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ANDROGENIC ALOPECIA:PATHOPHYSIOLOGY, CLINICAL FEATURES AND RECENT THERAPEUTIC APPROCHES

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ABSTRACT

By the age of 50, approximatelyone-half of all males and females get androgenic alopecia (AGA), a condition characterized by progressive hair loss on the scalp, impacting self-esteem and physical appearance. AGA is attributed to the increased activity of 5-reductase enzyme in scalp hair follicles, leading to conversion of testosterone to dihydrotestosterone (DHT). Finasteride, a synthetic 4-aza-3-oxosteroid with low water solubility, inhibits this conversion, resulting in reduced DHT levels and hair loss mitigation.Although minoxidil, potassium channel opener and vasodilator, promotes hair growth by enhancing blood flow and nutrient delivery to the scalp,its precise mechanism for stimulating hair growth remains ambiguous and seems to operate separately from its vasodilatory effects. The investigations on both medications found that combining minoxidil and finasteride had a superior effect on hair loss than either therapy alone. Combining finasteride and minoxidil has shown superior efficacy compared to either drug alone in treating hair loss. To address limitations of current formulations, a topical preparation combining finasteride and minoxidil is needed, optimizing drug-to-scalp contact, reducing administration frequency, enhancing penetration, stimulating hair follicles, and improving hair growth. Utilizing niosomes, which act as localized drug depots, could prolong drug release and improve therapeutic outcomes while minimizing systemic adverse effects of finasteride.

Keywords: Androgenic alopecia, Testosterone, Dihydrotestosterone, Minoxidil, Finasteride, Vasodilator

INTRODUCTION

In the realm of dermatology, hair loss presents itself through diverse manifestations, often prompting concern among patients seeking medical attention.Predominantly, diagnoses commonly encountered include androgenetic alopecia, telogen effluvium, and alopecia areata, among others. However, the range of potential diagnoses extends beyond these primary categories. Notably, within dermatology clinics, there appears to be a rising incidence of alopecia areata accompanied by scarring, indicating a remarkable trend. Moreover, it is pertinent to underscore that hair loss in both men and women is predominantly attributed to androgenetic alopecia (AGA), emphasizing its pervasive nature across genders.AGA progresses differently in males and females, with different classification scales. While the cause may be similar in both genders, the evidence for androgens is stronger in males and there are variations in hair loss patterns. **(Androgenetic alopecia: An update)**

In general, approximately 70% of men and 40% of women can experience AGA at some time in their life, depending on ethnicity. Negative image assessments suggest that even if the condition is prevalent, affected individuals may be highly willing to seek early diagnosis.[1]Finasteride (FNS) and Minoxidil, two medications that encourage hair growth, are now available to treat patients with specific types of hair loss (MXL). Hair length and breadth can be increased by both medications, although their mechanisms of action are different.[2]Types of alopecia are Androgenic alopecia, Alopecia areata, Alopecia totalis, Alopecia universal and alopecia cicatricle. Among these, the two alopecia areata and androgenic alopecia are common.

ALOPECIAAREATA

Alopecia areata is an autoimmune disorder where the immune system erroneously attacks hair follicles, leading to hair loss. The severity of hair loss varies widely, from small, circular patches that often regrow on their own to extensive, persistent patchy areas. In some cases, this can result in the total loss of all hair on the scalp, known as alopecia totalis, or the complete loss of hair on the scalp, face, and body, referred to as alopecia universalis. This condition can affect individuals of any age and gender equally. However, alopecia areata is more commonly seen in children and adolescents. Patients often experience spontaneous remission, with hair regrowing after treatment. Generally, these patients are in good health, though they do have a higher incidence of atopy, thyroid disease, and vitiligo compared to the general population. Children with alopecia areata and those with a family history of thyroid disease should have their serum thyrotropin levels tested. These observations, along with the ability of T cells to transfer anagen hair bulbs affected by alopecia areata from mice with severe combined immunodeficiency, support the theory that the disease is autoimmune in nature, specifically targeting anagen hair bulbs. Additionally, alopecia areata is linked to certain HLA class II alleles, such as DQB1*03* and DRB1*1104*, which suggest a general susceptibility to the condition. This genetic predisposition is similar to that seen in many other autoimmune disorders.

ANDROGENICALOPECIA

Androgenic alopecia is a condition in which genetically predisposed males and females experience hair thinning due to exposure to androgens. In males, this condition manifests as male-pattern hair loss, commonly referred to as “ordinary baldness,” while in females, it appears as female-pattern hair loss. Hair thinning typically begins between the ages of 12 and 40 in both genders, with about half of the population experiencing some degree of hair thinning by this age. The inheritance pattern of androgenic alopecia varies among individuals.[3]

HAIR GROWTH CYCLE

Hair follicles are mini organs that continually experience growth and remodelling cycles throughout a person's life. Hair plays several vital roles, including regulating body temperature, shielding against ultraviolet radiation, aiding in sensory perception, and contributing to personal identity. The hair growth cycle primarily

includes three stages: the growth phase (Anagen), the transition phase (Catagen), and the resting phase (Telogen).

The anagen phase of hair growth lasts between 1 to 6 years on the human scalp. During this period, dermal papilla cells release signaling molecules that activate dormant hair follicle stem cells, including hair follicular stem cells and melanocyte stem cells, located in the bulge region. A small portion of these hair follicle stem cells undergo asymmetrical division, differentiating into transient amplifying cells. These cells migrate downward and differentiate into follicular keratinocytes, forming the matrix cells, inner root sheath, and lower part of the hair follicle. Meanwhile, melanocyte stem cells divide to produce mature melanocytes, which generate and distribute pigmented granules to the follicular keratinocytes. Throughout this phase, the hair shaft continues to grow, becoming longer and thicker.

The catagen phase, which follows the anagen phase, lasts 1–4 weeks. In this phase, the lower two-thirds of the hair follicle shrink and regress as the keratinocytes and melanocytes in the follicle matrix undergo apoptosis, leaving the dermal papilla and bulge intact. The dermal papilla condenses and moves upward towards the bulge. By the end of catagen, the base of the terminal hair becomes keratinized and detaches from the bulb, forming a club hair.

During the telogen phase, the club hair remains in the follicle's orifice, and hair follicular stem cells are quiescent. The dermal papilla stays in contact with the bulge, facilitating epithelial-mesenchymal interactions (EMIs) between the hair follicular stem cells in the bulge and dermal papilla cells. These interactions trigger the formation of the secondary germ layer and initiate the next anagen phase. In the exogen phase, the club hair is shed from the follicle orifice, with approximately 50–100 hairs lost daily.

PATHOPHYSIOLOGY OF ANDROGENIC ALOPECIA

Dihydrotestosterone (DHT) binds to the androgen receptor in susceptible scalp hair follicles. This hormone-receptor complex subsequently activates genes responsible for the gradual transformation of large,terminal follicles to gradually shrink into smaller follicles.[4]

As anagen shortens with each hair cycle, follicles shrink and produce finer hair, eventually leading to bald spots. Shrunken hairs of varying lengths and diameters are characteristic indicators of androgenic alopecia. The number of follicles per unit area remains unchanged. Dihydrotestosterone (DHT) is produced when testosterone is converted peripherally by 5α-reductase. Types 1 and 2 of 5α-reductase, along with other enzymes in the epidermis, regulate steroid transformations. DHT has five times the binding affinity of testosterone for androgen receptors, resulting in greater downstream activation potency.[5]

In women, dehydroepiandrosterone (DHEA) and other lesser androgens serve as precursors, while in men, testosterone is the main precursor. Binding to androgen receptors increases the synthesis of cytokines such as TGF-beta1 and TGF-beta2, which induce telogen phase and promote senescence of dermal papilla cells. However, the intracellular signaling cascade that follows receptor binding remains not fully understood.[6]

In young men and women suffering from androgenic alopecia, hair follicles in the frontal scalp exhibit higher levels of the enzyme 5α-reductase and increased levels of androgen receptors. Conversely, they have lower levels of the enzyme cytochrome P-450 aromatase, which converts androgens into estrogen. These variations may result from differing amounts of 5α-reductase, androgen receptors, and aromatase in various areas of the scalp at different times in life. Androgenic alopecia affects men and women differently.

CLINICALFEATURES

To diagnose alopecia generalis, or AGA, which is characterized by varying hair shaft diameters without scarring, a detailed patient history and dermoscopy are used. When investigating hair loss, it's crucial to gather a thorough medical history. A comprehensive and methodical inquiry can reveal key elements for differential diagnosis and guide specific research directions. To avoid premature conclusions and bias, one should refrain from accepting anything as true unless it is clearly verifiable, either from the patient or the referring physician. This approach ensures that decisions are well-informed and free from questionable assumptions.

Hair loss often has a genetic component, so taking a detailed family history is necessary to rule out hereditary conditions. It is also important to gather comprehensive information about your medical history. This includes knowing when the hair loss began, how often it occurs, and the rate at which it has progressed. Additionally, understanding your current and past health status, any medications you are taking (including hormonal treatments like oral contraceptives or hormone replacement therapy), and your hair care practices is essential.7

Iron deficiency, thyroid disorders, and lupus erythematosus are among the most common causes of hair loss in women. These conditions should be thoroughly examined in the patient's medical history. Factors such as using an intrauterine device (IUD), experiencing heavy menstrual bleeding, having a history of iron deficiency anaemia, and consuming an iron-deficient diet all contribute to the risk of developing iron deficiency anaemia, which can lead to hair loss.

Additionally, it is important to gather information about the patient's history of significant stress, exposure to ultraviolet (UV) light, smoking habits, alcohol use, poor nutrition, substance abuse, and high-risk sexual behaviours, which could result in infections such as syphilis or HIV.Collecting and analysing skin and hair samples can also assist in diagnosing the underlying cause of hair loss. Ultimately, identifying all relevant factors involves a comprehensive assessment of the patient's medical history and a detailed observation of their condition.

The ability to observe may seem so basic that it is often overlooked. However, advancing to a higher level of diagnostic creativity requires active and skilful observation. Once a problem is identified, the true expertise lies in interpreting what has been seen and investigating the underlying cause. It is beneficial to examine a situation for the first time without any biases or preconceived notions from previous diagnoses or laboratory results. When a diagnosis hinges solely on recognition, it can be made almost instantaneously. Dermatologists aim to develop a well-informed perspective grounded in their education, clinical experience, and the capacity to remember a patient's visual presentation.

Dermatological screening techniques and laboratory analysis are examples of diagnostic procedures performed when a diagnosis cannot be determined at first glance. Alopecia is the medical term for significant hair loss over time. During a scalp examination, observe the pattern and distribution of hair loss, check for skin and nail lesions, and look for signs of inflammation or scarring. Note any irregularities in the width of hair parts. To estimate current hair loss, conduct and repeat the pull test. This involves holding about 50 hairs between the thumb, index, and middle fingers. If more than 10% of these hairs can be pulled out, the test is positive. Keep in mind that the cleanliness of the hair after shampooing can affect the results of the test.

During a scalp examination, multiple areas are assessed. Individuals with active androgenetic alopecia (AGA) typically show a positive pull test only in the affected region, while a diffusely positive pull test indicates the need for further diagnostic evaluation to rule out conditions like telogen effluvium or diffuse alopecia areata. Trichoscopy, also known as scalp dermoscopy, is a noninvasive diagnostic technique that allows the detection of morphological features not visible to the naked eye. Dermoscopy has proven valuable for dermatologists who deal with hair and scalp issues regularly. For patients experiencing hair loss, undergoing a dermoscopic examination of the scalp is essential, as it ensures a thorough assessment and addresses their concerns about inadequate examination. Trichoscopy can identify characteristic patterns in the scalp and hair under various conditions. For instance, in AGA, trichoscopy can reveal varying hair shaft diameters, peripilar signs, and empty hair follicles. A variation in hair shaft diameter greater than 20% was traditionally considered indicative of female AGA. Studies have shown that trichoscopy is an effective method for diagnosing female AGA, especially in early stages, with high accuracy independent of the previously recommended 20% hair shaft diameter variability threshold.

Trichoscopic imaging has recently become a tool for diagnosing pattern hair loss (PHL) in women. To meet the diagnostic criteria, the frontal region must show more than four empty follicles across four images (at 70x magnification), be thinner than the occipital region, and have over 10% thin hairs (0.03 mm in diameter) compared to the occipital area. Minor criteria include the fronto-occipital ratio of single hair pilosebaceous units, the presence of vellus hairs, and peripilar signs. The diagnosis of PHL in women is 98% specific when

two major criteria are fulfilled.In non-invasive hair examinations, the trichogram maps the hair growth cycle. This involves using forceps to remove 50-100 hairs from specific scalp areas to determine the ratio of anagen to telogen roots. This test is particularly useful when identifying loose anagen hair or dystrophic anagen effluvium. Accurate clinical suspicion and expertise in dermatology are crucial for this process, as they help minimize the risk of false-positive or irrelevant results, emphasizing the need for precise lab testing. Environmental factors may have a minor impact on AGA susceptibility.

Additionally, genes related to hormone metabolism, such as reductase, aromatase, and sex hormone-binding globulin (SHBG), might influence androgen responsiveness, though their significance remains uncertain 10.

One company claims to have developed a gene polymorphism-based screening test (Hair DXTM) that may predict the risk of developing androgenetic alopecia (AGA) in the future, although the complete genetic picture is not yet fully understood[11,12]. This test could help young patients who are worried about hair loss recognize the importance of starting treatment early. Additionally, there is a test available that predicts the effectiveness of finasteride treatment, which may be more immediately useful.

For women, checking serum ferritin levels can help rule out iron deficiency, thyrotropin levels can be checked to screen for thyroid dysfunction, and free testosterone levels can be measured if there is a suspicion of excessive androgen production. If serum ferritin levels are low, iron supplementation is recommended as it enhances the response to other treatments 14.

PSYCHOLOGICAL IMPACT

The psychosocial impact of AGA can be profound, leading to decreased self-esteem, anxiety, and depression. Studies indicate that individuals with AGA often perceive a significant impact on their quality of life, underscoring the importance of addressing these aspects in clinical practice.

TREATMENT OF ANDROGENICALOPECIA

For the treatment of androgenetic alopecia (AGA), only minoxidil and finasteride are currently approved. These two medications are effective when used together. Additionally, various other drugs are used off-label, and many over-the-counter treatments with unproven claims for hair growth are available.

Minoxidil

Minoxidil (Rogaine®), initially developed as an antihypertensive medication, is now repurposed as a topical treatment for hair loss, available in strengths from 2 percent to 12 percent. Its effects, which include vasodilation, angiogenesis, and enhanced cell proliferation, are likely mediated by potassium channel activation 15. During the first four months of use, potential side effects include contact dermatitis and temporary shedding. Using 5% minoxidil in formulations that do not contain propylene glycol, a possible irritant, can reduce the incidence of pruritus. Additionally, other active ingredients, such as tretinoin, may be used with minoxidil to enhance hair growth 16.

Finasteride

Finasteride (Propecia®) is the most commonly prescribed treatment for male pattern baldness. A daily dose of one milligram of this synthetic type II 5α-reductase inhibitor blocks the conversion of testosterone into DHT, with results typically improving over 6 months to a year17. However, studies indicate that finasteride may increase the risk of unwanted sexual side effects. Finasteride is not approved for use in women due to its potential to harm the development of male embryos. Nevertheless, it is sometimes prescribed off-label to women with androgen-induced female pattern hair loss, often in combination with a reliable oral contraceptive, as small-scale studies suggest it may be beneficial 7.

Dutasteride

Due to safety concerns, Phase III trials for dutasteride (Avodart®), a type I and type II 5α-reductase inhibitor, for treating androgenetic alopecia (AGA) have been suspended. Currently, it is only approved for benign prostatic hyperplasia. Phase II AGA studies demonstrated that dutasteride increased hair growth in a dose-dependent manner, with finasteride 5 mg/day being more effective than dutasteride 2.5 mg/day. Similar side effects to those of finasteride might be expected.

ProstaglandinAnalogues

Prostaglandin F2 analogues, such as latanoprost and bimatoprost, are used to treat ocular hypertension and glaucoma. Several small-scale studies have noted that a significant side effect is increased eyelash growth. Bimatoprost (Latisse®) is now available as the first treatment specifically for enhancing eyelash growth. Recently, research has explored the potential of latanoprost (Xalatan®) to promote scalp hair growth. Results showed that latanoprost could increase hair density and pigmentation compared to the control group and baseline 18.

Ketoconazole

A topical shampoo containing 2 percent ketoconazole (Nizoral®) is available over the counter, unlike higher doses. Ketoconazole, an imidazole anti-fungal drug, effectively treats dermatitis and dandruff. Its impact on the scalp microbiota may help those with follicular inflammation associated with androgenetic alopecia (AGA) 19, 20. Additionally, ketoconazole acts as an anti-androgen and has been shown to promote hair growth in AGA patients through androgen-dependent mechanisms. It is typically used alongside other AGA treatments.

Anti-androgens

Synthetic anti-androgens are commonly used as 5α-reductase inhibitors and androgen receptor blockers. Although a few small studies have investigated the effectiveness of topical anti-androgen medications for androgenetic alopecia (AGA), this approach is not widely used. In treating female pattern hair loss, anti-androgens are often combined with estrogen. Oral anti-androgen treatment is much more common in Europe than in the United States 21.

Estrogens

Women with androgenetic alopecia may benefit from using estrogen, an indirect anti-androgen, in the form of birth control pills. Estrogen increases the production of Sex Hormone Binding Globulin (SHBG), which reduces the bioavailability of androgenic hormones like testosterone. In Europe, topical estrogen medications are also available 22. Research on hair follicle estrogen receptors suggests that topical compounds may promote hair growth both directly and by antagonizing androgen action. However, there are few large clinical studies demonstrating the efficacy of this approach, and topical treatments are not widely available.

LaserTreatment

Hair loss laser and light treatments have gained popularity recently and are also marketed as a preventive measure against androgenetic alopecia (AGA). Numerous companies offer lasers and light sources with different spectral characteristics and suggested applications for these technologies. Some devices are only available in clinics for periodic use and cannot be used at home. The biological mechanism by which laser light wavelengths stimulate hair growth has been demonstrated, but remains unclear. Large-scale, placebo-controlled trials have provided limited clinical data. While lasers may be an option individuals consider, they have not yet become a mainstream treatment choice in dermatological practices 24.

SurgicalTreatment

Hair follicles in the occiput region of the scalp exhibit higher levels of androgen resistance compared to follicles in other areas. This characteristic allows for hair follicles to be transplanted from this region to balding areas, offering a long-lasting solution to androgenetic alopecia (AGA). Hair restoration surgery has significantly evolved since its inception, with many countries offering follicular unit transplantation (FUT) through specialized transplant facilities. The development of follicular unit extraction (FUE) has aimed to reduce scarring from strip graft harvesting. While hand-held motorized graft extraction devices are already in

use, automated hair follicle extraction robots have recently been developed and are now commercially available 25.

Cell MediatedTreatment

Several companies and academic institutions are developing cell-mediated treatments for androgenetic alopecia (AGA). The two main approaches under investigation involve direct injection of cultured cells and the use of cell-released chemicals to stimulate hair growth. Studies indicate that mesenchymal tissue cells present in the scalp can be harvested and utilized to promote the growth of new hair follicles from epithelial tissue. Additionally, injected cells may migrate to nearby hair follicles and contribute to their enlargement 24.

Another approach involves cultivating cells and processing the supernatant to create a hair growth-stimulating treatment rich in Wnt proteins and other hair growth factors. While cell-mediated treatment is still in its early stages, it may become available in the next few years. Platelet-rich plasma (PRP), derived from whole blood, is currently popular in the market. Platelets contain various growth hormones and stimulatory mediators. Some hair transplant surgeons use PRP to promote faster growth of transplanted grafts 26. Additionally, some clinics offer PRP as a standalone treatment for androgenetic alopecia (AGA), although there is limited published research supporting its efficacy 27.

Alternative Treatments

Several supplements available on the market claim to promote hair growth through blends of herbal, vitamin, and mineral ingredients. However, there is a lack of independent studies supporting their efficacy. Popular herbal ingredients found in these supplements include saw palmetto, black cohosh, dong quai, false unicorn, chaste berry, and red clover. Other herbs like saw palmetto (Serenoarepens), black cohosh (Actaearacemosa), dong quai, and angelica sinensis are also common. Herbalists suggest that some of these plants may possess anti-androgenic or estrogenic properties. Additionally, various proprietary compounds, such as biotin, caffeine, melatonin, and copper complexes, are included in these products, each with reported modes of action 28.

CONCLUSION

Niosomes are considered one of the most stable vesicular drug delivery systems. They enhance the therapeutic index of both classic and new medicines by increasing specificity through drug targeting to specific tissues, cells, or intra/intercellular compartments, controlling release kinetics, protecting active agents, or a combination of these mechanisms. Being a colloidal drug carrier, niosomes can target macrophages, enhance intracellular penetration and residency, thus improving therapeutic effectiveness. Studies on treatment therapy have demonstrated that various combinations of niosomes have a greater impact on hair loss than either treatment alone. However, oral administration carries the risk of side effects such as mood swings, gynecomastia, reduced libido, and ejaculation problems. Therefore, the topical method is considered a viable option for delivering medication precisely where it's needed while minimizing the likelihood of adverse effects.

Administering finasteride via focused distribution may help minimize its systemic adverse effects to a greater extent. When a drug encapsulated in niosomes is applied topically to the scalp, it typically causes minimal or no discomfort. Combining medications may result in greater retention of scalp hair because baldness often returns after discontinuing medication therapy. Niosomes act as localized drug depots, releasing active compounds slowly into the skin and its appendages, thereby increasing therapeutic indices and reducing drug toxicity.

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