Role of Non Androgenic Factors in Hair loss and Hair Regrowth

Rajendrasingh Rajput[1*]

Plastic Surgeon, Hair Transplant Surgeon, FISHRS - USA, IAT, Past President AHRS India.

*Corresponding author

Rajendrasingh J Rajput, Hair Transplant Surgeon, 201, A Wing, Gasper Enclave, Pali Market, Ambedkar Road, Bandra west, Mumbai, 400 050, India, Tel: +91-22- 26415298; E-mail: drrajeshrajput@gmail.com

Abstract

Multiple nutritional, environmental and lifestyle factors can directly affect hair follicles, to weaken and make them sensitive to the action of androgens. Hair loss can be corrected and hair growth can be improved by addressing these non-androgenic factors. Patients having hair fall, thinning, loss of volume and poor growth can be precursors to androgenetic alopecia. Recent research has shown that androgens inhibit hair growth through release of Transforming Growth Factor (TGF) ß1. Further study of this mechanism reveals that generation of Reactive Oxygen Species (ROS) induced by androgens leads to release of TGF ß1 and use of ROS scavengers can block the release of TGF ß1, explaining beneficial role of antioxidants in hair growth. The binding of ROS to intracellular proteins also causes hair loss by altering the protein structure, changing their immune recognition and converting them to new antigens targeted by inflammatory and immune systems. Calorie restriction and individual micronutrient deficiencies lead to a new process of intracellular destruction or autophagy before cell apoptosis, which could explain cessation of hair growth. Telogen is not a resting phase but now defined as active conservation of follicles under unfavourable conditions. Thus any stress, trauma, metabolic change or insult causes telogen. Micronutrients zinc, copper, selenium maintains immunity, control inflammation and preserve antioxidant activity of the cells. Vitamins A, C, D have a role in phagocytosis and antibodies maintaining resistance. Vitamin D3 modulates the hair-inductive capacity of dermal papilla cells. Vitamin and micronutrient deficiencies are prevalent among all the population of the world. Nutritive value of the foods has reduced over the years by 30%. Endocrine Disrupting chemicals are creating further damage to the hormonal balance of the body. All these can be countered by use of antioxidants and a well-planned nutritional program which will ensure strengthening and regrowth of hair follicles, without the use of Finasteride.

Introduction

Clinically patients are seen presenting with varying degrees of hair fall, thinning, poor hair growth, loss of hair volume, change in texture, lack of shine, lack of bounce, limp hair which cannot be styled and remains flat. These conditions do not match the defined features of AGA, MPHL, FPHL or DUPA. All these complaints can be subclinical variations, partial presentations or precursors of any of the scientifically defined hair loss patterns [1]. The final clinical presentation depends on the severity of insult, extent of compromise and effective counter defence of the host. Prolonged, continued sever hair fall could precede development of AGA, or any of the defined hair loss conditions [1].

Hair loss can be due to androgens, genetics, nutritional, micro inflammation and disruption or deregulation of hair growth cycles. Apart from androgens many more factors affect hair growth.Stress, pollution, nutrition, lifestyle, prolonged illness, medications, metabolic disease, smoking, alcohol, which disrupt or deregulate the hair growth cycles, have been associated with hair loss, thinning and poor growth. These factors affect the hair growth directly and also make the hair roots more sensitive and susceptible to the action of androgens.

Understanding the different non androgenic mechanisms of hair loss

Role of Oxidative Stress in hair loss: Lipid peroxidation, glutathione derivatives and nitric oxide are indicators of cellular destruction by ROS through oxidation. All these markers have been identified to be significantly raised in hair loss patients, providing evidence of the role of ROS in the mechanism of hair loss [2-5]. Inui, Fukuzato and Itami established that androgens inhibit hair growth through secretion of TGF ß1 [6-8].

Hee, Shin, Yoo and Inui analysed details of this mechanism showing that androgens rise levels of ROS in the dermal papilla cells which in turn leads to secretion of TGF ß1 that inhibits hair growth. The experiment further demonstrated that, use of ROS scavengers blocked the release of TGF ß1 and reversed the inhibition of hair growth [9,10]. The evidence suggests that antioxidants can promote hair growth without the direct use of anti-androgens and utilizing anti androgens alone may not achieve complete clinical response in all patients of hair loss.

Kalkan, Seçkin, et al. proposed that the ROS forms covalent bond with endogenous proteins in the cells, producing structural changes in the proteins, leading to changes in their immune signature. The

normal proteins are now recognised as new antigens, making them targets of immunity, inflammation and autoimmune reactions. The study indicates the importance of ROS scavengers and provides a rationale, for benefit from the use of antioxidants in hair loss management and alopecia areata [11].

Apoptosis and Autophagy triggered by lack of calories, poor nutrition and mineral deficiencies

Studies by Kubibidila, Yu and the research by Fraker and King showed altered immune response in protein calorie malnutrition and individual nutrient deficiencies [12,13]. Trueb recognised these mechanisms in androgenetic alopecia where nutritional deficiencies could lead to apoptosis of hair follicle cells [1,14]. Guimaraes, Yoshimori and Freker described a newly defined process of internal cell destruction through autophagy before proceeding to programmed cell death and apoptosis [15-17].

Autophagy has been recognised to play a role for providing nutrients during metabolic stress, nutritional deficiencies and starvation like conditions. Autophagy is a process of regulated destruction of intracellular proteins and organelles by partial self-destruction to tide over amino acid, mineral and nutritional deficiencies. It is an attempt to prevent apoptosis. Autophagy arrests the progress of cellular metabolism, new cell division and growth. When applied to hair cycles, autophagy explains the mechanism leading to telogen effluvium after illness, high fever, surgical trauma, states of interrupted or poor nutrition etc. Autophagy is the mechanism by which body maintains normal blood levels of nutrients by arresting and discontinuing hair growth. Clinically the nutrient levels may not show frank deficiencies as they are compensated and maintained by arresting hair growth. Body is in a state of compensated failure. As soon as we provide stimulation and restore nutrition the hair regrowth begins. The evidence supports correction of nutritional deficiencies to prevent hair loss and promote hair growth [15-17]. Goette and Odumin 1976, reported alopecia in crash dieters which may be due to the role of mechanisms like autophagy and uncorrected nutritional balance [18]. Yoshinori Oshumiof Japanhas been granted the 2016 Nobel Prize in Medicine for his research on Autophagy.

Freker points out that zinc deficiency induces secretion of glucocorticoids leading to programmed cell death by initiating apoptosis. The effect is first seen in lymphocytes, T cells, B cells, thymus, liver, kidney, testes, it compromises host defence increases inflammation and propagates damage to other cell systems. Fibroblasts exhibit DNA breakage [17]. Zinc deficiency is a well-documented cause for hair loss [19,20]. The scientific facts suggest that providing adequate nutrients and avoiding deficiency states can play a role in preventing hair loss and achieving new hair growth.

Telogen recognized as a stage of active conservation of the hair follicles

Geyfman and Plikus have studied hair follicles in telogen. The new understanding has redefined Telogen not as a resting phase but a highly energy-efficient state of retaining hair follicles when conditions are unfavourable. These follicles are spared from destruction to launch a new hair regeneration cycle later, when conditions are more favourable. Regenerative responses of telogen hair follicles change as a function of time and can be divided into two sub-stages: early 'refractory' stage and the late 'competent' stage of telogen [21]. Clinically we see this telogen response after high fever, trauma, physical or emotional stress, crash dieting and a number of other factors that trigger telogen effluvium.

Role of micro inflammation and immunity

The genetic analysis of male pattern baldness and the 5 alpha reductase genes by Ellis [22], histopathological and histochemical correlation of male pattern alopecia by Lattanand [23], revelation of inflammatory infiltrates and pathogenesis by Jaworsky [24] and analysis of cutaneous immunopathology in male pattern baldness by Young [25]. All have led to Androgenetic Alopecia being recognized as a condition of altered hair growth due to lack of regulation of the natural cycles or premature aging of the hair follicle, affected by multiple factors.

Skin keratinocytes respond to antigens or trigger inflammation in response to repeated, exposure to pollution, UV damage, reactive oxygen species[26], nitric oxide [27], prostaglandins and histamine [28] leading to progressive inflammation. As mentioned earlier, Kalkan, Seçkin et al. [11], proposed that the ROS forms covalent bond with endogenous proteins in the cells, changing their immune signature and making them behave as new antigens, becoming targets of immunity, inflammation and autoimmune reactions. All these processes, lead to accumulation and release of intracellular cytokines. IL-1alpha, IL-1beta, which are shown to inhibit hair elongation in hair follicle cultures in vitro [29,30]. The same effect is also supported by cytokines and chemokine, monocyte chemo attractant protein-1(MCP-1), which has been identified to be active in hair follicles and sebaceous glands in androgenetic alopecia [31]. Surrounding fibroblasts too can respond to these pro inflammatory stimuli [32]. Fabio Rinaldi studied the levels of pollutants in the air and their effect on the scalp, leading to hair loss, poor growth and a clinical condition of sensitive scalp syndrome [33]. Our previous published review also analyses hair loss due to pollution [34]. All the research encourages use of antioxidants, vitamins and minerals which can prevent altered immune response, to prevent hair loss and promote hair growth.

Role of vitamins and minerals in immunity and inflammation

Eugenio Mocchegiani has shown that micronutrients zinc, copper, selenium maintain immunity, control inflammation and preserve antioxidant activity of the cells [35,36]. Thurnham studied the interactions of micronutrients with other nutrients in the diet, non-nutrients, prescribed medicines, and lifestyle factors like smoking, tea and alcohol etc, which can cause hair loss [37]. Ströhle, Wolters and Hahn studied micronutrients as essential structural elements of antioxidant system, enzymes cofactors, components of transcription factors, and epigenetic modulators. They reported the influence of Vitamin C and Vitamin D on immunity, T cells phagocytosis, formation of antibodies, autoimmune response and resistance to infection [38,39]. Reichrath, Lehmann, et al.

have regarded Vitamin A and Vitamin D as hormones due to the role in epithelial integrity and immunity [40]. Aoi, Inoue, et al. have demonstrated that Vitamin D3 modulates the hair-inductive capacity of dermal papilla cells [41]. Thus making Vitamin D an important inclusion for promotion of hair growth. Beoy, Woei and Hay studied the benefit of 100 mg mixed tocotrienol and alpha tocopherol resulting into 34% improvement in hair counts attributed to potent inhibition of lipid peroxidaiton and reduction of oxidative stress [42]. Jin, Zhu and Wu compared zinc, copper, iron and manganese contents in hair in patients with male pattern alopecia and healthy men confirming low levels of nutrients in patterned hair loss [43]. A recent study by Ozturk et al. compared BMI and levels of zinc, copper in hair, serum and urine of Turkish male patients with androgenetic alopecia, again confirming low levels in patients with androgenetic alopecia [20]. Ozturk pointed out that Zinc and Copper are required for enzymatic functions of Carbonic anhydrase, Superoxide dismutase, Polymerase, Collagenase, Cell division, Nucleic acid metabolism and several coenzymes. Zinc and Copper have antioxidant activity. Zinc stabilizes cell membrane prevents oxidative destruction by free radicals [20]. Skalnaya et al. showed a lower copper and zinc content in the hair of frontal area in comparison to the occipital area in women with AGA [43].

Harrison and Bergfeld mentioned the role of calorie restriction, fatty acids, crash dieting, starvation, zinc and iron deficiency in diffuse hair loss [45]. Betsy, Binitha and Sarita have directed attention to association between zinc, copper, selenium deficiencies and altered thyroid function leading to hair loss [46]. Rojas and Gosch studied zinc, iron, copper, selenium deficiencies as cause for hair loss following Bariatric Surgery and found that patients having lower hair loss had lower compromise of nutrients [47]. All these studies emphasise the role of micronutrients, vitamins, minerals in hair loss management.

Nutrition correction in hair loss management gaining attention
A Randomized, Double-Blind, Placebo-Controlled Study by Ablon G using shark cartilage and omega 3 showed decreased hair shedding in women [48]. Another randomized trial by Le Floc'h C et al. confirmed benefit with omega 3 and omega 6 in female pattern hair loss [49]. Simopoulos has presented a detail account of the benefits of omega 3 in inflammation and auto immune conditions [50]. There is rising interest in addressing hair loss with nutritional support leading to studies showing effective use of vitamin B6, calcium pentothenate, l-cystine, l-lysine and combination to treat hair loss and improve hair growth [51-55]. There are double blind placebo controlled trials showing benefit of nutritional supplements [56-62]. Dwyer 1994 indicated the role of subclinical dietary deficiencies in non scarring hair loss [63]. Dietary deficiencies are common in population. Calorie restriction is a day to day practice becoming a way of life [64-66].

Nutritional deficiencies are more common than we can perceive Vegetarianism and lactovegetarian diet leads to defined nutritional deficiencies. Raumaand Mykkänen, reported low antioxidant levels in vegetarian diet due to lack of zinc and selenium [67]. Dietetic association position statement considers vegetarian diets can be low in protein, omega 3 fatty acids, iron, zinc, iodine, calcium, and vitamins D and B-12, but these deficiencies can be carefully avoided [68]. Lacto vegetarian diets can lead to energy, protein, iron, calcium, zinc, beta-carotene, and vitamin C deficiency [69].

People today satisfy their hunger with selection of wrong foods leaving an un-quenched nutritional deficit which research workers have termed as the 'hidden hunger' [70]. Foods with good nutritional value are affordable only to high income groups. These are termed as income elastic protective foods [71-74]. Malnutrition is so common in adult and adolescent population around the world that an Adult Micronutrient Quality Index (AMQI) has been developed to study malnutrition in adults [75,76]. Chicken are fattened faster using hormones, antibiotics, oral contraceptives, tranquilizers which pass on to consumers creating hormonal imbalance and risk of disease [77]. Endocrine disrupting chemicals are contaminating food through processing and packing technology. These mimic the action of hormones and cause imbalance leading to disease conditions [78]. Such altered metabolism could cause hair loss.

Gradual loss of nutritive value of foods due to soil depletion and farming methods
The nutritive value of foods itself has reduced over the years. Various studies show more than 30% reduction in nutritional content of foods when compared over the past 50 years. Anne-Marie Mayer reported significant reductions in the levels of Ca, Mg, Cu and Na, in vegetables and Mg, Fe, Cu and K in fruits. The greatest change was the reduction of copper levels [79]. David Thomas has reported individual loss of nutrients in vegetables, fruits, milk and meat [80]. Davis Donald has compared the vitamin content showing loss of riboflavin and ascorbic acid over the past 50 years [81]. More data on reduced nutritive value of foods has been recently added by White and Broadley [82]. The author has published his own clinical experience with the use of low dose nutritional correction in hair loss management with a two year follow up showing consistent improvements in men and women [83,84] (Figures 1a, 1b and 2a, 2b).

Figure 1: Thinning and poor hair growth in female patient.

Figure 1b: Improved hair quality and regrowth with nutritional correction and peptide cream. No minoxidil, no anti androgens.

Figure 2a: Thinning and poor hair growth in male patient.

Figure 2b: Improved hair quality and regrowth with nutritional correction

and peptide cream. No minoxidil, no anti androgens.

Conclusion

Maintaining good nutritional balance of vitamins, micro nutrients, antioxidants can neutralize ROS, maintain immunity, phagocytosis, induce cell growth, counter effects of endocrine disrupting chemicals, prevent autophagy, apoptosis, derangement of body functions due to poor diet and loss of nutritional value of foods. Correction of these associated mechanisms must be included in our approach to successful hair loss management. Anti-androgens may not be the only basis of hair loss management.

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