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Update on the treatment of androgenetic alopecia

S. RINALDI[1], M. BUSSA[2], A. MASCARO[3]

[1]Department of Plastic and Reconstructive Surgery, "Sapienza" University of Rome, Rome, Italy
[2]O.U. of Anesthesia, Intensive Care and Pain Therapy of Sant'Antonio Abate Hospital, Casa Santa Erice, Trapani, Italy
[3]Institute of Anesthesiology and Intensive Care, Catholic University of the "Sacred Heart", Rome, Italy

Abstract. – OBJECTIVE: Androgenetic alopecia is the most common type of hair loss, affecting women (50% of menopausal women and a large number of women of childbearing age) as well as males (over 70% of adult men). Since the condition is of an evolutionary nature, it is important to intervene early in order to prevent the progression of the clinical picture. It is equally important to identify all the factors that may hinder the effectiveness of the therapy.

MATERIALS AND METHODS: A literature search was conducted using, as electronic bibliographic database, Medline and the Cochrane library from 1995 until present.

RESULTS: Patients who make use of certain supplements can be less responsive to medical treatments.

CONCLUSIONS: The therapeutic approach to the patient with androgenetic alopecia should be global as the effectiveness of valid therapies may be affected by the patient overlooking the information received from the specialist.

Key Words:
Androgenetic alopecia, Stimulants, Anabolics, Platelet-rich plasma.

Introduction

Androgenetic alopecia (AGA) is the most common type of hair loss, affecting women (50% of menopausal women and a large number of women of childbearing age, ~35%), as well as males (over 70% of adult men)[1]. Androgenetic alopecia is due to a process of involution of the hair follicles, mainly due to the combined effect of two factors:

1. Genetic predisposition (AR, EDA2R/Chr. X - WNT10A/2q35 - 20p11 - 3q25.1 and several other loci are involved);
2. Hormonal stimulation[2-9].

The hair growth cycle consists of an anagen phase (a growth period of 2-6 years on average), a catagen phase (a period of involution, of about 2-3 weeks) and a telogen phase (a rest period of about 1-3 months)[10]. With androgenetic alopecia, under androgenic stimulation, there is a progressive reduction of the average duration of the anagen phase, at each hair growth cycle. The hair follicles become progressively smaller and the hair, shorter and thinner, is absent for longer periods (increased physiological kenogen interval – between the loss of the hair in telogen and its replacement with new hair), which contributes to worsen the thinned appearance. This process does not occur uniformly and is described, for men, using the Hamilton-Norwood scale, and for women using the Ludwig Scale. Several investigators have demonstrated, in patients with androgenetic alopecia, an increased expression of isoform 2 of the enzyme 5-α reductase, as well as the androgen receptors (AR) in the scalp areas that develop baldness. Hereditary predisposition determines the sensitivity of the follicle to male hormones and thus influences the age of onset and severity of the clinical picture[2,3,11].

At present, finasteride and minoxidil are the only therapies approved by the Food and Drug Administration (FDA), together with low-level laser light therapy (LLLT), for the treatment of AGA[12]. The search for new therapeutic options has led many patients to undergo treatment with topically-administered blood components. Platelet-rich plasma (PRP) is a volume of the plasma fraction of autologous blood with a platelet concentration higher than baseline. The regenerative potential of PRP is due to the growth factors released, after activation, by platelet α-granules[13]. The main growth factors (GFs) involved in androgenetic alopecia are: platelet-derived growth factor (PDGF), vascular-endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and insulin-like growth factor (IGF). The growth factors bind to their receptors on follicular stem cells[14-16]. Primi-

Corresponding Author: Simona Rinaldi, MD; e-mail: dr.simonarinaldi@gmail.com

tive stem cells of ectodermal origin can be found in the region of the bulge. Germ cells of mesenchymal origin are found in the dermal papilla region[17]. PRP seems to prolong the anagen phase of the hair growth cycle, increase survival of follicular cells by inhibiting apoptosis, promote stem cell differentiation and enrich the perifollicular vascular plexus, through VEGF and PDGF, which have angiogenic potential[18-21]. The purpose of this review is to contribute to the dissemination of knowledge among clinicians of relevant pathophysiological mechanisms, for an increased understanding of the factors that may hinder the effectiveness of valid medical treatments for curing androgenetic alopecia.

Materials and Methods

A literature search was conducted using, as electronic bibliographic database, Medline from 1995 until present. Evidence based reviews, from the Cochrane library, were also included in this topical review. For each pathophysiologic mechanism a separate search was conducted. With the purpose of overviewing the known risk factors, the query 'androgenetic alopecia' was combined with the following terms: 'incidence', 'prevalence', 'genetic factors'. Abstracts were screened manually, and full test papers were considered if the abstract suggested an experimental or observational study related to the pathogenesis of androgenetic alopecia or a review concerning one or more pathogenetic mechanisms or an association between androgenetic alopecia and risk factors. Systematic reviews, review articles, randomized controlled trials, comparative cohort studies and case series were included. Recent guidelines were consulted. Only articles written in English were included.

Results

Current therapies for androgenetic alopecia if set correctly, on the basis of a careful medical history, a thorough physical examination and laboratory tests to rule out other conditions that cause hair loss, can prevent the progression of the clinical picture and determine an overall improvement in hair density and quality, with increased shaft thickness. However, different factors can play a negative role during the control period and in the post-treatment phase.

Several studies have shown the negative psychological effects that can occur in patients with androgenetic alopecia[22,23]. Usually more pronounced in young people, loss of self-esteem, depression, introversion and neuroticism may manifest. As a result, many people often develop a particular focus on personal care. Stimulant and anabolic substances are widely used in this context especially among professional athletes or those who for various professional reasons (models, actors, etc.) are keen to preserve/improve their body image. These include: Creatine, Weight gainers, Arginine and Ornithine, Growth hormone (GH), Somatomedin-C analogues, Fat burners, Whey protein isolate, Branched-chain amino acids, Steroids and Pro-hormones.

Testosterone, converted to the more active metabolite dihydrotestosterone through the work of the enzyme 5-alpha reductase, plays a determinant role in the onset of hair loss in genetically susceptible individuals. Various studies have shown a significant increase in total testosterone and, in men as well as in women, of free circulating testosterone, following intense anaerobic strength workouts[24]. Many take nutritional supplements to enhance physical performance. The most frequently used is *creatine monohydrate*. Creatine, however, is also contained in various *weight gainers*, taken by athletes to increase their daily caloric intake and develop muscle mass. Creatine is a non-protein, nitrogenous compound composed of three amino acids: arginine, glycine and methionine. In the human body, creatine is synthesized in the liver and pancreas (~ 1 g/day) and 95% of it is stored in skeletal muscle, mainly (2/3) as phosphocreatine (PCr). With the depletion of PCr stores during intense exercise, the availability of energy decreases due to the impossibility of resynthesizing ATP; consequently, the ability to maintain a constant level of effort is reduced and this explains the use of creatine as a supplement. Research has shown that creatine monohydrate generates a significant increase in dihydrotestosterone (56-40%) during training periods[25]. Other studies have stressed the role of the amino acid *arginine* in directly affecting DHT without increasing testosterone levels, probably by increasing the activity of 5-alpha reductase. Arginine, as well as *ornithine*, both contained in several supplements and often also in energy drinks, directly affect the GH/IGF-1/IGFBP-3 axis after power exercises[26]. The endogenous synthesis of *GH* is regulated by two hypothalamic peptides respectively called GHRH (soma-

totropin releasing hormone) and SRIH (somatostatin). The first hormone stimulates the production and release of GH by the somatotropic cells of the anterior pituitary gland. Somatostatin, on the other hand, has a negative feedback effect, as does IGF-1. Growth hormone can modulate gene expression of the target cells, ensuring increased levels of protein synthesis, with intense musculoskeletal anabolism and important metabolic glucose and lipid control, facilitating the mobilization of these reserves. GH secretion is pulsatile with more frequent and higher peaks in the early hours of nocturnal sleep. The plasma values range from 1 to 5 ng/ml with peaks of 10 ng/ml under stress or after physical exercise. Hyperaminoacidemia, α-adrenergic agonists, and serotonin also stimulate GH secretion. GH exerts its physiological action directly through interaction with specific receptors, or indirectly, by stimulating the release of *insulin-like growth factor-1* (IGF-1), whose production is regulated by other nutritional and hormonal factors.

Somatomedin C or insulin-like growth factor is synthesized primarily in the liver, although the IGF-1 produced locally in many tissues (e.g. hair follicles) can exert autocrine or paracrine effects on cell growth.

In blood, IGF-1 binds to specific molecules denominated *IGFBP or IGF-1 binding proteins*. IGF-1 promotes hair growth in the dermal papilla cells of the hair follicles of the scalp; in individuals with androgenetic alopecia, however, reduced local secretion of IGF1 has been confirmed[27]. Furthermore, in studies conducted on rats, serum IGF 1 was shown to directly induce an increase in DHT[28]. Finally, *IGFBP -3*, one of the main binding proteins in the blood, by binding both serum and cellular insulin-like growth factor, reduces its availability, thus negatively influencing hair growth[29].

The term "*fat burner"* is used to describe dietary supplements that have the purpose of increasing fat metabolism or energy expenditure, alter the absorption of fat, increase fat oxidation during exercise and induce weight loss. The most popular supplements include: caffeine, green tea, fucoxanthin, carnitine, conjugated linoleic acid and chromium picolinate. Caffeine may act synergistically with green tea catechins, influencing the activity of the sympathetic nervous system. This activation induces the production of pituitary ACTH and, subsequently, cortisol from the adrenal cortex. Glucocorticoids inhibit IGF-1 activity, increasing IGFBP-3 levels. Similar effect occurs over time with GH (dose-dependent) and Somatomedin-C analogues.

Catecholamines also act on the α1-adrenergic receptors located in the arterioles causing smooth muscle contraction and vasoconstriction with subsequent loss of blood flow and follicular deprivation[30].

Testosterone acts by changing the balance in the production of IGF-1/IGFBPs, inducing an increase in IGFBP-3[31]. *Whey proteins* are regularly marketed and taken as a dietary supplement. *Whey Protein Isolate* undergoes more elaborate processes, such as cross flow microfiltration (CFM) or ion exchange (IE), therefore, compared to whey protein concentrate, it has a lactose and fat content of less than 1%, lower content of calcium and other minerals but a high protein concentration, 85-90%[32]. It is absorbed quickly, providing the body with essential amino acids and promoting muscle growth. The high content of *branched-chain amino acids (BCAA)* – leucine, isoleucine and valine – allows the production of energy, by means of *gluconeogenesis*, important in prolonged fasting and continued physical activity, and causes an increase in testosterone levels in active subjects[33].

Despite strict legislation prohibiting the use of drugs or biologically active substances that can modify the psychophysical or biological conditions of the organism, the use of which is not justified by pathological conditions, the use of anabolic steroids, pro-hormones, growth hormone and IGF-1 analogues, is still widespread (black market, Internet), in spite of the significant side effects. From the chemical point of view, *anabolic steroids* are drugs that are derived from testosterone[34,35]. The *pro-hormones* (e.g. Androstenedione, DHEA) have lower anabolic activity than steroids; these undergo enzymatic conversion into testosterone. In humans, testosterone is partly converted into oestrogen. This conversion is performed by the enzyme aromatase which is localized mainly in adipose tissue but also in the gonads, liver, muscles and central nervous system. Therefore, *aromatase inhibitors* (e.g. Arimidex) or drugs that prevent the binding of oestrogen with its respective receptors (e.g. Tamoxifen) are often combined with the use of steroids. Anabolic steroids are administered orally or parenterally (i.m.). A cyclical form of administration is usually used, characterized by a progressive increase in dosage and a subsequent final decrease. The use *human chorionic gonadotropin (hCG)* at the end of the cycle has the aim of reactivating the endogenous production of testosterone.

Conclusions

The therapeutic approach to the patient with androgenetic alopecia should be global: combined treatments may obtain improvements in hair density and miniaturization, reduction in hair loss, reduction of pruritus and/or of trichodynia, where present. The data found, however, suggest that patients who make use of supplements, such as stimulant and/or anabolic substances, can be less responsive to medical treatments. Randomized controlled trials will be needed to confirm this correlation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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