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An Overview on Androgenetic Alopecia

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Abstract:

Androgenetic alopecia (AGA) is the most common form of non-scarring hair loss, affecting a significant proportion of both men and women worldwide. It is characterized by progressive miniaturization of hair follicles in a patterned distribution, primarily involving the frontal and vertex scalp. The pathogenesis of AGA is multifactorial, involving genetic predisposition, androgen metabolism—particularly the role of dihydrotestosterone (DHT)—and increasing evidence highlighting the contribution of environmental factors, inflammation, and oxidative stress. Clinically, AGA presents with distinct patterns in males and females and can be assessed using standardized classification systems such as the Hamilton–Norwood and Ludwig scales. Diagnosis is mainly clinical, supported by tools such as trichoscopy and, in selected cases, scalp biopsy. A wide range of therapeutic options is available, including topical and oral pharmacological agents, hormonal therapies, regenerative techniques, and light-based modalities. Despite advances in understanding its pathophysiology, AGA remains a chronic condition requiring long-term management strategies.

Keywords: Androgenetic alopecia; Dihydrotestosterone; Hair loss; Trichoscopy; Minoxidil; Finasteride; Platelet-rich plasma

Introduction:

Hair loss represents the most frequent and distressing clinical complaint encountered by dermatologists in clinical practice. AGA, telogen effluvium (TE), and alopecia areata (AA) are the three most common types of hair loss, with AGA being the most prevalent type in dermatology practice. AGA or pattern baldness, characterized by a progressive miniaturization of the hair follicle, is a nonscarring hair loss disorder that predominantly affects up to 80% of men and 50% of women during adolescence and post-adolescence **(1).**

The term "androgenetic alopecia" was the major word used to describe the common, gradual loss of terminal hair on the frontal scalp and/or vertex of the scalp in men and women. The term "andro" denoted a hormonal etiology, whereas "genetic" signified a contribution of heredity to the clinical phenotype **(2)**.

Female pattern hair loss (FPHL) is a common form of nonscarring hair loss that primarily occurs in adult women. The condition is characterized by the progressive loss of terminal hairs over the frontal and vertex regions of the scalp, resulting in a visible reduction in hair density. Unlike many cases of AGA in men or male pattern hair loss (MPHL), the loss of terminal hairs in affected areas is usually incomplete and the frontal hairline is often spared **(3).**

Epidemiology of AGA

White patients are most affected followed by Asians and African Americans, then Native Americans and Eskimos. The incidence approximates the age in Caucasian males, with 50% affected by 50 years old and up to 80% affected by 70 years old. In females, the disorder is quite common, with an increase in incidence after menopause **(4).**

Androgenetic alopecia of men can affect all races, but the prevalence rates vary **(5).** In the Indian context, a population-based study of 1005 subjects showed a 58% prevalence of AGA in males aged 30-50 years **(6).** In oriental races, a lower prevalence has been shown **(7).** In a Chinese study, the overall prevalence was 21.3% **(8).** All studies demonstrate a gradual increase in incidence with age**.**

Epidemiological studies of AGA in women are fewer in number **(9).** In a Chinese population study, the prevalence was only 6.0% and a Korean study had a relatively similar lower prevalence of 5.6%, suggesting that like in men, the prevalence is considered to be lower in oriental races compared to Caucasians **(10).** The incidence of AGA in women also tends to increase with age **(11).**

Etiopathogenesis of AGA

The etiology of AGA is multifactorial and polygenetic **(5).** For the development of AGA, the presence of androgens, in combination with genetically susceptible hair follicles, is necessary **(12).**

Although genetics and androgens are instrumental in the pathogenesis of this type of hair loss, it is increasingly recognized that inflammation, stress, and environmental factors play a central role **(13).**

Role of androgens and androgen receptors

The modulation of hair growth by androgens is very important. Androgens such as testosterone are responsible for the conversion of vellus hair into terminal hairs of facial, trunk, extremities, pubic and axillary areas. The growth of these areas is similar in both sexes and begin around puberty. The growth of scalp hair is not dependent of the androgens, although it is well known they are necessary for the development of balding **(14).**

Androgens have a different effect regarding location of hair follicle. They are able to stimulate both growth of hair (pubic, axillary, beard, chest) and also promote loss of certain hair in the scalp, in genetical susceptible individuals **(15).**

They function through intracellular signaling pathways, with testosterone being the main and most active androgen in males. Testosterone is converted by type 2, 5-alpha reductase (2, 5-ARD2) into dihydrotestosterone (DHT), leading to AGA. Excessive DHT shrinks hair follicles, replacing terminal hairs, with vellus hairs **(Figure 1) (16).**

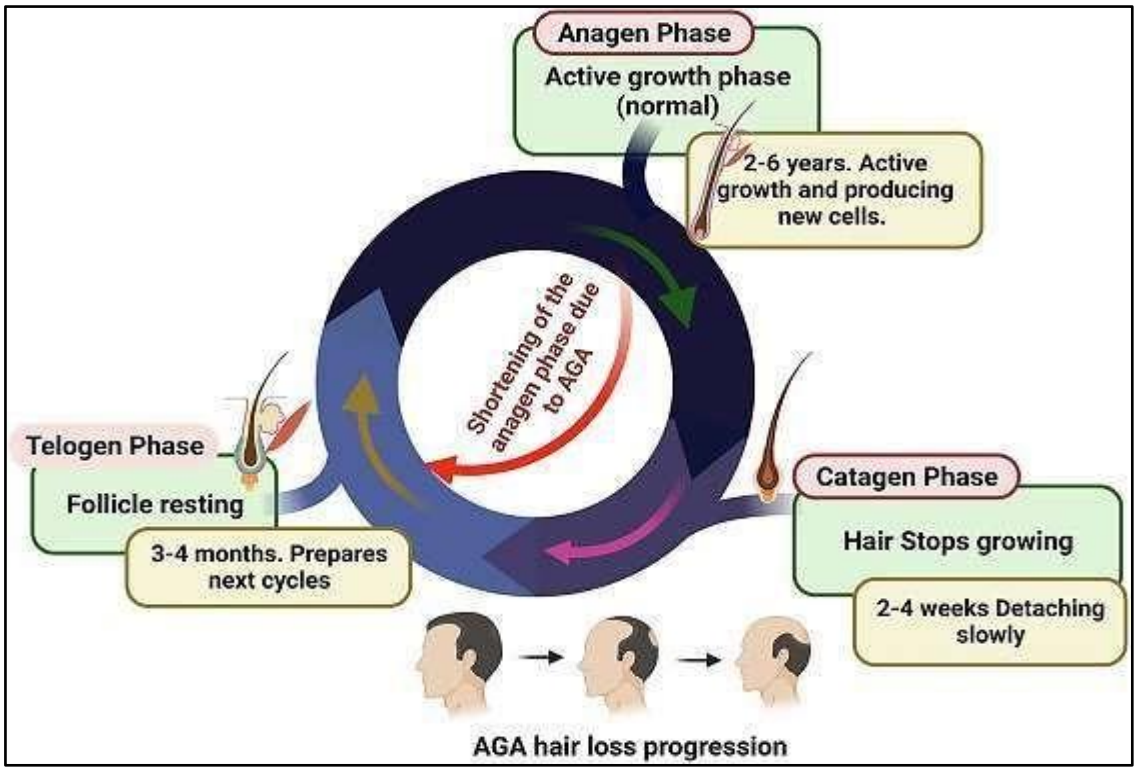

Figure (1): Androgen-mediated effect on the hair growth cycle leading to AGA: Excessive activation of the AR results in the miniaturisation of the follicles, shortening the

anagen phase of the hair cycle. The hair shafts become thinner and shorter and may not penetrate the epidermis **(16).**

Dihydrotestosterone is the most potent hormone among the androgens and is considered a pure androgen as it cannot convert into estrogen. It is formed primarily in peripheral tissues of the body, where it exerts its effects. Testosterone converts to DHT by the action of the 5-alpha-reductase enzyme at these target tissues. It plays a vital role in the sexual development of males. During embryonic life, DHT is involved primarily in the sexual differentiation of organs. Through adolescence and adulthood, DHT promotes prostate growth, sebaceous gland activity, male pattern baldness, and body, facial, and pubic hair growth **(17).**

In susceptible hair follicles, DHT binds to androgen receptor (AR) resulting in the activation of genes responsible for the transformation of anagen to catagen and the conversion of large terminal follicles to miniaturized follicles. AGA patients have elevated levels of 5-α reductase enzyme and AR in frontal hair follicles compared to occipital follicles **(18).**

The androgen receptors gene determines the sensitivity of cells to androgen. The ARs gene regulates the potency of androgen available to the hair follicle. Of the many ARs gene polymorphisms known, the Stu 1 polymorphism has the most significant association with AGA **(19).**

Androgen receptors in hair follicles bind to DHT, changing protein shape, and initiating a signaling cascade **(20).** Occipital hairs are less sensitive due to AR methylation, protecting them from miniaturization and loss. AR has a strong affinity for DHT compared to testosterone, explaining their binding strength **(21).**

Some studies found that patients with AGA have specific micro RNA (miRNA) expression profiles and that the abnormal expression of micro RNA- 133b (miR-133b) may inactivate the Wnt/β-catenin pathway and ultimately regulate hair growth **(22**).

Also, miR-221 was found to be significantly upregulated in balding hair follicles, thereby contributing to the suppression of hair growth and proliferation. The transcription of miR-221 was directly promoted by AR in combination with DHT in dermal papilla cells (DPCs) and dermal sheath cells (DSCs). Mechanistic analysis revealed that miR-221 could directly suppress IGF-1 expression, leading to the inactivation of the mitogen-activated protein kinase (MAPK) pathway in DPCs and the PI3K/AKT pathway in DSCs. Notably, miR-221 expression is positively correlated with both AR and IGF-1 expression in patients with AGA **(18).**

Role of genetics

Androgenetic alopecia susceptibility is primarily influenced by hereditary factors, contributing to around 80% of the predisposition to baldness (**23**). AGA follows a polygenic model, characterized by varying expression levels, which accounts for the diverse range of clinical phenotypes and initial variations observed in individuals affected by this condition **(24).**

Modifications of AR genes on the Xq12 chromosome leading to AGA through increased AR gene activity in hair follicles triggered by DHT binding **(16).** The mechanism of AR-mediated hair loss remains unknown **(25).**

Variation of the AR gene accounts for about 40% of the heritability of AGA in men, and variation in the DNA responsible for hair loss is close to the AR locus in regions responsible for the regulatory effect of AR, including the ectodysplasin A2 receptor (EDA2R) **(26).**

Role of steroid 5-alpha reductase (5ARD) enzyme

The 5AR enzyme is a full membrane-embedded protein with 5 members: 5ARD type 1 to type 3, the glycoprotein synaptic 2 (GSPN2) and GSPN2- like **(27).**

The 5ARD1 predominates in the liver, skin and scalp. 5-ARD2 is expressed in hair follicles, the prostate, and the genitourinary tract. 5-ARD3 is expressed in malignant human prostate tissues, prostate cancer, and breast cancer **(28).**

The 5-ARD mediates 3 metabolic pathways; bile acid biosynthesis, androgen, and estrogen metabolism. In androgen metabolism, 5-ARD reduces Δ^4-5 bond in substrates using nicotinamide adenine dinucleotide phosphate

(NADPH), for example, 5-ARD1 converts testosterone to DHT causing benign prostatic hyperplasia (BPH) and 5-ARD2 is involved in AGA. These 2 iso- enzymes reduce the Δ^4 group (double bond) of C-19 and C-21 steroids into 5α- stereoisomers – DHT **(Figure 2) (29).**

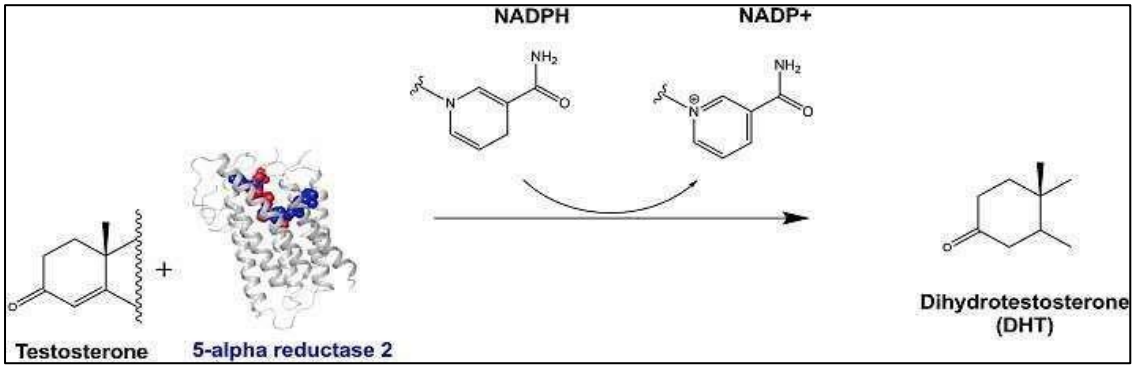

Figure (2): Dihydrotestosterone synthesis by 5-ARD2 in AGA. The 5-ARD2 synthesizes DHT by converting testosterone in the presence of NADPH to DHT **(16).**

Role of environmental factors

The hair follicle inflammation occurs due to several environmental factors; in which the implication of follicular inflammation has been brought out by several studies. The process is slow, subtle and indolent unlike the inflammatory and destructive process in the classical scarring alopecia. Microbial toxins related to Propionibacterium sp., Staphylococcus sp., Malassezia sp., or Demodex could be involved in generation of inflammatory response **(9).**

Alternatively, keratinocytes may respond to chemical stress from irritants in cosmetics and grooming agents, pollutants and actinic damage as in ultra violet (UV) irradiation by producing radical oxygen species and nitric oxide **(30).**

Oxidative stress is the latest candidate for a role in AGA pathogenesis, as DPCs from male AGA patients underwent premature senescence in vitro compared with occipital DPCs in response to environmental stress **(31).**

Environmental oxygen significantly alters DPC morphology, migration, proliferation, senescence and transforming growth factor-beta (TGF-β) signaling. Bald DPCs were significantly more sensitive to oxidative stress than were occipital DPCs and secreted higher levels of negative hair growth regulators, TGF-β1 and β2, in response to it **(5).**

Clinical features of AGA

The symptoms of AGA start to develop in the teenage after which the hair loss progresses gradually into different patterns. In males, AGA is genetically determined and presents as a reduction in hair density due to hair miniaturization, in a characteristic pattern. Initially, the frontotemporal area and vertex are two areas preferentially affected. As the hair loss progresses further, terminal hair is continuously replaced by vellus hair in an orderly manner without any skip areas, leading to hair loss in the mid frontal, temple and vertex areas **(10).**

The hair loss is not equal in all three mentioned areas; some men undergo hair loss in the frontal area while some are bald over the vertex. This gives rise to various hair patterns, which are defined further in the classification of AGA in males **(9).**

In females, hair loss is said to be multifactorial and the role of androgens is not well defined, so it is considered a different condition named FPHL. Just as in males, hair miniaturization in females begins in teenage, which progresses further with increasing age. There is diffuse hair loss, especially involving frontal, central, and parietal areas of the scalp in females too **(32).**

Patterns of hair loss in females included three patterns; in the first pattern diffuse thinning of upper biparietal and vertex areas of the scalp happens, while the frontal hairline is preserved. This pattern is included in different hair

loss scales, Ludwig's scale being the most commonly used among those **(33).** In the second pattern, described by Olsen has the involvement of frontal, bitemporal, and vertex areas of the scalp in a Christmas tree distribution **(34).** Finally, a third pattern presents with involvement of frontotemporal areas of the scalp as seen in males, but this is quite uncommon **(33).**

Classifications and Scales of AGA

There are several classifications that help to determine degree of AGA in male and female patients. This allows staging the degree of alopecia at time of diagnosis and control the evolution and response to treatment **(14).**

In male AGA, numerous classification systems have been described, each one having its own advantages and pitfalls. Over the years, many workers came up with their classification systems. Few important classifications in male and female patterned baldness developed over the years **(34) (Table 1).**

Table 1: Various proposed classifications of androgenetic alopecia (10).

1) Classification of male pattern baldness		
Name	**Year**	**Description**
Beck	1950	Frontal and fronto-vertical baldness
Hamilton	1951	Frontal and frontoparietal recession and thinning
Ogata	1953	Fifteen different types classified in six different subtypes
Setty	1970	Classification based on three subtypes
Norwood-Hamilton	1975	Medication of Hamilton classification by Norwood
Bouhanna	1976	Three basic presentations with two subtypes
Blanchard and Blanchard	1984	Six-stage classification based on scalp measurements
Dardour and Bouhanna	1996	Includes both morphological and dynamic parameters, but is difficult to apply
Koo	2000	Six subtypes with alphabetical letter shape of bald area
2) Classification of female pattern hair loss:		
Ebling and rook	1975	Five grades of hair loss
Ludwig	1977	Three-stage classification system
Savin	1992	Nine computerized images to quantify hair loss
Olsen	1994	Christmas tree pattern
Sinclair	2004	Five colored photographs were used as a measuring scale for self-reporting
3) Sex-neutral classification:		
Bouhanna	2000	Used in both sexes. Has multiple parameters
Basic and specific classification by lee	2007	Used in both sexes. Has two parts, basic and specific

The most widely used classification is Hamilton-Norwood classification, which was described by Norwood which is essentially an update to Hamilton's original classification. It has seven types, instead of eight as in the original Hamilton classification, with five subdivisions **(35) (Table 2, Figure 3).**

Table 2: Hamilton-Norwood classification (10).

Type	Description
Type 1	No or minimal recession along the frontotemporal region; anterior border
Type 2	Frontoparietal recession of the hairline, not extending further than 2 cm anterior to the midcoronal line
Type 3	Extension of frontoparietal recession occurs further than type 2 and may reach the mid coronal line
	Type 3 (vertex) is a subdivision, where along with features of type 3, the vertex is also involved
Type 4	The deep frontotemporal recession occurs and may extend beyond the mid coronal line
Type 5	Worsening of frontoparietal recession with hair loss occurring in the crown area
Type 6	Frontotemporal recession is akin to a horseshoe when seen from above. There is also hair loss in the crown area, the two areas being separated by a small island of hair over the mid frontal area
Type 7	Frontotemporal recession with hair loss over crown not separated by the island of hair. The bare area over the scalp is larger than that in type 6

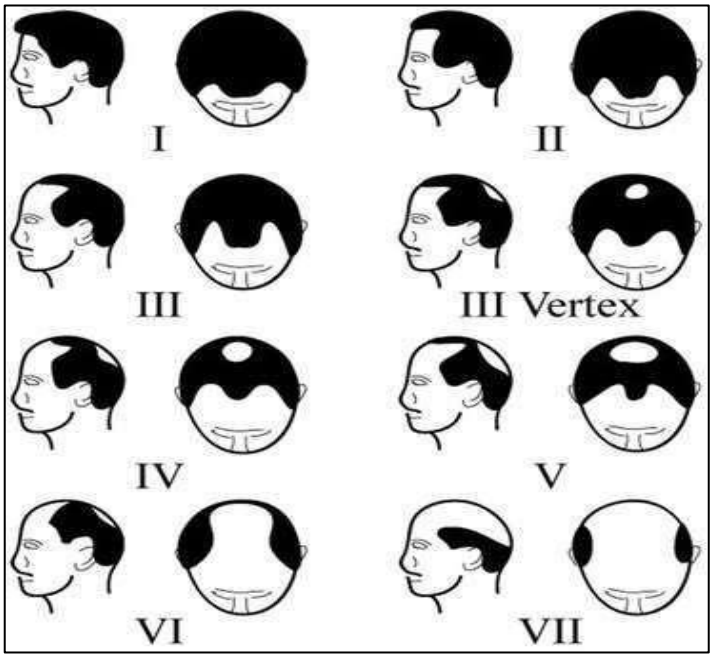

Figure (3): Hamilton–Norwood classification **(36).**

The commonest grading scales used for female AGA are the three-point Ludwig scale **(37) (Table 3, Figure 4).** and the five-point Sinclair scale **(S38) (Table 4, Figure 5)**.

Table :3 Ludwig's scale for female AGA (37).

Stage 1	Thinning of hair is seen mainly over the anterior part of the crown with minimal widening of the parting width[49]
Stage 2	Thinning of the crown becomes more evident because of an increase in the number of thin and short hairs
Stage 3	The crown becomes almost total bald. There is significant widening of the parting width, but the frontal hairline is still maintained

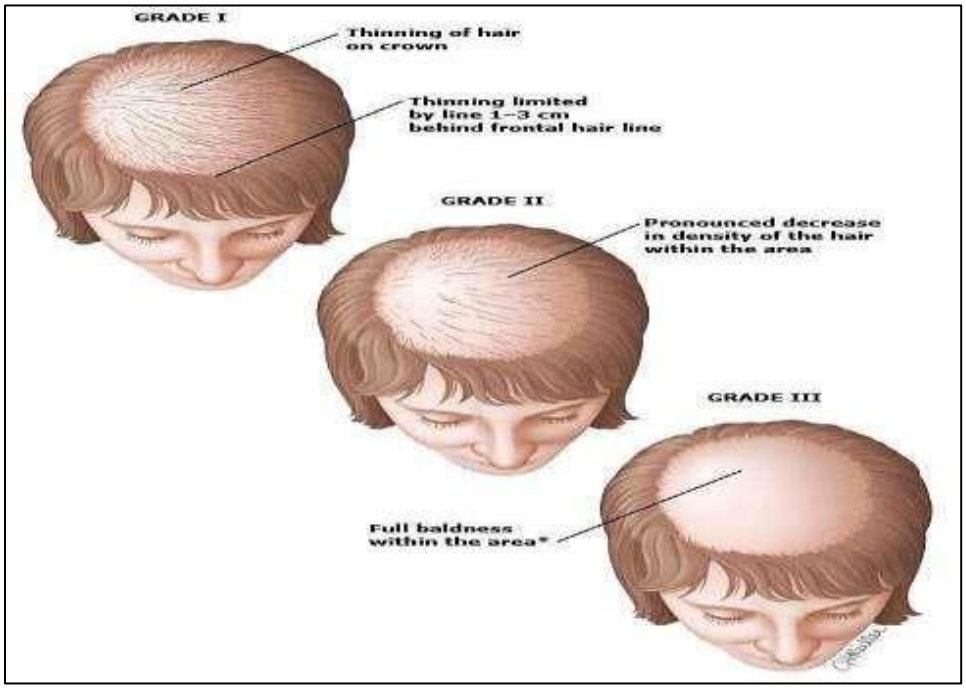

Figure (4): Ludwig scale for female pattern hair loss **(39)**.

Table 4: Sinclair scale for female pattern AGA (37).

Grade 1	Is normal. This pattern is found in all girls prior to puberty[50] but in only forty-five percent of women aged eighty or over
Grade 2	Shows a widening of the central part
Grade 3	Shows a widening of the central part and thinning of the hair on either side of the central part
Grade 4	Reveals the emergence of a diffuse hair loss over the top of the scalp
Grade 5	Indicates advanced hair loss

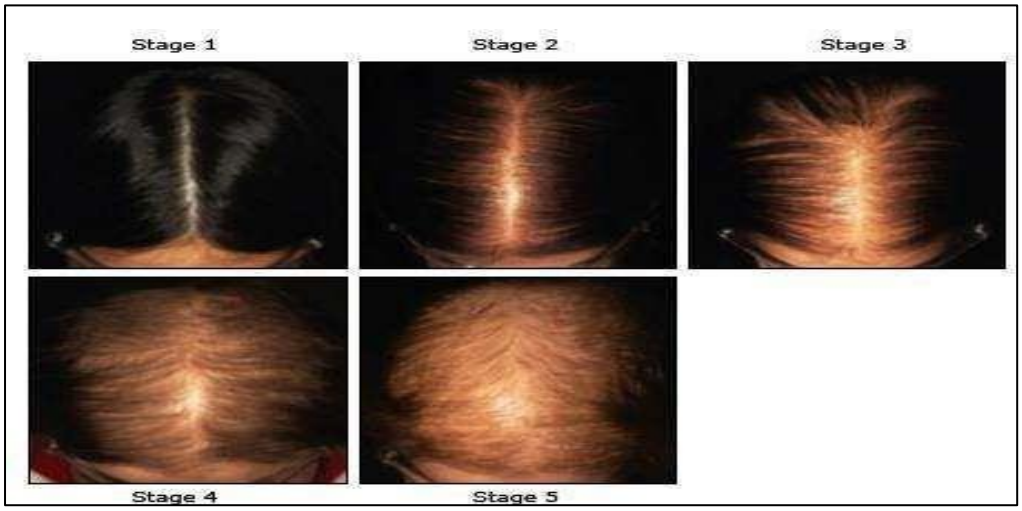

Figure (5): Sinclair scale for female pattern hair loss **(40).**

Diagnosis of AGA

History

Most patients with AGA are easily diagnosed by a clinical history and clinical examination, according to the condition of the characteristic distribution pattern**.** Male pattern baldness is characterized by a receding hairline at the temples and balding of the vertex, which gradually enlarges to link together. In FPHL, there is a diffuse decrease in density over the crown of the head and the frontal hairline is preserved **(14).**

History of systemic diseases, new medications especially within the previous year should be taken. Family history is usually positive for AGA. Diet is another important aspect of history, to rule out nutrition related effluvium **(41).**

Lifestyle related enquiries should cover effect of traction, smoking and ultraviolet exposure on AGA, all of which have been implicated as aggravating factors. In female patients, careful attention must be given to assess any associated hormonal dysfunction **(42).**

General scalp and hair examination

The scalp is usually normal in AGA, but look for factors which can aggravate AGA like seborrheic dermatitis and photo-damage**.** The main aim of clinical examination is to identify whether or not the hair loss is patterned **(37).**

Pull test

A hair pull test, also known as "traction test" or "Sabouraud's sign" helps distinguishes between active and non-active hair loss from follicles. To perform this test, around 50–100 hairs are grasped between the index finger and thumb and then lifted proximally to distally, with gentle traction **(43).**

This procedure is repeated in different areas of the scalp: frontal, occipital and temporal regions. The hair pull test is considered positive if more than 10% of telogen hairs are released, this means that if the pull test has more than 5 or 6 hair indicates ongoing hair activity **(44).**

Hair pull test is positive in TE. In patients with AGA, the hair pull test is usually negative, with the exception of active periods when a moderate telogen hair shedding is present in a pattern distribution. False positives can occur if the test is performed on a day in which hair has been washed. A positive hair pull test will indicate an active hair shedding **(42).**

Trichoscopy

Trichoscopy is a non-invasive technique performed using a handheld dermoscopy or a digital video dermatoscopy system. The handle dermoscopy usually has a 10-fold magnification of the skin surface while the video dermoscope, which is equipped with a software, will have the benefit of larger magnification (ranging from 10-

70 folds) and the conversion of measurement results into a database. Trichoscopy adds important information for establishing the correct diagnosis and it is also a useful tool for assessing disease activity and monitoring treatment efficacy **(45).**

Trichoscopy has emerged as a useful tool in the diagnosis of AGA. Important features of AGA on trichoscopy are hair diameter diversity greater than 20% (which corresponds to vellus transformation), perifollicular pigmentation/peripilar sign (the commonest change seen in Asians) and yellow dot **(Figure 6) (46)**.

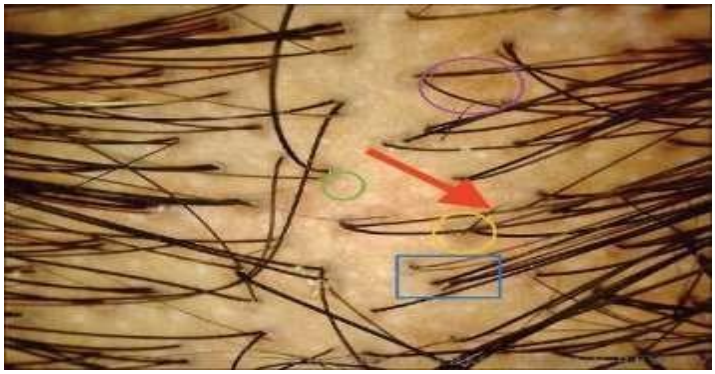

Figure (6): Tricoscopy ×10 showing increase hair diameter diversity, with prominent vellus transformation, perifollicular pigmentation and yellow spots in AGA **(10).**

There are some criteria which help to differentiate TE from AGA in females. Major criteria are ratio of (1) more than four yellow dots in four images (70-fold magnification) in the frontal area in female AGA compare to TE (2) lower average hair thickness in the frontal area compared to the occipital area in female AGA (3) more than 10% of thin hairs (below 0.03 mm) in the frontal area in female AGA. Minor criteria include- increased frontal to occipital ratio in AGA of (1) single-hair pilosebaceous units, (2) vellus hairs and (3) perifollicular discoloration. Fulfillment of two major criteria or one major and two minor criteria allows diagnosing AGA in females based on trichoscopy with 98% specificity **(47).**

Trichogram and Photo-trichogram

The trichogram is a quantitative technique that provides information on the ability of hair growth and its alterations. Although it is a useful technique, it requires prior training and is time consuming**.** Usually there is not a frequent diagnostic technique used for the diagnosis of AGA **(14).**

Phototrichogram (PTG) is a non-invasive method involving production of serial, close-up photographs of specific defined areas to assess hair growth rate, hair follicle density and hair shaft thickness. Variants of this technique include the contrast enhanced PTG and the automated PTG (Trichoscan) **(42).**

Hair wash test

Li et al. (48) have devised a test known as the AGA/TE wash test to distinguish between AGA and TE based on the count of vellus and terminal telogen hairs that are rinsed out on washing the scalp after a five days abstinence from washing and shampooing. The results are given in terms of total telogen hairs and the percentage of telogen vellus hairs. However, this method has definite disadvantages; hair breakage can occur leading to double counting, it is not useful in patients with curly hair and is very time-consuming.

Scalp Biopsy

Usually, scalp biopsy is the standard technique for diagnosing different types of scarring alopecia**.** In addition, scalp biopsy could give relevant information in difficult cases of non-scarring alopecia, where the diagnosis of the type of alopecia is uncertain. In few cases, the diagnosis of AGA is not clear, such as alterations of the scalp suggestive of scarring alopecia or diffuse AA, and a scalp biopsy may be needed to obtain the final diagnosis **(49).**

Biopsy is typically helpful when the pattern of AGA is not typical or to exclude TE or early scarring alopecia

(50). The scalp biopsy should be performed with a cylindrical punch of 4 to 6 mm in diameter, in an area representative of the hair loss. Biopsies taken with a smaller punch than 4 mm in diameter are not recommended as it would give less numbers of follicle units, and as the follicles are not always affected simultaneously by a such disease it would diminishes the probability of a correct diagnosis **(14).**

The biopsy specimen should include the entire follicular unit and reach into the subcutaneous tissue where normally are the bulbs of anagen hair follicles **(51).**

The prime feature found in scalp biopsies is the reduction in the terminal anagen hair count due to the replacement of terminal hairs with secondary pseudo-vellus hairs, and residual angiofibrotic tracts. There is a change in the ratio of terminal to vellus hairs from >6:1 to <4:1. Furthermore, the anagen to telogen hair ratio reduces from 12:1 to 5:1 **(52).**

In the connective tissue beneath the vellus follicles, small elastin bodies (Arão–Perkins bodies) which indicate sites of the papillae can be seen. These elastin bodies can be stained with the acid orcein method, but not the Verhoeff elastic stain. Erector pili muscles diminish in size and are seen attached to remnants of follicles. The number of sebaceous glands is generally decreased though some studies show increase in size, number, and lobulation of sebaceous glands **(53).**

Laboratory investigations

The general consensus is that extensive laboratory investigations are not required for AGA, especially in males. Testing for Prostate Specific Antigen prior to starting finasteride in men above the age of 45 are recommend. The main aim of laboratory investigations in women is to rule out any underlying hormonal dysfunction especially polycystic ovarian disease. The tests recommended are free androgen index test, dehydroepiandrosterone and prolactin. Further tests may be considered if necessary to rule out rarer conditions like congenital adrenal hyperplasia. The significance of measuring serum levels of ferritin in AGA is not clear as different studies have produced conflicting results **(42).**

Treatment of AGA

Although topical minoxidil, oral finasteride, and low-level light therapy are the only FDA-approved therapies to treat AGA, they are just a fraction of the treatment options available, including other oral and topical modalities, hormonal therapies, nutraceuticals, PRP and exosome treatments, and hair transplantation **(54) (Figure 7).**

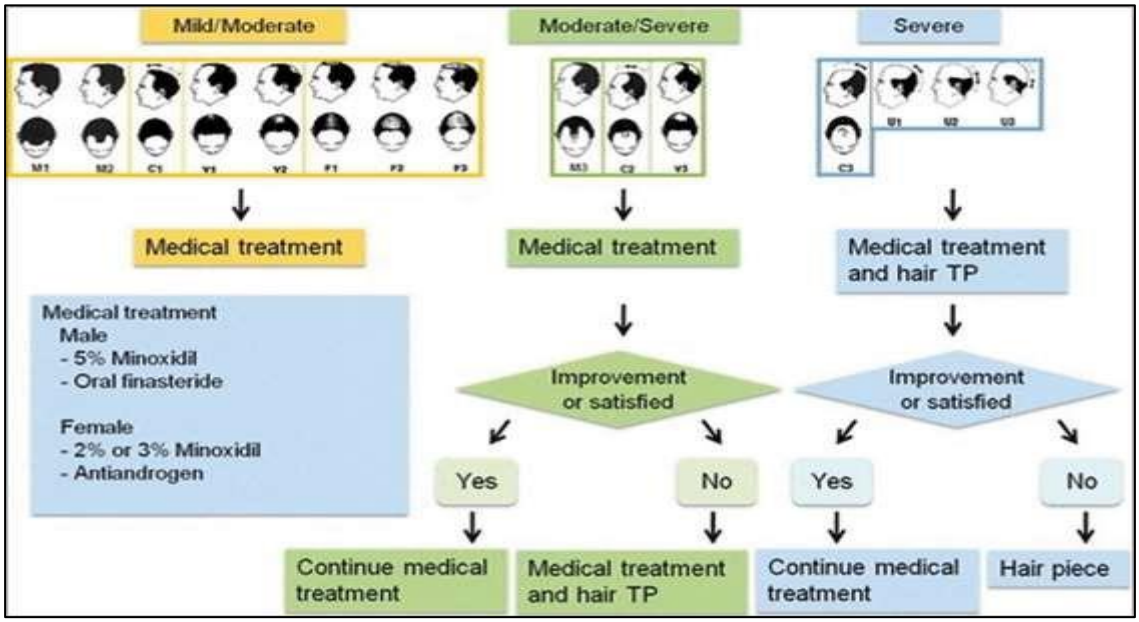

Figure (7): Algorithmic guideline for the management of androgenetic alopecia (AGA). Mild/moderate androgenetic = BASP type M1-2, C1, F1-3 or V1-2; moderate/severe AGA = BASP type M3, C2-3, U1-3 or V3;

severe AGA = BASP type C3 or U1-3 (**55).**

I. Topical therapies

For patients that have early or mild-to-moderate hair loss, and want to avoid oral medications due to the potential systemic side effects, topical therapies may serve as a viable first-line option or adjuvant for the treatment of AGA **(54).**

- **Topical Minoxidil**

Topical minoxidil is one of the FDA-approved treatments for male and female pattern hair loss. It was approved specifically for AGA in 1988 as a first- line treatment for men with mild-to-moderate AGA **(56).** It is also used off-label for many other hair loss conditions, such as central centrifugal cicatricial alopecia, AA, and TE, and others **(57).** The oral formulation was originally used in the 1960s as a vasodilator for the treatment of hypertension **(54).**

Hypertrichosis was discovered as a side effect with chronic use of oral minoxidil, which prompted the development of a topical formulation for hair growth stimulation **(58).** Minoxidil is readily available in both 2% and 5% foam and liquid solutions with varying efficacies **(59).** Compounding pharmacies may also provide higher concentrations, such as 6–7% liquid solutions, at the clinician's discretion **(54).**

Mechanism of action

Minoxidil elicits its greatest effect at the vertex and frontal regions of the scalp where it is known to slow the rate of hair loss by prolonging the anagen phase and promote hair regrowth by increasing both hair diameter and density **(60).**

Minoxidil is converted to its active metabolite, minoxidil sulfate, and functions as a potent arteriolar vasodilator that activates potassium channels on the smooth muscles of the peripheral artery, inducing cell proliferation. Furthermore, minoxidil was found to increase VEGF in dermal papilla cells in a dose-dependent fashion, as well as stimulate prostaglandin E2 production, leading to an increase in the duration of the anagen phase **(57).** It has also been shown to reduce pro- inflammatory cytokines such as IL-2 and prostacyclin's, which may play a role in the pathogenesis of AGA **(61).**

The topical application of minoxidil has been shown to stimulate cutaneous blood flow within 10–15 min. Minoxidil's effect is specific to the hair follicle as the conversion to its active metabolite is higher in hair follicles than in surrounding skin **(62).**

Efficacy

The earliest effects of minoxidil on hair growth begin at 6–8 weeks and reached maximal effect by 12–16 weeks without significant further improvement with additional time **(61).**

It has been estimated that 60% of male patients may not respond to topical minoxidil therapy due to decreased baseline levels of the sulfotransferase required to activate minoxidil to its active metabolite **(63).** Furthermore, analyzing sulfotransferase activity in plucked hair follicles was found to be an accurate predictor of female response to topical minoxidil treatment **(64).**

Side Effects

While topical minoxidil is considered safe, patients often experience an irritant contact dermatitis causing pruritis and scaling **(65).** It may also cause a transient increase in hair shedding at the beginning of the treatment, which can temporarily worsen physical appearance and dissuade patients from continuing the treatment regimen **(66).**

follicle enters the anagen phase prematurely, which requires it to pass through a shorter telogen phase and thus a period of hair shedding occurs before clinical improvement can be observed **(58).**

The most common adverse effect of topical minoxidil is hypertrichosis **(67).** The second most common adverse effect of topical minoxidil is headache, which affected 2–4% of the 153 patients in a large-scale study **(61).**

- **Topical Finasteride**

Finasteride is a member of a class of drugs known as 5-alpha-reductase inhibitors. These drugs block the enzyme 5-alpha-reductase, thus blocking the conversion of testosterone to its active form DHT. Finasteride is a type II 5-alpha-reductase inhibitor and dutasteride blocks both type I and type II so, it improves AGA conditions **(57).**

Topical finasteride is typically given as 0.25% finasteride spray, or 1% topical finasteride gel applied twice daily to the scalp. Furthermore, it was found to be well tolerated, particularly in comparison with its oral formulation **(68)**. Although the use of topical 0.5% finasteride combined with 2% minoxidil solution was found to be effective in FPHL **(69).** Scalp pruritus, burning, irritation, contact dermatitis, and erythema may occur. These side effects are rare and localized to the application site **(57).**

- **Latanoprost**

The use of prostaglandin analogs for alopecia came about when eyebrow and eyelash hair growth were observed in glaucoma patients. Prostaglandin F2 (PGF2) and PGE2 cause hair growth and prolong the anagen phase, whereas PGD2 inhibits hair growth **(70).**

Blume-Peytaavi et al. (71) conducted a randomized control trial using 0.1% latanoprost, a PGF2 analog, in 16 patients with MPHL. After 24 weeks, there was significantly increased hair density compared with baseline and placebo-treated areas.

II. Oral therapies

Oral therapies are often the easiest treatment options for patients with progressing and moderate AGA, but certainly have more potential side effects than topical agents. Since oral medications are convenient options, it is common for many medically based physicians to default to this treatment option while dismissing other complementary, invasive, or alternative therapies that may be more effective and better-suited to particular subsets of patients **(54).**

- **Oral Minoxidil**

The drug is available as a 2.5 mg tablet, and it can be cut in halves or quarters to achieve optimal safe dosing for the treatment of AGA. The combination of oral minoxidil 0.25 mg and spironolactone 25 mg was reported to be a safe and effective option in managing female pattern hair loss **(72).**

Oral minoxidil has shown equivalent efficacy in women compared to 5% topical formulation **(73). Jimenez-Cauhe et al. (74)** conducted a retrospective review of 41 men diagnosed with AGA undergoing oral minoxidil 5 mg daily treatment. Adverse effects were detected in 30% of the participants, but they were all tolerable. Another study using a 5 mg once daily regimen showed 100% improvement at week 12 and 24 with 43% patients achieving excellent improvement **(58).**

The systemic side effects of oral minoxidil were increased heart rate, weight gain, hirsutism, hypertrichosis, and lower extremity edema make it unfavorable compared to topical minoxidil as a first-line treatment **(54).** In a study of 1404 subjects, the most common side effect was noted to be hypertrichosis in about 15% of patients and the incidence of systemic adverse effects was noted in 1.7% of patients **(75).** Rare side effects include pericardial effusion, congestive heart failure and allergic reactions **(58).**

- **Oral Finasteride**

It is more effective at regrowing hair at the vertex scalp compared with the frontal/centroparietal scalp, and its efficacy does not reduce over time. Patients older than 30 years seem to have better hair growth than patients younger than 30 years **(76).**

Reported side effects include sexual dysfunction, altered libido, erectile dysfunction, ejaculatory dysfunction and gynecomastia. Some patients may have persistent sexual side effects for at least 3 months despite cessation of the drug, which may lead to increased rates of depression and suicidal thoughts **(77).**

- **Oral Dutasteride**

Dutasteride is a dual inhibitor of type I and type II 5-alpha-reductase and is a potential alternative to finasteride with reported improved efficacy in treating AGA. It is 100 times more potent at inhibiting type 1 5-alpha-reductase compared with finasteride and three times more potent at inhibiting type 2. Dutasteride is available in 0.5 mg tablets as treatment for AGA **(57).**

Dutasteride was found to improve hair growth within 3-6 months compared with finasteride which improve hair growth within 6 months **(78).** In addition, 0.5 mg dutasteride once daily was significantly more efficacious at increasing hair count at 24 weeks compared with 1 mg finasteride once daily and 0.25/5 mg minoxidil once daily **(79).** Side effects of dutasteride include sexual dysfunction, altered libido, erectile dysfunction, ejaculatory dysfunction and gynecomastia **(80).**

III. Hormonal therapies

- **Spironolactone**

Spironolactone has been widely used as a treatment for FPHL due to its anti-androgenetic properties. It works by decreasing testosterone production in the adrenal gland by affecting the 17α-hydroxylase and desmolase, as well as the competitive inhibitor of the androgen receptor **(81).**

In a retrospective survey of 166 patients with FPHL being managed with spironolactone, over 70% of patients noted stabilization or improvement of their disease **(82).** The side effects of spironolactone include electrolyte imbalance, worsening of renal function and hypotension **(54).**

- **Flutamide**

Flutamide is an oral antiandrogen medication rarely used in practice. Oral flutamide first reported to be an appropriate option for managing androgenetic alopecia. Oral flutamide 250 mg daily was noted to be effective in managing FPHL refractory to topical minoxidil and oral spironolactone in a 55-year-old female **(54).**

In a study by **Paradisi et al. (83)** found that there was a significant decrease in alopecia score and 4% of the patients dropped out the study in the initial phase due to liver toxicity. The common side effects of flutamide include hot flashes and potentially increasing the effect of warfarin **(84).**

- **Bicalutamide**

Bicalutamide is a nonsteroidal, antiandrogen medication. It has a more favorable safety profile than flutamide when treating prostate cancer. In a study of 17 women given oral bicalutamide with or without adjuvant therapies showed oral bicalutamide as a useful option in treatment of female pattern hair loss, especially patients with other comorbidities such as polycystic ovarian syndrome or hirsutism **(85).** The most common side effects of this drug were mild hepatic injury, peripheral edema, and gastrointestinal complaints **(86).**

- **Cyproterone acetate**

Cyproterone acetate inhibits gonadotrophin secretion and cutaneous 5- alpha-reductase activity and inhibits the androgen receptor. It has shown efficacy in treating AGA and acne vulgaris in female patients. Cyproterone acetate is associated with weight gain, breast tenderness, and decreased libido **(54).**

IV. Injectable medications

- **Platelet-rich plasma (PRP)**

Platelet rich plasma is a technique that has been employed in a variety of medical fields including orthopedic surgery, sports medicine, and cosmetic procedures. The regenerative properties of PRP have been used extensively to improve tendinopathy, tears in tendons, and disorders of bone structure **(87).**

Platelet rich plasma has become an increasingly popular therapeutic modality in dermatology for skin

rejuvenation, acne scarring and vitiligo **(88).**

Mechanism of Action

PRP are known to be a storehouse of growth factors. These growth factors affect the microenvironment of the tissue they are released in by causing cell proliferation, differentiation, migration and angiogenesis. Some of the most significant growth factors released by the platelets include PDGF, VEGF, fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor, IGF-1 and 2, and matrix metalloproteinases 2 and 9 (MMP 2 and 9) **(89).**

Another pathway that plays an essential role in human hair follicle growth is the WNT/β-catenin pathway. This pathway primarily functions during the embryonic hair morphogenesis **(90).** However, studies have also shown activation of the WNT/β-catenin pathway during adult hair growth, specifically during anagen activation **(91).**

Myung et al. (91) showed that activation of WNT pathway was essential for the conversion of telogen hair to anagen hair and the deletion of *Wntless* gene (a gene required for secretion of WNT ligands) led to the arrest of hair follicles in the telogen phase. This embryonic pathway is also activated in another process of hair regeneration called adult wound-induced hair neogenesis **(90).**

Ito et al. (90) demonstrated that new hairs could be generated *de novo* after wound healing. This follicular neogenesis required an intact WNT/β- catenin pathway and overexpression of WNT ligand increased the number of regenerated follicles.

The third pathway that has found relevance in the hair growth is the ERK/Akt pathway. The extracellular signal-regulated kinase (ERK) and the protein kinase B (Akt) signaling promotes cellular proliferation and prevention of apoptosis. PRP increased the proliferation of dermal papilla cells along with an increase in β-catenin levels and FGF-7 levels. PRP has also found to stimulate hair growth by angiogenesis and neovascularization **(34).** The downregulation of glycogen synthase–3 in PRP-treated dermal papilla cells was consistent with the activation of the WNT pathway **(92).**

The hair follicle growth occurs in the harmony of the various pathways. FGF-7 acts by prolonging the anagen phase, ERK signaling causes cellular proliferation, Akt activation leads to Bcl-2 release, which is antiapoptotic, and β-catenin stimulates hair follicle development **(93).**

Efficacy

In a review of 16 studies comprising a total of 389 patients with AGA, the majority demonstrated efficacy in promoting successful hair growth after 3– 4 sessions on a monthly basis **(94).**

The PRP is not curative for hair loss and must be continued long term for hair sustenance. However, patient satisfaction is typically very high and 60– 70% of patients continue to undergo maintenance treatments. Due to the relatively recent introduction of PRP injections for AGA, there are no long-term studies evaluating its effectiveness. Additionally, it is difficult to compare the efficacy with other remedies due to the lack of standardization in regard to PRP kits, treatment fractions, and regimens, including the use of newer multi-needle injectors **(54).**

Side effects

The PRP has emerged as a viable, minimally invasive alternative treatment for patients with AGA. The overall risk of adverse effects remains small, however there is a risk of infection. Additionally scalp sensitivity and mild scalp scaling are the most common adverse effects **(95).** Not all patients are candidates for PRP. PRP therapy should be avoided in patients with a history of malignancy, platelet disorders, anemia, bleeding disorders, pregnant woman, or immunocompromised patients **(96).**

- **Microneedling**

Microneedling is a minimally invasive procedure whereby small percutaneous wounds are induced with small needles, resulting in the release of platelet-derived growth factor and VEGF. These factors promote angiogenesis and wound healing and reverse fibrosis. It was used for wrinkles and atrophic scars treatment but was found to

have a beneficial effect as an adjunct treatment for hair loss through its effect on dermal papilla stem cell proliferation. Furthermore, the induced wounds form channels to improve absorption of topical treatments, such as 2–5% minoxidil or finasteride **(97).** Pain, bruising, and folliculitis have been seen with microneedling, as with other procedures involving injections **(98).**

- **Intradermal Botulinum Toxin**

The use of injectable botulinum A toxin has gained popularity as a treatment for AGA because of its ability to interfere with the suppressive effect of DHT on the hair follicle **(57).**

The mechanisms by which botulinum toxin may improve AGA are not yet established. However, there is speculation of at least 2 actions: decreased TGF-β1 activity in DPCS (through intradermal injections), and relaxation of the scalp perimeter muscles (through intramuscular injections). As such, researchers have hypothesized 2 possibilities: the unpinching of arterial branches that indirectly support balding regions and the reduction of tension across the galea aponeurotic **(99).**

- **Dutasteride Mesotherapy**

Injectable dutasteride has gained popularity over the last several years due to limited systemic absorption, and therefore, reduced side effects. A study assessed 541 patients that were treated with dutasteride mesotherapy every 3 months with at least 6 months of follow-up. Response to the therapy was assessed in 16% of patients after 1 year, and most reported improvement, with pain being the most frequent side effect (45.5%) **(100).**

- **Exosomes**

Mesenchymal stem cell (MSC) exosomes have shown promise in hair regrowth, as they contain cytokines and growth factors that play a role in hair restoration. A laboratory study that tested the efficacy of mesenchymal stem cell –extracellular vesicles (MSC–EVs) treatment on hair growth in an animal model demonstrated increased dermal papilla cell proliferation and increased levels of various growth factors. Injection of MSC–EVs intradermally into mice promoted hair follicle conversion from telogen to anagen **(101).**

Hair follicle-derived MSCs have also been shown to reduce inflammation and decrease hair loss in vitro in mice with Alopecia Areata **(22).** However, the use of exosomes in AGA is still not well supported, as data showing clear efficacy and safety of exosomes for alopecia is lacking **(102).**

Light therapies

- **Low-level light therapy (LLLT)**

Low-level laser therapy (LLLT) has been used in dermatology to reduce inflammation and promote wound healing, and to improve wrinkles, scarring from acne, improve blood flow, and improve hypertrophic scars and burns **(103).**

Due to its cost-effectiveness and noninvasive nature, LLLT is becoming a popular treatment line for AGA. LLLT uses light with wavelengths between 600 and 1100 nm to stimulate hair regrowth. While this mechanism is not completely understood, LLLT is believed to enhance hair growth by promoting anagen-phase reentry of telogen hair follicles, increasing the duration of anagen phase, and preventing premature conversion of anagen hairs to catagen-phase hairs (similar to minoxidil) **(104).** Reported side effects include scalp tenderness, paresthesia, and mild urticaria **(105).**

- **Light-emitting diode devices (LED)**

Light-emitting diode (LED) devices may emit a small band of wavelengths. In particular, an all-LED device that delivers dual dark orange (620 nm) and red light (660 nm) (Revian Red) to promote blood flow, reduce inflammation, and inhibit DHT via 5-AR downregulation **(54).** The mechanism of LED therapy was identified to involve an increase in hair growth follicles, VEGF, and leptin **(106).**

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