Changing the Cellular Environment Can Improve the Tissue Response of Follicles without DHT Blockers

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INTRODUCTION

Patients are losing faith in hair loss management due to fear of side effects. Researchers today agree that it is not simply a raised DHT level, but also the altered tissue response of the follicles at the tissue level, that is responsible for hair loss.[1,2] The altered response is in the form of a disturbance of metabolism and of ATP formation, energy utilization, and accumulation of free radicals (reactive oxygen species (ROS), reactive nitrogen species (RNS), peroxides, and other free radicals) creating inflammation, compromising immunity, and making the follicle weak and vulnerable. Hair loss is not only hormonal; it can occur without raised androgens, without a family history, and it can skip siblings and generations.[3,4] Therefore, it is no longer called androgenetic alopecia anymore by some authors and instead is referred to as male pattern hair loss (MPHL) or female pattern hair loss (FPHL). Should we still insist on treating it like pure androgenetic alopecia?

TABLE 1. Antioxidant Combination

Elemental Phosphorous	58.0 mg
Vitamin C	60.0 mg
Vitamin A (as palmitate)	2500.0 IU
Niacinamide	18.0 mg
Zinc (as Zinc sulphate)	15.0 mg
Iron (as Ferrous fumarate)	14.0 mg
Vitamin E Acetate	10.0 mg
Calcium Pentothenate	6.0 mg
Magnesium (as Magnesium Oxide heavy)	5.0 mg
Potassium Chloride	5.0 mg
Vitamin B12	1.0 mcg
Vitamin B6	2.0 mg
Copper (as coper sulphate)	2.0 mg
Vitamin B2	1.6 mg
Vitamin B1	1.4 mg
Manganese (as Manganese sulphate)	0.5 mg
Folic Acid	200 mcg
Biotin	0.15 mg
Iodine (Potassium iodide)	0.15 mg
Silicon (as colloidal anhydrous silica)	2.0 mcg
Vitamin K	30.0 mcg
Selenium (as selenium di oxide)	30.0 mcg
Chromium Picollinate	25.0 mcg
Molybdenum (as sodium molybdate)	25.0 mcg
Vitamin D3	200.0 IU
Lactic Acid Bacillus	500 lacs

TABLE 2. Amino Acid Combination

Alanine	11.9 gm
Arginine	23.5 mg
Asparti Acid	36.2 mg
Cysteine	3.9 mg
Glutamic Acid	61.8 mg
Glycine	12.8 mg
Histidine	7.7 mg
Isoleucine	14.6 mg
Leucine	23.8 mg
Lysine	19.6 mg
Methionine	3.9 mg
Phenylalanine	16.0 mg
Proline	16.0 mg
Serine	16.0 mg
Threonine	11.3 mg
Tryptophan	3.6 mg
Tyrosine	11.9 mg
Valine	14.0 mg

The male hormone was in focus in the beginning, when it was thought that only men go bald and hair loss runs in families. We were trying to search and treat a cause. But hair loss is neither a sickness nor a disease, it is more of a disturbance or slowing down of the biological cycles due to unfavourable conditions at the cellular level. Baldness progresses gradually over many years. Only the weak hairs are lost in a pattern or diffusely. We can strengthen the follicles, provide nutrition for energy, repair, restore, control hair loss, and achieve hair growth, as suggested by the data from our clinical trial and by other factors reviewed in the current literature below.

CLINICAL TRIAL DATA

We conducted a controlled clinical trial for hair loss management with 100 men and 100 women in each group. Men in the control group received 2% minoxidil application twice a day plus 1mg daily dose of finasteride and women were treated only with twice a day application of 1ml 2% minoxidil. The treatment group of 100 men and 100 women, who were of similar age and similar grades of hair loss, received antioxidants (Table 1), iron, calcium, amino acids (Table 2), B-complex, and biotin, without the use of any anti-androgens or DHT blocker or finasteride. All patients had computerized folliscope analysis for measurement of hair density and calibre at tattooed, fixed test spots over their perceived area of thinning, which was their area of most concern.

The treatment group (no minoxidil or finasteride) showed an average improvement in density of 18% at 2 months and 30% and at 4 months. Hair loss was controlled within 4-6 weeks.[6] The average improvement in calibre at 2 months was 9% and 21% at 4 months.[6,7] Improvement was seen in all the patients; there were no non-responders to this regimen, as are reported in finasteride and minoxidil studies.[8,9]

The control group (treated with minoxidil and finasteride) showed average improvement in density and caliber of 2% at 2 months and 4% at 4 months. There were 43% non-responders who had no improvement at all after 4 months of treatment, while 37% had increased hair fall (shedding) during treatment.[6]

The nutritional support program used in the treated group has also helped with hair loss due to smoking,[10] pollution,[11] and hair shaft disorders such as monilethrix due to poor hair structure.[12] It has also helped an unusual case of hair loss from exposure to cell phone radiation,[13] apart from being consistently effective in the management of hair loss routinely seen in clinical practice. Figure 1 shows improvement in hair density and calibre achieved in four months with the use of nutritional supplements, without the use of minoxidil or finasteride, in a male patient. Figure 2 shows results of

FIGURE 1. Male patient with thinning on vertex *(left)*; improved density, calibre, and hair quality with 4 months of nutrition without minoxidil and finasteride *(right)*.

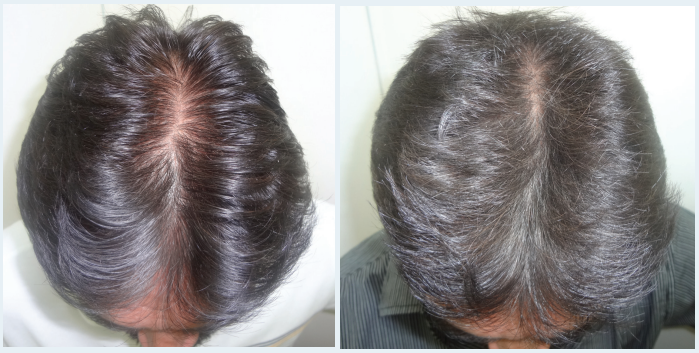
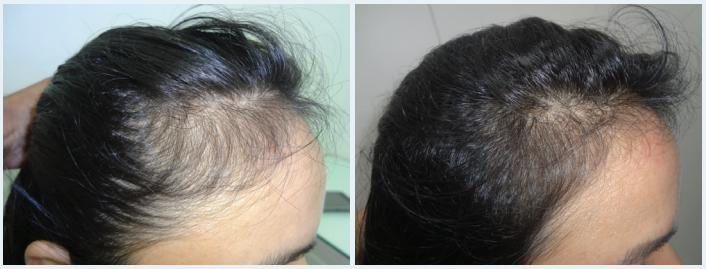


FIGURE 2. Female patient with temporal thinning *(left)*; hair regrowth and better hair quality with 4 months of nutrition without minoxidil and finasteride *(right)*



the same in a female patient. An improvement in density, calibre, and hair quality can be appreciated.

DISCUSSION

Researchers agree that hair loss is multifactorial. Hair loss is not only genetic and androgenic but also involves inflammatory, immune-mediated, nutritional, or other factors causing a dysregulation of the hair growth cycle.[14-16] Previous researchers have provided evidence on how nutrition can reduce inflammation, restore immunity, and improve genetic response.

Twins do not bald to the same extent

Studies of identical biological twin men and women show they do not lose hair in an identical pattern. The progress of hair loss in twins is influenced by such things as lifestyle, environmental factors (smoking, alcohol, caffeine, dandruff, Body Mass Index), physical activity, a history of skin disease, stress, diabetes, hypertension, smoking, multiple marriages, multiple children, divorce, separation, and use of sun protection.[17-19] These are studied as epigenetic factors that alter genetic expression without altering the nucleotide sequence of the genes.[5]

Improving the effect of epigenetic factors

Tronick & Hunter have reviewed Waddington's concept of epigenetics, which was introduced in 1942.[5] Epigenetics explains the effect of factors, such as pollution, stress, sleep, lifestyle, smoking, or obesity, influencing the genetic response. Trüeb has drawn attention to the influence of epigenetics in hair loss.[20] Jorge et al evaluated lifestyle as an epigenetic factor.[21] Nestler elaborated on the epigenetic contributions of stress.[22] Kiec-Wilk et al mentioned epigenetic influence of beta carotene on vascular endothelial growth factor (VEGF), which can induce anagen.[23] The studies suggest that correcting lifestyle can counteract the influence of epigenetic factors helping the management of hair loss.

Improving genetic response at tissue level

ThurnhamI studied how the immune system and genes interact with micronutrients to improve the functional internal environment and cell response.[24] Mocchegiani et al studied interactions of genes and the benefit of treatment with iron, zinc, copper, and micronutrients in the pathogenesis of inflammation and senescence.[25] A recent report by Mocchegiani et al studied micronutrient and gene interactions in inflammation, immune response with benefit from antioxidants.[26] The studies indicate that maintaining nutrition, mineral balance, and the use of antioxidants improves genetic interaction in inflammation, immunity, and senescence, all of which play a prime role in the progression of hair loss.

Hair loss pathways are mediators of inflammation and immunity

Androgens are known to cause inflammation throughout the body. DHT does not directly cause hair loss, but induces release of transforming growth factor beta (TGFβ), which causes hair loss.[27] TGF is a common mediator of inflammation which acts on lymphocytes, macrophages, activates naive thymic cells, and has a role in type 2 T-cell mediated immunity.[28,29] Regulation of Wnt by Dekoff1 (DKK1) is another hair growth pathway. DKK1 is a generalized mediator of immunity and inflammation involved in response from atopic dermatitis to psoriasis.[30] Sonic Hedgehog pathway (SHh) is responsible from embryogenesis of the hair follicle to proliferation, migration of cells, and induction of anagen. This SHh pathway is also involved in secretion of cytokines, interleukins in inflammation, and mediating immune response.[31,32] The three pathways linked with hair loss indicate scientifically that hair loss is an expression of altered inflammation and immunity rather than a specific mechanism of DHT alone.

Improving immunity

Trüeb has elaborated on the role of immunity in hair loss.[33] Kubibidila et al have confirmed altered immunity in malnutrition and in single nutrient deficiencies.[34] Fraker et al and Palmer et al have reported reprogramming of the immune system with correction of nutritional deficiencies.[35,36] We can assume that maintaining nutritional balance has a role in promoting immunity, protecting the hair follicle from damage and decreasing hair loss.

Nutrients can reduce inflammation

Magro et al have studied the role of inflammation in hair loss.[37] Benefits from omega-3 fatty acids in inflammation and autoimmune diseases are reported by Simopoulos.[38] Giugliano et al and Galland both suggested diets to prevent inflammation.[39,40] Sears and Ricordi have studied the role of fatty acids and polyphenols in transcription of inflammatory genes.[41] Maintaining nutrition can thus prevent inflammation and also correct the gene transcription helping in the management of hair loss.

Direct role of nutrient and antioxidants

Kalkan et al suggested that free radicals from the environment and internal metabolism, enter the cells as various ROS and form bonds with the intracellular proteins. The new molecular structure formed due to this combination changes the immune signature of the intracellular proteins making them recognized as new antigens, triggering auto immune response and micro-inflammation.[42] Therefore, neutralizing the free radicals and ROS with antioxidants has a role in prevention of hair loss.

Under predisposing conditions, even normal DHT causes miniaturization. Experiments by Hee established that DHT does not act directly but induces release of hair growth inhibiting factor TGFß1 (transforming growth factor beta 1), which in turn leads to miniaturization and hair loss.[27] As a paradoxical effect, exposure of DHT to the beard hair follicles and occipital hair follicles releases hair growth promoting factor, IGF (insulin-like growth factor), which leads to better hair growth. Continued experimental research on the same

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agenda by Shin et al demonstrated that exposure to DHT first leads to accumulation of ROS in the cells, which then triggers the release of TGFß1. The experiment further demonstrates that the ROS induced mechanism for the release of TGFß1 can be blocked by adding a free radical scavenger or antioxidant to the cell culture.[43] This documented research proves that use of antioxidants can block the mechanism of action of DHT at the tissue level. Morel et al confirmed that just like the events for TGF, the ROS act as second messengers to numerous cytokines, growth factors and ROS also regulate gene expression,[44] the same conclusion derived from the ROS research conducted by Dalton et al.[45]

Stefanato noted that peri infundibular inflammatory lymphocytic infiltrate in hair loss, followed by peri-follicular fibrosis being close to the epidermis suggested an external trigger factor generating ROS are responsible, as are UV rays, pollution, sebum, oxidation of scalp lipids or scalp microbes.[46] Liu et al showed that substance P induced hair loss due to stress is mediated through ROS.[47] Trüeb concluded that oxidative stress forms the hair aging phenotype and emphasised the role of oral antioxidants.[48] Experiments by Liang & Liao found that low dose omega 6, gamma lenolenic acid, can block 5-alpha-reductase activity and also is precursor to anti-inflammatory prostaglandin1.[49] Munkhbayar et al showed that arachidonic acid promotes mitosis, angiogenesis, hair elongation, and proliferation of matrix keratinocytes and improves expression of growth factors in the dermal papilla.[50] Aoi et al documented direct hair inductive capacity of Vitamin D3 on the dermal papilla,[51] while Beoy et al demonstrated that tocotrienol and alpha tocopherol supplements improved hair counts by inhibition of lipid peroxidation.[52] From these various scientific works, we can conclude that the use of antioxidants and nutrients have a role in the management of hair loss.

Do hair loss patients have nutritional deficiencies?

Goette & Odum reported alopecia in crash dieters in 1976.[53] Rushton has more than once presented evidence of nutritional deficiencies in hair loss.[54,55] Harrison and Bergfeld (2009) documented diffuse hair loss in zinc deficiency, iron deficiency, crash dieting, starvation, calorie restriction, and low fat diets.[56] Jin et al and Ozturk et al noted zinc, copper, iron, and manganese deficiencies in hair, serum, and urine of hair loss patients while Gowda et al noted amino acid deficiencies.[57-59] Betsy, Binitha, and Sarita have reported zinc deficiency causing hair loss along with hypothyroidism as an overlooked cause of alopecia.[60] Lengg, et al have published a double-blind, placebo-controlled trial showing benefits of nutritional supplements in hair loss.[61] The author has published a controlled clinical trial and reports on the benefit of nutrition in hair loss management, including a 2008 article in the ISHRS *Forum*.[6,7]

CONCLUSION

In conclusion, hair loss is not only androgenic or genetic. Hair loss occurs without raised DHT levels due to sensitivity and altered tissue response in the follicles. We should recognize there is a "non-hormonal" hair loss caused by non-hormonal factors. Epigenetics, inflammation, immunity, and accumulation of ROS lead to altered tissue response. Nutritional supplements can restore balance at the cellular level to improve immunity, reduce inflammation, neutralize ROS, improve cellular function, and improve genetic expression leading to better hair growth. We need not depend only on anti-androgens to fight hair loss. Providing effective treatment that can be followed long term without fear of side effects will win back the confidence of our patients.

Co-editor's note: This article gives an interesting overview about the multifactorial nature of hair loss. However, I would not be so quick to downplay the overwhelming evidence for the major effects of genetics and androgens on hair growth. I often explain to my patients that patterned hair loss, unlike diffuse effluvium, cannot merely be due to a general health problem or deficiency. Most mechanisms actually happen in the follicle itself, which is why laboratory tests are often normal.

On the other hand, hair follicle cells are characterized by a very active metabolism. I am sure that nutritional supplements may help treat diffuse hair loss or generally improve hair growth. They are actually part of my treatment plan for most of my hair patients, especially when they have idiopathic diffuse effluvium or active periods of androgenetic alopecia. Based on several studies, I recommend supplements containing the amino acid L-cystine combined with medicinal yeast, pantothenic acid, and B-vitamins. In addition, supplements with biotin, zinc, and other preparations may be helpful for some patients.

The presented study demonstrates the possible usefulness of nutritional supplements, which lead to improved hair parameters after 4 months. Long-term follow-ups would be needed to assess the actual efficacy compared to minoxidil and finasteride. There is certainly a role for anti-inflammatory and anti-oxidant approaches, too. Due to a lack of diagnostic techniques, we still don't have individually targeted hair therapy. Therefore, I believe that the key to success in treating our patients is combination therapy. —AF

References

1. Sawaya, M.E., and V.H. Price. Different levels of 5-alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of woman and men with androgenetic alopecia. *J Invest Dermatol.* 1997; 109:296.
2. Urysiak-Czubatka, I., et al. Assessment of the usefulness of dihydrotestosterone in the diagnostics of patients with androgenetic alopecia. *Advances in Dermatology and Allergology/Postepy Dermatologii i Alergologii.* 2014; 31(4):207-215.
3. Cranwell, W., and R. Sinclair. Male Androgenetic Alopecia. [Updated 2016 Feb 29]. In: L.J. De Groot, et al., eds. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278957/.
4. Lee, W-S, and H-J Lee. Characteristics of androgenetic alopecia in Asian. *Annals of Dermatology.* 2012; 24(3):243-252. doi:10.5021/ad.2012.24.3.243.
5. Tronick, E., and R.G. Hunter. (2016). Waddington, Dynamic Systems, and Epigenetics. *Frontiers in Behavioral Neuroscience*, 10, 107. http://doi.org/10.3389/fnbeh.2016.00107.
6. Rajput, R.J. Controlled clinical trial for evaluation of hair growth with low dose cyclical nutrition therapy in men and women without the use of finasteride. *Plast Aesthet Res.* 2017; 4. doi: 10.20517/2347-9264.2017.57.
7. Rajput, R. Cyclical medicine for hair loss Management and improving results in hair transplant. *Hair Transplant Forum Int'l.* 2008; 18(6):208.
8. Kaufman, K.D., et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. *J Am Acad Dermatol.* 1998.

9. Inadomi, T. Efficacy of finasteride for treating patients with androgenetic alopecia who are pileous in other areas: a pilot study in Japan. *Indian J Dermatol.* 2014(Mar-Apr); 59(2):163-165.
10. Rajput, R.S. Benefit from vitamin therapy in smoker's hair. *Hair Ther Transplant.* 2016; 6:141. doi: 10.4172/2167-0951.1000141.
11. Rajput, R. Understanding hair loss due to air pollution and the approach to management. *Hair Ther Transplant.* 2015; 5:133. http://www.omicsgroup.org/journals/understanding-hair-loss-due-to-air-pollution-and-the-approach-to-management-2167-0951-1000133.php?aid=47705
12. Rajput, R. Improvement in hair loss and better hair quality with vitamin therapy in monilethrix. *J Cosmo Trichol.* 2016; 2:113. doi: 10.4172/2471-9323.1000113.
13. Rajput, R. Hair loss due to electromagnetic radiation from overuse of cell phone. *J Cosmo Trichol.* 2016; 2:114. doi:10.4172/2471-9323.1000114.
14. Wolff, H., et al. The diagnosis and treatment of hair and scalp diseases. *Dtsch Arztebl Int.* 2016; 113:377-386. doi: 10.3238/arztebl.2016.0377.
15. Trüeb, R.M. Pharmacologic interventions in aging hair. *Clinical Interventions in Aging.* 2006; 1(2):121-129.
16. Rajendrasingh, J.R. Role of non-androgenic factors in hair loss and hair regrowth. *J Cosmo Trichol.* 2017; 3:118. doi:10.4172/2471-9323.1000118.
17. Rexbye, H, et al. Hair loss among elderly men: etiology and impact on perceived age. *J Gerontol A Biol Sci Med Sci.* 2005; 60(8):1077-1082.
18. Gatherwright, J., et al. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg.* 2012(Dec); 130(6):1219-1226. doi: 10.1097/PRS.0b013e31826d104f.
19. Gatherwright, J., et al. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg.* 2013(May); 131(5):794e-801e. doi: 10.1097/PRS.0b013e3182865ca9.
20. Trüeb, R.M. Oxidative stress in ageing of hair. *Int J Trichology.* 2009(Jan-Jun); 1(1):6-14. doi: 10.4103/0974-7753.51923
21. Alegría-Torres, J.A., et al. Epigenetics and lifestyle. *Epigenomics.* 2011(Jun); 3(3):267-277. doi: 10.2217/epi.11.22.
22. Nestler, E.J. Transgenerational epigenetic contributions to stress responses: fact or fiction? *PLoS Biol.* 2016; 14(3):e1002426. doi: 10.1371/journal.pbio.1002426.
23. Kiec-Wilk, B., et al. DNA methylation, induced by betacarotene and arachidonic acid, plays a regulatory role in the pro-angiogenic VEGF-receptor (KDR) gene expression in endothelial cells. *J Physiol Pharmacol.* 2009; 60(4):49-53.
24. Thurnham, D.I. An overview of interactions between micronutrients and of micronutrients with drugs, genes and immune mechanisms. *Nutr Res Rev.* 2004(Dec); 17(2):211-240.
25. Mocchegiani, E., et al. Micronutrient (Zn, Cu, Fe)–gene interactions in ageing and inflammatory age-related diseases: implications for treatments. *Ageing Research Reviews.* 2012; 11:297- 319.
26. Mocchegiani, E., et al. Micronutrient-gene interactions related to inflammatory/immune response and antioxidant activity in ageing and inflammation. A systematic review. *Mech Ageing Dev.* 2014(Mar-Apr); 136-137:29-49.
27. Hee, C.E. The involvement of ROS on androgen inducible TGF beta 1 regulation derived from dermal papilla cells; a suggestive implication of ROS on androgenetic alopecia. *J of the Amer Acad Derm.* 2008.
28. Han, G., et al. The pro-inflammatory role of TGFβ1: a paradox? *Int J Biol Sci.* 2012; 8(2):228-235.
29. Sanjabi, S., et al. Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. *Cold Spring Harb Perspect Biol.* 2017(Jun 1); 9(6). pii: a022236. doi: 10.1101/cshperspect.a022236.
30. Chae, W.J., et al. The Wnt antagonist dickkopf-1 promotes pathological type 2 cell-mediated inflammation. *Immunity.* 2016; 44(2):246-258.
31. Crompton, T., et al. Sonic hedgehog signaling in T-cell development and activation. *Nat Rev Immunol.* 2007; 7:726-735. doi: 10.1038/nri2151.
32. De la Roche, M., et al. Hedgehog signaling controls T-cell killing at the immunological synapse. *Science.* 2013; 342:1247-1250. doi: 10.1126/science.1244689.
33. Trüeb, R.M. Molecular mechanisms of androgenetic alopecia. *Exp Gerontol.* 2002.
34. Kubibidila, S., et al. The Immune Response in Protein-Energy Malnutrition and Single Nutrient Deficiencies. In: Human Nutrition: A Comprehensive Treatise, Vol. 8; 1993.
35. Fraker, P., and L. King. Reprogramming of the immune system during zinc deficiency. *Ann Rev Nutr.* 2004.
36. Palmer, A.C. Nutritionally mediated programming of the developing immune system. *Adv Nutr.* 2011; 2:377-395.
37. Magro, C.M., et al. The role of inflammation and immunity in the pathogenesis of androgenetic alopecia. *J Drugs Dermatol.* 2011(Dec); 10(12):1404-1411.
38. Simopoulos, A.P. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr.* 2002(Dec); 21(6):495-505.
39. Giugliano, D., et al. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol.* 2006(Aug 15); 48(4):677-85. Epub 2006 Jul 24.
40. Galland, L. Diet and inflammation. *Nutr Clin Pract.* 2010; 25(6):634-640.
41. Sears, B., and C. Ricordi. Role of fatty acids and polyphenols in inflammatory gene transcription and their impact on obesity, metabolic syndrome and diabetes. *Eur Rev Med Pharmacol Sci.* 2012; 16-N(9):1137-1154.
42. Kalkan, G., et al. Relationship between manganese superoxide dismutase (MnSODAla-9Val) and glutathione peroxidase (GPx1 Pro 197 Leu) gene polymorphisms and alopecia areata. *Int J Clin Exp Med.* 2015; 8:21533-21540.
43. Shin, H., et al. Induction of TGFß1 transforming growth factor-beta 1 by androgen is mediated by ROS, reactive oxygen species in hair follicle dermal papilla cells. *BMB Rep.* 2013(Sep).
44. Morel, Y., and R. Barouki. Repression of gene expression by oxidative stress. *Biochem J.* 1999(Sep); 15:342 Pt 3:481-96.
45. Dalton, T.P., et al. Regulation of gene expression by reactive oxygen. *Annu Rev Pharmacol Toxicol.* 1999; 39:67-101.
46. Stefanato, C.M. Histopathology of alopecia: a clinico pathological approach to diagnosis. *Histopathology.* 2010(Jan); 56(1):24-38.
47. Liu, N., et al. Chronic restraint stress inhibits hair growth via substance P mediated by reactive oxygen species in mice. *PLoS One.* 2013(Apr 26); 8(4):e61574.
48. Trüeb, R.M. Oxidative stress in ageing of hair. *Int J Trichology.* 2009(Jan); 1(1):6-14.
49. Liang, T., and S. Liao. Inhibition of steroid 5-alpha-reductase by specific aliphatic unsaturated fatty acids. *Biochem J.* 1992(Jul 15); 285 (Pt 2):557-62.
50. Munkhbayar, S., et al. Role of arachidonic acid in promoting hair growth. *Ann Dermatol.* 2016(Feb); 28(1):55-64.
51. Aoi, N., et al. 1α, 25-dihydroxyvitamin D3 modulates the hair-inductive capacity of dermal papilla cells: therapeutic potential for hair regeneration. *Stem Cells Transl Med.* 2012; 1(8):615-626.
52. Beoy, L.A., et al. Effects of Tocotrienol Supplementation on Hair Growth in Human Volunteers. *Tropical Life Sciences Research.* 2010; 21(2):91-99.
53. Goette, D.K., and R.B. Odum. Alopecia in crash dieters. *JAMA.* 1976; 235:2622-2623.
54. Rushton, D.H., et al. Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol.* 1990; 123:187-197.
55. Rushton, D.H. Nutritional factors and hair loss. *Clin Exp Dermatol.* 2002; 27:396-04.
56. Harrison and Bergfeld 2009; documented diffuse hair loss in calorie restriction, low fatty acids, crash dieting, starvation, zinc and iron deficiency.
57. Jin, W., et al. Determination of zinc, copper, iron and manganese contents in hair for MPA patients and healthy men. Guang Pu Xue Yu Guang Pu Fen Xi. 1998(Feb); 18(1):91-93.
58. Ozturk, P., et al. BMI and levels of Zn, Cu, in hair, serum and urine of male patients with androgenetic alopecia. *Journal of Trace Elements in Medicine and Biology.* 2014; 28:266-270.
59. Ambooken, B., et al. Zinc deficiency associated with hypothyroidism: an overlooked cause of severe alopecia. *Int J Trichology.* 2013. [Zn, Cu, Se, Fe, are required for thyroid hormone synthesis.]
60. Gowda, D., et al. Prevalence of nutritional deficiencies in hair loss among Indian participants: results of a cross-sectional study. *Int'l Journal of Trichology.* 2017; 9(3):101-104.
61. Lengg, N., et al. Dietary supplement increases anagen hair rate in women with telogen effluvium: results of a double-blind, placebo-controlled trial. *Therapy.* 2007; 4:59-65. ■