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Review Article

Caffeine and Its Role in Regulation the Androgenetic Alopecia.

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ABSTRACT

Androgenetic Alopecia (AGA) is the most diagnosed form of hair loss dysfunction in both men and women, causing significant psychological distress and reduction the quality of life. AGA is predominantly androgen dependent and genetically predisposed condition that take place when testosterone conversion to the more bioactive metabolite dihydrotestosterone (DHT), which is binds to the androgen receptors of the hair follicle causing a continuous minimization of the hair follicle and reduce in hair density. Nowadays, there are only two FDA-approved drugs for the treatment of AGA: finasteride (inhibit the synthesis of DHT) and minoxidil (opining potassium channels). Recently, newer advances have shown the caffeine which is methylxanthine alkaloids increasingly used for the production of many cosmetics also have potential clinical effects in patients suffering from AGA due to counteract DHT caused minimization of the hair follicle. Moreover caffeine inhibit the phosphodiesterase (PDE) enzyme lead to increases intracellular concentrations of cAMP, which activates several enzymes and transcription factors results in a stimulation of metabolic activity and improve cell proliferation via providing higher levels of energy to the new cells. This review aims to describe the caffeine and its role in regulation and treatment the disorders related to hair loss mainly Androgenetic Alopecia.

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INTRODUCTION

Androgenetic Alopecia (AGA) is the most diagnosed form of hair loss dysfunction in both men and women, causing significant psychological distress and reduction the quality of life [1]. This condition in male is also known as Male-Pattern Alopecia/Baldness/Hair loss, and in women is called Female-Pattern Hair Loss (FPHL) [2]. It affects 30–50% of men and around 30% of women in middle-aged. The AGA increased with age [3]. In Androgenetic Alopecia the term *"Andro"* refers to the androgens (testosterone and dihydrotestosterone) necessary for the improvement of AGA and *"Genetic"* refers to the potential inherited genes [4]. Although the causes are the same; AGA differ microscopically between men and women [3]. Male pattern hair loss (MPHL) commonly shows reduction in hair density and thickness in the both temples. With time, the hairline moves back to form "M" shape. Hair also thins at the top of the head and progressing to form partial or complete baldness. In women the hair becomes thinner all over the head and the hairline does not move back and rarely leads to complete baldness [4]. AGA is predominantly

androgen dependent and genetically predisposed condition that occurs due to the conversion of extra-follicular testosterone to the more bioactive metabolite dihydrotestosterone (DHT) via intrafollicular 5α-reductase enzyme. The DHT is the effector hormone binds to the androgen receptors of the hair follicle, causing a continuous shortening of anagen phase (hair follicle in the growth phase), longer telogen phase (hair follicle in the resting phase) followed by minimization of the hair follicle and decreased in hair density [5]. Although it is neither life threatening nor painful, AGA is commonly a distressful condition may lead to serious psychological concerns including the development of depression and anxiety and has a negative impact on the quality of life. It affects a self-confidence and lowered self-esteem [6].

Nowadays there are only two FDA-approved drugs for the treatment of AGA: finasteride (inhibit the synthesis of DHT) which is act as 5α-reductase type II inhibitor reduces conversion of testosterone to the more bioactive metabolite (DHT). And minoxidil (a drug that acts on the opining potassium channels). But 20-30% of patients with AGA does not respond to these drugs. These agents are able to achieve only limited hair regrowth also they are most useful in the management of early androgenetic alopecia.; as well as we must consider the contraindications and side effects associated with use of this agents, finasteride (oligospermia, teratogenicity) and minoxidil (hirsutism, hypotension, tachycardia), which limit their use in some patients [7,8].

Recently, certain newer advances have shown the caffeine increasingly used for the production of many cosmetics also have beneficial effects in patients suffering from AGA. Although the impact of caffeine on the human organs is well understood, the mechanism of the cosmetic action of caffeine has not been fully explained, so it is important to clarify whether caffeine is really able to improve the hair's condition or not and the ability of caffeine to penetrate the hair follicles is essential when discussing the mechanism of its action on hair [9,10].

Caffeine and Hair Loss

Caffeine is a methylxanthine belonging to the alkaloid family, a group of compounds present naturally in many plants such as coffee and tea, also produced synthetically in some soft drinks. Caffeine is the most widely psychoactive substance in the world due to stimulation the Central Nervous System [11]. In addition its consumed in beverages, foods and the various pharmaceutical products including over-the-counter and weight loss medications and a lot of prescription only medicines to treat menstrual symptoms, headache, general pain relief and muscle pain medication [12].

After its absorption in the stomach and small intestine the caffeine transported with blood and metabolized by the microsomal enzyme system into 3 main derivative paraxanthine speeds up lipolysis, theobromine blood vessels expanded and theophylline relaxes the smooth muscles of bronchi [13].

While in the brain, caffeine acts as a ligand blocks the adenosine receptors. Both ligands, caffeine and adenosine show a high chemical structures similarity. They can affect the release of neurotransmitters such as acetylcholine, dopamine, noradrenaline, gamma-aminobutyric acid, and serotonin, which enhances mood, improves concentration and eliminates physical fatigue [14]. Additionally, caffeine inhibits intracellular phosphodiesterase (PDE) enzymes: Inhibition of PDE increases intracellular concentrations of cyclic adenosine monophosphate (cAMP), which is activates several enzymes and transcription factors linked to fat oxidation and lipolysis. An increase in lipolysis results in a stimulation of cell metabolism. Therefore caffeine can increase metabolic activity and improve cell proliferation via providing higher levels of energy to the new cells [15].

Although it best known as a CNS stimulant, caffeine also acts on myocardial tissue, respiration, smooth muscles and kidney. Moreover anti-inflammatory and antioxidant activities of caffeine have been reported, earlier studies have shown a possible role of caffeine in regulation of AGA and treatment of hair

loss [16]. The phenomenon of hair loss in AGA can be explained by the physiology of hair growth. A single growth period of a hair follicle cycle can be divided into 3 characteristic phases: growth; anagen phase, involution catagen phase, and rest telogen phase [17]. The growth phase of the hair follicle cycle without being cut is proportional to the length of the anagen phase from 2–8 years [18]. The transition between the three phases of the hair follicle cycle is a well-regulated and controlled process [19]. The transition from anagen to catagen is regulated by hair growth regulatory factors including the growth-maintaining insulin-like growth factor 1(IGF-1) and the catagen promoting transforming growth factor-β2 – (TGF-β2) [19]. Hence, higher expression of IGF-1 and lower expression of TGF-β2 are favorable for maintaining the anagen phase. In AGA the presence of androgens leading to a transition from long anagen and short telogen phases to long telogen and short anagen phases, causing a continuous minimization of the hair follicle [20].

The role of caffeine on stimulating the growth of hair can be explained by its ability to counteract DHT causing minimization of the hair follicle and inhibit PDE enzymes. Inhibiting PDE activity increases the intracellular concentration of cAMP, stimulating cellular metabolism in a multitude of new cells. Caffeine decreases tension of smooth muscle near the hair follicle providing an easier delivery of nutrients through the blood vessels to the papillae of hair. Furthermore increase capillary vessel microcirculation in the skin of the head which stimulates rapid growth of the hair [21]. At the same time it is importance to select the optimal caffeine concentration to produce the best physiological response and avoiding inhibitory effects [22].

Pharmacological Role of Caffeine in The Regulation of AGA

Caffeine and its pharmacological role in the regulation of AGA have been investigated in numerous studies *in vitro* and *in vivo* penetration studies as well as in clinical trials all of this study shown the optimal caffeine concentration have important impacts against hair loss.

In vitro study by Fischer et al., (2007), showed that the hair follicle growth was suppressed by testosterone, and caffeine counteracts this testosterone-induced growth suppression. In the absence of testosterone, caffeine alone stimulate hair growth as well as proliferation in the dermal papilla [5].

Importance of follicular penetration of caffeine also observed in many studies, Otberg et al., (2007), showed that the penetration of a topical caffeine containing shampoo formulation (10 mg/ml) using Surface Ionization Mass Spectrometry (SI/MS) technique. After 2 minutes, the penetration of applied caffeine was detected via hair follicles. Hair follicles are the only pathway for fast caffeine absorption during the first 20 minutes after application, Caffeine can be detected up to 24 h after application; therefore, the hair follicles can act as a good reservoir [23].

Also Oberg et al, investigated that the rate of caffeine absorption by hair follicles which are closed by a small amount of a special varnish-wax-mixture *in vivo*, was found the rate of caffeine absorption when hair follicles were open is higher comparison to absorption when the hair follicles were closed [21]. Based on the observation from *in vitro* and *in vivo* penetration studies, randomized double blind clinical trial conducted by Bussoletti et al., (2020), measured the efficacy of a topical caffeine shampoo versus placebo in females with AGA and positive hair pull test, after 6 months of daily application approximately 180 days a significant improvement of hair loss intensity and reduction of number of hairs in the basin with caffeine shampoo compared to placebo [24].

Additionally, randomized double blind clinical trial studies showed by Golpour et al., (2013), topically applied caffeine plus minoxidil (25/25 mg/mL) lotion versus a topical minoxidil lotion alone (25 mg/mL) have been studied in men and women with androgenetic alopecia. After 150 days of application higher patients satisfaction and significant improvement in hair density and thickness with

topical caffeine plus minoxidil (25/25 mg/mL) lotion versus minoxidil (25 mg/mL) lotion alone [25].

CONCLUSION

In conclusion, androgenetic alopecia is recognized by reduction of anagen phase due to the conversion of extra-follicular testosterone to the more bioactive metabolite DHT via intrafollicular 5α- -reductase enzyme leads to minimization of the hair follicle and reduce in hair density, because there are only two hair-loss standard therapeutic drugs for treatment AGA (topical minoxidil and oral finasteride) which are not always provides the expected clinical outcomes. Caffeine new promoting candidate against the human hair loss, which is a well-known stimulant substance that promotes cell proliferation by increasing the metabolic activity. In the regulation of AGA caffeine enhances hair shaft elongation, prolongs anagen-phase duration, counteract the growth suppression of human hair follicles occurred by testosterone and enhances IGF-1 protein expression. All of these findings are supportive the potential clinical effects of caffeine on the regulation of androgenetic alopecia, a widespread problem of hair loss in all ages.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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