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An Overview of Current Trends in the Treatment of Androgenetic Alopecia

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ABSTRACT

Androgenetic alopecia (AGA) occurs in men and women, and is characterized by the loss of hair from the scalp in a defined pattern. Determining factors appear to be genetic predisposition coupled with the presence of sufficient circulating androgens. 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. Androgen-dependent processes are predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). DHT-dependent cell functions depend on the availability of weak androgens, their conversion to more potent androgens via the action of 5alpha-reductase. However, these therapies are variable in their effectiveness. Discovery of the involvement of the AR gene, and the identification of other genes contributing to the condition, might lead to the development of new and more effective therapies that target the condition at a more fundamental level. However the advances in the DNA technology and bioinformatics had revealed some information regarding the genetic influence of AGA which will reveal more information in near future and possibly a permanent cure by gene therapy. Surgical procedures such as hair transplantation had advanced to a modified technique follicular unit extraction (FUE) with more patient compliance and acceptability. Over the past several years there has been great interest in the potential role of laser/light-based treatments for male and female pattern hair loss. This article provides an overview of the underlying mechanisms of AGA and the current and developing treatment strategies.

Keywords: Androgenetic alopecia, finasteride, minoxidil, dihydrotestosterone, AR gene.

INTRODUCTION

Alopecia (from Classical Greek , *alōpēx*, meaning "fox") means loss of hair from the head or body. Alopecia can mean baldness, a term generally reserved for pattern alopecia or androgenic alopecia. Androgenetic alopecia occurs in men and women, and is characterized by the loss of hair from the scalp in a defined pattern. Determining factors appear to be genetic predisposition coupled with the presence of sufficient circulating androgens [1]. Symptoms of alopecia include hair loss, skin lesions, and scarring. In male-pattern hair loss, loss and thinning begin at the temples and the crown and either thins out or falls out. Female-pattern hair loss occurs at the frontal and parietal. Although there are no serious direct health consequences, the loss of scalp hair can be distressing . 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. Discovery of the involvement of the AR gene, and the identification of other genes contributing to the condition, might lead to the development of new and more effective therapies that target the condition at a more fundamental level.

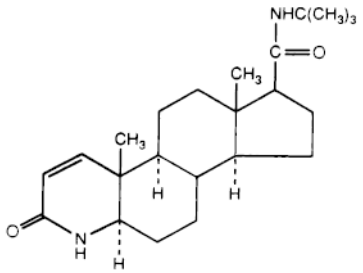
The real cause of hair fall [2] -

- **Hormonal factors**: Hereditary condition is most common cause of hair loss. Hormonal changes and imbalances can also cause temporary hair loss. This could be due to pregnancy, childbirth, discontinuation of birth control pills or the onset of menopause.
- **Medical conditions**: Thyroid problems. Alopecia areata. Scalp infections and other skin disorders
- **Medications**: Hair loss can be caused by drugs used to treat: Cancer, Arthritis, Depression, Heart problems, High blood pressure,
- **Other Conditions**: A physical or emotional shock, Hair-pulling disorder, certain hairstyles

Treatment Strategies -

1. Use of Anti-Androgen Drugs

Finasteride: Finasteride, is a specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5-dihydrotestosterone (DHT). The mechanism of action of finasteride in humans is also based on its preferential inhibition of the Type II isozyme [3]. In 1998 Finasteride becomes the second prescription medication approved by the FDA as a hair loss treatment. It is sold in pill form under the brand name Propecia in US. This medication now makes it possible for men in the early stages of hair loss to keep the hair they have, and even gain back some hair that was recently lost. Eighty-five percent of men stop losing their hair while taking Propecia



Mechanism of Action: Testosterone in males is produced primarily not only in the testicles, but also in the adrenal glands. The majority of testosterone in the body is bound to sex hormone-binding globulin (SHBG), a protein produced in the liver that transports testosterone through the bloodstream, prevents its metabolism, and prolongs its half-life. Once it becomes unbound from SHBG, free testosterone can enter cells throughout the body. In certain tissues, notably the scalp, skin, and prostate, testosterone is converted into 5α-dihydrotestosterone (DHT) by the enzyme5α-reductase [3]. DHT is a more powerful androgen than testosterone. So 5α-reductase can be thought to amplify the androgenic effect of testosterone in the tissues in which it is found. The androgens bind to androgen receptors (AR) in the hair follicle, which triggers a process reducing the anagen phase of the hair cycle. Gradually, over succeeding cycles, the terminal hair converts into a thinner and shorter vellus hair.

Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II 5α-reductase. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5-α reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. The Type II 5-α reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver.

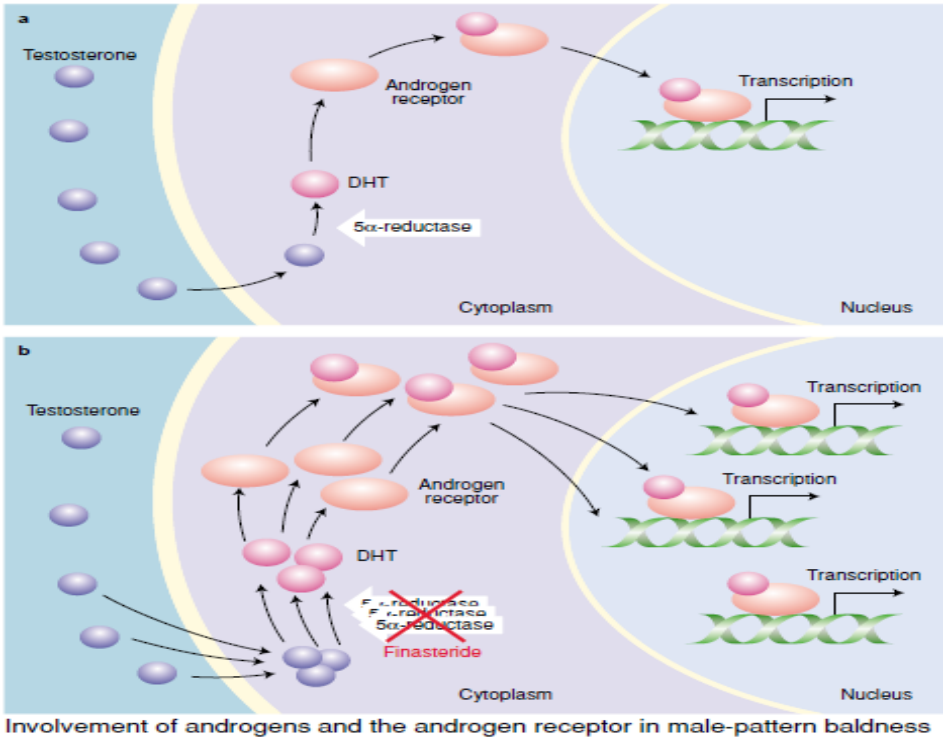


Fig.1: Involvement of androgens and androgen receptor in male pattern baldness.

Finasteride, a 4-azasteroid and analogue of testosterone, works by acting as a potent and specific, competitive inhibitor of one of the two subtypes of 5α-reductase, specifically the typeII isoenzyme[4]. In other words, it binds to the enzyme and prevents endogenous substrates such as testosterone from being metabolized. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed. *In vitro* binding studies that examined finasteride's ability to inhibit either isozyme of 5α-reductase documented a 100-fold selectivity for the human Type II over the Type I isozyme [5].

Indications and Usage: PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in men only. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area. Finasteride has been shown to be most effective in men with enlarged prostates and the most severe symptoms [6] .Finasteride is also approved for the treatment of male-pattern hair loss (androgenetic alopecia) and vertex baldness, and is generally prescribed at a lower dose of 1 mg [7, 8].

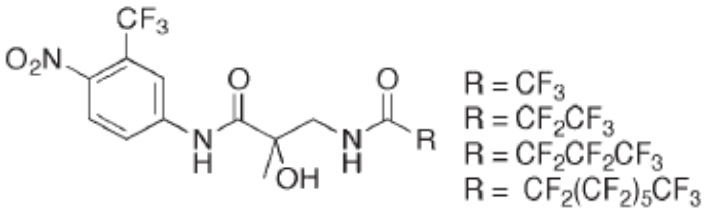
Adverse Effects: Side effects of finasteride include impotence (1.1% to 18.5%), abnormal ejaculation (7.2%), decreased ejaculatory volume (0.9% to 2.8%), abnormal sexual function (2.5%), gynecomastia (2.2%), erectile dysfunction (1.3%), ejaculation disorder (1.2%) and testicular pain.

Finasteride Hair Formulations: Finasteride is lipophilic[9], and development of a liposomal system of finasteride for topical application has been a subject of recent study[10].topical formulations show some effect in the reversal of androgenic effects on hair follicles, as well as in hirsutism[11] . More recent studies have looked at microemulsions and liquid crystalline nanoparticles for topical finasteride delivery. In the latter, addition of glycerol, propylene glycol, and polyethylene glycol 400, increased finasteride permeation, while addition of oleic acid made it decrease. Topical finasteride in combination with topical

minoxidil is more effective than topical minoxidil alone[12]. Topical finasteride gel has been shown as an effective formulation[13].

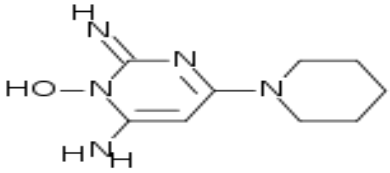
2. Androgen-Receptor Blockers: Although the involvement of the *AR* gene in androgenetic alopecia is a recent finding, the idea of blocking the action of the androgen receptor in an attempt to prevent the action of excess DHT in the scalp is not new. However, androgen-receptor antagonists that act systemically cannot be used to treat men, owing to the potential risks of gynaecomastia (an excessive development of the male mammary glands), feminization and impotence. Therefore, formulations must be developed that block the action of the androgen receptor only in scalp follicles.

Fluridil (topical suppressor of androgenic receptor): Fluridil was developed as a topical antiandrogen, suitable for the treatment of hyper androgenic skin syndromes. The drug belonging to the class of androgen receptor (AR) suppressors contain perfluoroalkyl moieties. The topical antiandrogen fluridil is a safe and effective alternative in the AGA treatment not only in men, but also in women, in whom long-term regular application of fluridil enlarges the hair stem diameter, thus improving the appearance, and arrests the progression of AGA. The product can be used both in monotherapy and in women also in combination with systemic hormonal treatment to potentiate the curative effect.



The cosmetic product Eucapil® containing 2% fluridil in isopropanol was tested in women with AGA in a 9-month open study. A total of 11 females (average age of 35 years) were enrolled into the study. Hair growth was evaluated using phototrichograms. The results after 6 months showed no significant changes, but after 9months there was no AGA progression[14]. Topical fluridil, owing to its hydrophobicity, dissolves in the sebum and blocks AR in the hair follicles. Fluridil in the aqueous environment rapidly decomposes into fragments which lack hormonal effects have acceptable systemic tolerance, and are rapidly eliminated. Neither fluridil nor its decomposition products were detected in the studies involving AGA in humans[15,16].

3. Minoxidil: Chemically, minoxidil is 2, 4-diamino-6-piperidinopyrimidine-3-oxide soluble in water to the extent of approximately 2 mg/ml, is more readily soluble in propylene glycol or ethanol, and is nearly insoluble in acetone, chloroform, or ethyl acetate.



Minoxidil was introduced in the early 1970s as a treatment for hypertension. Hypertrichosis was a common side-effect in those taking minoxidil tablets [17, 18] and included the regrowth of hair in male balding [19].This led to the development of a topical formulation of minoxidil for the treatment of androgenetic alopecia in men and subsequently in women. In 1995 the FDA approves two percent Rogaine lotion as an over-the-counter drug, meaning it can now be sold without a prescription. Generic versions of minoxidil lotion become available in concentrations up to seven percent, and are sold in supermarkets and drugstores. Minoxidil has been shown to stimulate hair growth in males and females with androgenic

alopecia. Minoxidil needs to be applied once or the recommended twice daily. The regrowth can be observed after approximately 4 or more months of use and is variable among patients. Upon discontinuation of treatment with Minoxidil, new hair growth stops and restoration of pretreatment appearance may occur within 3-4 months.

Molecular Mechanism: We have known for over 30 years that minoxidil stimulates hair growth. Yet our understanding of its mechanism of action on the hair follicle is very limited Minoxidil also causes prolongation of anagen and increases hair follicle size. Orally administered minoxidil lowers blood pressure by relaxing vascular smooth muscle through the action of its sulphated metabolite, minoxidil sulphate, as an opener of sarcolemma K^+ ATP channels. There is some evidence that the stimulatory effect of minoxidil on hair growth is also due to the opening of potassium channels by minoxidil sulphate, but this idea has been difficult to prove and to date there has been no clear demonstration that K ATP channels are expressed in the hair follicle. Minoxidil is a potassium channel opener, causing hyperpolarization of cell membranes and it is also a vasodilator. It is speculated that, by widening blood vessels and opening potassium channels, it allows more oxygen, blood and nutrients to the hair follicle. This can also cause follicles in the telogen phase to shed, usually soon to be replaced by new, thicker hairs in a new anagen phase.

Hair Growth Cycle

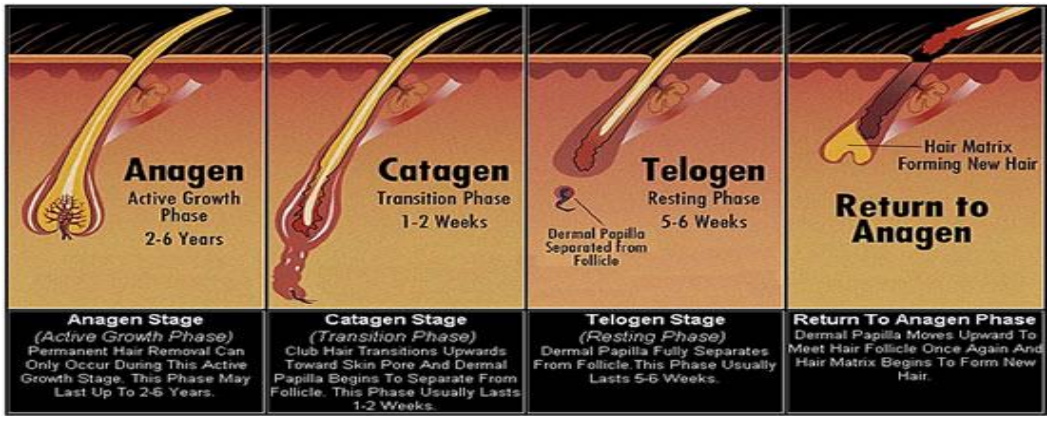


Fig.2: The hair growth cycle is composed by three phases: Anagen= growth phase; Catagen= degradation phase; Telogen= resting phase. Periods of growth (anagen) between two and eight years are followed by a brief period, two to four weeks, in which the follicle is almost totally degraded (catagen). The resting phase (telogen) then begins and lasts two to four months. Shedding of the hair occurs only after the next growth cycle (anagen) begins and a new hair shaft begins to emerge. On an average 50-100 telogen hairs are shed every day.

In male pattern balding (male androgenetic alopecia) there is a gradual reduction in the duration of anagen and a prolongation of the latent period of the hair cycle (the time between shedding of the telogen hair and the onset of the next anagen [20]. Hair follicles also become miniaturized [21]. Minoxidil stimulates hair follicles and growth, but does not reduce Dihydrotestosterone (DHT) or the enzyme responsible for its accumulation around the hair follicle, 5-alpha reductase, which is the primary mediator of male pattern baldness in genetically susceptible individuals. Therefore, when treatment is stopped, the DHT has its expected effect of shrinking and ultimately destroying the genetically predisposed hair follicles.

Side Effects

- **General:** Minoxidil topical is generally well tolerated. Dermatological adverse events are the only side effects reported more commonly.

- **Cardiovascular** Edema, salt and water retention, pericardial effusion, pericarditis, tamponade, tachycardia, and angina have been reported with oral minoxidil. Patients with underlying heart disease may be at increased risk for these or other cardiovascular adverse effects.
- **Local Exacerbation** of hair loss/alopecia has been reported.
- **Dermatologic** Rare cases of generalized hypertrichosis have been associated with topically applied minoxidil. Eczema, irritant dermatitis, and allergic contact dermatitis have also been reported.
- **Hypersensivity** Nonspecific allergic reactions, hives, allergic rhinitis, facial swelling, and sensitivity to minoxidil topical have rarely been reported.

Other Drugs for Treatment

- **Prostaglandin Analogues**

The prostaglandin F2α analogues latanoprost and bimatoprost are used in treating ocular hypertension and glaucoma. A noted side effect was increased eyelash hair growth, a feature that has been investigated in several small scale studies. Bimatoprost is now available as a treatment for eyelash growth. More recently, latanoprost has been investigated for its potential to promote scalp hair growth. Latanoprost significantly increased hair density compared with baseline and placebo and may also encourage pigmentation.

- **Spironolactone**

This medication has been widely used to treat high blood pressure and fluid retention in Australia since the 1960s. It blocks the effect of androgen hormones. In women, androgens can cause oily Skin, acne, unwanted facial and body hair, and scalp hair loss. Spironolactone can be used to treat all of these conditions, but it requires a prescription from your doctor. It is not recommended for men. Pregnant and breastfeeding women should not take spironolactone.

- **Cyproterone acetate**

This medication was also developed in the 1960s. It blocks the effect of androgen hormones. It is also a weak progestogen and is used as a component of some oral contraceptives (the pill). Cyproterone acetate can also be used to treat hereditary hair loss in women and is not recommended for men.

4. Hair Transplantations: Hair transplantation is a common operation especially for men with male pattern baldness. Hair transplantation involves removing a small strip of hair-bearing scalp from the back of the head (occipital area) which is then carefully sliced into tiny micro grafts (1-2 hair the front or top of the head where new hairs are needed the most). A typical 4 to 6 hours hair transplant session allows 800-1200 hair follicles to be successfully transplantated by a team of nurses and doctors under local anesthesia. More than one hair transplantation may be required depending on the density of hair expected. The survival of the successfully transplanted hair usually is longer than adjacent native hair upfront because the transplanted hair follicles behave like the original hairs in the occiput where they are less adversely affected by DHL and will continue to grow for many years.

History and Evolution of Hair Transplantation: Historically, male-pattern baldness (MPB) is the most common indication for hair transplantation. The severity of MPB varies dramatically and can be as mild as minor recession of the hairline or as severe as complete loss of the hair on the superior aspect of the scalp. Genetically determined differences in the sensitivity to dihydrotestosterone (DHT) explain these variations between people. The first description of hair transplantation was actually written by Okuda in Japan in the 1930s. He used hair transplantation to treat burn victims during World War II. In 1950 Norman Orientreich rediscovered the process and successfully performed the first hair transplant in the United States for patients with male pattern baldness(MPB)[22,23]. He proved when "donor" hair from the permanent horseshoe-shaped fringe area on the back and sides of the head was moved to the balding "recipient" area on the top of the scalp that it continued to grow and did not fall out. Donor hair from the fringe area remains insensitive to DHT and this property of donor hair and not local properties in the recipient area that enables transplanted hair to grow. Orientreich called this property "donor dominance" and it is the property that makes hair transplantation possible.

Types of Hair Transplantations

- Standard Punch Grafting
- Combination Mini-Micro Grafting
- Follicular Unit Transplantation.

Standard Punch Grafting: This procedure used large circular grafts (often called "plugs") that were harvested by round punches. Each graft was about the size of a pencil eraser and contained as much as 20 to 30 hairs per graft. Only 50–100 of these grafts were used at a time and they were placed into round recipient sites also created by punches. There were intrinsic problems with this technique that led to unnatural results. First, the large plugs had to be spaced rather far apart due to the constraints of blood supply and this led to the "doll's-head" look commonly associated with transplants of the past. The only way to at least partially resolve this doll's-head appearance was to do multiple procedures in an attempt to fill in the gaps between the plugs. Many patients frustrated and disappointed with the initial results simply did not finish the process.

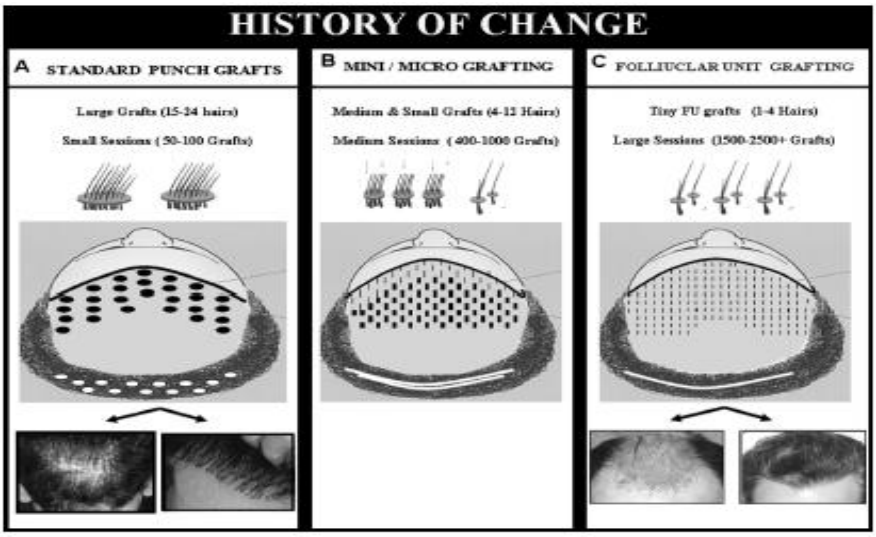


Fig.3: History of change.

(A) Standard punch-graft technique used large grafts (14–24 hairs) with small sessions (50–100 grafts). It created an unnatural look in both donor and recipient area.

(B) Mini-micro grafting used moderate to small size grafts (4–12 hairs) and moderate size sessions (400–1000 grafts). Donor hair was taken as a linear strip.

(C) Follicular unit grafting uses tiny 1–4hair grafts cut under a microscope in larger sessions of 1500–2500 grafts.

Combination Mini-Micro Grafting: In 1995 at United States, micrografting evolves into Follicular Unit Micro grafting and becomes the new state-of-the-art method of hair transplantation. The key to this technique is to identify and preserve the natural clusters of hair follicles from strips of donor tissue, minimizing cutting and risk of damage to the limited supply of donor follicles. The desire to improve naturalness led to the use of smaller grafts. Graft size had been reduced to 4–12 hairs per graft. The decreased vascular trauma associated with these smaller slit incisions enabled a larger number of grafts to be placed closer together in a single session. Procedure size increased to an average of 400 to 800 grafts per session. Donor tissue was no longer harvested with individual round punches but rather from a single strip of donor tissue (a process called strip harvesting). The harvested strip was subsequently divided into individual grafts. This produced less scarring, leaving behind a single linear scar rather than a checkerboard pattern.

Follicular Unit Transplantation : By the mid 1990 follicular unit transplantation (FUT) became the state-of-the-art procedure used in hair transplantation Follicular unit hair transplantation (FUT) is a widely accepted hair restoration surgical technique, with hair roots harvested under magnification, and its application is becoming widespread.

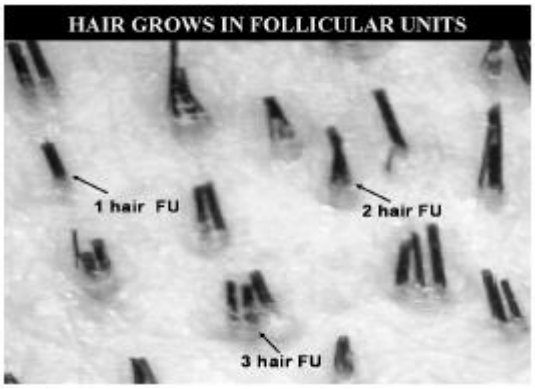


Fig.4

Procedure: Follicular unit transplantation can be divided into 4 major steps:

- donor harvesting
- graft preparation
- recipient site creation
- placing of grafts

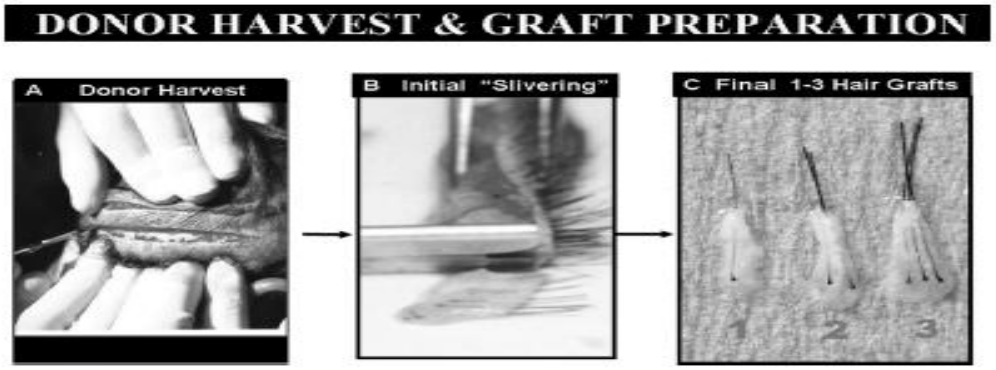


Fig.5: Donor harvest and graft preparation

Step 1: ***Donor harvesting (fig5A):*** The goal of donor harvesting is to remove scalp tissue from the permanent donor area in a way that limits transaction or waste of the hair and as small a scar as possible in the donor area. The donor is taken as a single strip using either a single scalpel or a two-bladed scalpel.

Step 2: ***Graft Preparation (fig5B &C) :*** The harvested donor tissue is converted into grafts in two steps. The first and most critical step is called slivering, during which the donor strip is cut into thin slices or "slivers," each about the width of one follicular unit. It can be visualized as similar to slicing a loaf of bread. It is important to use a dissecting microscope during this step to avoid transection. These slivers are then further dissected into individual 1–4-hair follicular unit grafts. They are placed in cooled saline until they are ready to be placed.

Step 3: ***Creating Recipient Sites:*** While the grafts are being cut, usually by highly trained assistants, the physician is making the recipient site incisions .Recipient site incisions vary in size from 7–1.2 mm wide with the smaller incisions used for the 1–2 hair grafts and the larger incisions used for the larger3–4 hair

grafts or hair that is tightly curled. A number of different instruments can be used to make these incisions. It is important for the physician to test the recipient sites to make sure the grafts fit properly and adjust the size of the blade if necessary. While making the recipient site the physician needs to create a pattern that imitates nature. The incisions also have to enter the scalp at the same angle and direction as normal hair.

Step 4: ***Placing:*** The ability to place grafts successfully is a critical step in the hair transplant procedure. The potential for graft trauma or dehydration occurring at this step is high. Placing large numberof tiny grafts into small incisions without trauma is technically difficult. The standard procedure is to use fine tipped micro-jewelers forceps to grab the graft at their base and then gently slide it into the incision. The use of surgical loops for magnification helps with this step. There is a tendency for grafts to get dehydrated if the process takes too long. Keeping grafts moist is critical as dehydration is probably one of the most common reasons for poor survival during placing.

Novel Techniques of Follicular Unit Extraction

Powdered-follicular unit extraction (P-FUE): Procedure [24]: This technique makes use of an instrument 'Ominigraft' which has been developed to optimize mini- and micro-graft transplantation. Ominigraft consists of three major parts: Hairtome, a pneumatic press device to generate mini- and micro-grafts; a hand-held pneumatic graft implanter; and a hollow-shafted micromotor handpiece used for making holes with a punch blade (0.8–1.25mm in diameter) .

Fig 6: Omnigraft

The patient is placed in a prone position, and local anesthesia is applied[25,26]. Usually tumescence with saline is not necessary for the P-FUE procedure. The 1.0-mm punch blade is attached to the micro motor headpiece, which is basically designed to create the recipient site, and the angle along the direction of the hairs is set .After careful visual adjustment of the direction of longitudinal axis of the hairs in follicular units and punch blade, the punch blade is rotated. The speed of rotations usually 700 to 1,500 rpm but varies with the patient's skin condition. When rotated, the punch blade penetrates the epidermis and dermis. Rotation should be stopped when the punch blade reaches the subcutaneous tissue. At this point, the operator senses a loss of resistance. Over penetration causes hair transection. The first harvested graft and the punch blade are arranged and compared. This is useful in estimating the proper depth of blade insertion. Then the headpiece is removed, the epidermis of the graft is grasped using forceps, and the graft is pulled out gently along the hair axis. The extracted follicular unit has no extra subcutaneous tissue, including fat. This fine grafting makes dense packing of the grafts possible. The P-FUE graft is slender

because it does not include surrounding tissue, which makes suitable for dense packing. After graft harvesting, the patient is changed to a supine position, and the recipient site is prepared in the usual manner with knives and needles. The handpiece of the Ominigraft (fig1A) is also used to create the recipient site. The 0.8-mm punch blade is suitable for this purpose. The graft is then implanted using a pneumatic implanter or forceps. To stop bleeding at the donor site, wound dressing with a bandage is applied overnight. After the overnight dressing, there is no need for wound dressing or any special treatment. Epithelization is completed within a few days after surgery.

Rassman and colleagues proposed the FUE method in 2002.The FU E method has several disadvantages; it is technically demanding, has limited patient candidacy, can result in high rates of follicle transection, has limitations on graft numbers. On the other hand, the FUE method also has many advantages, including faster surgical recovery and less noticeable postoperative scarring. Here we present an interesting case.

5. Laser Light Treatment

Fig 7: Hair Max Laser Comb

In Canada, 1998 a company marketed a laser-light treatment that promises to stop hair loss and stimulate hair. With just two thirty-minute sessions twice-weekly, along with regular use of their own branded shower head filter, shampoo, conditioner, and nutritional supplements, they claim that seventeen of eighteen patients in their study showed absolutely no further signs of hair loss, and fifteen of eighteen people showed signs of new hair growth. Later on a number of products using low-energy laser light beams have been marketed for hair growth. They are available without a prescription and are usually sold directly over the Internet or through late-night infomercials. Most are packaged like a hairbrush or comb which shines red light directly on the scalp while it is used to comb through the hair. Only one such device, called the Hair Max Laser Comb has obtained 510K FDA approval for use as a medical device[27].

Development of Low-Level Laser (Light) Therapy: A few years after the first working laser was invented, Endre Mester in Semmelweis University, Budapest, Hungary decided to test if laser radiation might cause cancer in mice[28]. He shaved the hair off their backs, divided them into two groups and gave a laser treablent with a low powered ruby laser {694-nrn) to one gloup .They did not get cancer and to his surprise the hair on the treated group grew back more quickly than the untreated group. His was the first demonstration of "laser biostimulation". Since then, medical treatment with coherent-light sources (lasers) or noncoherent light (light emifu diodes, LEDs) has passed through its childhood and adolescence. Currently, low-level laser (or light) therapy (LLLT), also known as "cold laser", "soft laser", .biostimulation" or "uphot biomodulation"- is considered

Mechanisms of Laser-Induced Hair Regrowth: The earliest evidence that low-level light therapy (LLLT) could help with hair growth was provided by Hungarian researcher Mester in 1967[29]. He found that by shining a low-powered ruby red laser (694nm) on the backs of shaved mice, he could increase their hair growth. This was the origin of biostimulation ,using ''cold laser'' or ''soft laser'' therapy administered at lower powers of 1 to 500 milliwatts .Since then, basic research has demonstrated that LLLT can improve wound healing, reduce inflammation, and reduce the symptoms of stroke[30,31,32]. Some have proposed that LLLT can enhance the local production of adenosine triphosphate by mitochondria. Indeed, there is evidence that it increases the activity of complexes II and IV in the

mitochondrial respiratory transport chain[33,34,35]. The low-level laser treatment will have an anti-inflammatory effect, thus reducing the inflammation in the hair follicles, and allowing hair re-growth to take place.

Biological Basis for LLLT: It was suggested in 1989 that the mechanism of LLLT at the cellular level was based on the absorption of Monochromatic visible and NIR radiation by components of the cellular respiratory chain[36]. The inner mitochondrial membrane contains 5 complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochiome c (Complex III), cytochrome c oxidase (Complex J), AIP synthase (Complex V) and two freely-diffusible molecules ubiquinone and cylochrome c that shuttle electrons from one complex to the next. The respiratory chain accomplishes the stepwise transfer of electrons from NADH and FADH (produced in the citric acid or krebs cycle) to oxygen molecules to form (with the aid of protons) water molecules harnessing the energy released by this transfer to the pumping of protons (H+) from the matrix to the outer membrane space. The gradient of protons formed across the inner membrane by this process of active transport forms a miniature battery. The protons can flow back down this gradient, re entering the matrix, only through another complex of integral proteins in the inner membrane, the ATP syntheses complex.

Absorption of photons by molecules leads to electronically excited states and consequently can lead to acceleration of electron transfer reactions[37]. More electron transport necessarily leads to increased production of AIP[38] . Light induced increase in ATP synthesis and increased proton gradient leads to an increasing activity of the Na./II* and Ca2*/l antiporters and of all the ATP driven carriers for ions. ATP is the substrate for adenylcyclase, and therefore the AIP level controls the level of cAMP. Both Ca'* and cAMP are very important second messengers. Ca* especially regulates almost every processing the human body (muscle contraction, blood coagulation, signal transfer in nerves, gene expression, etc.).

Sources for LLLT: Laser/light sources appear to be safe and effective in the treatment of male and female pattern hair loss. For many years He/Ne lasers (632.8-nm) were the preferred light source. Light emitting semiconductor diodes (GaAlAs, AlGaInE, InGaAsP etc) are used in both diode lasers and LEDs; the difference is whether the device contains the resonator (as the laser does) or not (LED). These diodes are available in a wide range of wavelengths from 630-nm to 980-nm.

6. Genetics Of Androgenic Alopecia (Aga) And Female Pattern Hair Loss (Fphl) With Implications of Molecular Diagnostic Techniques: Knowledge of the sequence differences between the ***AR* gene** in balding and non-balding men would allow the possibility of gene-therapy techniques that could selectively deliver the non balding *AR* gene to hair follicles, preventing hair loss without any systemic effects. This possibility has been advanced by the development of a topical cream containing liposomes to deliver entrapped DNA selectively to hair follicles in mice[39]. In this study, the *lacZ* reporter gene was successfully targeted to the hair follicles in mice after topical application of the gene entrapped in liposomes, demonstrating the feasibility in the future of the selective and safe targeting to the hair follicles. In addition, the variability in the age of onset and severity of baldness among individuals indicates that it is likely that various numbers and combinations of predisposing genes will be identified. Assuming this proves to be the case, such treatments could be designed on a case-by-case basis to target precisely those genes involved in each individual. AGA and FPHL are associated with strong heritability; however, the exact mode of inheritance of AGA and FPHL remains to be fully elucidated. Twin studies have shown that the development of hair loss is predominately determined by genetic predisposition. However, because of the high prevalence of AGA and FPHL, and the range of severity of the alopecia among affected individuals strongly suggest that this condition is not controlled by 1 gene (single gene traits rarely occur with a frequency 1 in 1000), rather follows a polygenic mode of inheritance[40,41]. Like many polygenic human disorders, the ultimate phenotypic expression of AGA and FPHL is likely dependent on the complex interplay between a number of genes throughout the genome. Each of these genes may contribute variably to the risk of hair loss in one's lifetime and may determine the age of onset, progression, patterning, and severity of the alopecia. The fact that the vast majority of men with premature hair loss

have the predisposing *AR* gene variant suggests that inheriting this variant seems to be a necessary prerequisite for developing AGA. In addition, up to 60% of the genetic predisposition remains unexplained, indicating that there are likely other genes contributing to the risk profile of AGA. In contrast to candidate gene methods, genome-wide genetic studies survey the entire genome in a nonbiased way for evidence of genetic contributions to disease. This methodology identifies genes on the basis of their position in the genome and does not depend on understanding the functionality of those genes. With the recent advent of the genome-wide association studies (GWAS) and in keeping with the purported polygenic transmission of this condition, several other susceptibility loci have been found to be associated with AGA. Prodi et al recently identified a locus near the androgen receptor at Xq11-12 containing the ectodysplasin A2 receptor gene (*EDA2R*), which was found to be independently and strongly associated with AGA[42].

Additionally, a positive gene test result can be found in a high percentage of men_50 years of age who have no evidence of hair loss as well as in the majority of balding men, leading to an uncertain clinical significance of a positive test result and ambiguity regarding whether to initiate treatment. By contrast, a negative test should not change the treatment offered to a patient. Therefore, for young patients concerned about hair loss, this test may have some potential in helping to define the value of early treatment initiation. However, it must be noted that because only a portion of AGA heritability can be explained by *AR* gene variation, testing the *AR* genetic Variation alone does not accurately predict risk for developing AGA. Genetic testing for FPHL risk estimates are currently based on CAG repeat polymorphism in exon 1 of the *AR* gene, and the strength of this association with FPHL risks also uncertain at this time.

CONCLUSIONS

Overall, there are a number of treatment options currently available to people with AGA, though the clinical data supporting their use is often very limited. Today currently, the most effective cosmetic treatments for hair loss are wigs and hairpieces, which work regardless of the cause of the hair loss. Finasteride and minoxidil are still the most common therapeutic drugs prescribed for AGA. The most effective surgical procedure for pattern baldness is follicular unit micrografting. The advances in the DNA technology and bioinformatics had revealed some information regarding the genetic influence of AGA which will reveal more information in near future and possibly a permanent cure by gene therapy. New treatment approaches are under active investigation.

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