Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (20) 2014, 59-64

REVIEW ARTICLE

Androgenetic alopecia and its remedies - a review

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Received 14 August 2014; Accepted 18 August 2014

ABSTRACT

Androgenetic alopecia commonly referred to as male and female pattern balding is the slow progressive loss of head hair in a discrete pattern, sometimes to the level of baldness. Androgenetic alopecia and alopecia areata are common disorders of the hair follicle which may heavily influence self esteem and self image. Human hair morphogenesis is a dynamic process caused by the remodeling of the skin. Hair growth is cyclic process; in which the mammals consisting of three distinct stages: an active stage (anagen), a regressive stage (catagen), and a resting stage (telogen). Current drug treatment approaches include the use of regrowth stimulators such as topical minoxidil and oral finasteride for androgenetic alopecia. This paper will focus on diagnosis, pathophysiology, growth cycle and medical treatment of androgenetic alopecia.

Key words: Finasteride, Minoxidil, Baldness, Androgenetic alopecia.

INTRODUCTION:

The skin of almost entire the human body contains hairs. Only the palms of the hands, the soles of the feet and the penis are hairless. Hair is composed of strong structural protein known as keratin. This is the similar variety of protein that create the nails and the outer layer of skin[1].

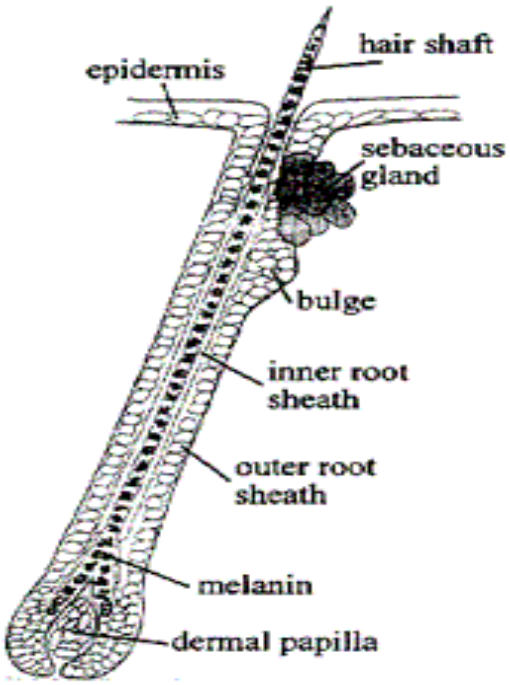

Figure 1: The structure of the hair follicle[1].

The hair follicle is a extremely organized composite biologic system consisting of epithelial components, which include the inner and outer root sheath, hair shaft, and mesenchymal components, namely the dermal papilla, the follicular matrix and connective tissue sheath[13,14].

Hair morphogenesis is dependent upon a series of mesenchymal-epithelial interactions in the embryonic skin[15,16]. In embryogenesis the establishment of a dermal papilla (DP) is vital to the development of all hair follicles and associated modified structures like sebaceous glands. For humans this initial aggregation begins when the embryo is approximately 60 days old[17]. The first hair follicles are formed from the ectoderm, an epithelial layer that will give rise to the epidermis, and the underlying mesoderm, a mesenchymal layer that will form the dermis.[1]

ANDROGENETIC ALOPECIA:

Alopecia (Greek word: Alepekia) means A disease in which the hair falls out.[8] Androgenetic alopecia, common dermatologic condition also known as male and female pattern baldness, affects at least 50% of men by the age of 50 years, and up to 70% of all males in later life[19]. The first signs of AGA may start after puberty.[10]

Androgenetic alopecia (AGA) (synonyms: calvities hippocratica, male pattern baldness, androgenetic effluvium) AGA) is an emotionally distressing and therapeutically frustrating dermatological problem characterized by patterned hair loss. It occurs as a result of progressive miniaturization of scalp hair with changes

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in hair cycle dynamics in genetically predisposed individuals[18]. Androgenetic alopecia is being recognized as a condition with significant effects including severe psychological stresses, depression, negative self image and outside perceptions.[2]

Androgenetic alopecia is caused by the heightened sensitivity of scalp follicles to post-pubertal androgens, particularly dihydrotestosterone. Sawaya and Price[20] showed that androgen receptor protein concentrations, within the outer root sheath and dermal papilla fibroblasts are some 30% greater in the balding frontal follicles than in the nonbalding frontal hair follicles. The resultant increased androgen binding at these receptor sites triggers pronounced effects on follicular physiology.[9]

Androgenetic alopecia has been reported to be a polygenic trait believed to involve several genes for male and female. This process is dependent process on the androgen hormone with continuous miniaturization of hair follicles in both genetically predisposed men and women. Systemically and also in the hair follicle cells, testosterone is changed in the additional active androgen dihydrotestosterone (DHT) by 5 α-reductase enzyme. The androgens bind to androgen receptors (AR) in the hair follicle, which produces a process reducing the anagen phase of the hair cycle. The terminal hair changes in the thinner and shorter vellus hair with time. The density of the androgen receptors (AR) in the hair follicles differs according to place or position, which is genetically determined. Age is also plays an important role in AGA[10].

TYPES OF ALOPECIA:

Table 1: Types of Alopecia[8]

TYPES OF ALOPECIA	
Alopecia adnata	Alopecia pityrodes
Alopecia areata	Alopecia universalis
Alopecia cicatrisata	Alopecia presinilis
Alopecia conginitalis	Alopecia senilis
Alopecia disseminate	Alopecia symptomatic
Alopecia leprotica	Alopecia syphilitica
Alopecia marginalis	Alopecia totalis
Alopecia medicamentosa	Alopecia toxica
Alopecia mucinosa	Alopecia triangularis

THE DIAGNOSIS:

Androgenetic Alopecia is diagnosed primarily on the basis of history and physical examination[21]. Men with a history of progressive hair loss that follows the pattern defined by the Hamilton-Norwood scale are highly likely to have male pattern baldness. Biopsies can be used as diagnostic aids but seldom are required for diagnosis. Histopathologic changes characteristic of male pattern baldness include a progressive increase in the density of vellus hairs (vellus hair shafts are ≤0.03 mm in diameter and thinner than the follicle's inner root sheath), a decrease in the density of terminal hairs (terminal hair shafts are >0.03 mm in diameter and thicker than the follicle's inner root sheath), and a decrease in the ratio of terminal to vellus hair from 7:1 to approximately 2:1.[6] These changes may be observed in the absence of an abnormal total number of hairs per unit area.

Androgenetic alopecia is not considered to be an inflammatory condition; however, superficial perifollicular infiltrate may be present[21]. The differential diagnosis of male pattern baldness includes diffuse alopecia areata recurring, nonscarring hair loss that may be linked with autoimmune disease. Unlike male pattern baldness, alopecia areata typically entails circumscribed and asymmetrical areas of baldness and can involve the eyebrows, face, and other body parts in addition to the scalp. A diagnosis of diffuse alopecia areata is suggested by findings of exclamation-point hairs, pitted nails, and/or a history of periodic regrowth of hair[21]. Alopecia areata, which is a reduced amount of common than male pattern baldness, reportedly affects 1.7% of the US population by the age of 50 years.[6]

Extra differential diagnosis comprise acute and chronic telogen effluvium (ie, excessive shedding of normal club hairs; may be idiopathic or associated with iron deficiency, papulosquamous scalp diseases, or stressors) and early cicatricial alopecia (ie, hair loss arising from the destruction of hair follicles by scarring from processes such as trauma, burns, lupus erythematosus, or lichen planopilaris)[6].

PATHOPHYSIOLOGY OF HAIR LOSS:

Normal hair growth takes place at the level of the hair follicle in a 3-phased cycle:

1. **Anagen,** A 2 to 7 year active growth phase during which hair is produced continuously via the division and growth of specialized keratin-producing epidermal cells that surround a dermal papilla at the base of the hair follicle.
2. **Catagen,** A 1 to 2 week transition and involution phase, In which the hair follicle contracts as a result of apoptosis occurs and the hair bulb ascends near the area of the skin, its result the development of a club shape end to form a club hair (ie, a hair in the resting state).
3. **Telogen,** A 5 to 12 week resting phase during which the old club hair is shack. At the ending of telogen, germinal cells of the hair follicle once again begin to grow to form a new hair bulb, which becomes the source of a new hair[22].

On average, in the normal scalp, at least 90% of hairs are in anagen, 1% is in catagen, and 9% are in telogen[24]. The basis of androgenetic alopecia in men is a progressive decrease in the density of terminal (thick and pigmented) hairs and a concurrent increase in density of vellus (short, fine, nonpigmented) hairs[24]. In effect; terminal hairs are turned off and are transformed into vellus hairs. This result is recognized to miniaturization of the hair follicle, which is linked with a substantial decrease in hair diameter. Miniaturization may happen rapidly in 1 or a few hair cycles[23]. In 1 illustrative study of biopsy specimens from 106 men with male pattern baldness and 44 nonbalding control subjects, the terminal ratio of vellus hairs was 7:1 in the nonbalding scalp compared with 2:1 in the balding scalp[25].

In male pattern baldness, the anagen phase condenses and the telogen phase extends or leftovers the same so that hair length which depends primarily on the duration of anagen decreases. Eventually, the hair does not reach the surface of skin. Also, the time among the telogen stage and the anagen stage lengthens so that the number of scalp hairs decreases[22]. Although the mechanisms of these changes have not been established definately, male pattern baldness is well-known to depend on androgens in particular, the androgen dihydrotestosterone (DHT). Dihydrotestosterone is synthesized from testosterone by 5α-reductase type I and type II, lipophilic enzymes are originates on intracellular (nuclear) membranes. Type II 5α-reductase, expressed in hair follicles and other androgen-dependent tissues such as the prostate gland, shows to be more important than type I in Androgenetic alopecia[6].

Numerous lines of circumstantial proof support of the crucial role of androgens and DHT in particular in Androgenetic alopecia.

Initially, this situation is not observed in eunuchs, who lack androgens; in individual persons who lack functional androgen receptors; or in pseudo hermaphrodites, who lack 5α-reductase. The absence of baldness in those lacking the gene for 5α-reductase type 2 suggests a essential role for Dihydotestosterone (DHT).

Second, the progression of Androgenetic alopecia in men is halted coincident with castration among postpubertal men.[21]

Third, balding scalp contains extreme concentrations of 5α-reductase, DHT, and the androgen receptor.

Finally, hair loss is mitigated or inhibited via finasteride, a medication that prevents the exchange of testosterone to dihydotestosterone by selectively inhibiting the activity of 5α-reductase type II. Although the presence of androgens and a genetic predisposition are necessary for androgenetic alopecia in male and female, a lot about the pathophysiology of this provision remains to be elucidated.

Androgenetic alopecia in men appears to be inherited, but the mode of inheritance is not yet understood. Hypothesized modes of inheritance include a single autosomal dominant gene, a particular couple of sex-linked factors, a dominant gene with amplified or changeable penetrance in men, and polygenic inheritance[21,24]. A family history of Androgenetic alopecia may be present on either side of the family; however, the absence of such a family history does not exclude the diagnosis.

HAIR GROWTH CYCLE:

In mammals including humans, lower portions of hair do not persist but are periodically shed and regrown in a "hair cycle". It is believed that the hair follicle cycle originally evolved as an adaptation to the seasons, which is why mammalian follicles are usually synchronized, leading to seasonal moults. But the human has largely retained hair as a social or secondary sexual characteristic, and individual follicles' cycling is largely asynchronous. The human hair follicle totally regenerates itself every 3-5 years[1].

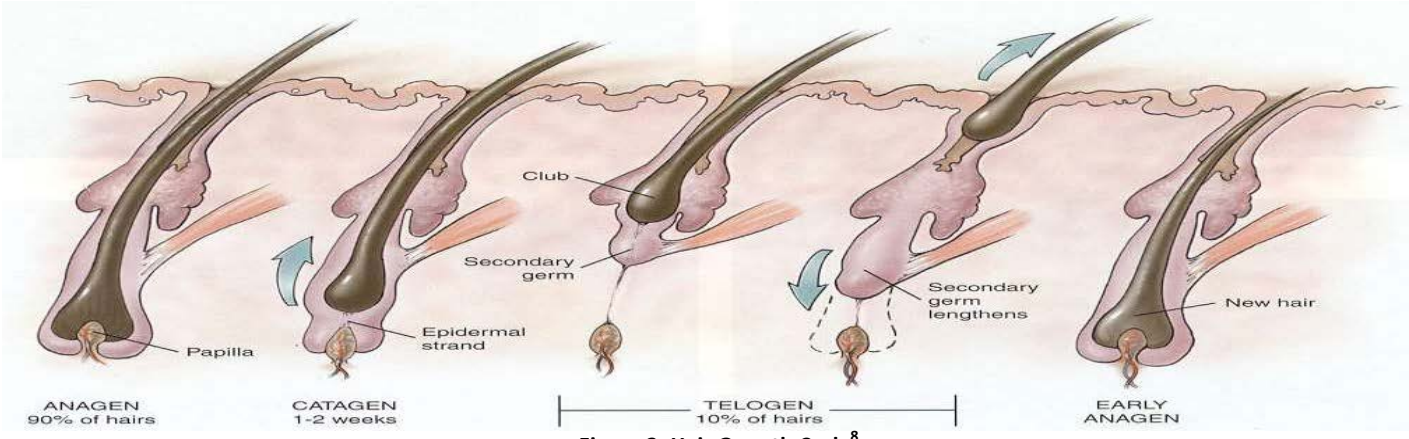

Figure 2: Hair Growth Cycle[8].

An active growth stage is **Anagen** (from the Greek *ana*, again and *genein*, to produce), followed by a regressive, **Catagen**, stage (from the Greek *kata*, down and *genein*, to produce) which gives rise to a resting, **Telogen**, follicle (from the Greek *telos*, end, and *genein*, to produce)[1].

Continuous self-renewal and cycling depend on pluripotent stem cells that reside in the bulge of the hair follicles, a portion of the outer root sheath. At the initiation of a new anagen stage, follicular stem cells shows to act in response to signals from the dermal papilla, and provide increase to the next generation of proliferating matrix cells.

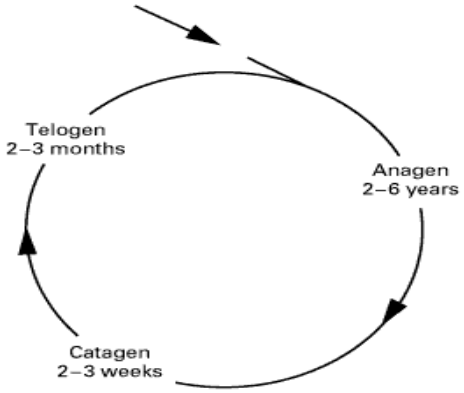

Figure 3: Stages of Hair Growth[8].

Matrix cells undergo lineage restricted differentiation to form the component structure of the hair fiber and its root sheats; during catagen the follicles undergo apoptosis, resulting in the formation of much smaller resting telogen follicles that after activation can again start the anagen phase. In human scalp hairs, the follicle spends some 90 % of the time in anagen[1]. On average, the amount of new scalp hair formation essentially matches the amount that is lost due to shedding (approximately 100/day), thereby maintaining a consistent covering.

MANAGEMENT OR TREATMENT:

Management of Androgenetic alopecia involves obtaining a medical history, performing a physical examination, assessing changes in scalp hair in the context of the age and occupation of the individual, assessing the importance of hair loss to the patient and functioning with the patient to decide the best treatment. Options for managing Androgenetic alopecia in men include doing nothing and accepting the cosmetic outcome pharmacotherapy, cosmetic aids and hair transplantation. It results progressive hair loss and does not improve or reverse without treatment.[6]

The Food and Drug Administration approved pharmacotherapies minoxidil and finasteride are available for treatment of male pattern baldness. These medications, which differ in mechanism of action and route of administration, are given as monotherapy or as combination therapy. These drugs often are prescribed for patients undergoing hair restoration surgery to reduce the amount of transplanted hair required to meet the patient's objectives and to help the patient maintain a relatively consistent and natural appearance. In a randomized study in which 99 patients treated with finasteride or minoxidil were monitored for up to 24 months, both agents appeared to be similarly effective for stopping the progression of Androgenetic alopecia.[26]

Table 2: Compilation of established and proposed treatments for androgenetic alopecia[9]

Drug treatment	Mode of action
Approved by US Food and Drug Administration (US FDA)	
Topical minoxidil (2 or 5%, twice daily)	Multiple mechanisms?
Oral finasteride (1mg, once daily)	Inhibits type II 5α-reductase
Unvalidated/proposed	
Topical minoxidil+penetration enhancers	Enhances delivery of active agent
Topical minoxidil + oral finasteride	Synergism
Topical vesicular minoxidil	Targets delivery of active agent to follicles
Topical finasteride	Inhibits type II 5α-reductase
Antimicrobials	Suppresses follicle inflammation
Herbal products	Induces vasodilation/unknown

MINOXIDIL:

Minoxidil, a pyrimidine derivative (2,4-diamino- 6-piperidinopyrimidine-3-oxide), was the first drug to become available for treating scalp hair loss. It is formerly synthesised for oral use, as an antihypertensive agent. Minoxidil was surprisingly found to induce hair growth in patients. This unexpected side effect led to the development of a topical minoxidil-containing lotion for alopecia treatment. The product is currently available as solutions containing 2% or 5% minoxidil, in formulations composed of 60% ethanol, 20% propylene glycol and 20% water.[9]

The mechanism(s) of minoxidil; promotes hair growth is still not well known, and mixed pathways are may be involved.

One theory proposes that minoxidil, metabolised to minoxidil sulfate in the hair follicles, acts as a potassium channel agonist to reduce the cytoplasmic free Ca2+ concentration. Minoxidil appears to increase the duration of the anagen phase, and its angiogenic effects reverse miniaturization of hair follicles.This prevents epidermal growth factor from inhibiting hair formation. Thus, hair growth is promoted.[9, 12].

Other researchers have documented that minoxidil is a potent activator of prostaglandin endoperoxide synthase-1 (a cytoprotective enzyme that stimulates hair growth)[11]. Immuno cytochemistry and autoradiographic analysis of primate scalp has indicated that minoxidil increases the number of DNA synthesising cells in the dermal papilla, bulbar matrix, outer root sheath and perifollicular fibrocytic cells[9]. These changes result in the prolongation of anagen and the conversion of vellus hairs to terminal hairs.

To maximize efficacy, minoxidil should be applied evenly to the entire affected area of the scalp. Patients should avoid wetting the scalp for at least 1 hour after minoxidil administration to allow the drug sufficient time to be absorbed; also, patients should apply minoxidil before any use of hair gel or hair spray so that absorption is not affected[7]. Minoxidil must be applied daily to maintain effectiveness. If treatment is discontinued over a period of a few months, the scalp appears to revert to the state that it would have been in without pharmacotherapy[6].

Generally, minoxidil is well tolerated with long-term daily use. Adverse events are primarily dermatologic and include irritant contact dermatitis and, less often, allergic contact dermatitis[5]. Transient and self-limiting telogen effluvium may begin approximately 3 to 5 weeks after initiation of treatment. Patients should be informed about the possibility of temporary telogen effluvium and advised to continue treatment should it occur.

FINASTERIDE:

Finasteride is initially introduced in a 5-mg dose for treatment of benign prostatic hyperplasia, finasteride is now marketed in a 1-mg dose for treatment of Androgenetic Alopecia Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of type II, 5-α reductase isoenzyme responsible for converting testosterone to dihydrotestosterone (DTH), the putative hormonal modulator of Androgenetic alopecia in male and female. Finasteride reduces serum and scalp DHT concentrations by approximately 60% to 70%[4]. Finasteride may inhibit or reverse miniaturization of hair follicles as shown by a trend toward improvement in the terminal-to-vellus ratio in a scalp biopsy study.

Finasteride is usually well tolerated. However, there is a small risk of transient impotence as an adverse effect, which is fully reversible upon treatment cessation[3]. Adverse effects could be further reduced if finasteride was applied topically to the affected scalp.

CONCLUSION:

Androgenetic alopecia is common dermatologic condition also known as male and female pattern baldness. Androgenetic alopecia is being recognized as a condition with significant effects including severe psychological stresses, depression, negative self image and outside perceptions. The differential diagnosis of male and female pattern baldness includes diffuse alopecia areata recurrent, nonscarring hair loss that may be associated with autoimmune disease. The US Food and Drug Administration approved hair loss pharmacotherapies the potassium channel opener minoxidil and the dihydrotestosterone synthesis inhibitor finasteride are safe and effective for controlling male and female pattern baldness with long-term daily use. In these days, topical minoxidil and oral finasteride are available as drug treatments for inducing hair regrowth in androgenetic alopecia. In this review, the compilation of established and proposed treatments for androgenetic alopecia is given with the mechanism of action.

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