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ANDROGENIC ALOPECIA: CURRENT PERSPECTIVES & TREATMENTS

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ABSTRACT

Androgenetic alopecia (AGA) is the most common form of hair loss in men and women. Determining factors appear to be genetic predisposition coupled with the presence of sufficient circulating androgens. The prevalence of this condition is high and although there are no serious direct health consequences, the loss of scalp hair can be distressing. Knowledge of the pathogenesis of androgenetic alopecia has increased markedly in recent years. Pre-programmed follicles on the scalp undergo a transformation from long growth (anagen) and short rest (telogen) cycles, to long rest and short growth cycles. This process is coupled with progressive miniaturisation of the follicle. These changes are androgen dependent and predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). Of the many treatments available for androgenetic alopecia, only two (finasteride and minoxidil) have been scientifically shown to be useful in the treatment of hair loss. However, these therapies are variable in their effectiveness. Hair transplantation is the only current successful permanent option, and it requires surgical procedures. Several other medical options, such as antiandrogens, ketoconazole, herbal therapy, Laser and light therapies are reported to be beneficial. Management of expectations is crucial and the aim of therapy, given the current therapeutic options, is to slow or stop disease progression with contentment despite patient expectations of permanent hair regrowth.

KEYWORDS: Androgenetic alopecia, Androgen, Androgen receptor, Dihydrotestosterone, Minoxidil, Finasteride.

INTRODUCTION

Androgenetic alopecia, the most common form of hair loss in men, involves the progressive loss of visible, pigmented terminal hair on the scalp, in response to circulating androgens. It may also occur in women & referred to as female-pattern hair loss in women and male pattern hair loss or common baldness in men.[1] Thinning usually begins between the age of 12 and 40 years in both sexes, and at least 50% of the men by the age of 50 and 50% of women by 60 years are more affected. It is more common in men. The pattern of inheritance is polygeneic.[2]

Androgens are important in regulating hair growth at puberty they increase the size of follicles in beard, chest and limbs and decrease the size of follicle in bitemporal regions which reshapes the hair line in men and women. In susceptible hair follicle of the scalp dihydrotestosterone binds to androgen receptor and this hormone receptor complex then activates the genes responsible for gradual transformation of large terminal follicle to miniaturized follicle. The density of the androgenic receptors in the hair follicles varies according to location and this is genetically determined. Age factors too play an important role in AGA, the first manifestation is usually appearing in the third decade. Further factors are probably involved.[3,4]

PREVALENCE

Approximately 20% of Caucasian men are affected by the age of 20 with incidence increasing 10% per decade. Fifty percent of Caucasian women are affected by age 50. Racial differences are noted with more Caucasian affected than Asian and African races.[5,6]

ETIOLOGY OF AGA

Although the clinical presentation is different in men and women, the underlying cellular processes causing AGA are thought to be similar. AGA is mediated by androgens in both men and women. Androgens are produced in men by the testes and adrenal glands. In women, androgens are produced by the ovaries and adrenal glands.

Androgens produced peripherally by endocrine-sensitive hair follicles and sebaceous glands also contribute significantly to circulating androgens in both men and women.

The androgen dihydrotestosterone (DHT), a potent metabolite of the androgen testosterone (T), causes a gradual, progressive shrinkage in the length and caliber of genetically

programmed hair follicles. This process is called "miniaturization". Miniaturization results from shortening of the anagen phase and a decrease in the size of the dermal papilla and volume of matrix cells. The three phases of the normal hair cycle are shown in Figure 1. Pre-programmed follicles on the scalp progress through long growth (anagen) cycles and short rest (telogen) cycles. With each passage through the hair cycle, the duration of the anagen phase decreases whereas the telogen phase elongates. Because the duration of the anagen phase is the main determinant of hair length, the maximum length of the new anagen hair is shorter than that of its predecessor. Eventually, the anagen phase is so short that the emerging hair does not reach the skin surface and the only testimony to the presence of a functioning follicle is a pore. In addition, the latency period between telogen hair shedding and anagen regrowth becomes longer, leading to a reduction in the number of hairs present on the scalp. The follicular miniaturisation that accompanies these hair-cycle changes is global, affecting the papilla, the matrix and ultimately the hair shaft. The dermal papilla is fundamental to the maintenance of hair growth and is probably the target for androgen-mediated changes in the hair cycle and miniaturisation of the follicle.[7, 8, 9]

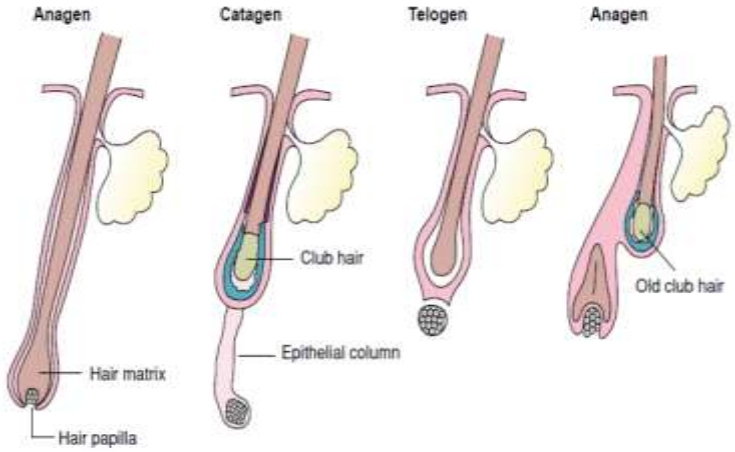

Figure 1. Diagrammatic representation of the scalp hair cycle.

(a) During the normal hair cycle, the active growth phase (anagen) can last from 2 years up to 6 years. This is followed by a short transition phase (catagen), which lasts 1–2 weeks and then by a resting phase (telogen), lasting 5–6 weeks. The hair is then shed, the anagen phase begins again, and a new hair is grown. In the altered hair cycle of the balding scalp (not shown), the phases of the cycle remain unchanged. However, the anagen growth phase becomes shorter and the telogen resting phase becomes longer with each passage through the hair cycle, resulting in diminishing hair length.

These biochemical events occur at the cellular level of the hair follicle. Because the dermal papilla is highly vascularized, it is continuously bathed in circulating androgens. It has been demonstrated that the dermal papilla is rich in androgen receptors and is the primary target of androgen action.[10, 11]

INVOLVEMENT OF ANDROGEN AND THE ANDROGEN RECEPTOR

Testosterone is a lipophilic compound that diffuses the cell membrane. It is irreversibly converted into its more active potent form DHT, by the cytoplasmic enzyme 5- alpha reductase (5-AR). There are two isozymes types of 5-AR. Type-I is found in keratinocytes, fibroblasts, sweat glands and sebocytes while Type – II is found in skin and inner root sheath of hair follicles. Androgens mediate their activities by binding to the human androgen receptor, a member of the steroid-thyroid hormone nuclear receptor superfamily. The structure of the androgen receptor includes a ligand-binding domain and a DNA-binding domain. Both testosterone and DHT can bind to the ligand domain, which activates the DNAbinding domain. The receptor–ligand complex then acts as a transcription factor, regulating the expression of androgen-sensitive genes. Activated genes are transcribed which are believed to stimulate the overlying matrix cells to mediate the androgen effects of miniaturization on the hair follicle.[12,13]

The involvement of androgens in androgenetic alopecia has been established for some time, and is well accepted. Eunuchs, who lack androgens, do not bald. Individuals who lack a functional androgen receptor are androgen insensitive and develop as females; again, these individuals do not bald. Similarly, no baldness is seen in pseudohermaphrodites, who lack 5α-reductase, the enzyme that converts testosterone to the potent androgen DHT.[14]

The concentration of DHT has been shown to be higher in the balding scalp than in the non-balding scalp. In addition, increased concentrations of both 5α-reductase and the androgen receptor have been detected in the balding scalp, suggesting that such changes contribute to hair loss. Although the exact mechanism and genes involved in hair loss are not known with certainty, some of the proposed genes responsible for hair growth(mainly studied in transgenic & knockout mice) are desoglein, activin, epidermal growth factor (EGF), fibroblast growth factor (FGF), lymphoid enhancer factor-1 (LEF-1) and sonic Hedgehock.[15, 16]

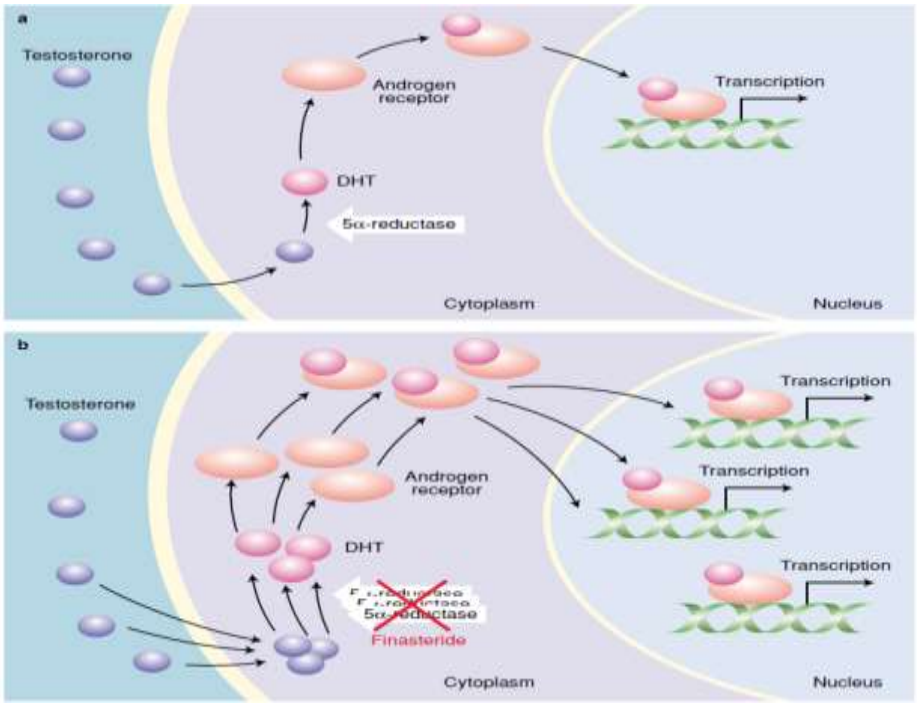

Figure 2. Involvement of androgens and the androgen receptor in male-pattern baldness.

(a) In the nonbalding scalp, testosterone enters the cell and is reduced to 5α-dihydrotestosterone (DHT) by 5α-reductase. DHT binds to the androgen receptor and the complex moves into the nucleus, where transcription control of androgen-dependent genes occurs. (b) In the balding scalp, the concentration of 5α-reductase is increased, resulting in the increased production of DHT. Because the concentration of the androgen receptor also appears to be increased, more complexes are formed between androgen receptors and DHT, augmenting the regulation of androgen-dependent genes in the nucleus.[17, 18]

PATTERNS OF HAIR LOSS

In Men

In men with androgenetic alopecia, the gradual replacement of long, pigmented, terminal hairs on the scalp by short, pale, *vellus* hairs normally occurs in a relatively precise pattern. Hamilton graded this progression from type 1, pre-pubertal scalp with terminal hair on the forehead and all over the scalp, through gradual regression of the frontal hairline and thinning on the vertex, to type VII where the bald areas became fully coalesced to leave hair only around the back and sides of the head. Norwood modified Hamilton's classification, including variations for the middle grades (see Fig. 3); this scale is used extensively during clinical trials.[1, 6, 19]

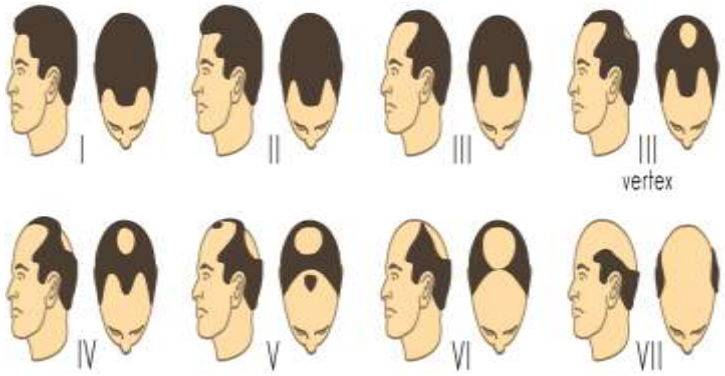

Figure 3. The Norwood–Hamilton scale of malepattern baldness.

The typical pattern of hair loss is divided into seven categories. No hair loss is termed ‘type I’. Minor recession of the frontal hairline is termed ‘type II’. Type III indicates further frontal loss, and is considered ‘cosmetically significant’. The subset of type III, termed ‘III vertex’, shows significant frontal recession coupled with hair loss from the vertex region of the scalp. Types IV–VI show further frontal and vertex loss, culminating in type VII, in which only the occipital scalp region maintains significant amounts of hair.

In Women

Androgenetic alopecia is also reported in women, although androgen involvement is less established. Although women can exhibit the “male” pattern, they usually show a different Ludwig pattern involving a progressive diffuse loss of hair from the crown while retaining the frontal hair line, but frontally and parietally hairs are thin. The density of hair remains the same in the occipital and parietal areas (Figure 4). Exceptionally, a retraction of the fronto-parietal hair line or the formation of a bald spot (as in men) may occur after the menopause. Clinical evaluation of AGA in women uses a three-level classification according to Ludwig.[1, 20]

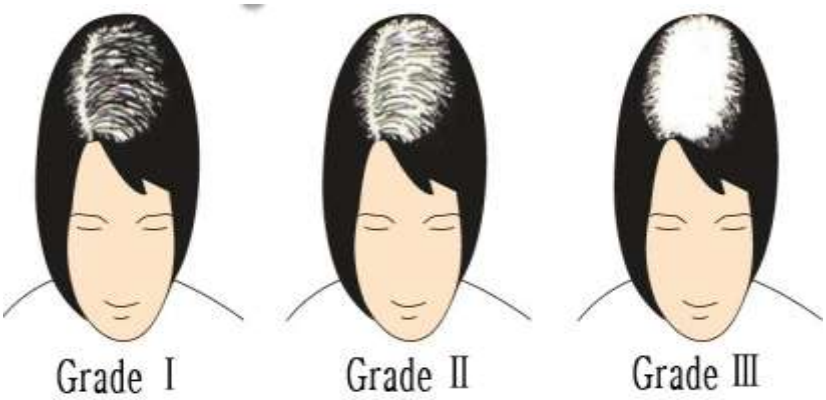

Figure 4. Ludwig Classification Scale for female pattern hair loss.

TREATMENT

Over the centuries, a wide range of remedies have been suggested for androgenetic alopecia and currently treatments include wigs and hairpieces, surgery, hormone action modifiers and non-hormonal therapy. Several of these are based on our understanding of the mechanisms of androgen action within the follicle.

Surgery

The hair follicles on the scalp occiput are relatively androgen resistant. This enables their transplantation to balding areas to provide a permanent treatment for AGA. Significant advances have been made in surgical hair restoration techniques. Follicular unit transplantation (FUT) is widely available from transplant clinics in North America and beyond. More recently, specialized techniques have been developed involving individual hair follicle and unit extraction (FUE) to avoid scarring from strip graft harvesting. Hand held motorized devices are now available for the extraction of grafts and most recently robots capable of automated hair follicle extraction have been developed and are commercially available. Hair transplant costs vary from $5,000 to $20,000 per session and sometimes more depending on the number of grafts and the surgeon. One or two sessions may be required depending on the extent of hair loss. Surgical treatment is limited by the hair density in the donor region and the reluctance of some patients to undergo what is a fairly invasive procedure.[21, 22]

Hormonal Treatments

5α - Reductase Inhibitors

Finasteride, a selective inhibitor of 5α- reductase of type II which reduces conversion of testosterone into DHT, is used for systemic therapy in males. It should be administered for a long period of time (a year at least), at a dosage of 1 mg per day. The level of DHT is reduced in the tissues as well as in the serum and slows hair loss progression and can promote hair growth in young men. Finasteride is more effective in the treatment of vertex type than in the treatment of the frontal type of androgenetic alopecia. Unfortunately, finasteride was not effective in postmenopausal women, and its use in pre-menopausal women is restricted, because 5α-reductase inhibitors may cause malformation of the external genitalia of male fetuses. The effectiveness of the drug has been demonstrated in a number of studies. The cost of the preparation however is a disadvantage. Adverse reactions such as erectile dysfunction,

loss of libido, a small volume of ejaculate or gynecomastia are rather rare. The mentioned side effects are however reversible.[20, 23]

Another promising remedy for AGA is oral administration of dutasteride. Dutasteride is a dual blocker of 5 alpha-reductase type 1 and 2. Although not definitive, a previous clinical trial has suggested an advantage of dutasteride compared with finasteride. However, dutasteride may be a future alternative for AGA cases refractory to oral finasteride therapy.[24]

Anti-Androgens

Blocking the activation of androgen receptors by antiandrogens is a theoretically useful approach, but not really practical because anti-androgens block all androgen actions, with unacceptable side effects on male masculinity and the potential to cause feminisation of a male foetus in a pregnant woman.[25] Hormonal contraception may also be used in the systemic treatment of AGA in childbearing women. The combination of estrogens and progestins with antiandrogen action, i.e. cyproteronacetate, chlormadinonacetate, dienogest and drospirenon should be prefered. In clinical practice the antiandrogen agents which block the DHT from binding to receptors in target tissues, activity of 5-alpha reductase and decrease production of androgens in ovaria, are frequently used. The effect is rather complex as the drugs are acting on various levels. The most potent antiandrogen is cyproteronacetate, which is applied as a preparation containing 2 mg cyproteronacetate + 35 µg ethinylestradiol in fertile women.[26,27] The estrogen component increases the liver production of sex hormone-binding globulin (SHBG) which reduces levels of free serum testosteron.

The combination of estrogen and cyproteronacetate (1 mg cyproteronacetate + 2 mg estradiolvalerate) is used for women who lack estrogens due to natural, premature or castration menopause. During menopause it is possible to administer cyproteronacetate separately, without estrogens. Oestrogen hormones in monotherapy can be used for systemic administration in women, in the form of hormonal replacement therapy, particularly when oestrogen production is reduced, especially during premenopause or menopause. Close cooperation with the gynaecologist is always needed.[28, 29]

Similarly, spironolactone, an aldosterone antagonist with mild anti-androgenic effects, is often used in the USA. Other pharmaceuticals with antiandrogen effects, i.e. ketoconazole or

the non-steroid antiandrogens, cimetidine and flutamide, are not recommended owing to the high risk of adverse reactions.[30]

Non-Hormonal Therapy

Topical and systemic drugs, individually or combined, may be used for the treatment. Minoxidil 2% or 5% solution is the most frequently used drug for topical application. Originally, minoxidil as a peripheral vasodilator was used in the treatment of hypertension. It was noted that systemic administration produced hypertrichosis as one of its side effects. Minoxidil has a specific direct effect on the proliferation and differentiation of follicular keratinocytes which leads to prolongation of the anagen phase.[20] In the case of AGA, topical application is necessary twice a day over a longer period of time. However, the therapeutic effect is usually only temporary. After discontinuing the drug the hair slowly falls out again. In adddition, irritative dermatitis or contact allergic dermatitis are mentioned as adverse reactions. Minoxidil may be combined with tretinoin in 0,025% - 0,05% concentration. The preparations are administered separately, e.g. minoxidil in the morning, tretinoin in the evening or vice versa. The combination of the two pharmaceuticals results in better stimulation of hair growth. However, the risk of an irritative reaction is also higher. A derivative of minoxidil – aminexil, as an antifibrotic agent is to inhibit collagen formation around the hair follicle and to maintain the follicle survival. Aminexil's primary claim is prevention of further hair loss.

The combined preparation containing *the patent RTH 16* molecule, extracted from *Ruscus aculeatus*, a phytotherapeutic agent containing ruscogenins and flavonoids. The RTH 16 molecule stimulates the production of VEGF (vascular endothelial growth factor) in the dermal papilla. Recently, topical antiandrogen fluridil which suppresses androgen receptors in hair follicles has been used. Owing to its lipophilic features it dissolves in the sebum. In environment containing water, it rapidly decomposes into an inactive substance, which lack hormonal effects have acceptable systemic tolerance, and are rapidly eliminated.[31]

Cell Mediated Treatment

Several companies and academic research groups are focused on the development of cell mediated treatments for AGA. Two main approaches are under investigation: the direct injection of cultured cells or the use of cell secreted factors as a hair growth promoting product. It has been shown that cells from the hair follicle mesenchymal tissue can be cultured and then used to induce new hair follicle formation from epithelial tissue. The

injected cells can also migrate to resident hair follicles to increase their size.[21] Alternatively, cells are cultured and the culture supernatant is processed to produce a compound rich in hair growth promoting factors, such as Wnt proteins, for use in treatment. These cell mediated treatment approaches are still in Phase I or II trials, but may be available in a few years. Also of note, currently gaining popularity in the marketplace is platelet rich plasma (PRP) isolated from whole blood. Platelets have multiple growth factors associated with them as well as other potentially stimulatory mediators. Some hair transplant surgeons use this product to encourage transplanted graft growth. PRP is also available from some clinics as a standalone treatment for AGA, though so far there is only one small published study in support of this approach.[32]

Laser Treatment

Laser/light treatment for hair loss has become very popular in the last few years; it has also been promoted as a preventative measure against AGA. Several different manufacturers provide lasers and light sources of varying wavelengths and with different suggested modes of use. While some laser machines are designed for use at home on a daily basis, others are only available through clinics for weekly or monthly use. Whilst there is evidence that laser light can stimulate hair growth at some wavelengths, the biological mechanism by which it occurs has not been defined. While lasers may be options that patients wish to independently explore, so far they have not become a significant treatment approach in most dermatology clinics.[33]

Herbal Therapies

There are many herbal preparations available that have been used to combat hair loss. It is recommended that the use of herbs that have pronounced DHT or 5-α-Reductase blocking activity can be used for the treatment of Alopecia (especially Androgenetic). Some of the more common herbs that patients may take include saw palmetto (*Serenoa repens*), black cohosh (*Actaea racemosa*), dong quai (*Angelica sinensis*), false unicorn (*Chamaelirium luteum*), chaste berry (*Vitex agnus-castus*), red clover (*Trifolium pratense*), *Pygeum africanum, Seneroa repens, Urtica dioic, Camellia sinensis,* and *Panax ginseng* etc. which are claimed to have anti-androgenic or estrogen promoting activity. Other products may contain biotin, caffeine, melatonin, copper complexes, and various proprietary compounds with diverse purported modes of action.[34, 35]

Aromatherapy

Aromatherapy can be used as a supplement to treat alopecia. It uses highly concentrated extracts which are derived from the flowers, leaves, bark and the roots of various plants like *Arnica montana, Cedrus atlantica, Lavandula agustifolia, Oscimum sanctum, Pilocarpus jabarondi, Rosmarinus officinalis, Thyme vulgaris etc.* In aromatherapy, the essential oils enter the body through the olfactory system (inhalation) and/or through your skin. As with herbs that are taken orally, the essential oils reach the circulatory system (the blood) where they bind to receptors and change the chemical composition. These oils work not only on a cellular level to strengthen/calm the nervous system, but also on a spiritual one, providing with a sense of well being. Topical herbal therapy stimulates hair follicles and it is proved as safest way to cope up with different type of hair loss (alopecia), however perfect pharmacological actions of these herbs and oils are yet not known.[34]

Nutritional supplementation

It has been suggested that nutritional supplements with vitamins, minerals, and antioxidants may help in hair growth and health. However, a list of nutrients such as Biotin (Vit. B7), B complex vitamins, Zinc, Copper, Iorn, Vitamin C, E, A and Coenzyme Q10 plays an important role in promoting hair growth and preventing hair loss. Medical practitioners should be familiar with those available so as to avoid potential side effects or drug interactions if employed. Supplementation may be beneficial in combination with evidence-based treatments.[24,34]

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