Research Article

Clinical Report of Acquired Androgen Sensitivity from Non Androgenic Factors

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ABSTRACT

Background: To understand the scientific mechanism of hair loss caused by non-androgenic factors and the importance of nutrients in prevention, reversal of damage and restoration of hair growth, without the use of anti-androgens.

Methodology: A total of 100 patients, 62 male and 38 female, who presented with Androgenetic Alopecia (AGA), Male Pattern Hair Loss (MPHL) and Female Pattern Hair Loss (FPHL), were included in the study. Early hair loss grades and patients with associated medical conditions were excluded. All patients were evaluated for DHT, DHEAS, SHBG, free testosterone, scalp trichoscopy, global photography and hair fall. The cause for initiation of hair fall was inquired and noted. All patients were treated with a low dose once in three days nutritional supplement combinations of Antioxidant, Calcium, vitamin D3 on day 1. Iron, folic acid, vitamin C, vitamin E on day 2 and amino acids with B-complex, biotin and omega 3 on day 3. The cycle repeated every 3 days for 4 months. Clinical progress was recorded every 2 months, hair fall was recorded every month.

Results: Levels of DHT, DHEAS, SHBG, free testosterone, in all the men and women were within normal limits. Hair loss commenced due to restricted eating, stress, lack of sleep, pollution, smoking, alcohol, late nights, circadian rhythm, poor scalp hygiene etc. but was now presenting as AGA or pattern hair loss. Peri pilar trichoscopic signs were seen only in the early months of commencement of hair loss and not after 3-4 months of progress. Focal atrichia was more common than expected. With the nutritional supplements, hair fall was controlled within 4 weeks–6 weeks. The average improvement in density in women at 4 months was 20% and the improvement in caliber was 25%. While in men the average improvement in density at 4 months was 24% and improvement in caliber was 18%, without use of minoxidil or finasteride.

Conclusion: All alopecias commence with simple hair fall triggered by non-androgenic factors. These factors act by generation of ROS leading to cellular dysfunction from damage to DNA and metabollism. The ROS also sensatize androgen receptors and pathways making the cells sensitive to normal androgens. The ROS can be neutralized, deranged metabolism and DNA damage can be repaired with restoration of cellular function, with combinations of nutritional supplements resulting in hair growth without the use of anti-androgens.

Key Words: Non androgenic, DHT, ROS, nutrition, hair loss, supplements, androgen receptors, anti-androgens.

Introduction

Clinical studies by Knussmann in 1992 and European Consensus Group, S1 guideline have concluded that AGA can present without family history and without raised androgens [1, 2]. Sreekumar et.al. (1999) and Cranwell (2016) have also found no correlation between genetics, androgen levels and AGA [3, 4]. Kondrakhina et.al. 2019 suggested AGA may be caused by hormone independent disorders affecting the hair follicle functions [5].

While Katzer et.al. (2019) pointed out that altered response of the follicles rather than raised androgens was responsible for hair loss [6].

The attention to testosterone was brought about by social observations and testosterone injection induced hair loss reported by Hamilton in 1942 [7]. Present research confirms that not testosterone but its conversion to Dihydrotestosterone (DHT) affects the hair follicles. DHT acts through release of Transforming Growth Factor Beta (TGFβ) and the release of TGFβ itself is mediated by the Reactive Oxygen Species (ROS) [8, 9]. Experiments have revealed that using free radical scavenger to neutralize the ROS can block the release of TGFβ, thus countering the action of DHT [9]. In the past, factors like stress, environment, lifestyle, diet, nutrition, sleep, loss of circadian rhythm, which were secondary are

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now on the rise and have assumed a primary role. These factors are known to generate ROS and alter cellular metabolism. Ten years prior to Hamilton, in 1932 Sabauroud reported acute reversible or chronic diffuse hair loss, which was a recognition of non-androgenic hair loss. Later these factors were addressed by Kligman as Telogen Effluvium (TE), which commonly presents as chronic TE, often associated with and difficult to distinguish from AGA [10].

Methodology

The prospective study includes 100 patients, 62 male and 38 female, presenting with Androgenetic Alopecia (AGA), Male Pattern Hair Loss (MPHL) and Female Pattern Hair Loss (FPHL). Patients on medication for thyroid, polycystic ovarian syndrome, obesity, diabetes, hypertension or history of COVID, were excluded. Men with early hair loss, Norwood Hamilton grade 1 and 2 were excluded, whereas women with all grades of Ludwig's hair loss were included. All the participants were evaluated for DHT, DHEAS (Dehydroepiandrosterone Sulfate), SHBG (Sex Hormone Binding Globulin), free testosterone, trichoscopy with computerized LeedsM Folliscope recording hair caliber and hair density with tagging for spot and global photography, which were repeated after 4 months. Hair fall was compared every month. The initial cause for hair loss was inquired and noted. All patients were treated with a low dose once in three days combination of Antioxidant, calcium and vitamin D on day 1. Iron, folic acid, vitamin C, vitamin E on day 2 and amino acids with B-complex, biotin and omega 3 on day 3. The cycle repeated every 3 days for 4 months. A controlled clinical on cyclical nutrition therapy has been published earlier [11].

■ Observations

The age group varied from 23 years to 54 years in men and 17 years to 42 years in women. The average duration of hair loss varied from 3 months to 10 months. It was noted that hair loss in all patients started as TE and gradually progressed to present as MPHL, FPHL, or AGA. Watching calories, restricted eating, exercising to burn out and control weight, meal replacements, skipping meals, stress, smoking and alcohol, sleep disturbances, night shifts, staying awake beyond mid night for work or net surfing, exposure to pollution, UV rays, oily scalp, dandruff, scalp hygiene, itching, trichodynia, redness were the initial causes for hair loss reported by men and women as described in table 1. Genetic history of hair loss was positive in 26% women and 38% men.

Grade of hair loss in men was recorded as per Norwood Hamilton scale. Grade 3 hair loss was noted in 37% men, grade 4 in 46% men and grade 5 in 17% on the male patients. Female hair loss was recorded as per Ludwig's scale. Grade 1 thinning was seen in 28% women, Grade 2 in 64% women and grade 3 in 8% of the women.

DHT levels in men varied from 32 ng/dl -72 ng/dl, the mean being 52 ng/dl (normal 30 ng/dl-85 ng/dl). In women the DHT levels varied from 4 ng/dl-16 ng/dl, the mean being 10 ng/dl (normal 4 ng/dl-22 ng/dl). The levels of DHEAS in men were reported between 100 ng/dl-390 ng/dl, the mean being 245 ng/dl (normal 95 ng/dl-530 ng/dl). In women the levels of DHEAS were reported between 40 ng/dl-180 mg/dl, the mean being 100 ng/dl (normal 32 ng/dl-280 ng/dl). The values of SHBG were tested to be between 10 nmol/l -36 nmol/l in men, the mean being 23 nmol/l (normal 10 nmol/l -57 nmol/l). In women the values of SHBG were tested to be between 20 nmol/l-110 nmol/l the mean being 65 nmol/l (normal 18 nmol/l-144 nmol/l). Free testosterone in men varied from 300 ng/dl-700 ng/dl, the mean being 500 ng/dl (normal 300 ng/dl-1000 ng/dl). In women the free testosterone varied from 15 ng/dl-50 ng/dl, the mean being 32.5 ng/dl (normal 15 ng/dl-70 ng/dl). All hormonal parameters DHT, DHEAS, SHBG and free testosterone were within normal limits for the men and women in the study. Trichoscopy revealed peri pilar halo, scaling, redness, yellow spots only in 7% cases of men and 16% of women who presented within 3 months-4 months history of hair loss. Focal atrichia was seen in 23% men and 41% women. Presence of individual villus hair, villus hair with a terminal hair in the unit, single hair units, hair diameter diversity and empty follicles were the most common trichoscopic findings in all the men and women. Trichoscopy counts were done at a fixed point of intersection of the sagittal plane with the coronal plane at the level of the tragus. Average hair density in men varied from 136 hair per square centimeter to 194 hair per square centimeter, while hair caliber was between 42 microns to 88 microns. Average density in women varied from 148 hair per square centimeter to 206 hair per square centimeter, while the hair caliber was between 36 microns to 82 microns. Patients were asked to refrain from shampoo for four days and hair loss was counted

Table 1: Non Androgenic causes for initiation of hair loss.

Causes	Men	Women
Watching calories, restricted eating, exercising to burn out and control weight	64%	72%
Skipping meals and meal replacements	44%	44%
Stress	72%	63%
Smoking	52%	11%
Alcohol	68%	19%
Sleep disturbances	32%	48%
Late night work or net surfing to well beyond mid night	64%	64%
Night shifts	35%	35%
Pollution	46%	46%
Oily scalp	54%	62%
Dandruff	28%	12%
Itching of the scalp, trichodynia, redness	9%	9%

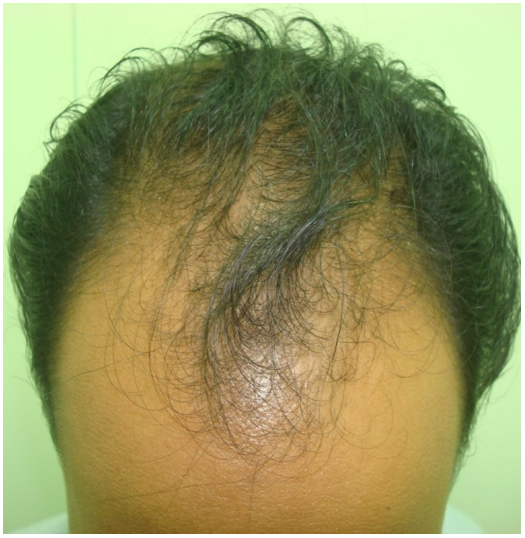

Figure 1a: Male Pattern Hair Loss Pre without Anti androgens.

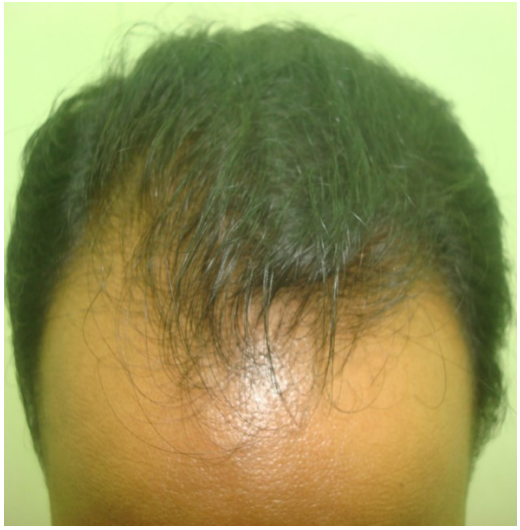

Figure 1b: Male Pattern Hair Loss 4 months post without anti androgens.

by brushing on the fifth day. Hair loss in men varied between 58 strands –102 strands while hair loss in women varied from 76 strands–124 strands.

Results

Hair loss was controlled by 40% -50% in the first month and another 16%-20% by the 2nd and 3rd month but some hair loss always remained as a complaint. There was 21% rise in density and 16% improvement of hair caliber in men at 2 months which progressed to 24% rise in density and 18% improvement in caliber at 4 months (Figure 1a and 1b). Women showed 17% improvement in density and 22% improvement in hair caliber at 2 months which progressed to 20% improved density and 25% better caliber at 4 months (Figure 2a and 2b).

Discussion

Hair loss in all men and women was initiated as simple TE from various non androgenic causes like calorie restriction, weight control, irregular meals, stress, smoking, alcohol, sleep, late nights, night shifts, circadian rhythm, pollution, scalp hygiene etc. in variable proportion. Women were

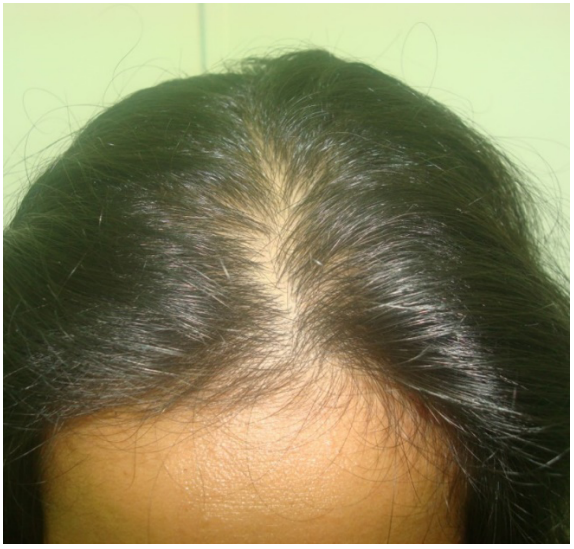

Figure 2a: Female Pattern Hair Loss Pre without Anti androgens.

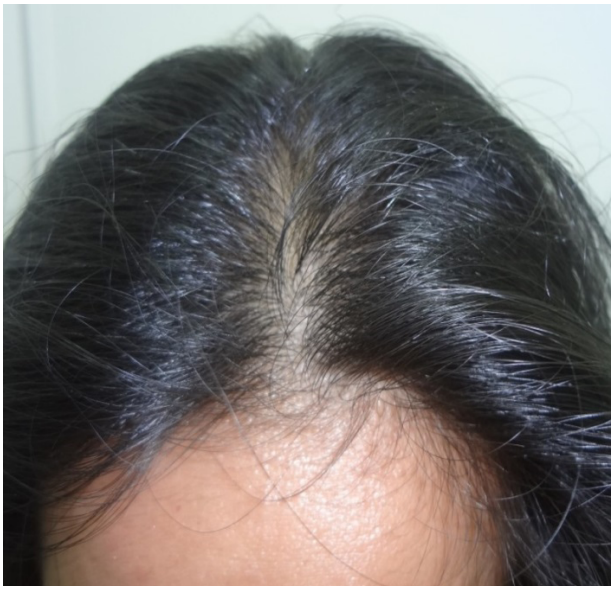

Figure 2b: Female pattern hair loss 4 months post without anti androgens.

affected at an earlier age than men. Trichoscopic signs of inflammation were active initially and later the pathology appears to progress at a subclinical level appropriately termed as micro inflammation. A large number of men (62%) and women (74%) had no genetic history of hair loss. The levels of DHT, DHEAS, SHBG and free testosterone were normal in all men and women.

What raised the curiosity was to know how the hair loss that was initiated as TE by non-androgenic factors later presented as AGA, MPHL or FPHL without raised androgens and without family history or genetic predisposition? When we focus on blocking conversion of testosterone to DHT, we neglect the accumulation of ROS from internal and external factors. These free radicals with an unstable electron combine with proteins, lipids, and other substrates leading to metabolic dysfunction and hair loss through multiple other mechanisms. In the past, factors like stress, environment, lifestyle, diet, nutrition, sleep, loss of circadian rhythm, which were secondary are now on the rise and have assumed a primary role. These factors are known to generate ROS which are secondary mediators for hair phenotypes created from cellular dysfunction due to metabolic slow down, inflammation, immunity, oxidative stress, aging and epigenetics. There is scientific evidence on the role of various non-androgenic factors.

■ Senescence inflammation immunity oxidative stress phenotypes and psychological stress

Inflammation, immunity, oxidative stress and mediators of psychological stress are common non androgenic factors that cause cellular dysfunction and interruption of the hair growth cycle. Lattanand et.al. (1975) and Jaworsky et.al (1992), studied histopathology and inflammatory infiltrates in male pattern alopecia [12, 13]. Young et.al (1991) and Margo et.al. (2011) have established the role of cutaneous immunopathology, inflammation and immunity in androgenetic alopecia [14, 15]. The oxidative stress hair loss phenotype leading to senescence of the hair follicles, has been reported by Trueb (2009) and Upton [16, 17]. Lee et.al in 2021 have described the cellular senescence and inflammaging phenotype [18]. The aging phenotype involving stem cells has been confirmed by Ji J [19]. Piccini et.al. recorded the metabolic quiescent phenotype [20]. Whereas Wang et.al. have documented how oxidative stress, in combination with psychological stress and substance P, induces autophagy leading to the arrest of hair growth [21]. The brain hair follicle axis, the effects of stress on keratinocyte proliferation, apoptosis and immunomodulatory effects of substance P have been described by Arck and Siebenhaar [22, 23]. Vitamin C attenuates raised cortisol and adrenaline in stress. DHA is a serotonin secretion activator. Tyrosine is precursor to nor-adrenaline, tryptophan to serotonin and phenylalanine to dopamine [24]. B-complex vitamins are essential for all cellular functions. Vitamin B5 pantothenic acid supports adrenal function making it an anti-stress vitamin. Requirements of all nutrients and minerals are raised in stress. A clinical trial on biomarkers of stress and benefits with nutrients has been published earlier [24]. The cellular changes in all the phenotypes resemble senescence, mediated through ROS and are amiable to reversal with nutrients [25]. Multiple pathologies may be active simultaneously creating various clinical presentation, distribution and combinations of hair loss.

■ Pollution and UV rays

Rinaldi in 2008 described hair loss and sensitive scalp syndrome from exposure to environmental pollution [26]. Kalkan suggested that ROS from pollution, bind with intracellular proteins to change the immune signature of these molecules, making them recognized as antigens and triggering autoimmune reactions [27]. While Jun et.al established that Trans follicular and transdermal penetration of pollutants, caused increased production of ROS and inflammatory cytokines, leading to apoptosis of follicular keratinocytes [28]. Hruza et.al. and Sebetić have studied the mechanism of UV inflammation, generation of ROS, Nitric Oxide (NO), and hair damage [29]. These non-androgenic pathologies leading to hair loss are mediated through generation of free radicals or ROS which makes them accessible to neutralization and repair with nutrients. A study of hair loss due to pollution and management with nutrients has been published earlier [30].

■ Sleep seasonal variation and circadian rhythm

Yi Y et.al and Liamsombut et.al have studied the correlation between poor sleeping habits and androgenetic alopecia with reference to changes in cortisol levels, growth hormone and inhibition of the Hypothalamus Pituitary Axis

(HPA) [30, 31]. Vitamin C regulates raised cortisol [24]. Sejbuk 2022 reported benefits of macro and micronutrients, vitamin C, zinc, B-complex, natural precursors of tryptophan, melatonin and serotonin to improve sleep quality and help in hair growth [32]. Randal and Ebling proposed seasonal changes in the hair growth cycle [33]. Deshayes et.al. demonstrated that prolonged deregulation of circadian rhythm alters the regenerative properties of skin and hair precursor cells [34].

■ Smoking alcohol

Su et. al. 2007 reported higher incidence of hair loss in smokers [35]. While Kavadya et.al. 2022 proposed that smoking could cause androgenetic alopecia from nicotine induced vasoconstriction, ROS induced nuclear damage, mitochondrial DNA damage, oxidative stress, phospholipid cell membrane damage, apoptosis, and senescence due to smoking and also rise in testosterone levels [36]. Gather wright et.al. 2013 found alcohol consumption to be one of the factors responsible for balding in twins [37]. While Galan et.al detected common deficiencies of beta carotene, vitamin C, vitamin E, zinc and selenium influenced by alcohol consumption and smoking which could lead to hair loss [38].

■ Lifestyle and epigenetic factors

Lifestyle and epigenetic factors may include stress, physical activity, sleep, obesity, smoking, alcohol, tobacco, food habits, night shifts, exposure to pollution, UV rays etc. [39]. Gatherwright and Koyama in 2013 reported that biological twins do not bald the same due to the influence of lifestyle and epigenetic factors [37, 40]. Epigenetic mechanisms create an acquired phenotype different than the genetic genotype by influencing gene expression through DNA methylation and histone modification [41]. DNA methylation is a measure for biological aging, detected during major surgery, pregnancy, COVID-19, stress, lifestyle, environmental exposure etc. and noted to be reversible with anti-aging nutrients [25]. ROS are involved in the mechanism of senescence and altered gene expression which can be prevented and reversed with antioxidants and micronutrients [42].

■ Acquired androgen sensitivity from continued exposure to non-androgenic factors

We propose the hypothesis of acquired androgen sensitivity. Lack of genetic history or normal androgen levels cannot rule out androgenetic alopecia [2]. Clinical incidence and progress of hair loss could never be linked to raised androgens or DHT [3, 43]. Clinically, every alopecia begins as simple hair fall or telogen effluvium, arising from non-androgenic causes like fever, stress, lifestyle, pollution, epigenetic, environmental factors, sleep, alcohol, smoking, diet etc. Continued exposure to these non-androgenic factors, promotes gradual cellular dysfunction and accumulation of ROS. The ROS are known to activate and lower the threshold of Androgen Receptors (AR) making the receptors sensitive to normal circulating androgens [44]. ROS also induces the release of inflammatory cytokines which further activate various AR sensitive pathways, despite normal androgen

Table 2: Progressive Effects of Non Androgenic Factors leading to Androgen Sensitivity

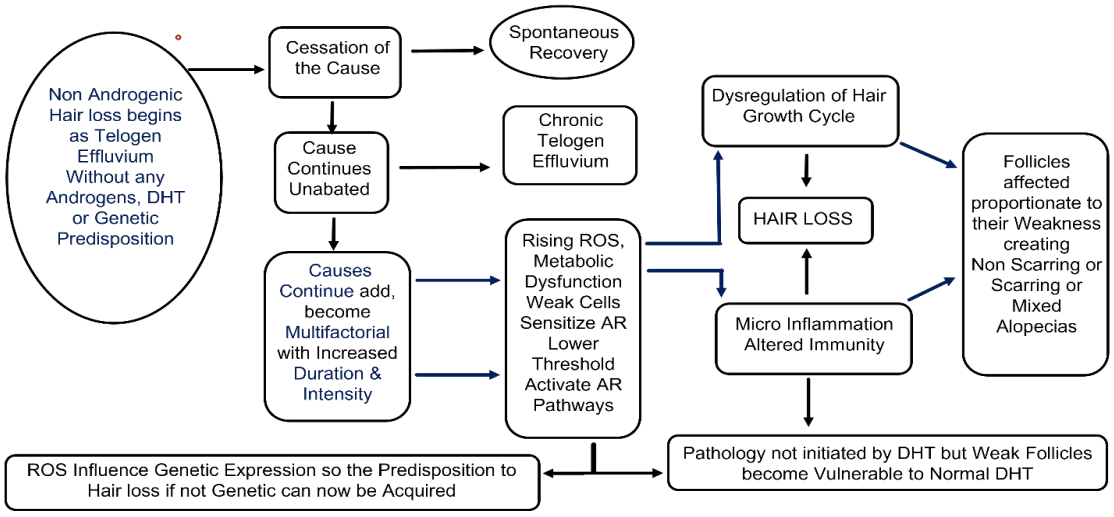

Figure 3: Progressive effect of androgenic factor leading to androgen sensitivity.

levels creating clinical presentation of AGA [44]. The hair loss phenotypes resemble changes of senescence and AR activation has been proven to accelerate premature senescence [45]. Thus, the follicles have now become sensitive to normal androgens and DHT from continuous insult and relentless exposure to non-androgenic factors. The predisposition to androgen sensitivity, if not genetic, is now acquired (Figure 3). The hypothesis explains common clinical presentation of hair loss with normal DHT and without any family history. Early intervention is called for to neutralize the ROS with antioxidants, repair and restore cellular functions with nutrients, correct the vulnerability of these cells and prevent hair loss.

■ Nutrients provide protection, repair, and continuation of cellular function

The clinical improvement hair density and caliber observed within 2 months-4 months with the use of nutrients is from conversion to resting follicles to active growth. Geyfman in 2015 describe hair follicles to prefer a phase of metabolic and proliferative quiescence, to reactivate growth on favorable changes in the intracellular micro environment and extracellular macro environment [46]. Non androgenic factors cause cellular dysfunction and DNA damage. Pro vitamin A, carotenoids, carotenes, β-cryptoxanthin and non-vitamin A, carotenoids, lycopene, lutein, astaxanthin and zeaxanthin protect against DNA damage [47]. Selenium is involved in cell growth, apoptosis, and cell signaling and transcription factors [48]. Biotin and biotin metabolites affect transcription of genes encoding cytokines, oncogenes, glucose metabolism and cellular homeostasis [49]. Hair follicles grow when the internal cellular environment has been corrected to achieve redox balance, energy generation, and repair of cellular damage and regulation of cellular function to meet the high metabolic demand [50]. Nutrients with one carbon metabolism, vitamins, B12, B6, folate, riboflavin, methionine, choline, betaine and bioactive compounds like retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols modulate epigenetic patterns by regulating universal methyl donor and enzymes that catalyze DNA methylation and histone modifications [39,25].

■ Benefits from nutritional management of hair loss

Several clinical trials have reported benefits from nutritional management of hair loss similar to our observations in this study. These reports support our hypothesis of neutralizing ROS, preventing release of TGFβ and restoring the cellular dysfunction induced from relentless exposure to non androgenic factors. A controlled, randomized, double blind, clinical trial with histological diagnosis of AGA in males by Lassus in 1992 showed 38% raise in non-villus hair counts with nutritional supplements for 6 months [51]. Thom in 2001, in randomized, placebo-controlled, double-blind, clinical trial reported 32.4% improvement in hair growth from various etiologies with 6 months of nutritional supplements [52]. Ablon (2016) reported improved quality of life and hair growth in 180 days (6 months) with the use of nutritional supplements in male pattern hair loss [53]. Our study concluded at 4 months, but clinical improvement was recorded as early as 2 months due to synergistic use of nutrients and a combination of antioxidants, vitamins, minerals, amino acids, omega 3 which provided a more comprehensive support to the repair and restoration of cellular function. Longer duration of nutritional supplements would have continued to deliver further improvement.

Conclusion

Androgenic actions are mediated through ROS. Multiple lifestyle, environmental and epigenetic factors promote generation of ROS and create cellular dysfunction interrupting the hair growth cycle. The ROS sensitize androgen receptors and upregulate androgen pathways resulting in acquired androgen sensitivity. The ROS can be neutralized and cellular function can be restored with nutritional supplements to achieve hair growth without the use of anti-androgens.

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