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Review Article:

Advancements in Hair Restoration: A Comprehensive Review of Emerging Therapies and Techniques for Androgenetic Alopecia

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Abstract

Context: Androgenic alopecia (AGA) is a common condition affecting both men and women, characterized by progressive hair loss due to genetic and hormonal factors. Hair loss has significant impacts on psychosocial well-being and quality of life.

Evidence Acquisition: A comprehensive review of peer-reviewed studies was conducted, including clinical trials, observational studies, and emerging treatment reports published from 2000 to 2024. Databases such as PubMed, Scopus, and Web of Science were searched using keywords related to AGA, hair growth, and therapies.

Results: Current treatments for AGA include topical agents like minoxidil and finasteride, oral medications, and advanced options such as hair transplantation. Emerging therapies, including platelet-rich plasma (PRP), low-level laser therapy (LLLT), JAK inhibitors, and gene therapy, show promising efficacy in promoting hair regrowth. Combination therapies often enhance clinical outcomes.

Conclusion: While traditional treatments remain effective, emerging therapies and combination approaches offer improved results for AGA management. Ongoing research in gene therapy and novel molecular interventions may transform future therapeutic strategies.

Keywords: Androgenic Alopecia (AGA), Dihydrotestesterone(DHT), Platelet Rich Plasma(PRP), Low Level-Laser Therapy (LLLP), Gene Theraphy, Hair Loss.

1. Context

According Androgenetic alopecia (AGA), commonly referred to as male-pattern baldness or androgenic alopecia, is the primary cause of gradual hair loss and is genetically driven. In women, late-

onset androgenic alopecia can occur in two age peaks: late twenties/early thirties or forties. It impacts a larger surface area, similar to telogen effluvium. In men, hair loss typically affects the temporal and crown areas but not simultaneously, leaving the occipital area untouched, creating a characteristic horseshoe shape [1].

In both men and women, androgens particularly the androgen receptor (AR) gene located on the X chromosome are crucial in AGA, contributing to the progressive miniaturization of hair follicles[2].

Around 50% of men are afflicted with AGA, and treatments like finasteride or minoxidil can slow progression and reverse hair loss in mild to moderate cases. Combining these treatments with hair restoration surgery offers the best outcomes for suitable candidates[3].

New treatments like JAK inhibitors, oral minoxidil, and platelet-rich plasma have shown potential for hair regrowth, but they require careful evaluation due to varying safety profiles[4].

Current treatments are often limited by effectiveness and side effects, and research continues to improve therapies targeting the cellular pathways involved in AGA[5]. Recent innovations include advanced oral minoxidil, dutasteride, prostaglandin modulators and low-level laser therapy [6].

To address this knowledge gap, the aim of this review is to summarize the current understanding of the pathophysiology of AGA, critically evaluate existing and emerging therapeutic options, and provide evidence-based recommendations for clinical management

1.Pathophysiology of Androgenic alopecia

The pathophysiology of AGA is heavily influenced by dihydrotestosterone (DHT), which miniaturizes hair follicles and leads to thinning and hair loss [7]. AGA involves the disruption of hair follicle signaling pathways, with inflammation playing a crucial role across various hair loss disorders, indicating that many conditions share broader mechanisms[8]. Over time, the shortening of the anagen phase in AGA leads to terminal hairs becoming vellus hairs [9].

2. Hair Growth Cycle

Average Hair growth cycle consist of 4 phases

2.1 Anagen phase

This is usually the active growth phase during the formation of the hair follicle and the production of the hair shaft. The phase begins with hair germ cells surrounding the dermal papilla, which send signals for the division of hair matrix cells to form the hair shaft and inner root sheath. This phase may last for several years and can, therefore, also include the proanagen and metanagen stages[10-11].

2.2 Catagen Phase

During this transitional phase, the lower part of the hair shaft disintegrates, and the follicle moves upwards with the dermal papilla until it rests below the bulge zone, forming the club hair. Apoptosis occurs, and If there is no contact between the dermal papilla and the bulge area, hair cycling stops, leading to permanent hair loss[9,12].

2.3 Telogen Phase

Lasting two to three months, about 9% of scalp hair and 40-50% of body hair are in this phase at any given time. Old hair rests, and new hair begins developing, eventually pushing out the old hair. Premature entry into the telogen phase can result in excessive shedding and thinning, known as telogen effluvium (TE). Managing this phase helps control hair loss. The hair follicle becomes inactive, with little DNA or RNA synthesis in the epithelial cells. Though often seen as a resting phase, telogen may actively regulate the transition to the anagen phase by releasing hair cycle inhibitors[13-14].

3. Role of Hormones in hair Growth

3.1 Testosterone

Androgens, especially dihydrotestosterone (DHT), play an important role in the miniaturization of hair follicles, especially those on the scalp. DHT is derived from testosterone by the enzymatic action of 5-alpha reductase. It binds to androgen receptors of the dermal papilla cells in hair follicles. This binding alters gene expression, leading to changes in hair growth. While androgens stimulate hair growth over the face, chest, and pubis, they inhibit scalp hair follicles and contribute to hair follicle miniaturization [15].

3.2 Estradiol

Estrogens, especially estradiol (E2), have a complex role in hair follicle biology and affect hair follicle miniaturization by modulating androgen metabolism. Estradiol reduces the amount of DHT produced from testosterone in hair follicles and may slow down or counteract androgen-induced hair

follicle miniaturization [16].

3.3 Progesterone

Progesterone acts on hair follicle growth through both central and local effects. Centrally, it blocks luteinizing hormone (LH) secretion, which reduces stimulation of ovarian theca cells and results in reduced androgen synthesis. Locally, in hair follicles, progesterone inhibits The process by which testosterone is converted into other biologically active forms or metabolites, such as dihydrotestosterone (DHT) by blocking the enzyme 5-alpha reductase [15].

3.4 Prolactin

The PRL gene, sharing a common ancestor with the growth hormone (GH) gene, provides insights into gene expression mechanisms. In female mink, a decrease in prolactin levels signals the start of autumn moulting, producing a denser winter coat. Bromocriptine treatment accelerates prolactin decline, inducing early moulting, while high prolactin levels from treatment shorten the moulting cycle and result in abnormal coat growth, indicating prolactin's role in hair growth during moulting [17-18].

3.5 Thyroid Gland Hormones

The hypothalamic-pituitary-thyroid (HPT) axis regulates metabolic processes, and both skin and hair follicles respond to thyroid hormones. Thyroid-stimulating hormone (TSH) prompts the thyroid gland to release thyroxine (T4) and triiodothyronine (T3), which are essential for skin and hair health. The presence of TSH receptors in scalp follicles suggests a direct impact on gene expression and hair growth [15,19].

3.6 Melatonin

Melatonin impacts hair growth by protecting hair follicles from oxidative stress and ultraviolet radiation-induced damage. Its receptor-dependent and independent actions in the skin contribute to stress response regulation, helping maintain hair follicle health and overall skin integrity [20].Melatonin and its metabolites protect hair follicles by reducing UVB-induced oxidative stress and DNA damage in melanocytes, stimulating the production of NRF2 and its protective target enzymes. These effects promote DNA repair and protect hair follicle cells from UVB damage, enhancing hair follicle resilience to environmental stressors [21].

3.7 Corticotropin-releasing hormone

Corticotropin-releasing hormone (CRH): CRH decreases hair shaft production, accelerates catagen phase, and modulates local inflammation. Chronic stress elevates CRH, contributing to hair thinning and telogen effluvium. Therapeutically targeting CRH may mitigate stress-induced hair loss [15].

3.8 Cortisol

Hair cortisol levels may serve as biomarkers for chronic stress, with higher levels associated with greater stress exposure. Frequent washing reduces cortisol levels, though no significant differences have been observed between treated and untreated hair [22].

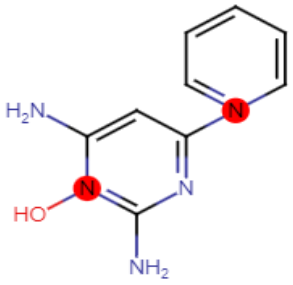
2. Evidence Acquisition

Comprehensive literature review details, search strategy, databases, inclusion criteria, study period, and screening methods for quality and relevance. PubMed, Scopus, and Web of Science were searched for studies between 2000 and 2024 using keywords such as 'Androgenic Alopecia', 'hair loss', 'PRP', 'minoxidil', 'finasteride', 'LLLT', and 'microneedling'. Studies were screened for relevance and quality.

3. Results

3.1 Topical treatments:

Minoxidil



Minoxidil was first discovered in 1970 as a potent vasodilator upon oral administration. Initial clinical investigations of the drug demonstrated its antihypertensive potential when administered together with β-blockers and diuretics [23].Minoxidil is a piperidino-pyrimidine derivative, 2,4-diamino-6 piperidino-pyrimidine-3-oxide, that exerts its action as a potent arteriolar vasodilator through opening potassium channels on smooth muscle cells of peripheral arteries[24]. The active metabolite, minoxidil sulfate, is responsible for its antihypertensive and follicular effects. Topical minoxidil has shown promise in treating male-pattern alopecia and alopecia areata. Clinical trials indicate that careful selection of patients with proper drug formulation is crucial for ensuring maximum efficacy. Adverse reactions are largely skin-related and generally occur in non-hypertensive or non-cardiovascular individuals. While the exact mechanism of minoxidil-induced hair growth is not well understood, it likely involves a synergistic effect on multiple cell types [25]. Normalization of hair follicles and increased blood supply to the scalp due to topical minoxidil may account for its effectiveness in promoting hair growth[26]. Topical minoxidil (Rogaine) has received FDA approval for the treatment of androgenetic alopecia and has been approved for this use in many other countries. The focus is on a realistic appraisal of its efficacy based on anecdotal and controlled clinical trials [27].

Minoxidil gained attention as a treatment for male pattern hair loss (androgenetic alopecia) after it was observed to reverse hair loss in a patient taking it for hypertension. While the mechanism by which minoxidil promotes hair growth is unclear, it reportedly provides cosmetic satisfaction with hair thickening in select individuals with the condition[28]. Although it cannot entirely halt or reverse hair loss, its use is generally safe, with no serious side effects reported, making it a viable option for some patients. Minoxidil promotes the transition of hair follicles from the telogen (resting) phase to the anagen (active growth) phase, enlarges follicles, and increases "non-vellus" hair count. Modern formulations with reduced propylene glycol have improved cosmetic acceptance and safety, solidifying minoxidil as a key treatment for androgenetic alopecia [29].

Available concentrations 2%, 5 % and 10%:

In a 48-week, randomized, double-blind, placebo-controlled multicenter study, researchers evaluated the effectiveness of 5% topical minoxidil compared to 2% topical minoxidil and a placebo in treating androgenetic alopecia (AGA) in men. The study's goal was to assess how varying minoxidil concentrations influence hair regrowth and patient outcomes, as shown in Table 1 [30].

Table 1. Comparison of Hair Regrowth and Patient Outcomes Across 5% Minoxidil, 2% Minoxidil, and Placebo Groups in a 48-Week Randomized, Double-Blind Study

Sr.No.	Criteria	5 % Minoxidil	2 % Minoxidil	Placebo
1	Change in Nonvellus Hair Count	Significantly superior	Less effective than 5%	Least effective
2	Patient Rating of Scalp Coverage	Higher satisfaction	Lower satisfaction	Lowest satisfaction
3	Patient Rating of Treatment Benefit	Higher perceived benefit	Lower perceived benefit	Lowest perceived benefit
4	Investigator Rating of Scalp Coverage	Higher improvement	Lower improvement	Lowest improvement
5	Onset of Treatment Response	Earlier response	Later response	N/A
6	Psychosocial Perceptions (Quality of Life)	Improved	Less improvement	Least improvement
7	Side Effects (Pruritus & Local Irritation)	Higher occurrence	Lower occurrence	N/A

The study was successfully completed, focusing on the comparison between 5% and 10% topical minoxidil for treating androgenetic alopecia. This research adds valuable insights into the efficacy and

safety of different minoxidil concentrations as mentioned in table 2 below [31].

Table 2. Efficacy and Safety Comparison of 5% and 10% Topical Minoxidil in Treating Androgenetic Alopecia Over a 48-Week Period.

Sr.No.	Parameters	5 % Minoxidil	10 % Minoxidil	Placebo
1	Change in Total Vertex Hair Count	0.47 ± 0.26	0.05 ± 0.13	0.01 ± 0.05
2	Change in Frontal Hair Mean Count	0.59 ± 0.64	0.45 ± 0.74	-0.03 ± 0.08
3	Pull Test (Negative Change After 6 Months)	37% of patients	37.5% of patients	0% of patients
4	Reported Sexual Dysfunction	None reported	None reported	None reported

One female patient, 2 years of age with LAHS, was treated with topical minoxidil 5% solution for 28 months, presenting marked improvement in hair density without any side effects. This case was thus indicative of the fact that minoxidil may be used as a first-line treatment for LAHS in order to accelerate clinical improvement [32]. Topical minoxidil (2% to 5%) is an effective standard therapy to cure androgenetic alopecia, permitting control of cosmetic distress and psychic disturbance associated with the condition.Morphometric studies have shown that topical minoxidil stimulates larger, normally configured hair follicle development by acting on follicular dermal papilla specialized mesenchymal cells [33].

Side Effects:

Topical application of minoxidil may result in adverse effects such as pruritus, scaling of the scalp, irritant contact dermatitis, allergic contact dermatitis, and exacerbation of seborrheic dermatitis. Allergic reactions are usually due to propylene glycol in the formulation rather than to minoxidil itself and a different solvent may be used for affected patients [34]. May lead to adverse effects that include pruritus, erythema, scaling, dryness, and, rarely, pustular allergic contact dermatitis. These side effects are always confined to the site of application and can be due to either irritant or allergic contact dermatitis, or both, and exacerbation of seborrheic dermatitis [35].

Topical minoxidil may lead to ACD and minoxidil is the main responsible allergen in 74.7% of cases, while propylene glycol is in 17.1%. Other identified allergens were estradiol, butylene glycol, and methylchloroisothiazolinone/methylisothiazolinone. Patch testing with 2% minoxidil in propylene glycol is advisable for an accurate diagnosis[36]. Allergic contact dermatitis is less frequent and, in most cases, a result of propylene glycol, rather than minoxidil itself. Those allergic to minoxidil must avoid the drug, but sensitive ones to the solvent may try alternative formulations [37]. Ingestion of topical minoxidil by children in the community can lead to severe poisoning, as demonstrated by this case—the girl developed prolonged hypotension, sinus tachycardia, and electrocardiogram changes following small amounts. This case emphasizes the danger of minoxidil in childhood and the need for its more secure packaging and safety precautions [38].

Toxicosis due to minoxidil occurred in a 2-yr-old female dog that had ingested a 5% minoxidil hair growth foam. The symptoms included vomiting, depression, tachycardia, and hypotension. The dog was treated with intravenous dopamine and esmolol to control the blood pressure and heart rate and with a lipid emulsion as a putative antidote for the lipophilic effects of minoxidil. After 36 h of hospitalization, the dog was well recovered, which established an effective clinical management in current veterinary practice. Table summarizing the clinical case of a dog with minoxidil toxicosis: as presented in Table 3 [39].

Table 3. Clinical Summary of Minoxidil Toxicosis and Treatment Outcomes in a 2-Year-Old Dog.

Sr.No	Parameter	Details

1	Patient	2 yr old female Dog
2	Incident	Ingestion of an unknown amount of Minoxidil foam
3	Initial Symptoms	Vomiting, lethargy, tachycardia (200-220 beats/min), hypotension (systolic BP 70 mm Hg
4	Initial Examination	Regular, narrow-complex tachycardia, no ventricular ectopy
5	Treatment Hypotension	Dopamine hydrochloride infusion (12.5 µg/kg/min)
6	Treatment Tachycardia	Esmolol hydrochloride infusion (40 µg/kg/min
7	Treatment toxicosis	IV lipid emulsion (1.5 mL/kg bolus, followed by 0.25 mL/kg/min infusion for 60 minutes)
8	Additional Medications	Maropitant citrate, ondansetron
9	Outcome	Clinical signs resolved; dog discharged 36 hours after admission
10	Follow up	Full recovery reported 4 days later, normal behaviour and activity level resumed

Finasteride functions by inhibiting the type II 5α-reductase enzyme, which decreases DHT (dihydrotestosterone) levels, thus offering therapeutic benefits in androgenetic alopecia by targeting DHT production in hair folliclesibition of 5α-reductas [40]. he enzyme that converts testosterone to DHT—a key androgen linked to androgenetic alopecia—helps prevent further hair loss and encourages regrowth [41]. In a 16le-blind, placebo-controlled trial involving 52 participants with androgenetic alopecia, a 0.005% topical finasteride solution led to increased hair regrowth and a reduction in balding areas, with no detectable percutaneous absorption or side effects, suggesting the potential of topical finasteride for treatment [42].Finasteride undnsive metabolism in the liver via cytochrome P450 3A4, producing two metabolites with minor 5α-reductase inhibitory properties. Although finasteride can cross the blood-brain barrier, seminal concentrations remain undetectable [43].

In this regard, one study of a new 0.25% topical finasteride solution called P-3074 reported scalp DHT reductions of 47-52% with lower doses of 100-200 µL, similar to these higher doses, yet with fewer systemic side effects. Thus, this may indicate that lower-dose topical finasteride could be an effective treatment for androgenetic alopecia with a reduced risk of sexual side effects from systemic DHT suppression [44].Topical finasteride has been shown to effectively reduce hair loss, resulting in a notable increase in both total and terminal hair counts, supporting positive hair growth outcomes. Additionally, DHT levels in both the scalp and plasma dropped significantly, with no observed changes in serum testosterone levels [43]. More recently, a novel powdered carrier microneedle delivery system for finasteride that is currently under investigation has shown a number of advantages compared to conventional topical formulations in the treatment of androgenetic alopecia. The broadening effect in this PCM system allows the FNS powder to be implanted directly into the skin, resulting in a sustained release for three days each, with increased efficacy of hair growth and higher density of hair [45]. In most studies on finasteride-loaded topical formulation, propylene glycol was employed as the main permeation enhancer, while less use was made of other ingredients such as poloxamer P407, monoolein, transcutol P, and choline in a limited number of formulations [46].

Some side effects

Finasteride represents an important drug in treating androgenetic alopecia and benign prostatic hyperplasia. It has been, however, implicated in PFS—Post-Finasteride Syndrome—which includes ED, decreased libido, fatigue, penile and scrotal atrophy, gynecomastia, muscular atrophy, and

emotional sensitivity, all of which are supposed to persist upon cessation of the drug [47]. A case of persistent gynecomastia following 1 month of low-dose finasteride for androgenetic alopecia in a 20-year-old man. Even after stopping the drug, there was no resolution of the condition, and so was subjected to surgery. Under-diagnosis of finasteride-induced gynecomastia is suspected in this case, which points to the fact that early diagnosis should be instituted [48]. Studies on male pattern hair loss have indicated that finasteride may cause sexual side effects, which are generally reversible. However, regulatory bodies in the UK and Sweden have issued warnings based on post-marketing reports, noting that erectile dysfunction could continue even after discontinuing Propecia [49].

A study involving men who experienced ongoing sexual side effects after using finasteride found that 96% continued to report these issues months or even years after stopping the drug. Additionally, 89% met the criteria for sexual dysfunction, highlighting the importance of informing patients about potential long-term side effects [50]. Finasteride has increasingly been associated with persistent sexual side effects and recently included depression in its product labeling. This article review discusses the ramifications of the side effects, especially on the prevalence of depressive symptoms and even suicidal thoughts from former users [51]. Finasteride has become more frequently linked to enduring sexual side effects, and depression has recently been added to its product labeling. This review article explores the impact of these side effects, particularly the increased incidence of depressive symptoms and, in some former users, even suicidal thoughts [52].

New Topical Agents:

Topical Dutasteride

New Topical Agents: Topical Dutasteride: More recent literature has assessed topical dutasteride using nanostructured lipid carriers, DST-NLCs, to reduce systemic absorption and lower irritation and cytotoxicity. It improved stability, retarded drug release, and had no irritation to skin because it was coated with chitosan oligomer and lauric acid; hence, it is safer [53]. The nanostructured systems increase topical delivery of dutasteride by enhancing drug penetration into hair follicles, prolonging its effect, and reducing skin irritation. Even though additional treatments, including microneedling, can further enhance its effectiveness, more clinical research has to be done to confirm safety and efficacy [54]. Intralesional dutasteride is a promising alternative to oral administration in the treatment of androgenetic alopecia, reducing systemic exposure. Although yielding a mean increase of 7.90 hairs in hair count, further studies comparing its efficacy and safety thoroughly with oral dutasteride, which gave a mean increase as high as 15.92 hairs, are needed [55].

Prostaglandin Analogues

Prostaglandins play a crucial role in hair growth regulation, with PGF2α promoting eyelash growth and PGE2 protecting against radiation-induced hair loss. Conversely, PGD2 has been found to inhibit hair growth, highlighting the complex effects of prostanoids on hair follicle activity and their potential clinical relevance in treating hair disorders[56]. Four major PGs—PGD2, PGI2, PGE2, and PGF2α—are expressed in hair follicles and are linked to hair growth dynamics. Understanding their physiological roles and pharmacological interventions may offer novel therapeutic insights for treating conditions like androgenetic alopecia (AGA) and alopecia areata, potentially enhancing treatment options beyond the temporary effects of FDA-approved medications like finasteride and minoxidil [57].

study examined the role of four prostaglandins (PGE2, PGD2, PGF2α, and prostacyclin) in androgenetic alopecia (AGA) by analyzing scalp biopsies from AGA patients and healthy individuals. Findings revealed that PGD2 and prostacyclin levels were elevated in bald areas, while PGE2 and PGF2α were reduced, suggesting a critical balance of these prostaglandins is essential for hair follicle function and indicating their receptors as potential therapeutic targets for AGA treatment [58].PGD2 acts as an inhibitor of hair growth by interacting with the GPR44 receptor. Its elevated levels in bald scalp and its role in triggering the regression phase of hair follicles targeting the PGD2-GPR44 pathway may represent a promising therapeutic approach for treating AGA [59].

Bimatoprost

Bimatoprost has shown effectiveness in encouraging eyelash regrowth in patients following chemotherapy, leading to visible improvements in eyelash length, thickness, and color. It has proven beneficial in restoring eyelash prominence with a favorable safety profile, presenting itself as a potential option for treating chemotherapy-induced hypotrichosis [60]. Bimatoprost in the 0.5% or 3% w/w BIM–TF#5 formulation increased skin permeability and dermal deposition, significantly promoting hair regrowth. It enhanced dermal papilla cell activity and outperformed both BIM in ethanol

and minoxidil in hair growth [61]. Bimatoprost shows potential for treating scalp alopecia, including androgenetic alopecia, though it is currently FDA-approved only for eyelash growth. Its benefits may extend to conditions like alopecia areata and frontal fibrosing alopecia [62].

Latanoprost

Latanoprost at a concentration of 500 µg/ml resulted in moderate to significant hair regrowth in a macaque model of androgenetic alopecia, with 5-10% of vellus hairs transitioning to intermediary or terminal hairs. In contrast, a lower dose of 50 µg/ml produced minimal growth, indicating that latanoprost warrants further investigation for treating human androgenetic alopecia [63]. Additionally, another study reported considerable increases in hair density and total hair strands after 24 weeks of treatment with a 0.1% latanoprost solution compared to placebo [64].

3.2 Oral Treatments:

Oral Minoxidil

Oral minoxidil (OM) shows potential benefits for treating various types of alopecia, but its effectiveness is uncertain due to low-quality evidence from existing studies[65].Low-dose oral minoxidil offers an effective option for treating hair loss, especially for patients who struggle with adherence to topical treatments. It has shown positive outcomes in conditions such as androgenetic alopecia and telogen effluvium. The typical dosage ranges from 0.25 to 5 mg per day, with women usually benefiting from lower doses compared to men for the best results [66]. A multi-center retrospective study involving 105 adult patients who received oral minoxidil (at doses of 0.625-2.5 mg daily for a minimum of 52 weeks) found that 52.4% of participants experienced clinical improvement, while 42.9% showed stabilization in their conditions related to androgenetic alopecia and telogen effluvium (70).Oral minoxidil demonstrates significant efficacy in treating androgenetic alopecia, with clinical improvement noted in up to 100% of male patients at higher doses. Lower doses are effective for females, but it is contraindicated in those with pheochromocytoma and poses risks for patients with hypotension or cardiac issues [67].

Nine female patients with allergies to topical minoxidil successfully tolerated low-dose oral minoxidil, showing good clinical efficacy without side effects. The study suggests that oral minoxidil, at a dose of 0.25 mg twice daily, is a safe alternative for those allergic to the topical formulation [68].Low-dose oral minoxidil is a safe and effective treatment for male-patterned and female-patterned hair loss, with doses ranging from 0.25 to 1.25 mg for females and 2.5 to 5 mg for males. Its low side-effect profile enhances patient adherence and promotes stabilization and improvement of hair loss[69]. Oral minoxidil has demonstrated effectiveness and good tolerance, making it a viable option for healthy patients who have difficulty using topical treatments [70]. Low-dose oral minoxidil (LDOM) could be a safe treatment alternative for hair disorders in children, while moderate to high doses may raise safety concerns [71].

Oral Finasteride

Oral finasteride is a 5-alpha-reductase inhibitor that prevents the conversion of testosterone into dihydrotestosterone (DHT), the androgen linked to male pattern hair loss (androgenetic alopecia) in genetically susceptible men. By lowering DHT levels, finasteride encourages hair growth and helps stop additional hair loss in those affected [40]. After six months of treatment with finasteride, there was a notable decrease in total sperm count and an increase in the number of abnormal sperm forms. However, these side effects seemed to improve by the 12-month follow-up, indicating that recovery may be possible following the discontinuation of the therapy [72].

Finasteride, originally developed for benign prostatic hyperplasia, Was subsequently approved as the first oral treatement for androgenetic alopecia (AGA) at a dose of 1 mg/day, demonstrating long-term efficacy and safety [73]. Finasteride 1 mg resulted in increased hair weight in men with androgenetic alopecia, with a more pronounced rise in hair weight compared to hair count. This indicates that the drug's beneficial effects are due to enhancements in hair thickness and growth rate, rather than merely shows an increase in the volume or number of hairs [74].

Oral Dutasteride

Dutasteride is a dual inhibitor of both 5α-reductase type 1 and type 2 enzymes, coming about in more than 90% suppression of serum DHT. This dual restraint gives more noteworthy suppression of DHT compared to finasteride, which inhibits only type 2, achieving around 70% suppression [75]. Dutasteride is a double 5-α-reductase inhibitor effective in reducing DHT levels, showing promise in treating androgenetic alopecia. It has demonstrated greater potency than finasteride in clinical trials [76].

Oral spironolactone promotes hair growth through its

antiandrogenic properties by blocking androgen receptors and decreasing the production of dihydrotestosterone (DHT), a key hormone responsible for hair loss in androgenetic alopecia[77]. spironolactone is a promising and well-tolerated treatment for Female Pattern Hair Loss (FPHL), particularly with long-term utilize. Its effectiveness, particularly in patients with more serious hair fall, supports its role as a viable option for improving hair density [78].

The combination of minoxidil with spironolactone is more benefical than minoxidil with finasteride in the treatment of AA in women, mainly in the improvement of hair density and reduction of hair loss. Spironolactone was far better in patient satisfaction and treatment outcomes in comparison with finasteride, mainly regarding male pattern hair loss[79]. Spironolactone is a synthetic aldosterone antagonist and potassium-sparing diuretic, which is effective against hirsutism and FPHL by its antiandrogenic action resulting in reduction of testosterone production. Although it has a very favourable long-term safety profile, it is contraindicated in pregnancy and should not be used in men because of the risk of feminization [80].

3.3 PRP

The concept of platelet-rich plasma (PRP) originated in the field of haematology. Haematologists coined the term in the 1970s to refer to plasma containing a higher platelet count than that found in peripheral blood. Initially, PRP was utilized as a transfusion product for treating patients with thrombocytopenia [81]. Platelet-rich plasma treatment for AGA is gaining interest in the medical literature based on the presence of growth factors such as EGF, IGF-1, and VEGF in PRP, which are considered very important in hair follicle growth [82]. Platelet-rich plasma is an autologous platelet concentration in plasma released by platelets during the Stimulation of hair regrowth. These growth factors exert their influence on the hair follicle stem cells to cause new follicle formation and neovascularization, hence making PRP a promising treatment for androgenetic alopecia (AGA) [83]. Platelet-rich plasma (PRP) has become a promising treatment candidate for dermatological treatments like alopecia and wound healing but lacks solid clinical evidence for widespread use. Despite this safety, its efficacy has not been consolidated yet because more research in that direction is required [84].

The PRP used stimulates hair growth through by stimulating the dermal papilla cells and key signalling pathways like ERK and Akt. In vivo, it hastened the change of phase from rest to growth in mouse hair [85]. Platelet-rich plasma is a concentrated plasma preparation containing an elevated level of platelets compared with peripheral blood and arising from the original use to treat thrombocytopenia [86]. For FAGA, studies evidence promising treatment results with high patient satisfaction and enhanced quality of life. It can be indicated for patients who are either unresponsive or intolerant to topical minoxidil or could be prescribed as an adjuvant therapy[87]. Recent literature on PRP for androgenetic alopecia is favourable; however, studies had methodologic limitations and data were not particularly robust. Nonetheless, the majority of patients were satisfied with the outcome, although additional research was required in better-designed, larger trials [88].

3.4 Low level Laser therapy

Low level Laser therapy: Low-level laser treatment, or LLLT, is a light therapy designed to boost cellular processes leading to tissue repair and regrowth. It involves the application of red to near-infrared laser light, typically within the wavelength range of 600–950 nm, which falls within the "optical window" for biological tissue. It is at these wavelengths where, in tissue, the penetration is optimized and hence photo biomodulation may occur - the overall therapeutic effect of LLLT on the body [89].

In this parallel-group study, Satino and Markou investigated whether LLLT promotes hair growth in patients with AGA by using low-level laser therapy to assess hair density and tensile strength in 28 male and 7 female patients with the condition. Each subject used a HairMax LaserComb®, which emits 655 nm light and was used at home for 5–10 minutes every other day over the course of six months. Tensile strength of the hair was measured by the VIP HairOScope by plucking three representative terminal hairs from a one-square centimetre section. The results demonstrated a significant increase in hair tensile strength in vertex area in males and temporal area in females with overall significant effects seen in all areas for both sexes [90].

Lucio Frigo researched on the vitro study of B16F10 melanoma cells. The study showed that LLLT can have adverse effects, particularly at high dosages (1050 J/cm²) as it was observed that remarkable increases in tumor volume, blood vessels, and cell aberrations were registered within the melanoma mouse model [91].

3.5 Microneedling

Microneedling: Microneedling, also called percutaneous collagen induction, is a minimally invasive treatment in which micro-injury to the skin is caused by the use of fine needles, inducing an inflammatory response that Favors the production of collagen and elastin. Though initially developed to treat scars, microneedling applications have evolved to include acne vulgaris, facial rejuvenation, dyspigmentation, alopecia and the enhancement of transdermal drug delivery [92]. Dhurat R etal The microneedling group revealed a much better increase in hair count at 12 weeks compared to the minoxidil-only group (91.4 vs. 22.2) [93]. Moreover, a higher number of subjects treated with microneedling showed a microneedling has emerged as a new transdermal drug delivery system for the treatment of alopecia, which avoids the limitations in the current FDA-approved anti-alopecia drugs, minoxidil and finasteride, due to unsatisfactory efficacy. Therefore, microneedles can improve the effectiveness of local drug delivery and patient compliance, thus enabling better therapeutic outcomes for hair-related disorders [94].

3.6 Exosome Therapy

Exosomes are tiny, cell-derived vesicles ranging from 30 to 200 nanometers in size and encased in a lipid bilayer. These vesicles are key players in cell-to-cell communication and show promise for treating hair loss. Exosomes play an essential role in hair follicle growth and cycling by facilitating interactions between hair follicle stem cells and dermal papilla cells. Their rich cargo, including bioactive molecules like microRNAs, offers therapeutic potential for enhancing hair regeneration and health [95]. Now, exosome therapy has emerged as a promising treatment in hair loss, particularly androgenetic alopecia, with encouraging positive results in hair growth sans the development of any side effects. Still a novel therapy, and hence further clinical trials are required to show its efficacy and safety profile [96]. Exosome treatment is an innovative treatment in hair loss using small vesicles secreted from cells called exosomes involved in intercellular communication. Whereas conventional therapies for hair loss include most disadvantages like repeated interventions and side effects, it has been noted that exosomes stimulate hair growth in animal models [97].

3.7 Hair Transplantation

Hair Transplantation: Most of the modern concepts in hair transplantation involve the use of follicular unit transplantation wherein the grafts used are individual follicular units for restoration [98].MARC R. AVRAM et al report that transplantation of air is an outpatient procedure done under local anaesthesia; the time required for transplanting 800 to 1500 grafts may take up to 3 to 4 hrs for natural-appearing results. Because of the limited amount of discomfort associated with procedures, normal activity can be resumed in a short period, and most people can return to work in 2 to 3 days [99].Problems that exist in hair transplantation include extreme competition, high training costs, and expertise in sophisticated surgical skills, especially for follicular unit extraction and hairline design. Amateurs struggle with precision techniques, anaesthesia application, and bearing long graft implantation times decreasing surgery outcomes [100]. Advancement of hair transplantation, specifically follicular unit transplantation, has increased the yield of the hair transplant operation. Innovations and modifications have made hair restoration surgery advance, while the applications are also increasing from traditional male pattern hair loss [101]. Hair transplantation surgery yields natural results; however, there is considerable debate regarding the superior donor harvesting methods: elliptical harvesting or follicular unit extraction [102].

3.8 Combination Therapies

Combination Therapies: Combination therapies comprising minoxidil with finasteride, low-level laser light therapy (LLLT), or microneedling were found to be more effective than minoxidil monotherapy for the treatment of androgenetic alopecia (AGA), with significant improvements in hair count and global assessments [103]. Parasa Abdi et al carried out a meta-analysis; combination therapy using minoxidil and microneedling significantly increased hair count in patients with androgenetic alopecia compared with minoxidil therapy alone. However, no statistically significant effect on hair diameter was observed in these studies [104].

3.9 Gene Therapy

Gene therapy for hair growth has shown promise in the delivery of genes either in vivo or ex vivo to hair follicles, targeting thereby the keratinocyte stem cells in manipulating the hair cycle and initiating anagen onset. Although gene therapy is still in its infancy, several studies have successfully used this technique in inducing hair growth or an alteration of hair follicle cycling [105]. Gene therapy can target the hair follicle progenitors, critical to hair follicle cycling and a diverse range of cell types during the early anagen stage. Thus, this technique offers hope

for the treatment of alopecia and other skin disorders; although success is influenced by the composition of liposomes used and the stage of the hair cycle [106].Hair restoration has evolved from scalp reduction techniques, mainly to hair transplantation and pharmacological treatments for androgenetic alopecia. Advancements in hair follicle biology and new molecular delivery techniques will ensure gene therapy as one of the possible options in alopecia treatments in the future [107].

4. Conclusion

Androgenic alopecia is a very common entity that, besides the pathophysiological interest, considerably affects the quality of life in subjects. While all the current treatments, both topical and oral, are effective, the new emerging therapies like PRP, LLLT, and advanced hair transplantation techniques offer new hope for better outcomes. The future management of AGA looks brilliant because the research into novel treatments such as gene therapy might completely revolutionize the approach to hair loss management.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used Grammarly to rectify grammar and language-related errors. After using this tool, the author(s) carefully reviewed and edited the content as needed and take full responsibility for the content of the published article.

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