Hair Restoration: Looking Beyond Minoxidil, Finasteride and Hair Transplantation

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**Editorial**

Hair loss is one of the most commonly encountered problems for dermatologists. Hair have a huge impact on a person's looks and self-esteem. Needless to say, hair loss and/or reduction of scalp hair density and thinning of hair have a profound negative impact on one's quality of life. Several studies have shown show that balding patients develop a negative self-perception, which appears to be consistent between Western and Asian cultures [1,2]. Advanced PHL, especially at an early age may even be a source of depression in young adults.

Androgenetic alopecia (AGA) is the most common form of hair loss in men and women; also known as the male (MPHL) and female (FPHL) patterned hair loss respectively. It has been suggested that up to 70% of men and 40% of women will experience some degree of AGA in their lifetime [3]. The hallmark of the condition is progressive and gradual miniaturization of hair follicles (HFs), which leads to transformation of terminal follicles into vellus-like thin hair. Follicle miniaturization is accompanied by progressive decrease in the duration of anagen with reduction of anagen to telogen ratio. Although, the exact etiopathogenesis of AGA remains unclear, evidence suggests that the major pathophysiological factor involved in the genesis of AGA is the undesirable androgen metabolism at the hair follicle level. The most significant factor in men is elevated activity of Type II isoform of the 5-alpha reductase (5AR) enzyme, which metabolizes testicular testosterone circulating in the blood into dihydrotestosterone (DHT) in the genetically predisposed hair follicles of the temporal and vertex regions. In women, the elevated local concentration of testosterone due to decreased activity of aromatase activity (the enzyme that converts ovarian testosterone circulating in the blood into 17 beta-estradiol) seems to be a significant contributory factor [4]. The androgen receptors that are abundantly expressed by predisposed hair follicles, bind to the increased local levels of DHT, resulting in progressive shortening of anagen and progressive miniaturization of the hair follicles. This eventuates the transformation of thick, pigmented terminal hair into thinner, non-pigmented vellus-like miniaturized hair [5].

Based on the hitherto held assumption of dysregulated androgen metabolism and its effect on genetically predisposed hair follicles being the major cause of AGA, only two therapeutic agents have been approved to date by the United States Federal Drug administration (FDA) and European Medicines Agency (EMEA) for treatment of AGA: topical minoxidil (MNX) in different percentages for both women and men, and oral finasteride (FIN) for men [6]. However, both options suffer the limitations of overall efficacy (which is often less than the patients’ expectations), delayed onset of effect and their specific adverse effects (AE). While FIN inhibits 5a-reductase (5AR) type II enzyme, resulting in reduced conversion of testosterone to DHT, the mechanism of MNX is not very clear. It has been suggested minoxidil increases follicular vascularity (as a potassium channel opener), prolongs anagen, shortens telogen, and converts partially miniaturized (intermediate) to terminal hair [7]. Despite regular use of MNX lotion and oral FIN, many patients are not fully satisfied with the response. Apart from the slow onset of effect, another limitation of MNX and FIN is that after 1-2 years of continuous use, the hair regrowth response of these medications reaches a plateau, after which further increase in density or thickness of hair fibres is not appreciable. Another deterrent to the use of these two medications is their adverse effects (AE) profile. Finasteride has the potential of resulting in sexual adverse effects (SAEs) in men, including decreased libido, ejaculatory dysfunction and impotence. While some cases represent true sufferers of these SAEs, another grave issue with FIN is the recently identified and appreciated phenomenon, called the nocebo effect [8]. The nocebo effect is best defined as the occurrence of adverse effects to a therapeutic intervention because the patient expects them to develop. Sexual adverse effects of finasteride have over time become well publicised and are often already known to the patients when they visit the dermatologist. Discussion with peers and notions derived from reading non-medical information freely available on the net (websites and blogs) skew the patient's thinking towards presuming that SAEs will occur [8]. In a recent study by Mondaini et al. in patients with benign prostatic hyperplasia, blinded administration of 5 mg finasteride was associated with a significantly higher proportion of sexual dysfunction in patients informed about SAEs, compared with those who were uninformed [9]. Certain studies have further documented a new long-term adverse effect of FIN, the ‘post-finasteride syndrome’[10,11]. This syndrome is characterized by sexual and certain non-sexual adverse effects experienced around 3 months after stopping the medication and persisting indefinitely. Although the true existence of this syndrome is debatable, it has generated a commotion in the scientific community as well patients and may further contribute to refusal of male patients to accept FIN as a treatment for their hair loss. However, pending a settling conclusion to the causal and statistical association between FIN and SAEs, the prospect of drug-induced impotence remains appalling for the layman, and a hindrance to the compliant use of this otherwise effective drug by the skeptical patients. [8].

Minoxidil tends to cause scalp irritation and dryness of hair in some users, sometimes to the extent of intolerance. Moreover, MNX is known to result in unwanted facial hypertrichosis in women, especially in those with polycystic ovarian syndrome (PCOS) due to an imbalance hormonal milieu [12]. Last but not the least, many patients report being prescribed the same drugs i.e., MNX and/or FIN, alone or in combination by different trichologists they consulted (with change of either the percentage of MNX or the brand). This also tends to reduce compliance and foster an alternate health seeking behavior;
ending up in the use of medically unproven home-based or complimentary medicine remedies.

Hair transplantation, despite being one of the best options of hair restoration, especially in advanced stages of AGA, has its own limitations. Besides the reluctance of many patients of getting a ‘surgery’ done, other issues that become a barrier for hair transplantation include – the down time needed for post-surgery healing, possibility of scarring over the donor site(s), sub-optimal results or failure resulting from follicular transaction sustained in the hands of an inexperienced surgeon, treatment cost, and the need of using MNX and/or FIN to maintain the growth of transplanted hair [13].

In view of the psycho-cosmetic importance of hair regrowth for patients suffering from AGA, and the limited efficacy and adverse issues associated with conventional treatment options, it became imperative to develop newer, efficacious and safe congeners and drugs other than MNX and FIN. Additionally, recent studies have brought to light, mechanisms other than the androgen-effect that significantly contribute to the pathogenesis of AGA. These relatively newfangled pathophysiological factors include:

Follicular microinflammation

The role of follicular microinflammation and fibrosis is being increasingly recognized. In FPHL as well male AGA, the miniaturization process may be accompanied by a mild to moderate lymphohistiocytic inflammatory infiltrate in the peri-infundibular region [14,15].

Oxidative stress

Natural aging process (senile AGA), unabated long-term exposure to ultraviolet radiation, smoking and environmental pollutants seem to contribute by generation of free radicals, resulting in oxidative stress that is damaging to the hair follicles [16-18].

Loss of extracellular matrix (ECM)

In recent past, the loss of ECM proteins in the follicular bed contributing to progressive reduction in the size of the hair follicle and loss of hair anchoring has gained attention as an additional pathogenetic factor for AGA [19].

Thus, therapies targeting these latterly pathophysiological phenomena have been developed. While many such therapies have already been launched for patient use after their efficacy was proven in completed clinical trials, the evidence for the efficacy of other drugs is being eagerly awaited. In the review article focussing on this aspect, being published in the maiden issue of Journal of Cosmetology and Trichology, I shall dwell in detail upon novel approaches to stimulate hair growth and discuss the established as well as tentative alternative treatment options for PHL, beyond minoxidil, finasteride and hair transplantation.

References