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An Analysis on Whether or Not Baldness Can Be Reversed

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Abstract

Many men experiencing hair loss often wonder: is there a cure? Can I get my hair regrown? This thesis addresses these very issues, the anatomy of the pilosebaceous hair, the hair growth cycle, and the suggested causes of male male pattern hair loss are examined. Finally, the Various drugs that have been suggested to reduce hair loss and even cause hair regrowth are reviewed. After examining the various treatments, it can be concluded with reasonable certainty that hair loss can be halted and often reversed by using FDA approved drugs finasteride and minoxidil. Other drugs such as ketoconazole and dutasteride have also demonstrated effectiveness in treating hair loss, however no FDA approval has yet to be issued, either due to lack of evidence demonstrating their efficacy, or due to concerns of negative side effects. The major disadvantage of using hair loss drugs is that one must continuously use the drug to maintain its benefits. It is therefore plausible to conclude that as of yet hair loss cannot be cured, rather its progression can be prevented as long as one uses the drug.

Introduction

Hair loss, known medically as alopecia, is a very common phenomenon, affecting both males and females. Demographically, it effects about half of males and a quarter of females by the age of 50 (Vary , 2015) This makes it very likely we will be affected by hair loss during our lifetime. Hair loss can manifest itself in various forms, the most common being male pattern baldness defined as the progressive loss of hair beginning in some cases at puberty, and proceeding throughout adulthood (Berman, 2015). Another form of hair loss is alopecia areata, an autoimmune condition where the body mistakenly attacks healthy hair follicles. Alopecia areata effects men, women and children with hair loss occurring in the form of patches on the scalp, and in extreme forms, a complete loss of hair (subtype known as alopecia totalis) (Moskowitz , 2014). True, hair loss is not a disease in a sense that it effects our physical wellbeing, however, it is a condition which may cause severe psychological distress, particularly anxiety and depression upon the affected individuals (Hunt, McHale, 2005). These psychological effects, combined with the widespread prevalence of hair loss make it imperative for us to find a cure. In this paper, the primary focus will be on exploring whether or not hair loss can be prevented, and if hair lost hair can be regrown. Since hair loss due to hormonal causes is the most prevalent and studied form, it will be the focus of this paper.

Anatomy of the Hair Follicle

To get a better understanding of the mechanisms responsible for hair loss, it is vital we discuss how hair growth occurs in a healthy individual. In mammals, formation of the hair follicle takes place during fetal skin development. Cells which form the hair follicle, sebaceous and apocrine glands (responsible for producing oils and sweat) are all derived from ectodermal stem cells. In contrast, cells derived from mesodermal stem cells will develop into the follicular dermal papilla and the connective tissue sheath, while the neural crest derived melanocyte progenitors produce the pigmentary cells, which are responsible for the coloring of hair (Fuchs, 2008).

Although hair follicles vary in shape and size, they all have the same basic structure. The base of the follicle known as the papilla, is primarily composed of connective tissue and a capillary loop which supplies nutrients to the hair follicle. Cell division at the papilla is very rare (Pawilna, Ross , & Kaye, 2003).

Superficial to the papilla, lies the hair matrix, the site of hair formation. In mammals the matrix contains trichocytes, the cells responsible for hair production. These epithelial cells produce modified keratin proteins, which contain ample amounts of the amino acid cysteine. Cysteine has a reactive sulfhydryl group which creates both inter and intra-chain linkage within a protein structure, thereby giving hair high tensile strength, and flexibility (Langbein & Schweizer, 2005). Also, contained within the matrix are scattered melanocytes.

Just superficial to the matrix, lies the root sheath. The root sheath is further subdivided into the inner and outer root sheath. The inner sheath contains three different layers, a cuticle layer, Huxley, and Henle's layer. The outer layer contains the bulge, a stem cell rich area which supplies the entire follicle with new stem cells. These stem cells are vital in the healing process of an epidermal wound. Also, contained in the outer sheath is the sebaceous gland, responsible for hair lubrication. In the uppermost region of the outer sheath are the attachment sites of the arrector pili, smooth muscles that serve to help the hair maintain a vertical position (Ma & Yang, 2004). The entire unit consisting of the hair, hair follicle, pili muscles and sebaceous gland is referred to as the pilosebaceous unit (PSU).

Hair Growth Cycle

There are three phases of hair growth, the anagen, catagen, and telogen. The anagen phase is what is known as the growth phase. During this stage the cells in the root divide rapidly. After dividing, the cells produce a new hair that pushes the old hair out of the shaft. At this time, the hair grows approximately 1cm every 28 days. The anagen phase is active for about 2-6 years.

Individuals who have trouble growing their hair to a proper length might have a short anagen phase, whereby their hair falls out to a renewed anagen phase. In contrast, individuals who have the ability to grow their hair exceedingly long are likely have a growth phase lasting very long. It should be noted that auxiliary hair such as that of the eyebrows, eyelashes and arms have a very short growth phase, lasting 30-40 days. This is why we don't have eyelashes that are more than a few millimeters in length.

The catagen phase is a transitional stage, which lasts from two to three weeks. At any given time about 3% of all hair are in this stage. During the catagen stage, hair growth stops, and the outer root sheath shrinks due to its detachment from the nutrient rich capillaries. At this point, a hard, club begins to form at the base of the hair, which is composed of hard keratinized tissue. This club holds the hair in place for as long as three months.

The telogen phase is the resting phase and usually last for about 100 days on the scalp and longer for the hair of the eyebrow, eyelash, arm and leg. During this phase the hair follicle is completely inactive, and the club becomes more solidified. If one pulls out a hair at this stage, a hard, dry and solid root will be visible. In a normal individual, about 25-100 telogen hairs shed each day (Elzouki, et al. ,2012). People with androgenetic alopecia don't have regrowth occurring at the same rate. Typically, the hair loss begins above the temples and vertex of the scalp, and as it progresses, a rim of hair remains at the side and the back of the scalp.

Causes of Male Pattern Baldness

Androgens and their role in hair loss

Androgens (the hormones responsible for the characteristic male appearance) play an important role in some, but not all hair growth. During puberty, the body produces significantly greater amounts of androgens to stimulate male development. One of the more noticeable effects androgens have is on the pilosebaceous units in the pubis, axilla (armpit), and lower face. In these regions, the hair goes from a fine, straight and almost colorless appearance, to a darker, thicker and curlier appearance. Additionally, in the areas of the upper face and trunk, the pilosebaceous units respond to these same androgens, by drastically increasing the size of the sebaceous gland, thereby increasing the amounts of oils they produce (Alonso & Rosenfeld, 2003).

In the male body, the major bioavailable form of androgens is testosterone. Testosterone can also be converted to a similar compound know as dihydrotestosterone (DHT) by the enzyme 5α–reductase, which reduces the 4,5 double bond. DHT has a significantly greater binding affinity and lower dissociation constant with the androgen receptor when compared to testosterone, hence DHT is a lot more potent. In men, approximately 5% of all testosterone molecules get converted by 5α–reductase into DHT (French, et al., 1990).

The importance of DHT in males is clearly demonstrated in individuals who have a deficiency in the 5α–reductase. Such individuals display phenotypical pseudohermaphroditism, a condition where the male genitalia and prostate are underdeveloped, even though they have a genetic makeup of a male (Imperato-McGinleyet al., 1979).

The androgen receptor is a 110kD protein with a ligand bonding domain, a DNA binding domain and two activation function regions that confer transcriptional regulatory activity. When a ligand binds to the androgen receptor in the cytoplasm, it exposes the nuclear localization signal. This allows it to dimerize with another androgen receptor and then be transported to the nucleolus. In the nucleus, the androgen receptor complex binds to a specific region of DNA known as the hormone response element, where it either up-regulates or down-regulates translation of specific genes. The effects of mediation by the androgen receptor complex are highly variable (Alonso & Rosenfeld, 2003).

It is widely believed that DHT is the major cause of baldness. Paradoxically, individuals with a genetic predisposition to baldness have an opposite response in some of their pilosebaceous units. In such individuals, the units in the scalp revert from being thick and darker in color, to being thin and lighter. However, the exact mechanism as to how DHT causes baldness remains to be determined. Furthermore, we have yet to understand why DHT acts in a paradoxical manner when affecting hair growth, creating baldness in some areas while stimulating new hair growth in other areas.

Although no definitive theories exist, Ustuner (2013) has proposed that gravity might play a role in causing baldnesss. He seeks to explain the unique pattern of manifestation in effected individuals by which is hair loss starts at the temples and the vertex of the scalp and proceeds to other areas. Ustuner believes that the weight of the facial tissue, which is supported by the scalp, causes damage to the hair follicles after puberty. During youth, there is sufficient fat tissue under the skin, which acts as a buffer to the hair follicles, and protects them from scalp pressure. However, this buffer gets diminished after puberty. The increase in DHT levels causes the fat layer to becomes increasingly thinner, essentially losing its buffering ability. As a result, pressure in the hair follicles increases causing follicular damage, eventually leading to hair loss. He notes that women have a lower incidence of balding, due to the effect estrogen has on maintaining the subcutaneous fat, thereby preventing baldness until at least menopause (when estrogen levels decrease) (Ustuner, 2013).

Ustuner continues to say that resulting increase in pressure weakens the follicle. To compensate for the increased pressure, the follicle sequesters more DHT more testosterone to make the hair follicle stronger. As a result, the subcutaneous fat layer becomes even thinner, creating a vicious cycle. Ultimately, the hair follicle becomes smaller and smaller, resulting in greater amounts of hair loss. According to this theory, areas in the front of the scalp should have greater pressure, due to greater amounts of soft tissues (the face) pulling down the scalp. This is consistent with the actual pattern observed (Ustuner, 2013).

One should be skeptical about this theory for several reasons. First, Ustuner does not explain the mechanism of how testosterone decreases the subcutaneous fat in the scalp. Even though there is a correlation between an increase in testosterone and its derivatives and a decrease in subcutaneous scalp fat following puberty, it is not proof of causation. Additionally, Ustuner does not address why or how testosterone causes an increase in hair growth in axillary areas (paradoxical effect of DHT).

Prostaglandin D2 and their suspected role in Hair Loss

Recently, there has been a new hypothesis as to what causes baldness. Researchers have found that individuals with androgenetic alopecia have elevated levels of prostaglandin D2 (PGD2) in areas of the scalp that are balding, while not having elevated PGD2 levels in haired areas of the scalp in the same individual. They note that in normal individuals, PGD2 is elevated in the catagen (regression) phase. This alludes to PGD2 having an inhibitory effect on hair, as the catagen phase is the transitional stage where the hair begins the process of falling out (Garza, et al., 2012). Additionally, when researchers targeted prostaglandin synthase (enzyme responsible for prostaglandin synthesis) in transgenic mice, the mice displayed symptoms characteristic of androgenetic alopecia due the increased synthesis of PGD2.

Genetic Factors

Many different genes have been suspected to play a role in hair loss. Thus far, most genetic studies investigating genetic causes have implicated the androgen receptor (AR) gene. This gene lies on the X chromosome, and its biological identifier is Xq11-12 (Ellis , et al., 2001). This is very intriguing, since as we have mentioned above, the most widely accepted cause of male pattern baldness is increased DHT levels. It would therefore be expected that the 5α–reductase gene be responsible for hair loss.

Treatments:

Finasteride (5α–reductase inhibitor)

In accordance with the theory that DHT is responsible for male pattern baldness, a 5α–reductase inhibitor should reduce male pattern baldness. Indeed, finasteride, a 5α–reductase inhibitor, has been one of only two FDA approved drugs used to treat hair loss. The recommended dosage for male pattern hair loss treatment is 1 mg/day taken orally. During trials conducted to determine the efficacy of finasteride in treating male pattern baldness, a placebo controlled study was conducted with 42 healthy participants. The trial demonstrated that administration of finasteride from 0.4 to 100 mg/day for up to 2 weeks significantly reduced the mean serum DHT from a baseline level. The reduction reached a maximum at the 1mg/day dosage. However, the study also found that 14 days after drug withdrawal, DHT returned to baseline levels. (Gormley, et al., 1990). In another study, individuals who were taking 1mg/day finasteride had a mean reduction in DHT of 68.4% versus the placebo (Kaufman , et al., 1998).

In the phase III placebo-controlled studies, the effects of finasteride on hair regrowth was assessed. Three studies were conducted in this phase; all were randomized, double-blinded and placebo controlled, and included 1879 male patients ages 18-41 years. All the individuals reported active shedding of hair at least 3 years prior to volunteering for the study. Hair loss among subjects ranged from mild to moderate. After categorically classifying subject's hair loss based on severity, they were given either a placebo or 1mg/day finasteride for 1 year. To detect whether or not finasteride increased hair growth, a baseline hair count was obtained before and after treatment, using macro-photographs of a 5.1cm2 area of the leading edge of the vertex with hair loss.

After analyzing these photographs, finasteride was found to cause significant progressive increase in hair counts in all areas of the scalp studied (vertex, mid and frontal) during 12 months of treatment. There was an 11% increase in hair count in subjects taking finasteride, compared to a 2.7% reduction in hair count during the same 12-month period in placebo subjects. Subjects taking finasteride for an additional year maintained their hair count, while those on the placebo continued to lose hair. After the 2-year period, 83% of those taking finasteride had no further hair loss, compared to only 28% of those taking the placebo. (Waldstreicher, et al., 1997).

Overall, tolerability was the same for both the placebo and finasteride receiving groups. The only difference was in sexual function disorders which were reported in a higher percentage in the group receiving finasteride. It should be noted that although there was a difference between both groups, the difference was relatively small, 3.8% in the placebo group and 2.1% in the group receiving finasteride. Additionally, of the subjects reporting sexual disorders during therapy, many cases were resolved even though they continued taking finasteride. All subjects who withdrew from the trial due to sexual disorders reported that the problems were resolved after discontinuing

the drug (Waldstreicher, et al., 1997). Based on these studies, it appears that finasteride does indeed reduce hair loss in most men. And since finasteride causes hair regrowth by altering DHT levels, it supports the DHT theory of baldness.

More research has to be carried out to determine whether there is a link between male breast cancer and the use of finasteride, as has been suggested by the UK Medicines and Healthcare Products Regulatory Agency. They have suggested that male breast cancer might be linked to the decrease in the ratio of testosterone to estrogen when taking finasteride. For individuals using finasteride to treat hair loss, this suggestion should be taken with a bit of skepticism, as a majority of cases of male breast cancer was found in males taking the 5mg/day dose as a form of treatment for benign prostatic hyperplasia. In contrast, only a small percentage of prostate cancer was reported in individuals taking the 1mg/day dose suggested for hair loss treatment (Shenoy & Prabhakar, 2010). However, as one must continue using the drug to prevent further loss of hair, there is a need for long term studies of possible side effects.

It should also be noted that non-Caucasian participants appeared to have less regrowth of hair compared to Caucasians. However, one has to be cautious in interpreting this, since only a small portion of the study subjects were non-Caucasian. To definitively state that non-Caucasians experienced less hair regrowth, future studies conducted must include a representative number of non-Caucasian subjects.

Dutasteride

Similar to finasteride, dutasteride is also a 5α–reductase inhibitor, however, dutasteride inhibits not only type II, but also type I forms of 5α–reductase. Scientists don't exactly know the effect type I 5α–reductase inhibitor has on hair loss, since no deficiency has been found for it. However, evidence suggests that dutasteride is three times more potent than finasteride in inhibiting type II, and more than 100 times more potent in type I enzyme. (Clark , et al., 2004). This would suggest that dutasteride would have a greater ability preventing hair loss, and promoting hair regrowth. Indeed, dutasteride has been found to decrease serum levels of DHT by more than 90% when compared to only 70% in finasteride. (Dallob, et al., 1994).

In 2002, the FDA approved dutasteride as a treatment for benign prostatic hyperplasia. Phase trials were also conducted on its use as a treatment for male pattern baldness. During the phase II trails, researchers found increased hair growth on the scalp. They also found that a 2.5mg dosage of dutasteride was more effective than a 5mg dosage of finasteride (Olsen , et al., 2006). However, the phase III trials were put on hold due to concerns of side effects. For this reason, one should be hesitant in using this drug.

Minoxidil (Vasodilator)

Minoxidil, the second of only two drugs the FDA approved for treating hair loss, was initially developed as a treatment for ulcers. When minoxidil was applied to dogs during the trail phase, the ulcers did not improve, however, minoxidil was found to be a strong vasodilator. As a result, the FDA approved minoxidil tablets as a treatment for high blood pressure in 1979 (Conrad , 2008). Initially, when studies on the effectiveness of minoxidil as a vasodilator in humans were conducted, researchers found unexpected hair growth. That is when it occurred to researchers that minoxidil might be an effective treatment for hair loss (Gilmore, et al., 1970)

Although the mechanism of minoxidil's ability to cause hair growth is poorly understood, some theories have been suggested. Minoxidil might increase hair growth by either shortening telogen or prolonging the anagen phase. Others propose that minoxidil is a potassium channel opener. When the potassium channel opens, it causes a hyperpolarization in cell membranes, this widens the blood vessels surrounding the hair follicle, thereby allowing more oxygen and nutrients into the follicle (Goren, et al., 2015).

In the 1980s, studies reported that a 2% topical solution of minoxidil reduced baldness in about 50% of patients. Although the study found that few mature terminal hairs were regrown, the number of fine, non-pigmented villus hairs were reduced. These studies acknowledged that the ideal candidates for minoxidil therapy were those who had been bald for less than five years, and whose baldness was less than 10cm in diameter and located on the vertex. They found that minoxidil was not useful for frontal hair loss. Additionally, patients who discontinued treatment showed a rapid loss of the newly regrown hair. After 3 months of discontinuing therapy, their hair count was below baseline levels (Savin , 1987).

After getting approved by the FDA as a treatment for hair loss in men, minoxidil became available under the name Rogaine, and was obtainable only by prescription. In 1996, Rogaine was approved for over-the-counter sale, and for the production of generic versions. Eventually a 5% topical solution was approved by the FDA (Conrad , 2008).

Two studies have been conducted comparing the 2% versus the 5% solution. One of the studies measured hair mass before and after a two-year period. This study found a greater hair mass in individuals taking the 5% solution. The difference was most apparent early in the study. After taking the 5% solution for five months, these individuals experienced a 55% increase in total hair mass compared to the baseline, while those on the 2% solution only experienced a 25% increase. After the end of the 2-year

period, the 5% group had an increase of 25% over the baseline, while those on the 2% had only 15% (Price, 1996). The second study found that the 5% minoxidil produced a significantly greater amount of non-villus hair by count as compared to the 2% group. They also found that patients using the higher dosage had an increased likelihood of noticing more hair coverage on the scalp in their assessment of treatment benefits (Trancik, 1998).

Generally, minoxidil is well tolerated, however, some side effects have been reported. The most frequent side effect is itching, redness, or irritation of the scalp in the treated area. Unwanted hair growth elsewhere on the body has also been reported. Some individuals reported exacerbation of hair loss after applying minoxidil.

Severe allergic reactions have also been reported including, rash, hives, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue, chest pain, dizziness, fainting, tachycardia, headache, sudden and unexplained weight gain, and swelling of the hands and feet (Rogain Side Effects, 2015). Overall, it seems safe to say that minoxidil is a somewhat effective treatment for male pattern hair loss, however, compared to finasteride, it is less effective but has the advantage of being a topical.

Ketoconazole (anti-fungal)

Ketoconazole, a common anti-fungal shampoo widely used in treating seborrheic dermatitis (dandruff), has also been suggested to contain hair regrowth properties. Recently, a study demonstrated that individuals applying a 2% solution of ketoconazole produced comparable levels of hair growth when compared to those using 2% minoxidil. Both groups achieved greater levels of hair growth compared to those using un-medicated shampoo (Pierard-Franchimont, et al., 1998). Similar results were obtained when treating model mice with androgenetic alopecia with 2% ketoconazole, when compared to the placebo group (Jiang, et al., 2005).

Why ketoconazole causes hair regrowth is not clearly understood. Some have suggested that ketoconazole plays a role in local disruption of the DHT pathway. They have suggested that when used in combination with finasteride, it may have a greater affect in reducing DHT levels compared to using finasteride on its own. (Perez, 2004). Its effect on DHT has been used to explain why some individuals using ketoconazole experience gynecomastia (enlargement of the breasts) (Wolverton , 2002).

Clearly, it seems like ketoconazole has some hair regrowth abilities, however, there is a need for more studies to be carried out to demonstrate how effective it is compared to placebo and other treatments. Additionally, more research needs to be done on the mechanism behind how it causes hair growth. Finally, studies have to demonstrate whether or not using ketoconazole for an extended period of time is safe.

Low-level Light Therapy

Use of a ruby red laser (694nm) , resulted in increased hair growth in mice who had their backs shaved (Mester, et al., 1968). Although light therapy has been shown to effectively reduce inflammation, improve wound healing and reduce stroke symptoms, the mechanism behind it is poorly understood. Some have hypothesized that the light increases levels of ATP synthesis in the mitochondria. There has been evidence that there is an increase in activity in complexes II and V in the electron transport chain (Oron , et al., 2007).

Many light therapies are marketed as treatments for hair loss. Typically, these devices are brushes or combs that have a red light shining out of the tips onto the scalp. Such devices are available for purchase over the counter. So far only one such device has been approved by the FDA as not being harmful, but does attest to its ability to treat hair loss. Such approval is sought after, as using certain wavelengths of light can be harmful.

Companies have capitalized on the little research showing hair regrowth abilities and have produced light therapy devices for consumers, despite the little research that has been conducted to determine the safety and efficacy of it. As a consumer, one must therefore be very skeptical of buying such light therapy devices. More research must be done before anything definitive can be said about using light therapy to treat hair loss.

Discussion

In light of research indicating that drugs can prevent further progression of hair loss, we may effectively conclude that hair loss can be treated. We cannot however conclude that hair loss can be cured, for a cure implies a reversal of a problematic medical phenomenon. Hair loss as of yet cannot be cured because the effectiveness of hair loss drugs is only for as long as they are administered. To find a cure, a definitive theory explaining the causative mechanisms behind hair loss is necessary. Once we understand the mechanism behind hair loss, most certainly a cure will follow.

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