Evidence for Supplemental Treatments in Androgenetic Alopecia

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ABSTRACT

Currently, topical minoxidil and finasteride are the only treatments that have been FDA approved for the treatment of female pattern hair loss and androgenetic alopecia. Given the incomplete efficacy and sife effect profile of these medications, some patients utilize alternative treatments to help improve this condition. In this review, we illustrate the scientific evidence underlying the efficacy of these alternative approaches, including biotin, caffeine, melatonin, a marine extract, and zinc.

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INTRODUCTION

Female pattern hair loss (FPHL) and androgenetic alopecia are estimated to affect at least 40% of women and 50% of men by the age of 50.[1,2] Without intervention, FPHL may be expected to progress at a rate of 10% per year and can cause significant psychological distress for patients.[1] Androgens and genetic factors are both involved in male pattern hair loss, but their role has yet to be elucidated in women. In men, testosterone is converted to dihydrotestosterone by 5-alpha reductase, which then binds to the androgen receptors of the hair follicle dermal papillae and activates the genes responsible for follicular miniaturization.[3] In women, FPHL is the term that has been used to describe this type of hair loss, since the role of androgens is unclear.[4] Although recent evidence has shown that females and males share similar genetic polymorphisms,[5] in this paper, we will use AGA to refer to both male and female pattern hair loss, but use FPHL when specifically referring to studies in women.

Topical minoxidil and oral finasteride are the mainstay of therapy for men. Placebo-controlled randomized trials have revealed both therapies to be efficacious and well-tolerated. A meta-analysis of randomized trials demonstrated treatment with finasteride results in a 24% increase in hair count after 48 months when compared to placebo administration.[6] Finasteride acts as a competitive inhibitor of 5-alpha reductase, and minoxidil increases the length of the anagen phase and decreases the telogen phase. For women, topical minoxidil is currently the only FDA approved treatment for FPHL but primarily halts progression of hair loss.[7] Anti-androgen therapy such as spironolactone has also been suggested as effective therapy for FPHL. In a small study, 88% of 80 women showed either no progression or improvement of their FPHL with anti-androgen therapy.[8]

Given the partial results obtained from these medications and potential adverse effects, both men and women often seek alternative treatments for AGA and FPHL. While a wide array of alternative therapies exists, here we present a review of biotin, caffeine, melatonin, marine protein extract, and zinc solution and their potential role in androgenetic alopecia treatment.

Biotin

Biotin is an essential water-soluble vitamin that acts as a cofactor in carbon dioxide transfer in some carboxylase enzymes which are involved in fatty acid synthesis, amino acid catabolism, and gluconeogenesis.[9] Biotin is also a coenzyme for mitochondrial carboxylases in hair roots.[10] Biotinidase is a critical enzyme in releasing biotin from foods and biotin-containing peptides so that the body can absorb biotin.[10] Genetic causes of biotin deficiency, such as both partial and profound biotinidase deficiency, result in a variety of symptoms including seizures, hypotonia, ataxia, dermatitis, hair loss, mental retardation, ketolactic acidosis and organic aciduria.[11] Interestingly, alopecia resulting from valproic acid administration in rats, likely due to biotin deficiency, was shown to reverse with biotin supplementation.[12] Biotin administration in children who had experienced alopecia after valproic acid treatment also produced a beneficial effect. Interestingly, no significant differences in biotin or biotinidase levels were found in 20 children treated with valproic acid and 10 children treated with carbamazepine when compared to 75 controls. Despite this, the alopecia was reversed in 3 patients treated with oral biotin administration for 3 months.[13] In 32 pediatric patients treated with valproic acid, the mean biotinidase activity was found to be reduced in the first three months of treatment but returned to normal in the sixth month of treatment, although the difference was not statistically significant.[14] In another study of 75 pediatric patients treated with valproic acid, the biotinidase activity was significantly reduced as compared with controls ($P<0.001$) and again alopecia was improved with biotin (10 mg/day) administration.[15] These results suggest that valproic acid therapy may cause alopecia through an initial reduction in biotinidase activity, which may account for the utility of biotin therapy in reversing this type of alopecia.

Isotretinoin - associated telogen effluvium may also be attributed to an effect on biotinidase activity as evidenced by a study of 42 patients under isotretinoin (Roaccutane 0.5 mg/kg/24 h) who showed significantly reduced biotinidase levels ($P<0.001$) when compared to 52 controls.[16]

Biotin supplementation has also been used successfully in the treatment of hair loss in dogs.[17] In 119 dogs with symptoms including dull coat, brittle hair, and loss of hair due to unknown factors, 60% showed resolution of all symptoms, 31% showed improvement, and only 9% showed no change. These results suggest that biotin may help improve alopecia in humans, but it is unclear if it would help in all types of alopecia, or only in some cases. In vitro studies have shown no effect on the proliferation and expression of differentiation specific keratins K1 and K10 in cultures of outer root sheath cells after administration of low dose and pharmaceutical doses of biotin.[18] Biotin concentrations likewise had no effect on the expression of keratin K16, involucrin, and filaggrin. To date there have been no clinical trials that have evaluated the efficacy of biotin in AGA, or any other type of alopecia. Biotinidase levels also have not been evaluated in AGA.

Caffeine

Caffeine appears to have several medicinal uses. Caffeine citrate has been used in the treatment of idiopathic apnea of prematurity, and caffeine and sodium benzoate have been used in the treatment of acute respiratory depression.[19,20] Caffeine has also been evaluated for cosmetic purposes as it has antioxidant properties and appears to increase the microcirculation in the skin.[21] Recent studies have elucidated a possible role for caffeine in the treatment of AGA as it was shown to stimulate hair growth in vitro. When cultures of hair follicles from male AGA patients were administered different concentrations of testosterone and caffeine, it was discovered that testosterone at a concentration of 5 mg/ml had an inhibitory effect on hair growth that was reversed by caffeine at a concentration of 0.005% (P<0.001). In addition, caffeine at concentrations of 0.001% significantly induced hair follicle growth when added to a testosterone-containing medium (P<0.001).[22] Although in vitro conditions are missing the vitamins, minerals, and other structures present in natural growth conditions, these results suggest a potential benefit of caffeine for AGA treatment, but it is important to note that higher levels of caffeine had an inhibitory effect on hair growth. The authors proposed that caffeine inhibits phosphodiesterase, enhancing cAMP levels, and thereby inducing cell metabolism that results in cellular proliferation.[22]

The topical application of a caffeine shampoo was evaluated for 6 months in 30 men with AGA.[23] Self-reported and dermatological assessments revealed hair loss to be substantially reduced compared to baseline assessments. Furthermore, the hair pull test demonstrated increased tensile strength, with 7.17% reduction in hairs pulled after 3 months and 13.45% reduction after 6 months. However, the results were reported without the performance of statistical analysis and the study was limited by lack of a control group. Placebo controlled randomized trials are needed to better assess the efficacy of caffeine in AGA.

Melatonin

Melatonin is secreted by the pineal gland and regulates the sleep cycle. Indeed, impaired melatonin synthesis is linked to poor quality of sleep among the elderly, and treatment with prolonged release melatonin for three weeks was shown to improve quality of sleep and morning alertness when compared to placebo.[24] Melatonin has also been implicated in the hair cycle, growth, and pigmentation across many species. Murine and human follicles express the melatonin membrane receptor and the nuclear melatonin receptor, whose stimulation inhibits keratinocyte apoptosis and estrogen receptor-a expression.[17] Murine and human hair follicles are also an important site for melatonin synthesis.[17] Melatonin may also reduce DNA damage which can initiate apoptosis in the especially sensitive anagen hair follicle by protecting against free radicals.[25-28] Furthermore, melatonin production in hair follicles may play a role in the regulation of pituitary prolactin synthesis.[29] Stimulation of prolactin receptors in human hair follicles induces the catagen phase.[30,31]

In vitro studies have revealed conflicting results on the effect of melatonin on hair growth. In cultures of male and female human hair follicles, hair shaft elongation was observed with administration of 30 μM melatonin and hair growth inhibition occurred with melatonin in the mM range.[32] Another in vitro study showed no change in human hair follicle growth or proliferation with different melatonin concentrations.[25]

Clinical studies have been conducted to evaluate the safety and efficacy of melatonin in humans. In an open-label observational study, 15 men and 15 women with Stage I or II AGA/FPHL showed significant reduction in severity of hair loss (P<0.001) based on dermatological examinations and self-reported questionnaires after 30 days of daily application of a melatonin solution.[33] To obtain more objective assessments, an extension of the study utilized the TrichoScan digital software to assess hair count and hair density in 35 men with Stage I or II AGA with daily application of a melatonin shampoo for six months. After three months, 54.8% of patients experienced 29% increase in hair density; after six months, 58.1% of patients showed 41% increase in hair density (P<0.001). Hair count was increased by 29.2% after three months and 41.7% after six months (P<0.001). An open-label, multi-center study of 901 men with stage I or II AGA and 990 women with stage I or II FPHL was also conducted[33] The hair pull test was used to measure clinical response. The percentage of patients who were identified as having severe or moderate hair loss decreased from 61.6% to 33.7% after 30 days and to 7.8% after 90 days (P<0.001). The percentage of patients who were assessed as having no hair loss increased from 12.2% to 25.5% after 30 days and 61.5% after 90 days (P<0.001). Treatment with melatonin was also associated with reduction in seborrhea. The percentage of patients experiencing moderately severe or severe seborrhea was reduced from 35.7% to 18% after 30 days, and further decreased to 5.4% after 90 days. The topical melatonin solution was also considered highly tolerable by most physicians and patients.[33]

A placebo-controlled, double-blind, randomized study was performed in 40 women with FPHL or diffuse alopecia defined as

diffuse thinning over entire scalp not due to thyroid disease or iron deficiency.[34] After application of a 0.1% melatonin or placebo solution, anagen hair rate was significantly increased in the occipital region of 12 women with FPHL and in the frontal region of 28 women with diffuse alopecia when compared to placebo (P<0.001). Although not statistically significant, the anagen hair phase was also increased in the frontal region of patients with FPHL and in the occipital region of patients with diffuse alopecia. Measured blood levels of melatonin showed increased levels but these levels were not beyond the physiological night peak. This was the first placebo-controlled study to demonstrate the efficacy and tolerability of melatonin in FPHL or AGA treatment and suggests its potential benefit to be attributed to induction of the anagen phase.

Marine Extract

There are two products that each have a proprietary blend including a marine extract: Hairgain and Viviscal. A compound containing a marine extract was initially shown to be beneficial in brittle hair and nail therapy, which has led to investigations evaluating its effects in AGA and FPHL. A double blind placebo-controlled study of sixty patients comprised of 55 men and 5 women, 56 of whom had AGA, was performed using a dietary supplement with a marine protein extract (Hairgain®) for six months followed by open-label extension for another six months.[35] Clinical response was evaluated using investigator assessments based on internationally accepted scales, close-up photographs, and subject assessments based on a 10 point Visual Analog Scale (VAS). Hair counting in close-up photographs demonstrated 32.4% increase in hair growth in the treatment group and insignificant change in the placebo group after six months. By the end of 12 months, an average hair growth of 63.9% was observed. The group initially receiving placebo experienced 60.8% increase in hair growth. This suggests continued improvement with continued treatment exposure. The VAS scores were also significantly higher in the treatment group compared to the placebo group (P<0.001). No serious side effects were reported by the end of the study. The mechanism of action for this supplement is unknown. Further studies are needed to evaluate the effect of treatment discontinuation with response maintenance. Furthermore, 55 of the 60 patients were men, which limits the generalizability of the results to the female population.

To better assess the efficacy of a marine extract supplement among females, a double-blind placebo controlled study was conducted using another marine protein extract (Viviscal®) for 180 days among 15 women with self-perceived hair thinning.[36] Clinical assessments were based on close-up photographs of designated 4 cm^2 region and self-assessment questionnaires. The mean number of terminal hairs in the target region increased from 271.0 at baseline to 571 after 90 days and 609.6 after 180 days which was significantly higher than the placebo treated group with P<0.001. In self-assessment questionnaires, significantly more subjects in the treatment group reported increased hair volume after 90 days. After 180 days, patients also reported enhanced hair shine and skin smoothness. No adverse events occurred with treatment. Thus, this study supports the efficacy and tolerability of this marine extract supplement among females, although not specifically for those with FPHL. While these two studies suggest that marine protein extract may be helpful in hair loss, information on whether they contain the same marine protein extract is not available since these are proprietary formulas.

Zinc

Zinc is crucial for proper enzyme functioning and its deficiency is also associated with alopecia.[37,38] In one case report, a child whose hair loss was attributed to zinc deficiency no longer experienced hair loss progression with zinc supplementation.[39] Serum zinc levels were assessed in patients with AGA, FPHL, alopecia areata, and telogen effluvium and were found to be significantly lower in all groups as compared to the control group, but were lowest in those with alopecia areata and telogen effluvium, so the role of zinc deficiency in AGA and FPHL is unclear.[40] In a randomized, double-blinded study of 200 men with type III and type IV AGA, the efficacy of 1% pyrithione zinc shampoo, 5% minoxidil topical solution, and a combination of the two treatments were compared to placebo treatment.[41] Subjects and investigators rated their hair growth based on photographic depictions. After 9 weeks, all treatment groups demonstrated a significant increase in hair count as compared to placebo (P<0.05). Increase in hair count for the 1% pyrithione zinc shampoo was slightly less than half that for the 5% minoxidil solution. No increase in hair count was observed with the combination treatment versus the 5% minoxidil solution. In addition, the increase in hair count by pyrithione zinc shampoo use was only appreciated by the investigators. Thus, daily use of 1% pyrithione zinc shampoo may induce some improvement in AGA, although not comparable to minoxidil treatment, and possibly not cosmetically acceptable. It is possible that pyrithione zinc shampoo improved mild hair loss related to seborrheic dermatitis. Furthermore, this study provides no information on the efficacy of pyrithione zinc shampoo for the treatment of FPHL. Longer and larger clinical trials are needed to better assess the safety and efficacy of this treatment.

While oral zinc supplementation has been found to be helpful in some cases of telogen effluvium and zinc-deficiency related hair loss, no studies have been done on AGA or FPHL.

CONCLUSION

The challenge of cosmetically acceptable and complete medical treatments for AGA and FPHL often leads patients and physicians to seek alternative therapies. Among these treatments, randomized placebo-controlled studies are only available for melatonin treatments, two marine extract protein dietary supplements, and a pyrithione zinc shampoo. However, to date only one study has compared pyrithione zinc to currently FDA approved treatments. Limitations in hair research include length of treatment and study periods, difficulty in assessing response, and phenotypic diversity, which may lead to variability in treatment response. Thus, while patients and clinicians may choose to supplement

TABLE 1.

Efficacy of Supplemental Treatments

	Possible Mechanism of Action	Evidence for Efficacy
Biotin	coenzyme for mitochondrial carboxylases in hair roots	No clinical trials have been conducted
Caffeine	inhibits phosphodiesterase which enhances cAMP levels, inducing cell metabolism	In vitro studies and open-label studies have shown efficacy
Melatonin	Free radical scavenger; modulates pituitary prolactin synthesis	Efficacy and tolerability shown in one randomized placebo-controlled study (solution)
Marine Extract	unknown	Efficacy and tolerability shown in two randomized placebo-controlled studies of different proprietary blends (oral)
Zinc	Essential for enzyme functioning	Efficacy shown in one randomized placebo-controlled study (shampoo)

standardized treatments with these therapies, their long-term efficacy and safety has not yet been determined. Long-term, multi-center studies are needed to assess these factors and compare them to standard FDA-approved treatments.

DISCLOSURES

The authors have not declared any relevant conflicts.

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