Clinical Patterns of Hair Loss in Men

Is Dihydrotestosterone the Only Culprit?

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KEYWORDS

• Alopecia • Androgenetic alopecia • Pathway • Oxidative stress • Inflammation • Prostaglandin • Comorbidities • Risk factors

KEY POINTS

- Pathways and factors, including oxidative stress, inflammation, prostaglandins, vasculogenesis, Wnt/β-catenin, and transforming growth factor-β, have increasingly been shown to be important in the pathophysiology of androgenetic alopecia in men.
- There is limited but increasing evidence of the potential safety and efficacy of treatments targeting these pathways for androgenetic alopecia.
- Lifestyle factors and comorbidities including cardiovascular risk factors have been shown to be associated with male androgenetic alopecia.
- Changes in hair characteristics related to aging, termed senescent alopecia, often coexist with male androgenetic alopecia with advancing age.
- Further study of these pathways, risk factors, and comorbidities is important to better understand the pathophysiology, find potentially useful therapeutic targets, and ensure a comprehensive approach to the management of androgenetic alopecia in men.

INTRODUCTION

The pathophysiology of male androgenetic alopecia (AGA) has focused on the role of androgens, mainly dihydrotestosterone (DHT) and its production by 5α-reductase. Inhibitors of 5α-reductase have been developed and studied for male AGA including finasteride, which was approved by the US Food and Drug Administration for the treatment of male AGA in 1998. Overall, the important role of DHT in the pathophysiology of male AGA and as a therapeutic target has been well-established. However, there is increasing evidence of other important pathways and factors in the development and pathophysiology of male AGA, which are discussed herein.

OXIDATIVE STRESS

Reactive oxygen species (ROS) are created during normal cellular function and have important physiologic functions, including maintenance of β-catenin

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and notch signaling during normal hair follicle development and in the cycling of fully developed hair follicles from anagen to catagen.[1–4] Oxidative stress occurs when there is an imbalance between ROS production and normal methods of reduction such as antioxidant function to avoid damage to cell membranes, lipids, protein, and DNA.[4] Lipid peroxidation in particular has been shown to lead to the induction of apoptosis and early catagen in murine hair follicles.[5]

In vitro human studies of men with AGA have shown increased markers of and increased sensitivity to oxidative stress in dermal papilla cells from a balding scalp compared with those from a nonbalding scalp.[6,7] A study analyzing microarray gene expression data from balding and nonbalding scalps in 5 male patients with AGA found upregulated genes in the oxidative stress pathway.[8] In cultured human hair follicles, oxidative stress has been shown to lead to apoptosis and matrix growth inhibition.[9] Activation of the transcription factor, nuclear factor erythroid 2-related factor 2, has been shown to prevent this growth inhibition following ROS exposure, and nuclear factor erythroid 2-related factor 2 activators, including metformin and sulforaphane, have been suggested as potential therapies.[9–11] However, studies of their effect on hair growth have been limited to murine studies, and there is evidence that these agents additionally act on hair growth through other pathways.[10,11]

A number of small case control studies compared serum markers of oxidative stress, including oxidant levels, antioxidant levels, and oxidative stress index. Although the individual methods of measuring oxidative stress differed between studies, generally there were indicators of higher serum oxidative stress in patients with AGA, including early-onset AGA in some studies, compared with age-matched controls.[12–14] Of note, limitations of these studies include small size, lack of prospective data, and measure of serum not follicular oxidative stress. Larger and prospective studies are still needed to better characterize the association and determine the clinical significance and causal or temporal relationship between oxidative stress and AGA.

The demonstration of the importance of oxidative stress in AGA has led to the investigation of a number of antioxidants for the treatment of AGA. There have been limited in vivo human studies on the efficacy of systemic antioxidants; these include a case series on systemic dexpanthenol, a few nonrandomized prospective studies on topical antioxidants, topical melatonin, and oral nutritional supplements, as well as randomized controlled trials on oral tocotrienols, topical procyanidin B-2, topical melatonin, topical herbal extracts, and oral nutritional supplements.[15–28] However, these studies are relatively small with short follow-up periods, some were performed in mostly females, and many include combination therapies with multiple antioxidant, anti-inflammatory, and antiandrogenic agents. Further investigation into their safety and efficacy for male AGA, ideal methods of delivery, dosing, combinations, and larger prospective studies including further comparative studies are still needed.

Additionally, a number of largely speculative studies have proposed that UV exposure may be linked to AGA through direct damage of hair follicles by way of the generation of oxidative stress and a proinflammatory state.[4,29,30] More recently, an in vitro study by Lu and colleagues[31] characterized the response of human hair follicles to UV exposure and found evidence to support oxidative stress, inflammation, and reduced proliferation of hair follicles following UV exposure. Of note, the in vivo clinical significance of UV exposure in AGA has not been studied. Other sources of oxidative stress include inflammation, smoking, poor nutrition, and aging (see corresponding sections elsewhere in this article).[4,30–33]

Further study of the role of oxidative stress and antioxidants in AGA is required to both better understand the pathophysiology of AGA and to determine the potential usefulness of various antioxidants in the treatment of AGA.

INFLAMMATION

The role of inflammation in AGA has been investigated by a number of small studies that performed direct immunofluorescence and histopathologic studies on scalp biopsies from patients with AGA. These studies have reported clear evidence of inflammation including granular deposits of immunoglobulin M or complement component 3 at the basement membrane, activated T-cell infiltrates at the follicular infundibula and follicular bulge, mast cell degranulation and fibroblastic activation in the fibrous sheath, and ultimately fibrosis.[34–38] This inflammation has been termed follicular microinflammation because the process involves a slow, subtle, and indolent course, in contrast with the more robust inflammatory and destructive process in inflammatory scarring alopecias.[29,39]

The precise pathophysiology of this microinflammatory process has yet to be established; however, biopsies from areas of clinically uninvolved scalp in patients with AGA already demonstrate the presence of inflammatory infiltrates and fibrosis, indicating that follicular

microinflammation is not a secondary phenomenon but an active participant in pathogenesis.[36,37,40,41] Additionally, there is a correlation between inflammatory infiltrates and apoptosis in miniaturized follicles, suggesting that inflammation can play a role in the pathogenesis of follicle miniaturization.[42] Proinflammatory cytokines like interleukin-1 and tumor necrosis factor-α are also known to induce premature catagen, liberate ROS, cause apoptosis, and further propagate inflammation.[29,43] Transforming growth factor-β may also be implicated because it plays a role in perifollicular fibrosis and miniaturization.[44] Alterations in cytokine and protein expression might not be immediately destructive, but over time they may chronically dysregulate physiologic cycling dynamics and follicle stem cell homeostasis.[29,36,37,41,45,46]

Additionally, more recent studies have found that the extent of inflammation correlates with the most severe clinical forms of AGA, and the addition of anti-inflammatory therapies to AGA treatment has led to improved treatment outcomes.[37,38] Clearly the presence and role of inflammation cannot be ignored in the pathophysiology of hair loss, and future therapeutic approaches to AGA should comprehensively address the multiple factors that affect the follicle including inflammation.[46]

PROSTAGLANDINS

Prostaglandins (PGs) have been actively studied in AGA given their role in inflammation, vasculogenesis, and wound healing.[47] Their generation starts with the release of arachidonic acid from cell membrane phospholipids by phospholipase A_2.[48,49] Arachidonic acid is then metabolized by either PG H synthases (PGHS) or lipoxygenases to form PGH_2 or leukotrienes, respectively.[50] PGH_2 is the precursor of PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), and thromboxane A_2.[51]

Although the exact role of prostanoids in the regulation of hair growth and cycling is unknown, it is clear that there exists a complex homeostasis at the follicular level of products of the arachidonic acid pathway. PGHS enzymes are expressed in hair follicles and sebaceous glands.[52–54] This expression includes the widely distributed PGHS-1 and inducible PGHS-2 isoforms, which have been immunolocalized to the dermal papilla during anagen and catagen.[55] Murine studies have shown evidence of PGD_2 inhibiting hair growth, and a human study in men with AGA found higher protein and messenger RNA levels of PGD_2 synthase enzyme and PGD_2 in bald scalp compared with nonbald scalp.[56,57] Studies in cultured dermal papilla cells have demonstrated that minoxidil stimulates PGE_2 and leukotriene B_4 production and inhibits PGI_2 synthesis.[58]

Perhaps the strongest evidence of the role of PGs on hair cycling has been the serendipitous discovery that topical synthetic $PGF_{2\alpha}$ analogues, including latanoprost and bimatoprost used in the treatment of glaucoma, cause eyelash hypertrichosis.[59] Human clinical trials have found topical bimatoprost, in multiple concentrations and dose frequencies, to be inferior to minoxidil but superior to placebo.[59]

VASCULOGENESIS

The dermal papilla, which controls hair growth, is characterized in the anagen phase by a highly developed vascular network and in the telogen phase by a disappearance of blood vessels in the dermal papilla and the hair bulb.[60] Two studies have investigated the effects of minoxidil on the balding scalp in regards to skin blood flow using laser Doppler velocimetry, with 1 study finding evidence of increased blood flow after the application of a 5% solution and a second failing to find any change in blood flow after the application of a 3% solution.[61,62] Although the effects of topical minoxidil on skin blood flow are nonconclusive, the concept of increased vasculogenesis and its role in hair growth and hair cycling has sparked further research interest.

Vascular endothelial growth factor (VEGF) has a pivotal role in promoting angiogenesis as well as influencing a vast array of cell functions, such as promoting cell survival, proliferation, and generation of nitric oxide and PGI_2.[63] Capillary proliferation during anagen phase has been demonstrated to be temporally and spatially associated with expression of VEGF in the outer root sheath of murine follicles.[64] Additionally, in cultured human dermal papilla cells, minoxidil has been shown to increase VEGF expression in a dose-dependent manner.[60]

Platelet-rich plasma is gaining steam as a new strategy for the treatment of AGA. Although limited by great variation in the methods of its preparation and administration, there is increasing evidence of its efficacy in the treatment of AGA.[65] Additionally, platelet-rich plasma has been shown to contain and lead to increased endogenous expression of a number of growth factors, including VEGF, platelet-derived growth factors, insulin-like growth factor, and epidermal growth factors, which promote angiogenesis and differentiation of cells in the scalp microenvironement.[65]

It is clear that there exists a temporal and spatial relationship between the capillary follicular

network and the cycling of hair follicles. Perhaps VEGF plays a central role in this pathway, and minoxidil and platelet-rich plasma may increase VEGF and other growth factors, thereby helping to promote follicular angiogenesis. However, further study is still needed.

WNT/β-CATENIN AND TRANSFORMING GROWTH FACTOR-β PATHWAYS

Decreased Wnt/β-catenin and increased transforming growth factor-β pathway signaling are known to be important in the development of miniaturization and decreased hair growth in AGA through both DHT-dependent and DHT-independent pathways, and recently crosstalk between the Wnt and transforming growth factor-β pathways has been demonstrated in follicles from balding scalp in males with AGA.[8,44,66–69] DHT has been shown to decrease Wnt activity through the upregulation of the Wnt inhibitor, dickkopf-1 (DKK-1).[66] This DKK-1 activity has been shown in in vitro studies to be key to the inhibition of outer root sheath keratinocytic growth by DHT; the inhibition was reversed with neutralizing antibodies to DKK-1.[66] Additionally, balding scalp has been shown to have higher levels of DKK-1 compared with nonbald scalp in patients with AGA.[66] L-Ascorbic acid 2-phosphatase and L-threonate have been shown to repress DHT-induced DKK-1 protein expression in human dermal papilla cells, and L-threonate led to reversal of growth inhibition of outer root sheath cells by DHT.[70,71] These agents show potential in the treatment of AGA although no in vivo studies have been performed.[70,71]

AGING

The scalp is subject to both intrinsic and extrinsic aging, including increased oxidative stress.[4,32,72–75] Intrinsic factors are related to genetic and epigenetic mechanisms, whereas extrinsic factors include ultraviolet radiation, pollution, and chemical treatments, among others.[76] Natural aging is characterized by weathering of the hair shaft, decrease in melanin and hair production, and the development of increasingly dry, thin, dull, and brittle hair.[77] Although many people assume that AGA is associated with aging, some people may never develop it no matter how long they live.[78] Senescent alopecia refers to diffuse scalp hair thinning seen with advanced age in individuals without a family history of hair loss or evidence of pattern balding.

Senescent alopecia was described as a distinct process in the 1980s and is characterized histologically by a modest reduction in the size of otherwise normal hair follicles.[79] This process was contrasted with the miniaturization, inflammation, and fibrosis seen with histologic evaluation of male pattern baldness.[79] However, there has been controversy regarding the existence of senescent alopecia as a distinct clinical entity; some studies suggest that many cases of alopecia in older individuals are AGA and that aging itself is not a cause of hair loss.[80] And although it is true that natural aging does not contribute to a significant loss in the number of hairs, most now accept that the main features of senescent alopecia are decrease in hair diameter and length.[81,82] Additionally, there is now evidence of differential gene expression in senescent alopecia and AGA.[83] Senescent alopecia can also be present concurrently with other types of alopecia, including AGA. In older individuals, this overlap can be quite common.[78,84]

Although much of the dermatology literature on age-associated hair changes focuses on hair loss, it is also important to consider that the diameter, length, curvature, and other structural properties of the hair fibers can impact the overall cosmetic appearance of hair.[39] To limit the effects of natural aging on hair health and combat senescent alopecia, it is important to take a holistic approach. Extrinsic components of natural hair aging can be treated with topical antiaging compounds, including photoprotectors and antioxidants, with varying levels of success.[76] Intrinsic components can also be addressed. When concomitant medical hair loss conditions are present such as AGA, seborrheic dermatitis, or psoriasis, they should be treated accordingly with appropriate medical therapy.[39] It is also important to manage age-related general health problems that can affect the condition of the hair: nutritional, endocrine, psychological, drug-related, substance abuse (including smoking), and multimorbidity (see the Lifestyle and Comorbidities section elsewhere in this article).[39]

LIFESTYLE FACTORS AND COMORBIDITIES

Smoking is hypothesized to contribute to hair loss through reduced blood flow to the follicle, DNA damage, pro-oxidant and proinflammatory effects, effects on collagen and elastin, effects on the protease/antiprotease system, inhibition of aromatase, and increased hydroxylation of estradiol.[4,85] Additionally, nuclear factor erythroid 2-related factor 2 may provide a link between smoking and oxidative stress and be a potential therapeutic target based on studies in other cell types, although further study in hair is still needed.[86,87]

A number of observational cross-sectional studies, case-control studies, and a single study of identical twins have shown a potential association between either smoking, alcohol consumption, diet, working hours, and/or stress and AGA.[85,88–97] Importantly, this research provides an opportunity to counsel AGA patients who smoke on the importance of smoking cessation given the potential connection to AGA in addition to the other numerous well-established negative health outcomes. However, other cross-sectional and case-control studies of male patients with AGA have shown no association between either smoking, alcohol consumption, diet, sleeping habits, and/or work and the incidence of AGA.[91,95,96,98,99]

The link between AGA, including early-onset AGA, in men and cardiovascular disease risk factors has been studied over the last 48 years.[100] Numerous case-control studies, cross-sectional studies, meta-analyses, and 1 prospective cohort study among different populations have investigated the association between AGA and various cardiovascular risk factors, including coronary artery disease, metabolic syndrome, insulin resistance, type II diabetes mellitus, an unfavorable lipid profile, systolic or diastolic hypertension, arteriolosclerosis, and increased body mass index or obesity.[101–112] The majority of studies have concluded that there was an association between male AGA and at least 1 of these cardiovascular risk factors; however, which risk factors have been shown to have a significant association with AGA have varied among different studies. Conversely, a few case-control studies have not found a statistically significant association between AGA and any of the risk factors they evaluated.[113,114] Further, a number of studies not only found an association between AGA and at least 1 risk factor, but also found a correlation between the severity of early-onset male AGA and the degree of cardiovascular risk with largely greater than grade III on the Norwood–Hamilton scale and vertex balding associated with higher risk.[101,104,106–108] Both AGA, especially early-onset AGA, and many cardiovascular risk factors, including metabolic syndrome, insulin resistance, coronary artery disease, and obesity, have been linked to oxidative stress, and a better understanding of oxidative stress and AGA may help to explain its association with other conditions. Additionally, in family clusters of women with polycystic ovarian syndrome, evidence shows that men are also affected with the disease—phenotypically expressed as early-onset AGA.[115–117] In fact, a number of clinical and biochemical profile abnormalities, including insulin resistance, low sex hormone–binding globulin, low follicle-stimulating hormone, and high luteinizing hormone, have been noted to be similar between early-onset male AGA and female polycystic ovarian syndrome, suggesting a possible link and providing a potential mechanism for the association between male AGA and cardiovascular disease risk.[115–119]

Variations in the results of studies investigating associations between AGA and numerous lifestyle factors and comorbidities may reflect differences among different populations studied. Additionally, limitations based on study design include the potential for confounding factors. Clearly, further large well-designed studies adjusting for confounding factors and prospective studies are needed to further try to elucidate what factors are not only associated but potentially causative of alopecia. Additionally, further study into the pathophysiology of potential causative factors are needed to better understand their role in the development of AGA.

SUMMARY

The role of 5α-reductase activity and DHT and its usefulness as a therapeutic target for male AGA has been well-established. Additionally, a number of other contributing factors and pathways have been investigated and shown to be involved in AGA in men. Further studies of these pathways in how they relate to AGA and how these translate to potential therapeutic options are still needed.

CLINICS CARE POINTS

- A number of pathways and factors including oxidative stress, inflammation, prostaglandins, vasculogenesis, Wnt/β-catenin, and transforming growth factor-β have increasingly been shown to be important in the pathophysiology of AGA in men.
- There is limited but increasing evidence of the potential safety and efficacy of treatments targeting these pathways including antioxidants, anti-inflammatory agents, prostaglandins, growth factors promoting vasculogenesis, and promoters of the Wnt/β-catenin pathway for AGA.
- Lifestyle factors and comorbidities including cardiovascular risk factors have been shown to be associated with male AGA.
- Changes in hair characteristics related to aging, termed senescent alopecia, often coexists with male AGA with advancing age.

- Further study of these pathways, risk factors, and comorbidities is important to better understand the pathophysiology, find potentially useful therapeutic targets, and ensure a comprehensive approach to the management of AGA in men.

DISCLOSURE

The authors have nothing to disclose.

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