved after the first treatment. Time and, in some instances, regular usage seem to enhance finasteride's effectiveness (24).

#### Levitra orally

Dutasteride is an example of a secondgeneration 5-alpha-reductase inhibitor; it selectively competes with both the type 1 and type 2 isoenzymes, therefore blocking their activity. It has been shown that compared to finasteride, dutasteride is three times more effective at inhibiting the type I enzyme and one hundred times more effective at inhibiting the type II enzyme. There are two dosage options for the medicine, 2.5 and 5 mg, and both of them have shown more effectiveness than 5 mg of finasteride (25, 21).

#### Oral medrol dose

Several studies looked at the efficacy of oral minoxidil in treating AGA in men and women, although it is not FDA-approved and is not nearly as popular as finasteride. If you want to treat AGA with the safest possible dosage, you may divide the 2.5 mg pill in half or quarters. When it comes to treating female pattern hair loss, Sinclair was the first to suggest a safe and successful combination of 0.25 mg of minoxidil and 25 mg of spironolactone taken orally (21).

#### Hormonal treatment Stronolactone dose

The antiandrogenic characteristics of spironolactone have led to its extensive usage as a therapy for female pattern hair loss, despite the drug's original indication as a cardiovascular disease medication. By influencing the 17ahydroxylase, desmolase, and the androgen receptor competitive inhibitor, it reduces adrenal testosterone synthesis (26).

#### Ibuprofen with bicarbofur

Oral flutamide is an antiandrogen drug that is seldom prescribed. A 55-year-old woman with FPHL that did not respond to topical minoxidil and oral spironolactone was successfully treated with 250 mg of oral flutamide one day (27).

#### Acetate of cyproterone

An androgen receptor inhibitor, cyproterone acetate (CA) also blocks the release of gonadotrophins and the activity of cutaneous 5-alpha-reductase. In female patients, it has been effective in treating acne vulgaris and AGA. Topical minoxidil and cyproterone acetate are both good choices, although CA could be better for people with additional symptoms of hyperandrogenism and a high body mass index (28).

# Light therapy

# Low-power laser treatment

The discovery of hair growth in mice exposed to a low fluence red laser in the 1960s was a happy accident that led to the development of low-level laser treatment (LLLT). The development of LLLT as a commercially viable therapy for AGA follows decades of research. Combs, helmets, and hats are some of the common home-use devices used to deliver LLLT. The FDA has approved a number of devices for the treatment of AGA, including the Capillus® laser cap and the Hairmax® Lasercomb/Laserband (29).

gadgets that use light-emitting diodes

Unlike LLLT, which only uses one collimated wave length of light, LEDs may really generate a narrow spectrum of light. For example, a device that uses all-LED technology and emits a combination of dark orange (620 nm) and red (660 nm) light (Revian Red) to decrease inflammation, increase blood flow, and limit DHT by controlling 5-AR levels (30).

#### Intravenous medications Treatments using cells

One of the newer and more promising ways to treat androgenetic alopecia is using stem cell treatment (SCT). Clinical trials provide the option to employ either allogenic or autologous cell sources, whereas SCT makes use of foreign cells. Fat, the scalp, bone marrow, and peripheral blood are among the many possible sources of adult stem cells (31). The poor yields of cell detachment protocols and the invasiveness of the technique to extract bone marrow stem cells (BMSC) make them an unsuitable choice for treating hair loss, despite their popularity due to their ease and speed of harvesting. The limitations of BMSC have led to the suggestion of adipose-derived stem cells, which may develop into cells of the mesenchymal lineage and secrete a number of growth factors (32).

#### plasma high in platelets

AGA patients also have the option of undergoing cell-based therapy using plateletrich plasma (PRP). Patients with early-stage AGA are often good candidates for PRP since the hair follicles are still intact and the restorative impact might be more noticeable. In order to separate the plasma from the red blood cells, the technique involves drawing 10–30 mL of blood from the patient's vein and centrifuging it for 10 minutes (33).

# Plasma rich in platelets for use in hair transplantation

A number of studies have shown that plateletrich plasma (PRP) used in conjunction with hair transplantation has positive results. Twenty male pattern baldness patients were the subjects of the first study to show that pretreatment of the harvested donor with platelet plasma growth factors derived from the patients' autologous plasma increased hair yield in follicular unit density by 15% compared to normal saline (18.7 follicular units per cm2) (34).

# Toxin A from botulinum

The neurotoxins known as botulinum toxins are produced by the bacterium Clostridium botulinum. There are eight distinct toxins in this group: A, B, C1, C2, D, E, F, and G. There are several medical uses for toxin type A, the most potent of the bunch. The use of botulinum toxin A as a substitute therapy for androgenetic alopecia has been investigated in a small number of trials. It seems that the activity is based on the relaxing of scalp muscles, which in turn increases blood flow (35).

#### Additional treatment

#### Needling on a smaller scale

It seems that micro needling activates wound healing systems, causes collagen synthesis as a result of physical mild injury from the needles, and creates channels to improve topical penetration by releasing growth factors and dermal papilla-associated stem cells. Research has shown that micro needling may improve the uptake of topical treatments and is a safe adjuvant therapy option. One hundred male patients with mild to moderate AGA were first observed in a study that randomly assigned them to either a group that received 5% minoxidil lotion twice daily or a group that received 5% minoxidil lotion twice daily in addition to micro needling once weekly. According to investigator and subject assessments and hair count results, the combined treatments group showed significant improvement (19).

#### As a medicine, ketoconazole

Androgenetic alopecia has responded well to topical ketoconazole treatment when used consistently over time. When used to treat seborrhoeic dermatitis, ketoconazole not only kills Malassezia yeast and inflammation, but it also inhibits DHT, making it antiandrogenic. Following therapy, comprehensive а evaluation of ketoconazole for AGA showed that the hair shaft diameter and pilary index (percent anagen phase  $\times$  diameter) both rose. Research has also shown that AGA, when evaluated via photographs, may enhance therapeutic outcomes. One potential adjuvant or alternative treatment for AGA is the use of shampoos containing 2% ketoconazole, which may be administered to the scalp (36).

#### Surgical procedures

Although there are many options for treating androgenetic alopecia, surgical procedures may be necessary for those who do not find relief from their symptoms after trying the aforementioned treatments. Scalp reduction surgery, hair transplantation, or a mix of the two may be part of the surgical strategy. Scalp reduction surgery, sometimes called alopecia reduction, has seen limited use since the advent of hair transplants; the major drawbacks of this operation are its high invasiveness and poor risk-benefit ratio. Patients with cicatricial alopecia, a kind of alopecia that does not leave a secondary defect to repair, are the only ones who may undergo scalp reduction surgery (37).

Surgical hair restoration with a transplant is the gold standard for treating hair thinning. The two most popular methods for hair transplants are follicular unit extraction (FUE) and follicular unit transplantation (FUT), which is sometimes called the strip procedure. The Follicular Unit Transplant (FUT) method involves removing hair-bearing donor tissue and separating it into individual follicular units. Small individual follicular grafts are harvested using either manual or motorised punches in the Follicular Unit Extraction (FUE) technique, which is also called the FOX process, Wood's technique, follicular isolation technique, and individual follicular group harvesting. reduced scarring, reduced recovery time, and low risk of nerve damage are some of the benefits that the FUE procedure may give compared to FUT (38).

Although hair transplant is an effective longterm method for regrowing lost hair, its exorbitant price tag discourages its adoption. In addition, extensive surgical training is necessary. Even though it's been around for a while, there are still certain obstacles, such as getting enough hair from a donor (39).

# Various forms of treatment

Some patients may show substantial improvement considering the expense and hazards of using more than one medication, while there is currently a lack of research on combination therapies and none of them are FDA-approved. A popular combination for AGA treatment is topical minoxidil and oral finasteride. Research has shown that topical minoxidil does not work as well as oral finasteride (40).

#### 5. Conclusion

AGA has several causes and progresses over time. Multiple diagnostic tests may corroborate a patient's symptoms and signs that point to a diagnosis. A variety of treatment methods were available, including surgical interventions, oral and topical therapies, and combination therapies, the latter of which showed encouraging results. The key to the best results is prompt intervention and ongoing treatment. New management avenues are opened up by emerging therapies such cellbased treatments and low-level laser therapy, although their long-term efficacy and safety need further research.

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