**Chapter 18 – Male Androgenetic Alopecia**

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**18.1 INTRODUCTION**

Male androgenetic alopecia (MAA, Male pattern baldness) is the most common cause of hair loss in men. The hair loss is progressive.  Gradual conversion of terminal hairs into vellus hairs occurs in a highly reproducible pattern, denudes the scalp and leads to baldness. While some degree of androgen dependent hair loss is universal after puberty, the prevalence of alopecia of sufficient severity to warrant a diagnosis of balding increases with advancing age. Twin studies confirm that hair loss is a genetically determined phenomenon. Observational studies in eunuchs have established the androgen dependent nature of this condition.

The morbidity of MAAis predominately psychological, although baldness is a significant risk factor for both melanoma and non-melanoma skin cancer of the scalp.  MAA has a variable psychosocial impact on the affected individual however premature MAA is more likely to cause emotional distress.  MAA is reported to be associated with increased incidence of myocardial infarction, hypertension and hypercholesterolaemia.

Topical minoxidil and finasteride(5 alpha reductase type II inhibitor) are the only FDA approved treatments for MAA. Both agents arrest progression of hair loss and stimulate partial regrowth of hair. Dutasteride (dual 5 alpha reductase I and II inhibitor) is more potent and has been more effective than finasteride in phase II trials but phase III trial data are limited. Hair transplantation is widely practised in the USA and takes advantage of the relative sparing and androgen resistant nature of donor occipital hairs.

New insights into the pathophysiology, genetic basis of MAA and, the role of androgens may help in the discovery of additional treatments for androgenetic alopecia.

**18.1.1 Epidemiology**

Hamilton estimated that 30% to 50% of men developed MAA by the age of 50 (1). Many Western studies have shown that there are racial as well as age-related differences in the incidence and pattern of hair loss in MAA (2).

The incidence and severity of MAA is reported to be more common in Caucasian men than other nationalities. It has been observed that advanced degrees of alopecia are more frequent and develop at an earlier age in Caucasian than in Mongolian populations (3). The onset of MAA in the Japanese occurs one decade later than in Caucasians (4).  Black, Oriental and Native American, African-American men are more likely to have preservation of their frontal hair lines, less extensive and late onset baldness than Caucasians (5-8).  Chinese men are reported to have a lower incidence of MAA and this has been supported by a population study done in Singapore. (9)

Age prevalence of MAA has been documented in different study populations. In Australia a study of 1390 men between the ages of 40 and 69 was conducted to determine the prevalence and risk factors for MAA. The prevalence of vertex or full baldness [Figure 1][ Norwood Hamilton scale] increases with age from 31% [age 40-55] to 53% [age 65-69]. A receding frontal hairline was found in 25% of men aged 40-55 and 31% aged 65-69 (10). A survey done in USA (11) reported a prevalence of moderate or severe MAA of 53% in the age group 40-49. Increased incidence of MAA with aging has also been reported in Korean population with type III-vertex involvement being the most common type in the third to seventh decades (12).  The prevalence of MAA in Singaporean males was reported to be 63%, increasing with age, from 32% at 17-26 years to 100% after 80 years. (9)

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| 5 males final 24th sept |
| **Figure 1.** Androgenetic alopecia patterns in men |

**18.1.2 Psychosocial impact of MAA**

The main significance of hair relates to socialization and hair is an essential part of an individual's self-image. Thus the consequences of MAA are predominantly psychological. Several studies show that the negative self-perception of balding patients appears to be consistent between Western (13, 14) and Asian cultures (15). The negative impact of MAA is often trivialized or ignored by unaffected people (16). However, there is evidence that perception by others may compound the psychological problems suffered by balding men. A Korean study (15) of the perception of balding men by women and non-balding men found that their negative perception of men with MAA was similar to the psychosocial effects reported by the patients themselves. Of note a perception of bald men looking less attractive was found in more than 90% of subjects surveyed. Importantly, this view was more common in women than non-balding men. Such negative perceptions may further impair the social functioning of balding men. It is important to note however, that most affected men cope well with androgenetic alopecia, without significant impact on their psychosocial function. Thus those who do seek help are likely to be in greater emotional distress and have been dissatisfied with any treatment they have received. The most distressed balding men are those with more extensive hair loss, those who have very early onset and those that deem their balding as progressive. (13).

**18.1.3 MAA and disease associations**

The idea that male pattern baldness may be a risk factor for cardiovascular disease was first suggested by Cotton et al. (17). This has been subsequently supported by several other studies (18-21).  However, most of these studies were conducted bynon-dermatologists and no dermatologic expertise was included for confirmationof the accuracy of these studies. These statistically-significant, though weak,associations were discovered in epidemiological, cohort and case control studies. Severe early onset of MAA in subjects before their30s may have a higher risk for ischaemic heart disease. In a recent retrospectivestudy of 22,071 American subjects who had predominantly vertexbalding as opposed to frontal hair loss were shown to be have an increased incidence of myocardial infarction (22). One study revealed that frontal male pattern baldness in young men was associated with an increased serum cholesterol levels and higher blood pressure compared to men of similar age with no hair loss (23).  An increased incidence of hypertension and elevated aldosterone levels also have been found in women with - female pattern hair loss. (24, 25)

An increased incidence in benign prostatic hypertrophy has been associated with MAA (26,27), and MAA could be an early marker of the disease.(28) Prostate cancer has also been found to be positively associated with MAA in various studies (29,30) . A large scale Australian case-control study (30) found that vertex balding was associated with a 50% increase in risk of prostate cancer and 11 year follow up data suggests thatvertex androgenetic alopecia at age of 40 years might be a marker of increased risk of early-onset prostate cancer (31) .A meta-analysis done using Medline and Cochrane data base suggest that increased risk of prostate cancer was seen only in association of vertex baldness and any other pattern seem to have no association. (32). However, associations with high-grade prostate cancer were found in all patterns of MAA, being especially significant in men aged 60-69 years.No clear link between above mentioned diseases and MAA has been found. High androgen levels have been postulated to cause bothMAA as well as atherosclerosis and thrombosis, however some data has shown no association between baldness and established coronary risk factors(33). An association and a pathophysiological mechanism for the link between MAA and prostate cancer also remains to be established but may involve the dual dependence of these conditions on dihydrotestosterone (34).

**18.2  ETIOLOGY**

Genetic factors and androgens play a key role as described by the adjective "androgenetic" in causing hair loss

**18.2.1 Genetics and androgenetic alopecia**

A familial tendency to MAA is well recognized as is the racial variation in the prevalence of balding (35,36). Twin studies identified heredity as accounting for around 80% of the predisposition to baldness(37) . Genetic factors modify the magnitude of the hair follicle response to circulating androgens. Those with a strong predisposition go bald in their teens, while those with a weak predisposition may not go bald until they are in their 60s or 70s. Fewer than 15% of men have little or no baldness by the age of 70 (38).. Osborne in 1916 (39)suggested that the baldness gene behaved in an autosomal dominant manner in men and an autosomal recessive fashion in women. Happle and Küster(40) were unable to demonstrate a bimodal distribution of phenotypes with clearly unaffected and clearly affected individuals as is usually seen in autosomal dominant disorders. In contrast they observed a range of phenotypes for men and women that seem to follow a normal distribution. This, together with the finding that baldness risk increases with the number of affected family members is more consistent with polygenic inheritance. Furthermore, they noted that inherited traits due to single gene defects rarely have an incidence greater that 1:1000, whilst polygenic diseases are much more common, as is the case with androgenetic alopecia. The current concept of it being a polygenic inheritance is supported by an Australian study that examined the frequency of baldness in the fathers of balding men(41). Of the fifty-four father-son relationships, 81.5% of balding sons had fathers who had cosmetically significant balding. This figure greatly exceeded the proportion expected of an autosomal dominant pattern of inheritance. The same authors also described an association of male pattern baldness with a polymorphism of the androgen receptor gene on the X chromosome (42) (41). The androgen receptor gene restriction fragment length polymorphism [RFLP] was found in almost all (98.1%) young bald men, older bald men (92.3%), but only in 77% of non-bald men. This polymorphism appears to be necessary for the development of MAA, but its presence in non-bald men indicates that it is necessary but is not sufficient to cause the phenotype (41). In addition several shorter triplet repeat haplotypes were found in higher frequency in bald men than in normal controls. These RFLP's appear to be associated with a functional variant of the androgen receptor gene. Of note, the androgen receptor gene is located on the X chromosome, which is passed on from mother to a male child. However family studies have shown resemblance of hair loss between fathers and sons which cannot be explained by AR gene mutations alone.

These data suggest that other autosomal genes may also be contributing to the phenotype. Several studies have been done to examine the other candidate genes and chromosomal regions that can contribute to the hair loss.

Genetic association studies of 5 alpha reductase genes SRD5A1 on chromosome 5 and SRD5A2 on chromosome 2, examined using dimorphic intragenic restriction fragment length polymorphisms in 828 families, failed to show an association between these genes and MAA (41). However the role of the 5 alpha reductase enzyme in MAA is evident from its role in themetabolism of testosterone to DHT and the effect of 5 alpha reductase inhibitors in treating hair loss.The cytochrome p450 alpha aromatase enzyme has also been found to contribute to androgenetic alopecia. Aromatase diminishes intrafollicular testosterone by catalysing the conversion of testosterone to estradiol. Differences exist in the expression of aromatase in balding and non-balding scalp (43). Yip L. et al suggests that aromatase gene (CYP19A1) might predispose to hair loss in women (44).  

Hillmer et al sought to identify new susceptibility genes in MAA. In a genome wide scan and fine mapping linkage study performed on 95 families, they found that there is strong evidence for an MAA susceptibility locus on chromosome 3q26 (45). This study could not confirm or rule out the relevance of chromosomes 11q22-q24, 18p11-q22 and 19p13-q13 in causing MAA. Another genome-wide association study done by Hillmer et al found that a highly significant  association  on chromosome 20p11  suggesting that the 20p11 locus has a role in a yet-to-be-identified androgen-independent pathway.(46)  A new susceptibility variants on chromosome 7p21.1 suggest HDAC9 as a new and 3rd candidate gene for male-pattern baldness. (47)

**18.2.1.1 Genetic testing in MAA**

A gene polymorphism-based diagnostic test that will predict the chances of future AGA development is now in the market (48,49).For young patients concerned about hair loss this test may help to define the value of early treatment initiation.

In males, the gene test can predict the chances for [Male Pattern Hair Loss](http://www.drshellyfriedman.com/hair-loss-in-men.html) by reporting the presence or absence of a specific variation in the androgen receptor (AR) gene found on the X chromosome. The variant AR gene causes changes in the hair follicle’s response to dihydrotestosterone, resulting in alterations in the hair growth cycle. A positive test result indicates a 70% chance of developing Male Pattern Hair Loss (MPHL), whereas a negative test result indicates a 70% chance of not developing MPHL. The test is of value as a screening test in predicting the future chances of developing MPHL rather than a confirmatory test.

Recently, a gene test has been developed that is designed to evaluate an individual’s response to finasteridetherapy.The test is based on significant association of specific variations in the androgen receptor (AR) gene and the likelihood that a man will respond to finasteride therapy (49a). The test provide the patient’s CAG repeat length score in the androgen receptor gene and a shorter CAG repeat length (<22) is associated with a greater likelihood that the patient will experience a significant benefit by using finasteride for the treatment of AGA. The genetic test for finasteride response helps in determining if the patient will have a slight, moderate, or great response to finasteride.

**18.2.2 Hormones and androgenetic alopecia**

The role of androgen in male pattern hair loss is well established. American anatomist James Hamilton observed that castrated males did not develop MAA unless they were treated with testosterone (50).

Measurements of serum androgens, testosterone, dihydroepiandrosteronesulphate (DHEA), and free testosterone levels have failed to demonstrate a reproducible difference between cases and controls (51)A study which assessed different hormonal levels in MAA and age-matched controls showed elevated levels of cortisol and androstenedione in the cases (52). This study further suggests a broad range hormone may influence androgenetic alopecia.   Even though scalp hair loss and hirsutism are essential features of hyperandrogenism in women, several investigations failed to demonstrate raised androgen levels in women (53)and therefore it is suggested that normal levels of androgens are sufficient to cause hair loss in genetically susceptible individuals.

The demonstration that eunuchs(54) patients with androgen-insensitivity syndrome (55) and 5 alpha-reductase deficiency (56) do not bald suggests that MAA is induced by activation of follicular androgen receptors by dihydrotestosterone [DHT]. Patients affected by Kennedy's disease, who have a functional abnormality of the androgen receptor gene, have a reduced risk of MAA (57).Increased levels of DHT have been found in balding scalp compared to non-balding scalp. (58).

Intrafollicular androgen over-activity may also be the result of local factors such as an increased number of androgen receptors(59), functional polymorphisms of the androgen receptor, increased local production of DHT, or reduced local degradation of DHT.

Similar to the classical steroidogenic organs, such as gonads and adrenal glands, the skin and its appendages, including hair follicles, sebaceous glands, and eccrine/apocrine glands, are armed with all the necessary enzymes required for androgen synthesis and metabolism. The 5 alpha reductaseenzyme plays a central role through the intrafollicular conversion of testosterone to more active metabolite DHT (60).Dihydrotestosterone binds the androgen receptor with 5 times the avidity of testosterone and is more potent in its ability to cause downstream activation (61).Two 5 alpha reductaseisoenzymes have been characterized, based on their different pH optima and tissue expression patterns (62). Type 1 5 alpha reductase is found immunohistochemically in sebaceous glands, epidermis, eccrine sweat glands, apocrine sweat glands, and hair follicles. In the skin the activity of the type 1 5 alpha reductase is concentrated in sebaceous glands and is significantly higher in sebaceous glands from the face and scalp compared with non acne-prone areas. Northern blot studies reveal an abundance of type 1 mRNA in neonatal foreskin keratinocytes, followed by adult facial sebocytes, and stronger expression in dermal papilla (DP) from occipital hair cells than from beard (63).`It is also found in the liver, adrenals and kidneys. Despite the wide expression pattern of type 1 enzyme, its physiological function is uncertain. The type 2 enzyme has been found by immunohistochemistry to be in the dermal papilla, the inner layer of the outer root sheath, the sebaceous ducts and proximal inner root sheath of scalp hair follicles(64).It is also found in the prostate, testes, and liver. Type 2 5 alpha reductase accounts for about 80% of circulating DHT (61)

However, recent studies done by Hoffmann et al demonstrate  that there are number of other  enzymes involved in the pathogenetic steps leading to androgenetic hair loss. 17 beta- and 3beta- hydroxysteroid dehydrogenases (HSD), with  type 2 5 alpha reductase within the dermal papilla playing a central role by the intrafollicular conversion of testosterone to DHT(65).Fritsch et al suggest that small levels of some isoenzymes found in normal states, may have important implications in disease states. Steroid sulfatase, 3beta-HSD1, 17beta-HSD3, and the type 1 5 alpha reductase are the major steroidogenic enzymes responsible for the formation of potent androgens, whereas 17b-HSD2, 3a-HSD, and aromatase seem to inactivate the excess androgens locally in order to achieve androgen homeostasis in the hair follicles (66).

Human hair follicles, distributed in specific sites of the body, appear to have an inherited susceptibility for androgen-dependent growth which starts during puberty. Depending on the body sites, androgens have paradoxically different effects on human hair follicles. Androgens stimulate hair growth in some sites such as the beard, axillary, and pubic areas and suppress the growth of frontal scalp hair of genetically disposed individuals. Itami et al proposed that the second messenger system determines whether androgen sensitive follicles will respond to androgens by either miniaturization or enhancement.(67) Androgen stimulation of cultured beard dermal papilla cells (DPC) lead to increased transcription of insulin like growth factor (IGF-1) and enhanced growth of co-cultured keratinocytes.  Androgen stimulation of DPC derived from balding scalp lead to suppression of growth of co-cultured keratinocytes.  This growth suppression of keratinocytes was mediated by transforming growth factor-beta1 (TGF-beta 1) derived from DPC from men with MAA, suggesting that TGF-beta1 is a paracrine mediator for MAA (68).Beard dermal papilla cells are known to secrete growth-inducing autocrine growth factors in response to testosterone, leading to an increase in dermal papilla size and enlargement of the hair follicle and hair cortex.  Insulin-like growth factor-1 has been identified as a major component of secreted cytokines (69)

Hair loss on the scalp progresses in an orderly and reproducible pattern, and is a function of factors intrinsic to each hair follicle. In vitro experiments have shown that the hair follicles are able to self-regulate their response to androgens by regulating the expression of 5alpha-reductase and androgen receptors (70,71,72) This self regulation is postulated to produce the quantifiable difference in androgen receptor numbers (70,73)   and  5 alpha reductase activity(71,74) that is observed between balding and non-balding areas of the scalp. This intrinsic regulation is best demonstrated in hair transplantation experiments: occipital hairs maintain their resistance to MAA when transplanted to the vertex, and scalp hairs from the vertex transplanted to the forearm miniaturise at the same pace as hairs neighbouring the donor site (75)

**18.3 PATHOPHYSIOLOGY**

Large terminal hairs are shed and replaced by small vellus hairs in androgenetic alopecia.  Three areas of the scalp are affected preferentially: the temples, vertex scalp and mid frontal scalp.[Figure 2]  Within these areas the process is strictly patterned.  Bitemporal hair loss starts at the anterior hair line and moves posteriorly over the scalp.  Hair loss over the vertex scalp begins centrally and radiates outwards circumferentially.   Over the mid frontal scalp hair follicle miniaturization leads to a pattern of hair loss reminiscent of a Christmas tree (76). These three zones are not affected equally leading to clinical variations in the pattern of hair loss with some men balding more to the front while other bald more over the crown.

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| http://www.endotext.org/male/male18/figures/figure2.png |
| **Figure 2.**Areas of the scalp. F-Frontal / M - Mid frontal / T-Temple / V-Vertex |

The 3 key features of MAA are alteration of hair cycle dynamics, follicular miniaturization and inflammation.

**18.3.1 Hair cycle dynamics and androgenetic alopecia**

Hair is lost and replaced cyclically.  Follicles undergo corresponding cyclic phases of growth, involution, quiescence and regeneration. (Figure 3) The growth phase (anagen) last for 3-5 years.(77)As hair elongation is relatively constant at 1 cm per month, the duration of the growth phase is the primary  determinant of the final hair length. At the end of anagen the involutional phase is known as catagenlasts for few weeks. The period of hair follicle quiescence that follows catagen and lasts approximately 3 months is known as telogen(78)Hair follicle regeneration occurs in the first week or so of anagen, and  once regenerated, the anagen phase continues until the hair reaches its final (possibly predetermined) length.

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| http://www.endotext.org/male/male18/figures/figure3.png |
| **Figure 3.**Normal hair cycle- Each telogen hair is replaced by a new anagen hair |

Hair cycle in mammals has an intrinsic rhythmic behaviour and this is modified by systemic and local factors. Humans have an asynchronous hair cycle and the duration of anagen and the final length of hair differ between regions of the body. A number of molecular signals including growth factors, nuclear receptors, cytokines and intracellular signalling pathways are involved in controlling the hair cycle. Growth factors such as insulin like growth factor (IGF-1), hepatocyte growth factor, keratinocyte growth factor and vascular endothelial growth factor (VEGF) promote anagen phase of the hair cycle. Similarly transforming growth factor-β (TGF β), interleukin 1-α, tumor necrosis factor -α promote onset of catagen. (78)

In androgenetic alopecia, the duration of anagen decreases with each cycle, whilst the length of telogen remains constant or is prolonged. This results in a reduction of the anagen to telogen ratio(79).Balding patients often describe periods of excessive hair shedding, most noticeable whilst combing or washing. This is due to the relative increase in numbers of follicles in telogen. As the hair growth rate remains relatively constant the duration of anagen growth determines hair length. Thus, with each successively foreshortened hair cycle, the length of each hair shaft is reduced. Ultimately, anagen duration becomes so short that the growing hair fails to achieve sufficient length to reach the surface of the skin, leaving an empty follicular pore. Prolongation of the kenegen phase, the lag phase or the delayed replacement of telogen hair(80) seems to last longer in MAA leaving a higher percentage of empty hair follicles contributing to balding.(81) Further,  the kenegen or the latent phase is prolonged in MAA, reducing hair numbers contributing to the balding process(82)

In MAA tiny, pale hairs gradually replace large, pigmented ones. Androgens appear to reduce alopecia hair colour by inhibiting dermal papilla stem cell factor (SCF) production which is important in embryonic melanocyte migration and bulbar melanocyte pigmentation. (83)

**18.3.2 Hair follicle miniaturization**

Hair follicles consist of mesenchymal and ectodermal components. The ectodermal part consists of an invagination of epidermis into the dermis and subcutaneous fat. The hair bulb contains the hair matrix which produces the hair shaft. The mesenchymal component is the dermal papilla, a small collection of specialised fibroblasts that is totally surrounded by the hair bulb.

In association with the changes in hair cycle dynamics, there is progressive, stepwise miniaturization of the entire follicular apparatus  in MAA (**Figure 4**).The mesenchyme-derived dermal papilla, located in the middle of the hair bulb at the follicle base, regulates many aspects of the epithelial follicle and determines the type of hair produced.(84,85) As the dermal papilla is central in the maintenance and control of hair growth, it is likely to be the target of androgen-mediated events leading to miniaturization and hair cycle changes (86,87,88) The constant geometric relationship between the dermal papilla size and the size of the hair matrix (89) suggests that the size of the dermal papilla determines the size of the hair bulb and ultimately the hair shaft produced (90) .

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| http://www.endotext.org/male/male18/figures/figure4.png |
| **Figure 4.**Progressive miniaturization of hair in each cycle |

A greater than tenfold reduction in overall cell numbers is likely to account for the decrease in hair follicular size (91) The mechanism by which this decrease occurs is unexplained, and may be the result of either apoptotic cell death, decreased proliferation of keratinocytes (92) cell displacement with loss of cellular adhesion leading to dermal papilla fibroblasts dropping off into the dermis, or migration of dermal papilla cells into the dermal sheath associated with the outer root sheath of the hair follicle (90) In vitro studies demonstrate that human balding dermal papilla cells secrete inhibitory factors which affect the growth of both human and rodent dermal papilla cells and factors which delay the onset of anagen in mice in vivo. These inhibitory factor(s) probably cause the formation of smaller dermal papillae and smaller hairs in male pattern baldness.(93) Insulin-like growth factor binding protein 3 (IGFBP3) has demonstrated an antagonistic effect on keratinocyte proliferation in the hair follicle in transgenic mice studies(94).

Smaller follicles result in finer hairs. The calibre of hair shafts reduces from 0.08mm to less than 0.06mm. On the balding scalp, transitional indeterminate hairs represent the bridge between full-sized and miniaturised terminal hairs(95). Traditional models of MAA show follicular miniaturization occurring in a stepwise fashion. This has recently been contested, and it is now believed that the transition from terminal to vellus hair occurs as an abrupt, large step process (96). Either way the cross-sectional area of individual hair shafts remains constant throughout fully developed anagen(95), indicating that the hair follicle, and its dermal papilla, remain the same size. Therefore follicular miniaturization occurs between anagen cycles rather than within the anagen. This short window of androgen effect may also explain the lengthy delay experienced between clinical response and the commencement of therapy, as any pharmacological intervention will only have effect at the point of miniaturization(95).

Follicular miniaturization leaves behind stellae as dermal remnants of the full sized follicle. These stellae, also known as fibrous tracts or streamers, extend from the subcutaneous tissue up the old follicular tract to the miniaturized hair and mark the formal position of the original terminal follicle (97). Arao-Perkins bodies may be seen with elastic stains within the follicular stellae. An Arao-Perkins body begins as a small cluster of elastic fibres in the neck of the dermal papilla. These clump in catagen and remain situated at the lowest point of origin of the follicular stellae. With the progressive shortening of anagen hair seen in androgenetic alopecia, multiple elastic clumps may be found in a stella, like the rungs of a ladder (98).

In addition to the hair follicle miniaturization that leads to thin fibres in androgenetic alopecia, a reduction in anagen duration leads to shorter hair length, while an increase in telogen duration delays regeneration. This results in hairs so short and fine that they fail to achieve sufficient length to reach the surface of the scalp.

While miniaturized hairs are also seen in alopecia areata, that condition is potentially fully treatment reversible.  In contrast, MAA is only partially reversible at its best. The mechanism for the difference may be related to the attachment of arrectorpili muscle and the hair follicle which will be discussed later in this chapter.

**18.3.2.1 Pattern of hair loss**

There are 2 concurrent patterns in the hair loss; a macroscopic pattern and a microscopic pattern. The macroscopic pattern of hair loss is highly reproducible with certain zones of the scalp being affected preferentially.  This is best seen over the vertex scalp where the baldness begins at a central focus and hair loss progresses radially in all directions.  There are no-skip lesions. Hair transplantation studies have demonstrated that this pattern is not due to a local signal or a diffusible chemical but rather genetically imprinted in the follicle.  The orderly and systematic progression of hair loss is retained even when follicles are relocated to distant sites.

The microscopic pattern of hair loss refers to the pattern of hair loss within scalp follicular units. (99) In contrast to beard hairs, scalp hairs exist as compound follicles with between 2 and 5 hairs emerging from a single pore.  Miniaturization within these follicular units is also ordered and leads to a reduction in the number of terminal hairs per follicular unit which can be demonstrated by using a dermatoscope. ( **Figure 5**). This is perceived by the affected individual as a loss of hair volume.  When all the hairs within a follicular unit have miniaturized, additional denuded scalp is visible and perceived by affected individuals as baldness

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| http://www.endotext.org/male/male18/figures/figure5.png |
| **Figure 5.**Dermatoscopic  images of scalp in different stages  of alopecia   1. Normal scalp with 2-4  hairs in most follicular units 2. Early androgenetic alopecia with mixture of multiple  and single hair in follicular units 3. Advanced androgenetic alopecia with  thin and single hair in most follicular units |

**18.3.3 Inflammation**

Studies suggest that inflammation is a feature in MAA even though its significance in the pathogenesis of the disease is controversial. Activated T-cells infiltratingabout the lower portions of follicular infundibula have been demonstrated in scalp biopsies (100). A moderate perifollicular, lymphohistiocytic infiltrate, perhaps with concentric layers of perifollicular collagen deposition, is present in some 40% of cases of androgenetic alopecia, but only 10% of normal controls (97) Occasional eosinophils and mast cells can be seen. The cellular inflammatory changes also occur around lower follicles in some cases and occasionally involve follicular stellae. A considerable difference in the inflammatory infiltrate has been observed between balding and non-balding scalp(101)

A modest degree of chronic inflammation around the upper part of hair follicles has been well described by many investigators. (98,101,105)

**18.3.4 Scarring**

The possibility of slow inflammatory  scarring process has been suggested by the irreversibility of the hair loss,  the histological evidence of fibrous tracts and the histological similarity seen between MAA and lichen planopilaris (102).

**18.4. Histopathology**

Histological diagnosis is rarely necessary for male androgenetic alopecia. In patients where the diagnosis is equivocal, 4mm punch vertex scalp biopsies are the ideal specimen. Horizontal scalp biopsies have more diagnostic information than vertical biopsies.(103) Triple horizontal biopsies have showed  98% diagnostic accuracy compared with 79% in a single biopsy in female androgenetic alopecia.(104)

The prime feature found in scalp biopsies is the reduction in the terminal anagen hair count. The apparent reduction in the number of terminal hairs is due to progressive replacement of terminal hairs with secondary pseudo-vellus hairs with residual angiofibrotic tracts (105). There is a change in the ratio of terminal to vellus hairs from greater than 6:1to less than 4:1.   Also, the anagen to telogen hair ratio reduces from 12:1 to 5:1.(97)

Messenger et al reported that there is an increase in vellus follicle numbers with increasing severity of hair loss in women with FPHL, suggesting that terminal follicles do indeed miniaturize(106).

Considering that hair follicle miniaturization is the key point during androgenic alopecia onset and development, diversity in hair diameter represents an important feature histologically reflecting the different stages of miniaturization  and this accurately correlates with the clinical  hair diameter diversity(107).

**18.4.1 Arrectorpili muscle and androgenetic alopecia**

Hair exist as follicular units consisting of 3-5 terminal hair per follicular unit nourished by a single arborizing arrectorpili muscle that attaches circumferentially around the primary follicle with variable attachment to other follicles. (99)(93) A study done by Yazabadi et al demonstrate that in MPHL and FPHL, where follicle miniaturization is either irreversible or only partially reversible, there was a consistent loss of attachment of the APM to vellus hair follicles(Figure 6).. This was in contrast to potentially reversible AA, in which the APM maintained contact with the miniaturized secondary vellusfollicles( Figure 7a,b). The study suggests that the persisting contact between the APM and follicular unit predicts reversibility of miniaturization. (108)

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| http://www.endotext.org/male/male18/figures/figure6.png |
| **Figure 6.**(a,b,c,d,e)   Illustrations showing the progressive miniaturization within the follicular units and the detachment with the arrectorpili muscle |

**18.5 CLINICAL SYNDROME**

The clinical appearance of male MAA is universally and instantly recognizable in most cases. The progression of the hair loss occurs in an orderly manner and has been well documented by Hamilton(109) and Norwood(110) [**Figure 8].** A modified grading scale for MPHL is used by the authors [**Figure 9**]. Affected hairs are miniaturized and there is decreased hair density. Progressive replacement of terminal hairs by vellus hairs leads to an overall decrease in hair density in affected zones as a precursor to total baldness. The scalp is generally normal and periods of increased hair shedding may be accompanied by a positive hair pull on examination. A family history of MAA on either side of the family is seen in around 80% while in 20% of cases, there is no family history.

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| http://www.endotext.org/male/male18/figures/figure7.png |
| **Figure 8.**The  Hamilton-Norwood classification of male androgenetic Alopecia |

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| **http://www.endotext.org/male/male18/figures/figure8.png** |
| **Figure 9.**Modified MPHL grading scale |

**18.6. MANAGEMENT**

A number of options are available to balding men. Firstly, as the condition is not life threatening and the morbidity are variable, a reasonable option is to have no treatment and allow the balding to progress naturally. In fact, this is what the vast majority of men elect to do. Regardless of whether or not patients pursue treatment, an adequate explanation of the pathogenesis of the disease, how common it is in the community and the various treatment options available form an important part of the support and counseling that should occur with each patient. It is very important to ascertain whether patients' expectations regarding treatment outcome are achievable before embarking on medical therapy. Patients should also be educated about the advantage of early treatment and the necessity of prolong therapy.

**18.6.1 Camouflage and wigs**

Camouflage is the simplest, easiest way to deal with mild degree of MAA. Changing the hair styling to cover the balding scalp, adding small fibres held in place electrostatically and dyeing the scalp the same colour as hair are important and cheap measures that can also be easily done. Modern wigs can be styled, washed and give the natural look.

**18.6.2 Medical Management**

Topical minoxidil and oral finasteride are the only two treatments currently approved by the Food and Drug Administration [USA] for MAA in men. Both of these medications prevent further hair loss but are only able to partially reverse the baldness. Both require continuous use to maintain the effect. As clinical response may take 6-12 months to become apparent, these agents should be used for at least 1 year before deciding whether to continue treatment.

**18.6.2.1 Minoxidil**

Oral Minoxidil has been used to treat hypertension since the 1960s (111). Hypertrichosis as a consequence of minoxidil treatment was observed shortly thereafter and has been said to occur in 100% of the users(112,113,114). These observations led to the development of topical minoxidil as a treatment for hair loss (115). It was approved by the FDA for the treatment of male androgentic alopecia in 1984.

A number of investigators have advanced hypotheses as to the mechanism of action of minoxidil. One important hypothesis is that it has vasodilatory properties. Cutaneous blood flow was observed to increase after 10 to 15 minutes of applying topical minoxidil (116). Up-regulation of vascular endothelial growth factor (VEGF)is another important action of minoxidil which help in maintaining dermal papilla vasculature and hair growth (117). Li et al proposed a possible mechanism for minoxidil stimulation of VEGF from experiments on dermal papilla cells (118). They suggest that binding of minoxidil to adenosine receptors A1 and A2 as well as the sulphonylurea receptor SUR2B activate adenosine signalling pathways and increase the release of VEGF. Over expression of VEGF increase peri follicular vascularisation and accelerate hair growth.

The prevailing view is now that minoxidil promotes hair regrowth through its action tp open potassium channels(119,120). It is postulated that minoxidil sulfate, the active metabolite, opens the adenosine triphosphate (ATP) sensitive potassium channels (KATP channel) thereby having a relaxant effect on vascular smooth muscle and also rendering the intracellular potential more negative. This negative gradient promotes depletion of intracellular calcium. In the presence of calcium, epidermal growth factor has been shown to inhibit hair follicular growth in vitro. The conversion of minoxidil to minoxidil sulfate is higher in hair follicles than in the surrounding skin and may suppress EGF-induced inhibition of growth, prolonging the anagen growth phase of hair follicles (118). The effect on the cell cycle is to initiate the onset of anagen (and thereby shorten telogen duration) and to prolong the duration of anagen by delaying initiation of catagen. 

Several studies have shown the effect of topical minoxidil in promoting hair growth(121,122,123).  A five year follow up with topical minoxidil has shown the sustained effect of minoxidil on long term use(124). Minoxidil works as a non-specific promoter of hair growth, but the slow miniaturization of hair follicles induced by androgens continues in spite of treatment. Evidence for this is seen in a 120-week double-blind study (123) comparing the clipped hair weight of men treated with 5% minoxidil, 2% minoxidil and placebo and a group with no treatment. As expected, the minoxidil groups experienced a surge in hair weights at the induction of therapy. The 5% group was superior to the 2% group in terms of the initial peak in hair weights. Both were superior to placebo and no treatment groups. However, all groups [minoxidil, placebo and no treatment] showed a progressive 6% per annum decrease in hair weights during the treatment period. This would mean that patients using minoxidil as mono-therapy for MAA continue to bald in spite of treatment. If treatment is ceased, any positive effect on hair growth is lost in 4-6 months (125).   
Minoxidil topical preparations are available in 2% and 5% solutions. Both 2% and 5% solutions are currently in use for treatment in males and the 5% minoxidil solution has shown higher efficacy than the 2% solution(126).A recent advancement in the use of minoxidil as a hair loss treatment is the development of a 5% topical foam. The traditional topical solution consists of a liquid vehicle with a tendency to spread beyond the intended site of treatment, and that takes time to dry. It also contains a high concentration of propylene glycol, a potential irritant. The newly developed topical hydroalcoholic foam is propylene glycol-free, and has been shown to be more easily applied specifically to target areas. Placebo controlled double-blind trials have demonstrated that the hydroalcoholic foam is efficacious, safe and well accepted cosmetically by patients(127).

On commencing treatment, minoxidil may cause a surge in the growth of miniaturized hairs and induction of anagen from resting hair follicles. This may produce a rapid hair shedding of previous telogen hairs 2-8 weeks after treatment initiation. This temporary shedding may be interpreted as a clinical indication that the minoxidil is having a beneficial effect and the hair shedding usually resolves after few weeks.

Hypertrichosis on the face and hands is a common side effect observed following topical minoxidil.  Itching of the scalp, increased dandruff and erythema are commonly reported. Contact allergic dermatitis to minoxidil can occur and it could either be due to minoxidil itself  or more commonly to propylene glycol in the vehicle(128) . Patch testing is worthwhile in differentiating the cause of contact dermatitis and the new minoxidil form which does not contain propylene glycol is an alternative in these patients.

**18.6.2.2 Finasteride**

Finasteride is a synthetic azo-steroid that is a potent and highly selective antagonist of type II 5 alpha reductase. It is not an anti-androgen. It binds irreversibly to the enzyme and inhibits the conversion of testosterone to dihydrotestosterone. Thus, while the pharmacokinetic half-life is about eight hours, the biological effect persists for much longer. It was initially FDA approved to be used in benign prostate hyperplasia (BPH) and FDA approved finasteride to treat MAA in 1997. The underlying principle for its use in MAA is the reduction of DHT production and thus this limits its action on scalp hair follicles.

Various studies(129-137)have demonstrated the beneficial effects of finasteride in MAA with the most benefits seen in patients with primarily type III vertex or type IV Hamilton/Norwood hair loss. Finasteride has been reported to slow the progression of MAA and to produce partial regrowth in about 2/3 of men (129). A study measuring hair counts using macrophotographs (130)found that both total and anagen hair counts increase with treatment of finasteride. A significant increase in the anagen to telogen ratio was also achieved. This demonstrates the ability of finasteride to stimulate conversion of hair follicles into the anagen phase, possibly through reversion of the decrease in anagen phase and the increase in lag phase. A study looking at scalp biopsies(131) shows that finasteride stimulates an increase in terminal hair counts and a decrease in vellus hair counts. Other studies have used hair count and hair weight as objective measures of outcome (132,138) and demonstrated that both increase, with a larger extent of increase achieved in hair weight. Factors that affect hair weight include the number of hairs, hair growth rate and hair thickness. These findings show the ability of finasteride to reverse the miniaturizationprocess, producing hair of greater length and thickness, and possibly with a greater growth rate

A daily oral dose of one milligram finasteride reduces scalp DHT by 64% and serum DHT by 68% (133) Finasteride was originally given for benign prostatic hyperplasia at 5mg daily. For the treatment of androgenetic alopecia, dose ranging studies have found no significant difference in clinical benefit between five and one milligram daily regimens(134) nor is there any significant further reduction of scalp or serum DHT levels. In practice, finasteride can be administered at either at a dose of one milligram per day, or at longer intervals. A 5-year multinational study looking at the effect of finasteride on treatment of MAA found it to be superior to placebo(136). The placebo group suffered a progressive decline in hair count, losing about 26% of terminal hairs compared to baseline counts at the end of the 5-year study. In contrast, patients on finasteride have a 10% increase in hair count at the end of the first year. Hair count declined somewhat thereafter but remained above baseline throughout, remaining at 5% above the baseline hair count after 5 years of treatment. This decline rate of hair count in the finasteride group is significantly less than that of the placebo group. Taken together, there is a progressive increase in the difference between treatment and placebo group over time. This demonstrates the effects of finasteride in stimulating a substantial amount of hair regrowth, reaching its peak efficacy after one year of treatment, and slowing the progression of hair loss thereafter. At the end of the first year, some in the placebo group were swapped onto receiving finasteride for the remaining four years. These patients demonstrated a decrease in hair count during the first year with placebo, followed by an improvement in the subsequent four years with finasteride. The improvement is similar to that of the group who received finasteride for five years throughout the study. However, mean hair count level is less than that of the patients who have taken finasteride "a year earlier" at all comparable time points, with the difference being similar to the amount of hair loss sustained during the year of placebo treatment. This shows the relative benefits of early commencement of treatment with finasteride. Some of the finasteride patients were also crossed-over to receive placebo after a year of finasteride treatment. A decrease in hair count was observed twelve months later, demonstrating the reversal of the beneficial effects of treatment obtained during the first year.

Further evidence of the efficacy of finasteride in the treatment of MAA is seen in a randomized, double-blind, placebo-controlled twin study(137).At month 12, all subjects in the finasteride group demonstrated an increase in hair count, while a decrease was found in 44% of the placebo group. Serum DHT levels were significantly decreased in the finasteride group, with no significant change observed in the placebo group. Global photography assessment shows significant improvement on hair growth in vertex and superior-frontal scalp in the finasteride group, with no significant differences between treatment groups observed in the temporal or anterior hairline views. This finding shows the relative effectiveness of finasteride on protecting hair loss over the vertex and superior-frontal regions of the scalp, in compare to the minimal response over the temporal and the anterior hairline regions. An open randomised comparative study with 5% topical minoxidil and oral finasteride 1mg a day showed a significant more hair growth in the finasteride group(139).

One Japanese study shows that the hair growth with finasteride continues to increase with continuing treatment without significant side effects.(140) A recent 10-year study of 118 men treated with 1 mg/day finasteride for androgenic alopecia found that 86% of men continued to benefit from treatment over the entire course of 10 years — showing increased or stable rates of hair growth and only 14% experiencing any further hair loss (141). Sexual side effects are a main concern when treating patients for male pattern baldness with finasteride.The evidence available up to date about the safety of the drug is controversialand needs to be further evaluated. In view of this, it is very important to properly counsel patients before the treatment.

Long term studies have reported few adverse effects when using finasteride. In the finasteride group loss of libido was reported in 1.9% and erectile dysfunction in 1.4% in the first year. The placebo groups reported these same events with frequencies of 1.3% and 0.6% respectively. These events appeared to resolve on cessation of the drug and, in some ceased with continued treatment. It has been suggested that even these figures overstate the true incidence of sexual dysfunction (142) (132) (96).

A recent study by Irwig MS *et al*,(143) which has been widely reported in internet after conducting standardized interviews with 71 otherwise healthy men aged 21-46 years. The subjects reported the onset of sexual side effects associated with the temporary use of finasteridewith symptoms persisting for at least three months despite stopping the drug. The study revealed that the subjects reported new-onset persistent sexual dysfunction (low libido, ED, and problems with orgasm) associated with the use of finasteride. Total sexual dysfunction score increased for both before and after finasteride use (*P*< 0.0001 for both). The small number of patients, selection bias, recall bias for before finasteride data, and the absence of serum hormone analyses were the limiting factors of the study. The study recommended that physicians treating male pattern hair loss (MPHL) should discuss the potential risk levels with patients while prescribing the drug.

In view of the conflicting and continuing data and importance of the subject, the International Society of Hair Restoration Surgery (ISHRS) established a Task Force on Finasteride Adverse Event Controversies to evaluate published data and make recommendations. ISHRS recommend that finasteride use for MAA is entirely at the discretion of the patient given that the male pattern hair loss is largely a cosmetic condition. However the treating physician should provide full information about the drug to enable the patient to make an informed decision.

Of note, older men on finasteride experienced a 50% reduction in serum prostate specific antigen [PSA] levels, which could result in an underestimation of prostatic cancer risk. Previous recommendations in the urology literature state that PSA levels remain valid whilst patients are on finasteride, but the value should be doubled to correct for the finasteride effect(144,145,146). Men between 18 to 41 years old are thought to have a negligible decrease in measured PSA levels(147).More recent studies (148) now suggest that finasteride treatment at the 5mg/day dose affects the serum PSA concentration in a time-dependent manner. In the Prostate Cancer Prevention Trial,the adjustment factor needed to be increased from 2 at 24 months to 2.5 at 7 years after the initiation of finasteride. (149). A study done in men aged 40-60 years, 1mg finasteride /day for 48weeks suggest  that existing recommendation for the adjustment of serum PSA concentration in prostate-cancer screening in men taking 5 mg/day finasteride should also apply to men taking the 1 mg/day preparation for male-pattern hair loss.(150) Limited data suggest that reduction in PSA of malignant origin appears to be no greater than the percentage reduction in PSA of benign origin.(151) The free/total PSA (f/tPSA) ratio, currently used to help differentiate benign from malignant processes in the prostate, remains valid during treatment with finasteride; finasteride  does not affect the f/tPSA ratio.(144)

### The effect of finasteride on the incidence and severity of prostate cancer has been extensively investigated and conflicting evidence of the risk of increased incident of high grade prostate cancer associated with finasteride  prevent its use as a chemoprevention agent. In a  trial where  18,882 men older than 54 years with a normal digital rectal examination and a serum PSA equal to or less than 3ng/ml were randomized to finasteride 5mg daily vs placebo. There was a 25% reduction in prostate cancer prevalence in those taking finasteride(152). However, 6.4% of the men taking finasteride developed histologically high grade cancer (Gleason score 7-10) compared with 5.1% of those on Placebo. Recent data suggest that several confounding factors could have contributed to the above results. It is suggested that morphological and histological alterations, ,the degree of sampling error induced by the reduction of prostate volume, differential sensitivity of the biopsy between placebo and the drug groups and increased sensitivity of PSA in detecting prostate cancer with finasteride may have contributed to an apparent increase of higher grade cancers.(153-159)Finasteride use has also been suggested to significantly improve prostate cancer detection with digital rectal examination (160).

Topical finasteride has been investigated as potential variation in drug delivery. While a 0.05% of finasteride solution applied to the scalp was well absorbed and produced a 40% reduction in serum DHT, it had shown no effect on hair regrowth. One explanation for this observation is that inhibition of prostatic DHT production is an important factor in preventing hair loss with finasteride, i.e. a significant reduction in circulating DHT is required in addition to the local blockade of 5 alphareductase at the hair follicle(161) . However a double blind, randomized clinical study between oral finasteride and topical finasteride showed similar efficacy after 18 months in one study.(162) Further studies are needed to assess the efficacy of topical finasteride.

Medical treatment should be continued indefinitely, as the benefit will not be maintained upon ceasing therapy. Up to one year of treatment may be required before any clinical response is noticeable.

Baseline and follow up photographs are helpful in monitoring the response to treatment, but unlikely to detect changes of less than 20% in hair density. The authors make use of a camera mounted on a stereotactic device; a system that is identical to the set-up used in the phase III finasteride trials(161). Photographs are taken of the vertex and frontal hairline at six-monthly to yearly intervals; hair densities at these time points can be readily compared. This set-up is proving to be useful in the long-term monitoring of treatment response. [Figure 10 & 11] Patients are able to observe their regrowth during treatment; the photographs serve as a motivating factor, improving long-term patient compliance to medical treatment. Similar set-ups using digital photographs also appear useful(163) .

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| --- |
| http://www.endotext.org/male/male18/figures/figure9.png |
| **Figure 10.** Photographic evaluation of treatment response to finasteride      a - pre treatment      b - post treatment |

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| --- |
| http://www.endotext.org/male/male18/figures/figure10.png |
| **Figure 11.**Hair photography using the stereotactic device |

Finasteride is a teratogen, pregnancy category X drug and is contraindicated in pregnancy. Male rats exposed to finasteride in utero develop hypospadias with cleft prepuce, decreased anogenital distance, reduced prostate weight and altered nipple formation(150).As the drug is secreted in the semen and can be absorbed through the vagina during intercourse, it was originally advocated that men taking finasteride should avoid unprotected intercourse with pregnant women. In practice, the concentration of finasteride in the semen is well below the minimum effect dosage, and no recommendations regarding the use of condoms are made in the product information leaflet. To date there are no reports of adverse pregnancy outcomes among women whose partners take finasteride.

Finasteride has demonstrable modest transient effects on semen parameters in normal men including decreased total sperm count, semen volume, sperm concentration, and sperm motility but no apparent effect on sperm morphology.(164) With regards to long term safety, finasteride has now been in use for over 10 years. Many recipients are elderly men taking 5mg per day. Very few side-effects have been observed. There is no effect of long term use on bone mineral density (165,166) Reversible painful gynaecomastia has been reported(167) and the incidence is thought to be around 0.001%.(168) Depression measured by increased Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) before and after treatment has been reported.(169)

**18.6.2.3 Dutasteride**

Dutasteride inhibits both type I and type II 5 alphareductase and  it is approximately 3 times more potent than  finasteride at inhibiting type II 5 alphareductase and more than 100 times more potent at inhibition of the type I isoenzyme(170). Dutasteride can decrease serum DHT by more than 90% (171)), while finasteride decreases serum DHT by 70% (172).

The serum half-life of dutasteride is 4 weeks as compared with a serum half-life of 6-8 hours for finasteride. There is persistent suppression of DHT level after dutasteride is ceased. For this reason, patients taking dutasteride should not donate blood until at least 6 months after stopping their medication, to prevent administration to a pregnant transfusion recipient (173). Dutasteride 0.5mg dose is FDA approved for the treatment of benign prostatic hyperplasia while its use in maleandrogenetic alopecia is ‘off label’.

A phase II randomized placebo-controlled study of dutasteride versus finasteride (173) showed that the effect of dutasteridewas dose dependent and 2.5mg of dutasteride was superior to 5mg finasteride in improving scalp hair growth in men between the ages of 21 and 45 years. It was also able to produce hair growth earlier than finasteride. This was evidenced by target area hair counts and clinical assessment at 12 and 24 weeks. In addition, a recent randomized, double-blind, placebo-controlled study on the efficacy of dutasteride 0.5mg/day in identical twins demonstrated that dutasteride was able to significantly reduce hair loss progression in men with MAA (174) A single case report showed improvement of hair loss with dutasteride 0.5mg in a woman who had failed to show any response to finasteride (175)

In one phase III study dutasteride 0.5mg daily showed significantly higher efficacy than placebo based on subject self-assessment and by investigator and panel photographic assessment. There was no major difference in adverse events between two groups. However this study was limited to only 6 months.(176)

Side effects including decreased libido, impotence and gynecomastia are slightly higher with dutasteride than with finasteride (173) Reduction in the sperm count and the volume has been reported with dutasteride(150) (176). There is no effect on the bone density(177. The issue to 5 alpha reductase inhibitor use and prostate cancer is considered in Chapter 10.

**18.6.3 Emerging medical therapy**

**18.6.3.1 Topical antiandrogens**

Oral anti-androgens (e.g. spironolactone, cyproterone acetate) have been widely used to treat women with androgenetic alopecia. However it is contraindicated in men due to its feminization effects. A topical anti-androgen, fluridil has been rationally developed for use in male androgenetic alopecia. It is designed to be locally metabolized, not systemically resorbable, and degradable into inactive metabolites without systemic anti-androgenic activity (178)A double-blind, placebo-controlled study showed that patients using topical fluridil had an increase in the anagen to telogen ratio, and the maximum  attainable effect was achieved within the first 90 days of daily use. No side effects on libido and sexual performances have been found. Nevertheless, a long term study is required to further investigate fluridil's long-term safety and effectiveness in male androgenetic alopecia.

**18.6.3.2 Latanoprost**

The prostaglandin analogue latanoprost stimulates hair growth supposedly by prolonging the anagen phase of the hair cycle.  Lengthening of eyelashes and eye brows has been observed when latanoprost is used topically for glaucoma(179). In a recent placebo controlled studylatanoprost was able to significantly increase hair density compared with baseline and placebo and may also encourage pigmentation.(180)

**18.6.3.3 Topical antibiotics and antifungal**

The role of inflammation in the pathogenesis of MAA is not clear. In particular, the significance of inflammatory cells close to the infra infundibulum of transitional hairs remains obscure. A study conducted in 20 men who used a lotion containing the antimicrobials, piroctoneolamine and triclosan, regularly for 18 months  showed a decrease in the density of activated T cells in the region of the follicular infrainfundibulum and isthmus over time and the trichograms taken at 3-month intervals suggested signs of hair regrowth with moderate increase in density of transitional hairs.(181)Further studies are needed to confirm the effect of topical antimicrobials as a therapeutic option for MAA.

Topical ketaconazole shampoo has been shown to increased hair growth in both humans and in rodents when compared with placebo.(182)Oral ketoconazole has been beneficial in treating hirsutism but the potential side effects does not warrant its use for androgenetic alopecia. Ketoconazole shampoo is a good additive treatment and thought to be having anti-inflammatory and anti-androgenetic properties(183)and will also help associated seborrheic dermatitis.

**18.6.3.4 Growth factors**

### The growth and development of hair follicles is influenced by a number of different growth factors and cytokines. Use of such growth factors to promote hair growth, topically or subcutaneously, is a potential therapeutic target. Preliminary investigations using animal models have shown positive resultsA phase 1, double-blind clinical trial designed to evaluate the safety of a bioengineered, nonrecombinant, human cell–derived formulation containing follistatin, keratinocyte growth factor (KGF), and vascular endothelial growth factor (VEGF) was performed to assess the efficacy in stimulating hair growth. Twenty-six subjects were entered into the study and none showed an adverse reaction to the single intradermal injection. After 1 year, a statistically significant increase in total hair count continued to be seen.(184)

 Platelet rich plasma (PRP) isolated from whole blood can be used for its growth factors and stimulatory mediators. Some hair transplant surgeons use this product to encourage transplanted graft growth(185).PRP is also available as a standalone treatment for AGA, though there is only limited data in its support. (186)

#### 18.6.3.5 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 MPHL.. Several different manufacturers provide lasers and light sources of varying wavelengths and with different suggested modes of use. Whilst there is evidence that laser light can stimulate hair growth at some wavelengths (187,188), the biological mechanism by which it occurs has not been defined andclinical data from large scale, placebo controlled trials is lacking.

**18.6.4 Surgical treatments**

Hair transplantation involves removal of hair from the occipital scalp and reimplantation into the bald vertex and frontal scalp.  With modern techniques graft survival in excess of 90% can be reliably achieved.  Prerequisites for the procedure are stabilization of the hair loss with medical treatment and good donor hair population on the occipital hair.

The modern hair transplant technique was started in Japan in 1930s where small punch grafts were used to cover damaged eyebrows or lashes (189).Norman Orentreich reported on the use of autografts and proposed the term "donor dominance" (190).in that the hair taken from the androgen resistant occipital scalp remain androgen resistant when implanted into the androgen sensitive bald areas of the scalp.

In 1995, Bernstein  and  Rassmanintroduced  "[Follicular Unit Transplantation](http://en.wikipedia.org/wiki/Follicular_Unit_Transplantation)," where hair is transplanted in naturally occurring units of 1-4 hair (191) In "[Follicular Unit Transplantation](http://en.wikipedia.org/wiki/Follicular_Unit_Transplantation)"donor hair can be harvested in two different ways;

Strip Harvesting - a strip of scalp 8 - 14 mm and 20-30 cm is removed under local anaesthesia, from the occipital scalp and the wound is then sutured back together. The donor hair is then separated into follicular units and then transplanted in to the balding area. The main disadvantage of this method is that it will leave a linear scar in the donor occipital area.

FUE (Follicular Unit Extraction) Harvesting - individual follicles of occipital hair are removed under local anaesthesia with 1mm punch biopsies. Each unit is then reinserted back in to the scalp in the bald areas using a micro blade. In this technique, there are no visible scars as single follicular units are removed instead of large amount of tissue and take a short time to heal than strip harvesting. 

Both techniques can achieve good results, but follicular unit transplantations have the advantage of being able to achieve much greater hair densities. It is preferable that surgical candidates have frontal or mid-frontal hair loss as opposed to hair loss at the vertex and their donor hair density needs to be adequate to support the surgery (i.e. > 40 follicular units/cm2). Also, thicker donor hairs are able to create better coverage compared with finer hair. Disadvantages of hair transplants are increased time and labour requirements, which translates to greater cost for the patient. Transplanted hairs seem to immediately go into a telogen resting phase after insertion. Thus surgical results can only be adequately assessed after no less than three months after surgery. There is always a degree of graft failure. Various reasons account for dead grafts including the skill of the surgeon, the density of graft placement, careless handling and preparation of the graft units, and desiccation of the grafts whilst awaiting insertion. 

Scalp reductions result in a more unnatural look with excision scars tending to be more noticeable over time. In addition, the inability to predict further hair loss over time in each patient has meant that the procedures are now uncommonly performed.

**18.6.5  Combination of medical, medical and surgical therapy**

An open, randomized, parallel-group study comparing the efficacy of available medications as monotherapy or combined therapy (finasteride alone, finasteride and 2% topical minoxidil, topical minoxidil alone and finasteride and ketokonazole shampoo) showed that finasteride in combination with either topical minoxidil or ketoconazole showed significantly better hair regrowth than with finasteride as monotherapy and showed no difference in the incidence of side effects. It is inferred that the combination of medication with different mechanisms of action enhance the efficacy (192).. A recent case study showed that adding dutasteride 0.5mg in a patient who had poor response to finasteride had marked improvement of hair loss.(193).

Topical minoxidil and finasteride can be a useful adjunct to hair transplant surgery for MAA. Without adjuvant medical therapy to prevent progression of balding process an unnatural appearance can evolve over time. Studies have found that topical use of minoxidil in perioperative period could prevent the usual shedding that occurs 1 to 2 weeks after transplantation and speed the time for regrowth (194). These results were confirmed by double-blind trial, which showed that significantly less grafted hair was lost during the shedding period(195)Use of topical minoxidil as a premedication in hair transplant surgery has the advantage of stabilizing the hair loss, increasing the number of hair in anagen phase and decreasing post surgicaltelegon effluvium. Minoxidil should be stopped 2 to 3 days before surgery to minimize skin irritation and to reduce the theoretical risk of intraoperative bleeding caused by vasodilation. Therapy should be restarted in 1-2 weeks.Randomized, double-blind trial using finasteride 1 mg daily or placebo in 79 men with MAA 4 weeks before and 48 weeks after hair transplantation demonstrated that the treatment group had significant improvement from baseline, in comparison with placebo group (196).

**7. CONCLUSION**

MAA is increasingly common among men as they age. Many men find it a distressing and unwelcome event and some seek treatment to prevent further hair loss and reverse the process. A number of therapeutic options are now available for these men. In addition, MAA may be a marker of increased risk of cardiovascular diseases. The hair follicle is a complex organ biologically. The changes in the hair follicles that lead to baldness have caught the interest of stem cell scientists, geneticists, developmental biologists and immunologists and hair biology has become an increasingly fruitful field of scientific endeavour.

**References**

1. Hamilton JB. Patterned hair loss in man: types and incidence. Ann NY Acad Sci 1951;53:708-28.

2. Oslen EA. Disorders of Hair Growth: Diagnosis and Treatment. New York. McGraw-Hill, lnc 1994;257-84  
   
3.  Montagna W, Ellis R. The Biology of Hair Growth. NY Academic Press 1958; 399-433.

4.  Ishino A, Uzuka M, Tsuji Y et al.Progressive decrease in hair diameter in Japanese with male pattern baldness. J. Dermatol 1997; 24(12):758-64.

5.  Hamilton JB. Patterned loss of hair in man: Types and incidence.Ann NY Acad Sci. 1951; 53:708-28.

6. Muller SA. Alopecia: Syndromes of genetic significance. J Invest Dermatol. 1973; 60:475-92.

7.  Smith MA, Wells RS. Male type alopecia, alopecia areata and normal hair in women: Family histories. Arch Dermatol.1964; 89:95-8.

8.  Setty LR. Hair patterns of the scalp in white and Negro males. Am J Phys Anthropol.1970; 33:49-55.

9. Tang PH, Chia HP, Cheong LL, Koh DA. community study of male androgenetic alopecia in Bishan, Singapore. Singapore Med J 2000; 41: 202-5.

10. Severi G, Sinclair R, Hopper JL etal. Androgenetic alopecia in men aged 40-69 years: prevalence and risk factors British Journal of Dermatology 2003; 149: 1207-1213.

11.  Rhodes T, Girman CJ, Savin RC et al. Prevalence of male pattern hair loss in 18-49 year old men. Dermatol Surg 1998; 24: 1330-2.

12.  Paik JH, Yoon JB, Sim WY et al. The prevalence and types of androgenetic alopecia in Korean men and women. Br J Dermatol 2001; 145: 95-9.

13.  Cash TF. The psychological effects of androgenetic alopecia in men. J Am Acad Dermatol 1992;26:926-31.

14.  Budd D, Himmelberger D, Rhodes T, et al. The effects of hair loss in European men: a survey in four countries. Eur J Dermatol 2000;10:122-7.

15.  Lee HJ, Ha SJ, Kim D, et al. Perception of men with androgenetic alopecia by women and nonbalding men in Korea: how the nonbald regard the bald. Int J Dermatol 2002;41:867-9.

16.  Passchier J. Quality of life issues in male pattern hair loss. Dermatology 1998;197:217-8.

17. Cotton SG, Nixon JM, Carpenter RG, et al. Factors discriminating men with coronary heart disease from healthy controls. Br Heart J 1972; 34: 458-64.  
  
18.  Herrera CR, D Agostino RB, Gerstman BB, et al. Baldness and coronary heart disease rates in men from the Framingham Study. Am J Epidemiol 1995;142:828-33.

19.  Ford ES, Freedman DS, Byers T. Baldness and ischemic heart disease in a national sample of men. Am J Epidemiol 1996;143:651-7.

20.  Lesko SM, Rosenberg L, Shapiro S. A case-control study of baldness in relation to myocardial infarction in men. Jama 1993;269:998-1003.

21.  Schnohr P, Lange P, Nyboe J, et al. Gray hair, baldness, and wrinkles in relation to myocardial infarction: the Copenhagen City Heart Study. Am Heart J 1995;130:1003-10.

22.  Lotufo PA, Chae CU, Ajani UA, et al. Male pattern baldness and coronary heart disease: the Physicians Health Study. Arch Intern Med 2000;160:165-71.

23.  Lotufo PA, Chae CU, Ajani UA, et al. Male pattern baldness and coronary heart disease: the Physicians Health Study. Arch Intern Med 2000;160:165-71.

24.   Arias-Santiago S, Gutirrez-Salmern MT,  Buendia-Eisman A etal. Hypertension and aldosterone levels in women with early-onset androgenetic alopecia [British Journal of Dermatology](http://www3.interscience.wiley.com/journal/117983344/home) 2010[;162 (4](http://www3.interscience.wiley.com/journal/123326221/issue)): 786 - 789

25.  Ahouansou S, Le Toumelin P, Crickx B, Descamps V. Association of androgenetic alopecia and hypertension.  Eur J Dermatol.  2007; 17(3):220-2

26.  Chen W, Yang CC, Chen GY, et al. Patients with a large prostate show a higher prevalence of androgenetic alopecia. Arch Dermatol Res 2004;296:245-9.

27.  Oh BR, Kim SJ, Moon JD, et al. Association of benign prostatic hyperplasia with male pattern baldness. Urology 1998;51:744-8.

28. Arias-Santiago S, Arrabal-Polo MA, Buendía-Eisman A, et al. Androgenetic alopecia as an early marker of benign prostatic hyperplasia. J Am Acad Dermatol. Mar 2012;66(3):401-8.

29.   Hawk E, Brewslow RA, Graubard BI. Male pattern baldness and clinical prostate cancer in the epidemiologic follow-up of the First National Health and Nutrition Examination Survey. Cancer Epidemiol Biomark Prev 2000;9:523-7.

30. .  Giles GG, Severi G, Sinclair R, et al. Androgenetic alopecia and prostate cancer: findings from an Australian case-control study. Cancer Epidemiol Biomarkers Prev 2002;11:549-53.

31..   Muller DC, Giles GG, Sinclair R, Hopper JL, English DR, Severi G..  [Age dependent associations between androgenetic alopecia and prostate cancer risk](http://scholar.google.com.au/citations?view_op=view_citation&hl=en&user=Sw84KV8AAAAJ&pagesize=100&sortby=pubdate&citation_for_view=Sw84KV8AAAAJ:8d8msizDQcsC).  Cancer Epidemiol Biomarkers Prev. 2012 Oct 16.

32. [Amoretti A](http://www.ncbi.nlm.nih.gov/pubmed?term=Amoretti%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23395589), [Laydner H](http://www.ncbi.nlm.nih.gov/pubmed?term=Laydner%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23395589), [Bergfeld W](http://www.ncbi.nlm.nih.gov/pubmed?term=Bergfeld%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23395589).Androgenetic alopecia and risk of prostate cancer: a systematic review and meta-analysis.[J Am Acad Dermatol.](http://www.ncbi.nlm.nih.gov/pubmed/23395589) 2013 Jun;68(6):937-43

33.Ellis JA, Stebbing M, Harrap SB. Male pattern baldness is not associated with established cardiovascular risk factors in the general population. Clin Sci (Lond) 2001;100:401-4.

34.Denmark-WahnefriedW, Schildkraut JM, Thompson D, et al. Early onset baldness and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2000;9:325-8.

35.. Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. Expert Rev Mol Med 2002;2002:1-11.

36.. Setty LR. Hair patterns of scalp of white and Negro males. Am J Phys Anthropol 1970;33:49-55.

37. Nyholt D.R., Gillespie N.A., Heath A.C., Martin N.G. Genetic basis of male pattern baldness. J. Invest. Dermatol. 2003;121:1561-64.  
  
38. . Ellis JA, Harrap SB. The genetics of androgenetic alopecia. Clin Dermatol 2001;19:149-54.

39..  Osborne D. Inheritance of baldness. J Hered 1916;347-55.

40..  Kuster W, Happle R. The inheritance of common baldness: two B or not two B? J Am Acad Dermatol 1984;11:921-6.

41. .Ellis JA, Stebbing M, Harrap SB. Genetic analysis of male pattern baldness and the 5alpha-reductase genes. J Invest Dermatol 1998;110:849-53.

42.Ellis JA, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. J Invest Dermatol 2001;116:452-5.

43. Sawaya ME, Price VH. Different levels of 5 alpha reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J. Invest. Dermatol. 1997;109:296-300.  
  
44. Yip L, Zaloumis S, Irwin D et al. "Gene-wide association study of the aromatase gene (CYP19A1) with female pattern hair loss" Br J Dermatol. 2009 ;161(2):289-94.  
  
45. Hillmer AM, Flaquer A, Hanneken S et al. Genome- wide scan and Fine-Mapping Linkage study of androgenetic alopecia reveals a locus on chromosome 3q26. The American Journal of Human genetics 2008;82:737-743.  
  
44. Hillmer AM, Brockschmidt FF, Hanneken S, Eigelshoven S et al. Susceptibility variants for male-pattern baldness on chromosome 20p11. Nat Genet. 2008 Nov;40(11):1279-81

47. Brockschmidt FF, Heilmann S, Ellis JA, et al. Susceptibility variants on chromosome 7p21.1 suggest HDAC9 as a new candidate gene for male-pattern baldness. Br J Dermatol. Dec 2011;165(6):1293-302.

48. JA, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. J Invest Dermatol. 2001 Mar;116(3):452–5.

49. AM, Hanneken S, Ritzmann S, et al. Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. Am J Hum Genet. 2005 Jul;77(1):140–8.49a  Sato et al. Correlation between Polymorphic CAG-Repeats in the Androgen Receptor Gene and Therapeutic Efficiency of Finasteride in Androgenetic Alopecia. Skin Surgery: 17(2); 80-86, 2008

50. Hamilton JB. Male hormone stimulation is prerequisite and an insitant in common baldness. AM J Anat. 1942;71:451-80.  
  
51. Pits RL. Serum elevation of dihydroepiandrosterone sulphate associated with male pattern baldness in young men.J Am Acad dermatol 1987;16:571-3.  
  
52. Jolanta B. Schmidt.  Hormonal Basis of Male and Female Androgenic Alopecia: Clinical Relevance. Skin Pharmacol 1994;7:61-66.  
  
53, Schmidt JB,Lindmaier A, Trenz A et al.Hormone studies in females with androgenetic hair loss. Gynecol Obstet Invest 1991; 31:235-9  
  
54. Hamilton JB.Effect of castration in adolescent and young adult males upon further changes in the proportion of bare and hairy scalp. J Clin Endrocrinol Metabol 1960;20:1309-18.

55.   Griffin JE, Wilson JD. The resistance syndromes: 5a reductase deficiency, testicular feminisation and related disorders. In:Baudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease.edn. New York. McGraw Hill; 1989. p. 1919-44.

56.  Imperato-McGinley J, Guerrero L, Gautier T, et al. Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 1974;186:1213-5.

57. Sinclair RD, Greenland K, van Egmond S, et al. Men with Kennedy’s disease have a reduced risk of androgenetic alopecia [unpublished observations]. In: St Vincent’s Hospital, Melbourne, Australia, 2007.

58.   Schweikert HU, Wilson JD. Regulation of human hair growth by steroid hormones. II. Androstenedione metabolism in isolated hairs. J Clin Endocrinol Metab 1974;39:1012-9.

59.   Randall VA, Thornton MJ, Hamada K, Messenger AG. Androgen action in cultured dermal papula cells from human hair follicles. Skin Pharmacol 1994; 7: 20-26.

60.   Kaufman KD. Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol Clin 1996;14:697-711.

61. Jones LN, Sinclair RD, Rivett DE.Androgen metabolism and human hair growth.  
Chem Aust 1997;64:12-3.

62.   Itami S, Kurata S, Sonoda T, et al. Characterization of 5 alpha-reductase in cultured human dermal papilla cells from beard and occipital scalp hair. J Invest Dermatol 1991;96:57-60.

63.   Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic researchand clinical perspectives. J Invest Dermatol 2002;119:992-1007.

64. Bayne EK, Flanagan J, Einstein M, et al. Immunohistochemical localization of types 1 and 2 5alpha-reductase in human scalp. Br J Dermatol 1999;141:481-91.

65. Hoffmann R, Happle R.  Current understanding of androgenetic alopecia. Part I: Etiopathogenesis European Journal of Dermatology. Volume 10, Number 4, 319-27.

66. Fritsch M, Orfanos CE, Zouboulis ChC: Sebocytes are the key regulators of androgen homeostasis in human skin. J Invest Dermatol 116:793-800, 2001.  
  
67.   Itami S, Kurata S, Takayasu S. Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-I from dermal papilla cells. Biochem Biophys Res Commun 1995;212:988-94.

68.   Shigeki Inui, Yoko Fukuzato, Takeshi Nakajima et al. Androgen-inducible TGF-from balding dermal papilla cells inhibits epithelial cell growth: a clue to understanding paradoxical effects of androgen on human hair growth][ Journal of Investigative Dermatology Symposium Proceedings (2003) 8, 69-71.

69. Thornton MJ, Hamada K, Messenger AG, et al. Androgen-dependent beard dermal papilla cells secrete autocrine growth factor(s) in response to testosterone unlike scalp cells. J Invest Dermatol 1998;111:727-32.

70.   Randall VA, Thornton MJ, Messenger AG. Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of scalp. J Endocrinol 1992;133:141-7.

71.   Thornton MJ, Laing I, Hamada K, et al. Differences in testosterone metabolism by beard and scalp hair follicle dermal papilla cells. Clin Endocrinol (Oxf) 1993;39:633-9.

72.   Itami S, Kurata S, Takayasu S. 5 alpha-reductase activity in cultured human dermal papilla cells from beard compared with reticular dermal fibroblasts. J Invest Dermatol 1990;94:150-2.

73.   Boudou P, Reygagne P. Increased scalp skin and serum 5 alpha-reductase reduced androgens in a man relevant to the acquired progressive kinky hair disorder and developing androgenetic alopecia. Arch Dermatol 1997;133:1129-33.

74. Sawaya ME, Price VH. Different levels of 5alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J Invest Dermatol 1997;109:296-300.

75.   Orentreich N. Autografts in alopecias and other selected dermatological conditions.  
Ann NY Acad Sci 1959;83:463-79.

76.   Oslen E. A. Female pattern hair loss: Clinival features and potential hormonal factors. J AM Acad Dermatol 2001;45:570- 580.  
  
77. . Kligman AM. The human hair cycle. J Invest Dermatol 1959;33:307-16.

78.    de Berker D A R, Messenger A G , Sinclair RD. Disorders of Hair. In Rook’s Textbook of Dermatology 7th Edition ( Volume 4) Burns T, Breathnach S, Cox N, Griffiths C( Eds) . Blackwell  Publishing 2004.  p  63.8 - 63.10.  
  
79.   Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. Expert Rev Mol Med 2002;2002:1-11.

80 . . Courtois M, Loussouarn G, Hourseau C, Grollier JF. Hair cycle and alopecia. Skin Pharmacol 1994;7:84-9.

81. Guarrera M, Rebora A. Anagen hairs may fail to replace telogen hairs in early androgenetic alopecia. Dermatology 1996;192:28- 31.

82.   Curtois M, Loussouarn G, Horseau C. Hair cycle and alopecia. Skin Pharmacol 1994;7:84-9.  
  
83.   Valerie A Randall, Tracey J Jenner, Nigel A Hibberts et al. Stem cell factor/c-Kit signalling in normal and androgenetic alopecia hair follicles Journal of Endocrinology(2008)197,11-23   
       
84. Jahoda CAB, Horne KA, Oliver RF. Induction of hair growth by implantation of cultured dermal papilla cells.Nature (London) 1984; 311:560-2.

85. Jahoda CAB, Reynolds AJ. Dermal-epidermal interactions.Adult follicle-derived cell populations and hair growth.Dermatol Clin 1996; 14:573-83.

86. Obana NJ, Uno H. Dermal papilla cells in macaque alopecia trigger a testosteronedependent inhibition of follicular cell proliferation. In:van Neste D, Randall VA, editors. Hair research in the next millennium.edn. Amsterdam. Elsevier; 1996. p. 307-10.

87.   Randall VA. The use of dermal papilla cells in studies of normal and abnormal hair follicle biology. Dermatol Clin 1996;14:585-94.

88.   Oliver RF, Jahoda CAB. The dermal papilla and the maintenance of hair growth. In:Rogers GA et al., editors. The biology of wool and hair.edn. London. Chapman and Hall; 1989. p. 51-67.

89. Van Scott EJ, Ekel TM. Geometric relationships between the matrix of the hair bulb and its dermal papilla in normal and alopecic scalp. J Invest Dermatol 1958;31:281-7.

90. Jahoda CA. Cellular and developmental aspects of androgenetic alopecia. Exp Dermatol 1998;7:235-48.

91.   Elliott K, Stephenson TJ, Messenger AG. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: Implications for the control of hair follicle size and androgen responses. J Invest Dermatol 1999;113:873-7.

92. Prieto VG, Sadick NS, Shea CR. Androgenetic alopecia: analysis of proliferation and apoptosis. Arch Dermatol 2002;138:1101-2.

93.   [Hamada K](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Hamada%20K%22%5BAuthor%5D), [Randall VA](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Randall%20VA%22%5BAuthor%5D). Inhibitory autocrine factors produced by the mesenchyme-derived hair follicle dermal papilla may be a key to male pattern baldness. Br J Dermatol.2006 ;154(4):609-18.

94.    Weger N,   Schlake T. Igfbp3 Modulates Cell Proliferation in the Hair Follicle.  Journal of Investigative Dermatology (2005) 125, 847-849;

95.   Sinclair R. Male pattern androgenetic alopecia. BMJ 1998;317:865-9.

96.   Whiting DA. Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss. J Am Acad Dermatol 2001;45:S81-6.

97.   Whiting DA. Scalp biopsy as a diagnostic and prognostic tool in androgenetic alopecia. Dermatol Ther 1998;8:24-33.

98.   Pinkus H. Differential patterns of elastic fibers in scarring and non-scarring alopecias.  
J Cutan Pathol 1978;5:93-104.

99.    Yazdabadi A, Magee J, Harrison S, Sinclair R. The Ludwig pattern of androgenetic alopecia is due to a hierarchy of androgen sensitivity within follicular units that leads to selective miniaturization and a reduction in the number of terminal hairs per follicular unit. Br J Dermatol 2008; 159: 1300-1302.

100.    [Jaworsky C](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Jaworsky%20C%22%5BAuthor%5D), [Kligman AM](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Kligman%20AM%22%5BAuthor%5D), [Murphy GF](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Murphy%20GF%22%5BAuthor%5D). Characterization of inflammatory infiltrates in male pattern alopecia: implications for pathogenesis. Br J Dermatol 1992 Sep;127(3):239-46.   
  
101.  [Sueki H](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Sueki%20H%22%5BAuthor%5D), [Stoudemayer T](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Stoudemayer%20T%22%5BAuthor%5D), [Kligman AM](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Kligman%20AM%22%5BAuthor%5D), [Murphy GF](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Murphy%20GF%22%5BAuthor%5D). Quantitative and ultrastructural analysis of inflammatory infiltrates in male pattern alopecia. [Acta Derm Venereol.](javascript:AL_get(this,%20'jour',%20'Acta%20Derm%20Venereol.');)1999 Sep;79(5):347-50.   
  
102. Martin S. Z,   Ralph M. T.  Fibrosing Alopecia in a Pattern Distribution  Patterned Lichen Planopilaris or Androgenetic Alopecia With a Lichenoid Tissue Reaction Pattern?  Arch Dermatol. 2000;136:205-211.  
  
103.  [Whiting DA](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Whiting%20DA%22%5BAuthor%5D). Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. [J Am Acad Dermatol.](javascript:AL_get(this,%20'jour',%20'J%20Am%20Acad%20Dermatol.');) 1993 May;28(5 Pt 1):755-63

104.  [Sinclair](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract) R,  [Jolley](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract) D,  [Mallari](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract)[c](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract" \l "ANC3" \o ")R, [Magee](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract)[d](http://www.eblue.org/article/S0190-9622(03)00045-8/abstract" \l "ANC4" \o ")J. The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. J Am Acad Dermatol 2004 [Volume 51](http://www.eblue.org/issues?Vol=51), [Issue 2](http://www.eblue.org/issues/contents?issue_key=S0190-9622(00)X0164-8), Pages 189-199.

105.   Kligman AM. The comparative histopathology of male pattern baldness and senescent baldness. Clin Dermatol 1986;6:108-18.

106.   A.G. Messenger and R. Sinclair. Follicular miniaturization in female pattern hair loss:  
clinicopathological correlations . British Journal of Dermatology 2006 155, 926-930

107.    de Lacharrière O,   Deloche C,   Misciali C. Hair Diameter Diversity A Clinical Sign Reflecting the Follicle Miniaturization Arch Dermatol. 2001;137:641-646.

108. A Yazdabadi, D Whiting, NW Rufaut, R Sinclair. [Miniaturized hairs maintain contact with the arrector pili muscle in alopecia areata but not in androgenetic alopecia: A model for reversible miniaturization and potential for hair regrowth](http://scholar.google.com.au/citations?view_op=view_citation&hl=en&user=Sw84KV8AAAAJ&pagesize=100&sortby=pubdate&citation_for_view=Sw84KV8AAAAJ:GtLg2Ama23sC). International Journal of Trichology 2012;4;154

109. Hamilton JB. Patterned hair loss in man: types and incidence. Ann NY Acad Sci  
1951;53:708-28.

110.   Norwood OT. Male pattern baldness: classification and incidence. South Med J  
1975;68:1359-65.  
  
111.  Kosman ME. Evaluation of a new antihypertensive agent: minoxidil. JAMA 1980;244:73-5.  
  
112. Devine Bl, Fife R, Trust PM. Minoxidil for severe hypertention after failure of other hypotensive agents.BrMed J 1977; 2: 667-9.  
  
113.    Jacobs D. Minoxidil Experience in Australia 1974-1980. Med J Aust 1981; 1:477-8.  
  
114.   Pennisi AJ, Takahashi M, Bernstein BH et al. Minoxidil therapy in children with severe hypertension. J Paediatr 1977;90:813-9.  
  
115.   Kreindler TG. Topical minoxidil in early androgenetic alopecia. J Am Acad Dermatol 1987;16:718-24.  
  
116.    Wester RC, Maibach HI, Guy RH, Nowak E. Minoxidil stimulates cutaneous blood flow in human balding scalp:Pharmacodynamics measured by laser Doppler velocimetry and photopulse plethysmography. J Invest Dermatol 1984;82:515-7.  
  
117.   Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. Br J Dermatol 1998;138:407-411.  
  
118.   Li M, Marubayashi A, Nakaya Y, Fukui K, Arase S. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. J Invest Dermatol. 2001 Dec;117(6):1594-600.  
  
119.   Buhl AE, Conrad SJ, Waldon DJ et al. Pottasium channel conductance as a control mechanism in hair follicles. J Invest Dermatol 1993;101:148s-52s.  
  
120. Buhl AE,  Waldon DJ,  Conrad SJ et al. Pottasium channel conductance: a mechanism affecting hair growth both in vitro and in vivo. J Invest Dermatol 1992;98:315-19.  
  
121.   Katz HI, Hien NT, Prawer SE, et al. Long-term efficacy of topical minoxidil in male  
pattern baldness. J Am Acad Dermatol 1987;16:711-8.

122. Rietschel RL, Duncan SH. Safety and efficacy of topical minoxidil in the management of androgenetic alopecia. J Am Acad Dermatol 1987;16:677-85.

123. Price VH, Menefee E, Strauss PC. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol 1999;41:717-21.

124. Olsen EA, Weiner MS, Amara IA, et al. Five-year follow-up of men with androgenetic  
alopecia treated with topical minoxidil. J Am Acad Dermatol 1990;22:643-6.

125. Olsen, E.A. and Weiner, M.S. (1987) Topical minoxidil in male pattern baldness:  
effects of discontinuation of treatment. J. Am. Acad. Dermatol. 17, 97-101]

126.   Roberts JL. Androgenetic alopecia: treatment results with topical minoxidil. J Am Acad Dermatol 1987;16:705-10.  
  
127.   Olsen, E.A. et al. A multicenter, randomized, placebo-controlled, doubleblind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men. J. Am. Acad. Dermatol. (2007) ; 57: 767-774.

128.   Friedman ES, Friedman PM,Cohen DE, Washenik K. Allergic contact dermatitis to topical minoxidil solution:atiology and treatment. J Am Acad dermatol 2002;46:309-12.  
  
129.   Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. J Am AcadDermatol 1998;39:578-89.  
  
130. Van Neste D, Fuh V, Sanchez-Pedreno P, et al. Finasteride increases anagen hair in  
men with androgenetic alopecia. Br J Dermatol 2000;143:804-10.

131.   Whiting DA, Waldstreicher J, Sanchez M, et al. Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies: results of finasteride 1 mg treatment of men and postmenopausal women. J Investig Dermatol Symp Proc 1999;4:282-4.

132. Price VH, Menefee E, Sanchez M, et al. Changes in hair weight and hair count in men with androgenetic alopecia after treatment with finasteride, 1 mg, daily. J Am Acad Dermatol 2002;46:517-23.

133.   Drake L, Hordinsky M, Fiedler V, et al. The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol 1999;41:550-4.

134.   Roberts JL, Fiedler V, Imperato-McGinley J, et al. Clinical dose ranging studies with finasteride, a type 2 5alpha-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol 1999;41:555-63.

135. Leyden J, Dunlap F, Miller B, et al. Finasteride in the treatment of men with frontal  
male pattern hair loss. J Am Acad Dermatol 1999;40:930-7.

136.   The Finasteride Male Pattern Hair Loss Study Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol 2002;12:38-49.

137.   Stough DB, Rao NA, Kaufman KD, et al. Finasteride improves male pattern hair loss in a randomized study in identical twins. Eur J Dermatol 2002;12:32-7.

138. Price VH, Menefee E, Sanchez M, et al. Changes in hair weight in men with androgenetic alopecia after treatment with finasteride (1 mg daily): three- and 4-year results. J Am Acad Dermatol 2006;55:71-4.

139. [Arca E](http://www.ncbi.nlm.nih.gov/pubmed?term=Arca%20E%5BAuthor%5D&cauthor=true&cauthor_uid=15316165), [Açikgöz G](http://www.ncbi.nlm.nih.gov/pubmed?term=A%C3%A7ikg%C3%B6z%20G%5BAuthor%5D&cauthor=true&cauthor_uid=15316165), [Taştan HB](http://www.ncbi.nlm.nih.gov/pubmed?term=Ta%C5%9Ftan%20HB%5BAuthor%5D&cauthor=true&cauthor_uid=15316165), [Köse O](http://www.ncbi.nlm.nih.gov/pubmed?term=K%C3%B6se%20O%5BAuthor%5D&cauthor=true&cauthor_uid=15316165), [Kurumlu Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Kurumlu%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=15316165). An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. [Dermatology.](javascript:AL_get(this,%20'jour',%20'Dermatology.');)2004;209(2):117-25.

140. [Sato A](http://www.ncbi.nlm.nih.gov/pubmed?term=Sato%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21980923), [Takeda A](http://www.ncbi.nlm.nih.gov/pubmed?term=Takeda%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21980923) . Evaluation of efficacy and safety of finasteride 1 mg in 3177 Japanese men with androgenetic alopecia..[J Dermatol.](http://www.ncbi.nlm.nih.gov/pubmed/21980923" \o "The Journal of dermatology.) 2012 Jan;39(1):27-32.

141.  Rossi, A.; Cantisani, C.; Scarnò, M.; Trucchia, A.; Fortuna, M. C.; Calvieri, S. "Finasteride, 1 mg daily administration on male androgenetic alopecia in different age groups: 10-year follow-up". Dermatologic Therapy  2011. 24 (4): 455–461.

142. Tosti A, Piraccini BM, Soli M. Evaluation of sexual function in subjects taking finasteride for the treatment of androgenetic alopecia. J Eur Acad Dermatol Venereol 2001;15:418-21.

143. [Irwig MS](http://www.ncbi.nlm.nih.gov/pubmed?term=Irwig%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=22789024). Persistent sexual side effects of finasteride: could they be permanent?.[J Sex Med.](http://www.ncbi.nlm.nih.gov/pubmed/22789024" \o "The journal of sexual medicine.) 2012 Nov;9(11):2927-32.

144. Matzkin H, Barak M, Braf Z. Effect of finasteride on free and total serum prostatespecific  
antigen in men with benign prostatic hyperplasia. Br J Urol 1996;78:405-8.

145.   Keetch DW, Andriole GL, Ratliff TL, et al. Comparison of percent free prostatespecific antigen levels in men with benign prostatic hyperplasia treated with finasteride, terazosin, or watchful waiting. Urology 1997;50:901-5.

146.   Andriole GL, Guess HA, Epstein JI, et al. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology 1998;52:195-201.

147.   Physicians circular for Propecia. West Point, NY: Merck; December 1997.

148. Marks LS, Andriole GL, Fitzpatrick JM, et al. The interpretation of serum prostate specific antigen in men receiving 5alpha-reductase inhibitors: a review and clinical recommendations. J Urol 2006;176:868-74.

149. Etzioni R, Howlander N, Shaw P et al.  Long term effects of finasteride on prostate specific antigen levels: results from the Prostate Cancer Prevention Trial. Journal of Urology, ;174 (3); 877-881

150. 140. Amico  AD , Roehrborn C.  Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenic alopecia: a randomised controlled trial .The Lancet Oncology, Volume 8, Issue 1, Pages 21-25  
  
151.   Guess HA  ,  Heyse JF,  Gormley GJ. The effect of finasteride on prostate-specific antigen in men with benign prostatic hyperplasia. [The Prostate](http://www3.interscience.wiley.com/journal/34304/home); 22(1); 31-37.

152.   Thompson IM, Goodman PJ, Tangen CM, et al.The influence of finasteride on the  
development of prostate cancer. N Engl J Med 2003;349:215-24.

153.   [Redman](http://cancerpreventionresearch.aacrjournals.org/search?author1=Mary+W.+Redman&sortspec=date&submit=Submit) MW, [Tangen](http://cancerpreventionresearch.aacrjournals.org/search?author1=Catherine+M.+Tangen&sortspec=date&submit=Submit) CM, [Goodman](http://cancerpreventionresearch.aacrjournals.org/search?author1=Phyllis+J.+Goodman&sortspec=date&submit=Submit) PJ et al. Finasteride Does Not Increase the Risk of High-Grade Prostate Cancer: A Bias-Adjusted Modeling Approach .Cancer Prevention Research August 2008 1; 174

154.   Lucia MS,  Epstein JI,  Goodman PJ et al. Finasteride and High-Grade Prostate Cancer in the Prostate Cancer Prevention Trial. Journal of the National Cancer Institute 2007 99(18):1375-1383.  
  
155. Lucia MS, Epstein JI, Goodman PJ, et al: Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. J Natl Cancer Inst 99:1375-1383, 2007.  
  
156. Cohen YC, Liu KS, Heyden NL, et al: Detection bias due to the effect of finasteride on prostate volume: A modeling approach for analysis of the Prostate Cancer Prevention Trial. J Natl Cancer Inst 99:1366-1374, 2007.

157.    Kramer BS, Hagerty KL,  Justman S et al. Use of 5--Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. Journal of Clinical Oncology2009; 27(9),1502-1516.

158. Elliott CS, Shinghal R, Presti JC  The Influence of Prostate Volume on Prostate-Specific Antigen Performance: Implications for the Prostate Cancer Prevention Trial Outcomes Clin. Cancer Res., July 15, 2009; 15(14): 4694 - 4699.

159. .Redman MW,Tangen CM,  Goodman PJ et al. Finasteride Does Not Increase the Risk of High-Grade Prostate Cancer: A Bias-Adjusted Modeling Approach Cancer Prevention Research, August 1, 2008; 1(3): 174 - 181.

160.   Thompson IM, Tangen CM, Goodman PJ, et al. Finasteride improves the sensitivity  
of digital rectal examination for prostate cancer detection. J Urol 2007;177:1749-52.

161. Sinclair RD, Dawber RP.Androgenetic alopecia in men and women. Clin Dermatol  
2001;19:167-78.

162. [Zohreh Hajheydari](http://www.ijdvl.com/searchresult.asp?search=&author=Zohreh+Hajheydari&journal=Y&but_search=Search&entries=10&pg=1&s=0),  [Jafar Akbari](http://www.ijdvl.com/searchresult.asp?search=&author=Jafar+Akbari&journal=Y&but_search=Search&entries=10&pg=1&s=0),  [Majid Saeedi](http://www.ijdvl.com/searchresult.asp?search=&author=Majid+Saeedi&journal=Y&but_search=Search&entries=10&pg=1&s=0),  [Leila Shokoohi](http://www.ijdvl.com/searchresult.asp?search=&author=Leila+Shokoohi&journal=Y&but_search=Search&entries=10&pg=1&s=0), Comparing the therapeutic effects of finasteride gel and tablet in treatment of the androgenetic alopecia. Indian J D V 2009:75;1: 47-51.

163. Trueb RM, Itin P. Photographic documentation of the effectiveness of 1 mg. oral finasteride  
in treatment of androgenic alopecia in the man in routine general practice in Switzerland]. Schweiz Rundsch Med Prax 2001;90:2087-93.

164.   Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, et al.The effect of 5alpha reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab 2007;92:1659-65.

165. Tollin SR, Rosen HN, Zurowski K, et al. Finasteride therapy does not alter bone turnover in men with benign prostatic hyperplasia--a Clinical Research Center study. J Clin Endocrinol Metab 1996;81:1031-4.

166.   Matsumoto AM, Tenover L, McClung M, et al. The long-term effect of specific type II 5alpha-reductase inhibition with finasteride on bone mineral density in men: results of a 4-year placebo controlled trial. J Urol 2002;167:2105-8.

167. Wade MS, Sinclair RD. Reversible painful gynaecomastia induced by low dose finasteride (1 mg/day). Australas J Dermatol 2000;41:55.

168. Ferrando J, Grimalt R, Alsina M, et al. Unilateral gynecomastia induced by treatment  
with 1 mg of oral finasteride. Arch Dermatol 2002;138:543-4.

169. Rahimi-Ardabili B,  Pourandarjani R, Habibollahi P,  Mualeki A Finasteride induced depression: a prospective study. Clin Pharmacol. 2006; 6: 7

170.   Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin Endocrinol Metab 2004;89:2179-84.

171.   Clark RV, Hermann DJ, Cunningham GR, Wilson TH, Morrill BB, Hobbs S. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5-alpha-reductase inhibitor. J Clin Endocrinol Metab 2004;89: 2179-84.

172. .Dallob AL, Sadick NS, Unger W et al. The effect of finasteride, a 5-alpha-reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. J Clin Endocrinol Metabol 1994;79:703-6.

173. Olsen EA, Hordinsky M, Whiting D, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol 2006;55:1014-23.

174.   Debruyne F, Barkin J, van Erps P, et al. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. Eur Urol 2004;46:488-94.

175.   Olszewska M, Rudnicka L. Effective treatment of female androgenic alopecia with dutasteride. J Drugs Dermatol 2005;4:637-40.

176.[Eun HC](http://www.ncbi.nlm.nih.gov/pubmed?term=Eun%20HC%5BAuthor%5D&cauthor=true&cauthor_uid=20605255), [Kwon OS](http://www.ncbi.nlm.nih.gov/pubmed?term=Kwon%20OS%5BAuthor%5D&cauthor=true&cauthor_uid=20605255), [Yeon JH](http://www.ncbi.nlm.nih.gov/pubmed?term=Yeon%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=20605255), [Shin HS](http://www.ncbi.nlm.nih.gov/pubmed?term=Shin%20HS%5BAuthor%5D&cauthor=true&cauthor_uid=20605255) et al.  Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: a randomized, double-blind, placebo-controlled, phase III study.[J Am Acad Dermatol.](http://www.ncbi.nlm.nih.gov/pubmed/20605255) 2010 Aug;63(2):252-8

176177.   Andriole GL, Kirby R. Safety and tolerability of the dual 5- alpha reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. Eur Urol 2003;44:82-8.

178. Sovak M, Seligson AL, Kucerova R, et al. Fluridil, a rationally designed topical  
agent for androgenetic alopecia: first clinical experience. Dermatol Surg 2002;28:678-85.

179. Wolf, R. et al. Prostaglandin analogs for hair growth: great expectations. Dermatol. Online J. (2003)  9, 7

180.Blume-Peytavi U, Lonnfors S, Hillmann K, et al. A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. J Am Acad Dermatol. 2012 May;66(5):794–800.  
  
181. Piérard GE,  Piérard Franchimont C‌ , Nikkels-Tassoudji N et al. Improvement in the inflammatory aspect of androgenetic alopecia. A pilot study with an antimicrobial lotion. [Journal of Dermatological Treatment](http://informahealthcare.com/loi/jdt)1996, Vol. 7, No. 3, Pages 153-157   
  
182. Inui S, Itami S. Reversal of androgenetic alopecia by topical ketoconzole: relevance of anti-androgenic activity. J Dermatol Sci 2007;45:66-8.

183.. Hugo Perez, B.S. (2004) Ketocazole as an adjunct to finasteride in the treatment of androgenetic alopecia in men. Med. Hypotheses 62, 112-115.

184.. Zimber MP, Ziering C, Zeigler F, et al. Hair regrowth following a Wnt- and follistatin containing treatment: safety and efficacy in a first-in-man phase 1 clinical trial. J Drugs Dermatol. Nov 2011;10(11):1308-12.

185..Rose, P. (2011). "The Latest Innovations in Hair Transplantation". Facial Plastic Surgery 27 (4): 366–377.

186. Takikawa M, Nakamura S, Nakamura S, et al. Enhanced effect of platelet-rich plasma containing a new carrier on hair growth. Dermatol Surg. 2011 Dec; 37(12):1721–9.

187.. Lee GY, Lee SJ, Kim WS. The effect of a 1550 nm fractional erbium-glass laser in female pattern hair loss. J Eur Acad Dermatol Venereol. 2011 Dec;25(12):1450–4.

188.. Leavitt M, Charles G, Heyman E, et al. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: A randomized, double-blind, sham device-controlled, multicentre trial. Clin Drug Investig.2009;29(5):283–92

189.   Okuda S. The study of clinical experiments of hair transplantation. Jpn J Dermatolurol.  1939;46:135

190.   Orentreich N. Autografts in alopecias and other selected dermatological conditions..Ann N Y Acad Sci. 1959 Nov 20;83:463-79.

191. Bernstein RM, [Rassman WR](http://en.wikipedia.org/w/index.php?title=Rassman_WR&action=edit&redlink=1), Szaniawski W, Halperin A: Follicular Transplantation. Intl J Aesthetic Restorative Surgery 1995; 3: 119-32

192..    [Khandpur S](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Khandpur%20S%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract), [Suman M](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Suman%20M%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract), [Reddy BS](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Reddy%20BS%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract). Comparative efficacy of various treatment regimens for androgenetic alopecia in men. [J Dermatol.](javascript:AL_get(this,%20'jour',%20'J%20Dermatol.');) 2002 Aug;29(8):489-9.

193..[Boyapati A](http://www.ncbi.nlm.nih.gov/pubmed?term=Boyapati%20A%5BAuthor%5D&cauthor=true&cauthor_uid=22686691), [Sinclair R](http://www.ncbi.nlm.nih.gov/pubmed?term=Sinclair%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22686691). Combination therapy with finasteride and low-dose dutasteride in the treatment of androgenetic alopecia.[Australas J Dermatol.](http://www.ncbi.nlm.nih.gov/pubmed/22686691" \o "The Australasian journal of dermatology.) 2013 Feb;54(1):49-51.

194.    Kassimir JJ. Use of topical minoxidil as a possible adjunct to hair transplant surgery.A pilot study. J Am Acad Dermatol 1987;16:685-7.

195.   Roenigk HH, Berman MD. Topical 2% minoxidil with hair transplantation. Face 1993;4:213-6.

196. Leavitt M, Perez-Meza D, Rao NA et al. Effects of finasteride (1 mg) on hair transplant. J Dermatol Surg 2005;31:1268-76.