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REVIEW

The Role of Vitamins and Minerals in Hair Loss: A Review

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ABSTRACT

People commonly inquire about vitamin and mineral supplementation and diet as a means to prevent or manage dermatological diseases and, in particular, hair loss. Answering these queries is frequently challenging, given the enormous and conflicting evidence that exists on this subject. There are several reasons to suspect a role for micronutrients in non-scarring alopecia. Micronutrients are major elements in the normal hair follicle cycle, playing a role in cellular turnover, a frequent occurrence in the matrix cells in the follicle bulb that are rapidly dividing. Management of alopecia is an essential aspect of clinical dermatology given the prevalence of hair loss and its significant impact on patients' quality of life. The role of nutrition and diet in treating hair loss represents a dynamic and growing area of inquiry. In this review we summarize the role of vitamins and minerals, such as vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, iron, selenium, and zinc, in non-scarring alopecia. A broad literature search of PubMed and Google Scholar was performed in July 2018 to compile published articles that study the relationship between vitamins and minerals, and hair loss. Micronutrients such as vitamins and minerals play an important, but not entirely clear role in normal hair follicle development and immune cell function. Deficiency of such micronutrients may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia. Given the role of vitamins and minerals in the hair cycle and immune defense mechanism, large double-blind placebo-controlled trials are required to determine the effect of specific micronutrient supplementation on hair growth in those with both micronutrient deficiency and non-scarring alopecia to establish any association between hair loss and such micronutrient deficiency.

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PLAIN LANGUAGE SUMMARY

Hair loss is a common problem that may be improved with vitamin and mineral supplementation. Vitamins and minerals are important for normal cell growth and function and may contribute to hair loss when they are deficient. While supplementation is relatively affordable and easily accessible, it is important to know which vitamins and minerals are helpful in treating hair loss.

Androgenetic alopecia (AGA), telogen effluvium (TE) are two common types of hair loss. Studies show that supplementing the diet with low levels of vitamin D can improve symptoms of these diseases. If a patient with AGA or TE has low iron levels (more commonly seen in females), supplementation is also recommended. These iron-deficient patients should also ensure their vitamin C intake is appropriate. At the present time there is insufficient data to recommend zinc, riboflavin, folic acid, or vitamin B12 supplementation in cases of deficiency. Neither vitamin E or biotin supplementation are supported by the literature for treating AGA or TE; in addition, biotin supplementation can also lead to dangerous false laboratory results. Studies show that too much vitamin A can contribute to hair loss, as can too much selenium, although more studies are needed to establish the latter relationship.

Alopecia areata (AA) occurs when the immune system attacks the hair follicle. Studies have shown a relationship between AA and low vitamin D levels. Vitamin D should be supplemented if levels are low. However, more studies are needed to determine the effect of iron and zinc supplementation on AA patients. There is currently not enough data to recommend supplementation of folate or B12. Biotin supplementation is not supported by available data for the treatment of AA. It is unclear if selenium plays a role in this disease; therefore, supplementation with this mineral is not recommended.

Iron, vitamin D, folate, vitamin B12, and selenium are vitamins and minerals that may be involved in hair graying/whitening during childhood or early adulthood. Supplementing these deficient micronutrients can improve premature graying.

INTRODUCTION

People commonly inquire about vitamin and mineral supplementation and diet as a means to prevent or manage dermatological diseases and, in particular, hair loss. Answering these queries is frequently challenging, given the enormous and conflicting body of evidence that exists on this subject. The latest findings promote new evidence-based recommendations for the prevention and treatment of atopic dermatitis, psoriasis, acne, and skin cancer and have highlighted the requirement for ongoing research studies [1, 2].

The human scalp contains approximately 100,000 hair follicles. Of these, 90% are in the anagen phase, where there is no alopecia, requiring essential elements, such as proteins, vitamins, and minerals, to efficiently produce healthy hair [3, 4]. Micronutrients, including vitamins and trace minerals, are therefore crucial components of our diet [5]. According to Stewart and Gutherie [6], in 1497 Vasco de Gamma recorded the deaths of 100 of his 160 sailors due to scurvy and 300 years later James Lind linked scurvy with vitamin C deficiency, noting skin hemorrhage and hair loss [6]. In protein-energy malnutrition, skin and hair changes are prominent, as seen, for example in children with kwashiorkor, marasmus, and marasmic-kwashiorkor conditions [7]. A severe reduction in carbohydrate intake results in hair loss [8].

Management of alopecia is an essential aspect of clinical dermatology given the prevalence of hair loss and its significant impact on patients' quality of life. Androgenetic alopecia (AGA), telogen effluvium (TE), and alopecia areata (AA) represent the three most common types of non-scarring alopecia [9]. There are several reasons to suspect a role for micronutrients in non-scarring alopecia. The most

noteworthy of these is that micronutrients are major elements in the normal hair follicle cycle, playing a role in the cellular turnover of the matrix cells in the follicle bulb that are rapidly dividing [10].

The role of nutrition and diet in treating hair loss represents a dynamic and growing area of inquiry. In this review we summarize the role of vitamins and minerals, such as vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, iron, selenium, and zinc, in non-scarring alopecia.

METHODS

We performed a broad literature search of PubMed and Google Scholar in July 2018 to compile published articles that study the relationship between vitamins and minerals, and hair loss. The search terms included "hair loss," "alopecia," "vitamin A," "vitamin B," "vitamin C," "vitamin D," "vitamin E," "iron," "ferritin," "biotin," "zinc," "selenium," "folic acid," "telogen effluvium," "alopecia areata," "androgenetic alopecia," "female pattern hair loss," "male pattern hair loss," and "premature hair graying." Only published articles on human subjects that were written in English were selected. After three authors had independently screened titles and abstracts for relevance and had thoroughly examined the clinical results, 125 articles were selected to be included in this review. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

VITAMIN A

Vitamin A represents a group of fat-soluble retinoids that includes retinol, retinal, and retinyl esters [11, 12]. This vitamin serves many roles in the body: it is critical for vision, involved in immune function, and is necessary for cellular growth and differentiation [13]. Vitamin A exists in the diet as preformed vitamin A (from animal sources) and as provitamin A carotenoids (sourced from plants). Both sources of vitamin A must be metabolized intracellularly to their active forms (retinal and retinoic acid). The majority of vitamin A is stored in the liver as retinyl esters. When measuring retinol and carotenoid levels, plasma levels are typically sufficient for determining adequacy. A plasma retinol concentration of < 0.70 μmol/L signifies vitamin A inadequacy [13].

In most cases, a balanced diet will supply a healthy amount of vitamin A [14]. The recommended dietary allowance of vitamin A for adults aged $\geq$ 19 years is 1300 mcg/day (4300 IU [international units]) for U.S. populations. While there is no upper intake level for provitamin A carotenoids, ingestion of very high levels of preformed vitamin A can be toxic. For adults aged $\geq$ 19 years, the tolerable upper intake level of preformed vitamin A is 10,000 IU [13]. It is therefore important to consider what form of vitamin A is contained in supplements (provitamin A carotenoids or preformed vitamin A) and in what proportion.

As a general rule, consuming too much or over-supplementing vitamin A can cause hair loss [15, 16]. Typically, fat-soluble vitamin A is stored in the liver where its dispersal is tightly regulated by anabolic and catabolic reactions between the inactive and active metabolite. When levels of vitamin A are too high, the capacity of the transport system is exceeded and vitamin A spills over into the circulation [17]. Maintaining homeostasis—and by extension the proper concentration of active metabolite—is important for healthy hair [18].

In one study with the aim to determine the effects of isotretinoin on acne vulgaris in the skin, special care was taken to evaluate changes in the hair and hair growth. Thirty patients were evaluated over a 4- to 7-month treatment period, with examinations carried out using a FotoFinder dermoscope (FotoFinder Systems, Inc., Columbia, MD, USA) with TrichoScan® Professional software. Consistent with other findings, the authors reported a decrease in hair count, density, and percentage of anagen hairs [19].

In a case documented in 1979, a 28-year-old woman undergoing renal dialysis noticed sudden hair loss. Further investigation revealed

that she had been taking a daily vitamin A supplement (5000 IU) and that her vitamin A serum levels were well above normal (140 μg/dL). Gentle traction yielded four to five hairs, all of which were in the telogen phase. One month after termination of vitamin A supplementation, hair loss was no longer a problem. The authors concluded that signs of hypervitaminosis A were misinterpreted as symptoms of chronic renal failure. The authors also highlighted the possible "insidious" effects of exogenous vitamin A on dialysis patients [20].

Consumption of vitamin A exceeding the recommended daily limit of approximately 10,000 IU a day can lead to vitamin A toxicity. In a case report, a 60-year-old male who had been taking excess vitamin A supplements experienced non-scarring fronto-central alopecia as well as decreased pubic and axillary hair. The patient also reported dystrophic nail changes and an erythematous rash. Taken together, these changes were concurrent with drug toxicity that aligned with the patient's over-consumption of vitamin A [21].

VITAMIN B

The vitamin B complex includes eight water-soluble vitamin substances—thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, biotin (B7), folate, and vitamin B12—that aid in cell metabolism. The recommended daily allowances of these vitamins can be reached by eating a balanced diet, with the exception of biotin, which is the only B vitamin produced by the body. In healthy individuals biotin does not need to be supplemented [14]. Only riboflavin, biotin, folate, and vitamin B12 deficiencies have been associated with hair loss.

Vitamin B2 (riboflavin) is a component of two important coenzymes: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) [22]. FMN and FAD represent 90% of dietary riboflavin, and both play roles in cellular development and function, metabolism of fats, and energy production [23]. The body stores only small amounts of riboflavin, in the liver, heart, and kidneys. Riboflavin deficiency—while extremely rare in the USA—can cause hair loss [24].

Vitamin B7 (biotin or vitamin H) is a cofactor for five carboxylases that catalyze steps in fatty acid, glucose, and amino acid metabolism. Biotin also plays roles in histone modification, cell signaling, and gene regulation [25]. Most dietary biotin is found in protein. Dietary protein must be broken down into free biotin, which is then stored in the small intestine and liver. An adequate intake of biotin for adults is 30 mcg/day in U.S. populations. The average dietary intake of biotin in Western countries is adequate, and biotin deficiency is rare. Severe biotin deficiency in healthy individuals eating a normal diet has never been reported [26, 27]. While there is no upper limit for biotin intake—as there is no evidence for biotin toxicity—high biotin intake can cause falsely high or falsely low laboratory test results [28]. Many supplements for hair, skin, and nails far exceed the recommended daily intake of biotin [28].

The presence of biotin can in fact interfere with tests that use biotin–streptavidin technology. The interaction between biotin and streptavidin is used as the basis for many biotin-based immunoassays, and these immunoassays are vulnerable to interference when they are used to analyze a sample that contains biotin. Exogenous biotin in the sample competes with biotinylated reagents for the binding sites on streptavidin reagents, creating false positive or false negative results [29]. Biotin interference in biotin–streptavidin immunoassays have been described in patient samples for thyroid-stimulating hormone, free tri-iodothyronine (FT3), free thyroxine (FT4), parathyroid hormone, estradiol, testosterone, progesterone, dehydroepiandrosterone sulfate, vitamin B12, prostate-specific antigen, luteinizing hormone, and follicle-stimulating hormone. Other non-hormonal tests include cardiac and tumor markers, infectious disease serologies, biomarkers of anemia and autoimmune diseases, and concentrations of immunosuppressive drugs [29–32].

Furthermore, according to the U.S. Food and Drug Administration, biotin interference (from supplemental biotin) caused a falsely low result in a troponin test that led to a missed diagnosis

of a heart attack and a patient's death [28]. In addition, a recent study showed that some human chorionic gonadotropin (hCG) devices are subject to biotin interference in individuals taking dietary biotin supplements. Therefore, clinicians and laboratory technicians need to be aware of this potential interference with qualitative urine hCG tests and should suggest quantitative serum hCG measurement. The latter is not subject to biotin interference [33].

Biotin deficiency can be genetic or acquired. Genetic causes of biotin deficiency can be either neonatal or infantile. The neonatal type is a life-threatening condition manifested during the first 6 weeks of life, and it is due to a holocarboxylase enzyme deficiency. It is usually manifested with severe dermatitis and alopecia, where there is loss of vellus and terminal hair on the scalp; eyebrows, eyelashes, and lanugo hair can also be absent. The infantile form of biotin deficiency occurs after 3 months of delivery and is due to a lack of the enzyme called biotinidase. In this form, hair of the scalp, eyebrows, and eyelashes is sparse or totally absent [34].

Acquired biotin deficiency can be due to increased raw egg consumption, where avidin particles attach to biotin and inhibit its absorption into the intestinal gut. In cooked eggs the avidin particles are destroyed [35]. Other causes of acquired biotin deficiency include states of malabsorption, alcoholism, pregnancy, prolonged use of antibiotics that interrupt normal flora, medications such as valproic acid, and isotretinoin intake. The aforementioned medications interfere with biotinidase activity [34]. Evidence suggests that 50% of pregnant women are deficient in biotin [36].

While signs of biotin deficiency include hair loss, skin rashes, and brittle nails, the efficacy of biotin in supplements for hair, skin, and nails as a means to remedy these conditions is not supported in large-scale studies [25, 26]. In fact, only case reports have been used to justify the use of biotin supplements for hair growth. These case reports were in children and found that 3–5 mg biotin daily could improve hair health after 3–4 months in children with uncombable hair syndrome [37, 38].

A recent review article evaluating biotin and its effect on human hair found 18 reported cases of biotin use on hair and nail. In ten of these 18 cases there was a genetic cause of biotin deficiency; the remaining eight patients had alopecia that was improved after they had taken biotin supplementation. There were three cases of uncombable hair syndrome, three cases of brittle nail syndrome, one case of alopecia due to valproic acid intake, and one case of an infant on a biotin-free dietary supplement. All of these 18 patients had underlying causes of biotin deficiency and, once treated with biotin supplement, showed clinical improvement in a variable time period [35].

Researchers in another study investigated the serum biotin level in 541 women participants complaining of hair shedding (age range 9–92 years). Low biotin levels (< 100 ng/L) were found in 38% of these subjects. Of this 38% with biotin deficiency, 11% were found to have an acquired cause of biotin deficiency, such as gastrointestinal disease, valproic acid, isotretinoin, and antibiotic use, and 35% were found to have associated underlying seborrheic dermatitis. These results suggest a multifactorial cause of hair loss [39].

A case–control study was conducted on 52 Indian subjects aged < 20 years with premature canities (graying of the hair), with a matched control for each patient. The authors assessed and compared biotin, folic acid and vitamin B12 levels in both groups. The results showed a deficiency of vitamin B12 and folic acid in the patients evaluated and lower levels of biotin without any obvious biotin deficiency in the cases [40].

Folate is another water-soluble B vitamin and includes naturally occurring food folate and folic acid (fully oxidized monoglutamate). Folate is a coenzyme in the synthesis of nucleic acids and in amino acid metabolism. It exists in the plasma as 5-methyl-tetrahydrofolate, while about half of the total body content exists in the liver [22, 41]. The recommended dietary allowance of food folate is 400 mcg daily for adults, which is supported by required fortification of some foods in the USA [22]. The tolerable upper intake level of folate is 1000 mcg [42]. While most people in the USA ingest adequate amounts of folate, certain groups are at risk for deficiency (usually in association with poor

diet, alcoholism, or a malabsorptive disorder). Folate deficiency can cause hair, skin, and nail changes [22].

Vitamin B12 is necessary for DNA synthesis, neurological function, and red blood cell formation [22]. The active forms of B12 are called methylcobalamin and 5-deoxyadenosylcobalamin. Vitamin B12 is a cofactor for methionine synthase and thereby affects the synthesis of nearly 100 substrates including DNA, RNA, and proteins [22]. The recommended dietary allowance of vitamin B12 is 2.4 mcg for adult U.S. populations. There is no established upper limit for vitamin B12 intake, as it has a low potential for toxicity [22].

The role of folate and vitamin B12 in nucleic acid production suggest that they might play a role in the highly proliferative hair follicle [43]. However, few studies to date have addressed the relationship between B vitamins and hair loss. Turkish authors investigated folate level in 43 patients with AA and 36 healthy controls and found no significant differences in serum folate and vitamin B12 levels between the AA subjects and the healthy controls [44]. Also, the authors found that serum levels did not vary with duration or activity of the disease [44]. In another study conducted in Turkey 75 subjects with AA and 54 controls were enrolled. Blood samples were taken to investigate the serum folic acid and vitamin B12 levels. The results were similar to those reported by the authors of the previous Turkish study [44], with the authors finding no significant differences in vitamin B12 and folate levels between affected and healthy patients [45].

A study including 29 patients with AA that involved > 20% of the scalp showed that mean red blood cell folate concentrations were significantly lower in the patient group than in controls and significantly lower in patients with alopecia totalis/alopecia universalis than in patients with patchy hair loss [46]. Of interest, a genetic study including 136 Turkish patients with AA and 130 healthy controls found that the affected patients had a higher prevalence of mutations in the methylene-tetrahydrofolate reductase (MTHFR) gene [47]. This gene regulates folate metabolism, influences nucleic acid synthesis and DNA methylation, and is associated with other autoimmune disorders. These results suggest that mutations in MTHFR might impact the risk of AA in the Turkish population. However, there was no difference between serum levels of folate or vitamin B12 in affected patients and controls [47].

A retrospective cross-sectional study evaluated folate and vitamin B12 levels in 115 patients with TE (acute and chronic). The results showed that 2.6% of subjects had vitamin B12 deficiency but none had folate deficiency. the lack of a control group is a major limitation of this study [48]. The authors of a case–control study attempted to determine the prevalence of trichodynia in 91 patients with diffuse hair loss, including those with AGA and TE. These researchers found no significant difference in folate and vitamin B12 levels between patients with hair loss and control patients [35]. Ramsay et al. reported a reduction in vitamin B12 levels in females with AGA treated with ethinyl estradiol and cyproterone acetate (Diane/Dianette and Androcur). This reduced vitamin B12 level resulted in vitamin B12-related anxiety, causing some patient to stop treatment. However, a daily 200 μg vitamin B12 supplement corrected the reduced B12 concentrations. Interestingly, the reduction in vitamin B12 levels had no adverse effects on hair shedding or hair growth [49].

VITAMIN C

Vitamin C, or ascorbic acid, is a water-soluble vitamin derived from glucose metabolism. It is a potent antioxidant preventing the oxidation of low-density lipoproteins and free radicals damage. It also acts as a reducing mediator necessary for collagen fiber synthesis through hydroxylation of lysine and proline. Vitamin C plays an essential role in the intestinal absorption of iron due to its chelating and reducing effect, assisting iron mobilization and intestinal absorption [50]. Therefore, vitamin C intake is important in patients with hair loss associated with iron deficiency.

Humans are naturally deficient in an enzyme called L-gulonolactone oxidase that is required for vitamin C synthesis, and should therefore

take vitamin C through their diet. Citrus fruits, potatoes, tomatoes, green peppers, and cabbages have particularly high concentrations of vitamin C [51]. Although vitamin C deficiency is typically associated to body hair abnormalities [52], there are no data correlating vitamin C levels and hair loss.

VITAMIN D

Vitamin D is a fat-soluble vitamin synthesized in epidermal keratinocytes [53]. Vitamin D obtained from the diet or synthesis in skin is inactive and needs to be activated enzymatically. Serum levels are primarily maintained through the UVB-mediated conversion of 7-dehydrocholesterol in the skin to cholecalciferol, which is hydroxylated in the liver and kidney to the active form of 1,25-dihydroxyvitamin D [1,25(OH)2D] [54, 55]. There is strong evidence that vitamin D exerts an anti-inflammatory and immunoregulatory effect, in addition to its important role in maintaining adequate serum levels of calcium and phosphorus [54, 56]. The mechanisms underlying the role of vitamin D in autoimmunity are not fully understood [54, 55]. Low vitamin D levels have been reported in several autoimmune diseases [54, 55, 57–60].

Vitamin D modulates growth and differentiation of keratinocytes through binding to the nuclear vitamin D receptor (VDR). Murine hair follicle keratinocytes are immunoreactive for VDR, showing their highest activity in the anagen stage [61]. The role of vitamin D in the hair follicle is evidenced by hair loss in patients with vitamin D-dependent rickets type II. These patients have mutations in the VDR gene, resulting in vitamin D resistance and sparse body hair, frequently involving the total scalp and body alopecia [62–64]. In addition, Forghani et al. identified novel nonsense mutations in the VDR gene in two patients that resulted in hereditary vitamin D-resistant rickets and alopecia [65].

Vitamin D and AA

Published data on AA suggest that vitamin D, due to its immunomodulatory effect, may be involved in AA [66, 67]. Lee et al. conducted a systematic review and meta-analysis of observational studies on the prevalence of vitamin D deficiency and/or serum vitamin D levels and AA [68]. These authors analyzed a total of 14 studies that involved 1255 patients with AA and 784 control patients without AA. The mean serum 25-hydroxyvitamin D [25(OH)D] level in patients with AA was significantly lower than that in the non-AA control group, by 8.52 ng/dL (95% confidence interval − 11.53 to − 5.50 ng/dL). Vitamin D deficiency was also highly prevalent in patients with AA, leading the authors to suggest that the vitamin D level has to be measured in patients with AA. These results also suggest that vitamin D supplements or topical vitamin D analogues should be considered for patients with AA and vitamin D deficiency. However, the meta-analysis did not find any clear correlations between extent of hair loss and serum 25-hydroxyvitamin D level [68].

Thompson et al. evaluated the association between AA and vitamin D in a prospective study. Survey data encompassing lifestyle and medical history from 55,929 women in the Nurses' Health Study were investigated. The authors found that there was no significant association between dietary, supplemental, or total vitamin D intake and risk of developing AA [69].

More recently, a cross-sectional study conducted by Gade et al. sought to assess serum vitamin D levels in patients with AA as compared to healthy controls, and to further identify the association between vitamin D levels and disease severity in patients with AA. The study included 45 adult patients with AA and 45 control subjects. Serum vitamin D was estimated using enzyme-linked immunosorbent assay (ELISA) kits. The severity of AA was determined using the Severity of Alopecia Tool (SALT) score. The mean vitamin D level was found to be significantly lower in patients with AA (17.86 ± SD 5.83 ng/mL) than in the healthy controls (30.65 ± SD 6.21 ng/mL) ($p = 0.0001$). The level of vitamin D showed a significant inverse correlation with disease severity ($p = 0.001$) [70].

Dorach et al. conducted a prospective study to correlate serum vitamin D levels with the

severity, pattern, and duration of AA and with the density of vitamin D receptor (VDR) expression over hair follicles in patients with AA. These authors evaluated 30 subjects with AA and 30 healthy controls with a mean age of 28.9 ± 9.96 and 31.17 ± 9.43 years, respectively. Of the 30 patients, 96.7% were vitamin D deficient (< 20 ng/mL), compared to 73.3% of the 30 healthy controls ($p = 0.001$). Serum vitamin D levels negatively correlated with the severity of the disease and duration of disease; however, vitamin D did not correlate with the pattern of AA and VDR expression in tissue samples. VDR expression was reduced in all patients and was normal in controls. There was an inverse correlation of VDR with the presence of inflammation, as assessed in histology studies ($p = 0.02$) [71].

Female Pattern Hair Loss and TE

Data on vitamin D in female pattern hair loss (FPHL) and TE contradict data derived from studies indicating that women with FPHL or TE have lower levels of vitamin D than controls, and studies showing no correlation or even opposite results [72–76]. To elucidate the role of vitamin D in FPHL and TE, additional large-scale trials are necessary [77].

VITAMIN E

Immune cells are extremely sensitive to oxidative damage. They also produce reactive oxygen species as part of the immune defense mechanism, which can induce a lipid peroxidation reaction. Antioxidant supplementation fundamentally reverses several age-associated immune deficiencies, leading to increased numbers of total lymphocytes and T-cell subsets, elevated levels of interleukin-2, increased natural killer cell activity, enhanced antibody response to antigen stimulation, improved mitogen responsiveness, decreased prostaglandin synthesis, and decreased lipid peroxidation [78].

Several clinical studies have implicated oxidant/antioxidant discrepancy in patients with AA, which is a disease dependent on autoimmunity, genetic predisposition, and emotional and environmental stress. These studies have been reviewed, with most reviewers reporting increased levels of oxidative stress biomarkers and decreased levels of protective antioxidant enzymes in patients with AA [79].

Vitamin E is involved in the oxidant/antioxidant balance and helps to protect against free-radical damage [80]. Ramadan and colleagues evaluated the serum and tissue vitamin E levels in 15 subjects with AA and found significantly lower levels of vitamin E in patients with AA than in the healthy controls ($p < 0.001$) [81]. These results were not confirmed by Naziroglu and Kokcam who found no statistical difference in plasma vitamin E levels between patients with AA and healthy controls [80].

IRON

The most common nutritional deficiency in the world is iron deficiency, which contributes to TE [82, 83]. The serum ferritin (iron-binding protein) level is considered to be a good indicator of total body iron stores and is relied upon as an indicator in hair loss studies [84]. However, serum ferritin levels may be raised in patients with inflammatory, infectious, and neoplastic conditions, and in those with liver disorders.

Iron deficiency is common in women with hair loss [85]. Nevertheless, the association of hair loss and low serum ferritin level has been debated for many years. There is an ongoing discussion of whether low serum ferritin levels ought to be designated as a nutritional deficiency triggering hair loss (mainly TE) [86]. Using serum ferritin levels as a marker for iron storage deficiency, the definition of iron deficiency (but not specifically iron deficiency anemia) in several studies has ranged from a serum ferritin concentration of ≤ 15 to < 70 μg/L [87–92]. A cut-off of 30 μg/L has a sensitivity and specificity in detecting iron deficiency of 92% and 98%, respectively; a cut-off of 41 μg/L has a sensitivity and specificity of 98% [93]. In order to reverse severe hair loss due to TE, some authors recommend maintaining serum ferritin

at levels of > 40 ng/dL [94] or 70 ng/dL [82]. There is insufficient evidence on the efficacy of the replacement of iron on the outcome of TE, although some benefits have been achieved in a few controlled studies [95]. Menstruation is the biggest cause of iron deficiency in otherwise healthy premenopausal women. The lower female serum ferritin reference ranges have been questioned due to confounding by widespread iron deficiency in premenopausal females sampled when determining population reference levels [96, 97].

The role of essential amino acids in anemia is well known, but just how amino acids affect iron uptake is the subject of ongoing research. Also, the possible impact of amino acids on hair growth has yet to be elucidated. The bioavailability of L-lysine is restricted primarily to fish, meat, and eggs. Little is known about the influence of L-lysine on iron uptake and utilization. In one study, some of the participating women achieved a modest increase in serum ferritin level after iron supplementation, i.e., supplementation with elemental iron 50 mg twice daily; adding L-lysine (1.5–2 g/day) to their existing iron supplementation regimen resulted in a significant ($p < 0.001$) increase in the mean serum ferritin concentration [85].

Trost et al. [82] and St. Pierre et al. [93] reviewed several studies that examined the relationship between hair loss and iron deficiency. Almost all of these studies had focused on non-scarring alopecia and addressed women [82, 93]. The authors of most studies suggested that iron deficiency may be related to TE [85, 94, 98–100], AA [94, 101], and AGA [88, 94]—but a few did not [86, 102–104]. Of note, Sinclair's paper [86] was criticized by Rushton et al. [105] since the study evaluated only five women with TE with a serum ferritin level of < 20 μg/L and presented no data on the final serum ferritin level. According to Rushton et al., the study was too short and did not achieve the increase in ferritin levels which is necessary to treat iron-induced chronic telogen effluvium (CTE) in women with a normal hair density [105].

Olsen and colleagues performed a controlled study on 381 women to determine if iron deficiency may play a role in FPHL or in CTE. Their results showed that iron deficiency is common in females, but not increased in patients with FPHL or CTE as compared with their control participants [106]. This paper was also a source of discussion as Rushton et al. [105] criticized the methodology of the study which may have led to selection bias as a potential significant confounder. According to Rushton and colleagues, the results of the Olsen et al. study instead showed significant differences between premenopausal women with FPHL ($p = 0.004$) or CTE ($p = 0.024$) and control subjects [107]. Consequently, Olsen and colleagues published a reply letter stating that the serum ferritin was performed in two different laboratories with same normal reference range. These authors also stated ''we were careful to evaluate difference in the iron status in both premenopausal and postmenopausal women with CTE versus FPHL and in each of these hair loss conditions versus controls at three different level of serum ferritin''. Olsen and colleagues noted a high percentage of iron deficiency in premenopausal controls versus patients using a cut-off ferritin level of ≤ 15 μg/L; the premenopausal controls however had a lower mean age, which might have affected the results [108].

Gowda et al. conducted a cross-sectional study to evaluate the prevalence of nutritional deficiencies in 100 Indian patients with hair loss. Their results indicate that a relatively higher proportion of participants with TE (20.37%) had iron deficiency compared to those with FPHL (16.67%) and male pattern hair loss (MPHL) (2.94%) ($p = 0.069$). Furthermore, transferrin saturation and ferritin levels were lower in patients with FPHL (41.67%) and TE (40.74%) than in patients with MPHL (11.76%) [109]. Iron deficiencies were found to be related to gender rather than to type of hair loss.

In contrast to the study of Gowda et al. [109], a study conducted by Deo et al. in India aimed to detect the prevalence of several forms of hair loss in females and to correlate these data with levels of hemoglobin and serum ferritin. This observational study involved 135 subjects, the majority (62.2%) of whom had TE, with the next largest group having FPHL (23.7%). Neither low hemoglobin (< 12 gm %; 73.4%) nor

low serum ferritin (< 12 μg/L; 6.7%) levels were found to be statistically significant [110].

In 2017, Thompson et al. reviewed five other studies investigating the relationship between AA and iron [55]. None of these studies supported an association between AA and iron deficiency [27, 44, 111–113].

A study was conducted in India on 35 students aged < 20 years who had premature graying of hair, who were matched with 35 healthy controls. The subjects were investigated for hemoglobin level, total iron binding capacity, and levels of ferritin, calcium, and iron, and vitamin B12 and D3 levels. The authors of the study reported that serum calcium, serum ferritin, and vitamin D3 levels may play a role in premature graying of the hair [114].

In 2008, Du et al. [115] described the role of hepcidin in iron regulation and hair loss in the 'mask mouse,' which was reversed with iron supplementation [85]. Hepcidin is a liver-derived protein that restricts enteric iron absorption; this protein is considered the iron-regulating hormone found in all mammals and to be responsible for iron uptake. Several proteins stimulate the expression of the gene encoding hepcidin (*HAMP*) in response to high levels of iron or infection. However, the mechanism of *HAMP* suppression during iron depletion is not well understood. Du et al. reported the loss of body hair and development of iron deficiency anemia in the 'mask mouse' as a result of a mutation in the *TMPRSS6* gene. The protein encoded by *TMPRSS6* (matriptase-2) was found to negatively regulate the *HAMP* gene. In mice, a mutation in *TMPRSS6* was associated with failure to downregulate the expression of *HAMP* and was associated with increased levels of the hepcidin, reduced absorption of dietary iron, and, consequently, iron deficiency. Interestingly, iron supplementation in these mice reversed the iron deficiency and induced hair growth [115].

The role of iron during the hair cycle has not been well studied. In 2006, an investigative study described gene expression specific to the bulge region of the hair follicle [116]. St. Pierre et al. [93] reviewed the literature for the function of genes that may be affected by fluctuating iron levels. The genes *CDC2*, *NDRG1*, *ALAD*, and *RRM2* are upregulated in the bulge region and can be regulated by iron. The genes *Decorin* and *DCT* are downregulated in the bulge region and can also be regulated by iron. The authors hypothesized that iron deficiency might change the normal progression of the hair cycle. However, whether these six genes play a role in iron-dependent processes in the hair follicle remains to be elucidated. Although not yet proven, there is a prevailing view that hepcidin upregulation diverts iron from the hair follicle to support the essential iron requirements. The 33% of women experiencing CTE in the study of Rushton [85] might well represent this group, which could explain why some women with a serum ferritin below the lower male reference range (≤ 40 μg/L) do not experience any change in hepcidin-induced hair follicle regulation.

SELENIUM

Selenium is an essential trace element required for the synthesis of more than 35 proteins. Glutathione peroxidase (antioxidant enzyme) depends on selenium as a co-factor. Selenium deficiency occurs in low-birth-weight infants and in patients requiring total parenteral nutrition (TPN). It can also occur among people living in a location where the soil lacks selenium [34].

Venton et al. described the loss of pigmentation of the hair in four patients receiving TPN without selenium supplementation. The serum and hair selenium levels were 38 ± 11 ng/mL and 0.34 ± 0.13 μg/g, respectively. Hair started to re-pigment after 6–12 months of therapy with intravenous selenium [117]. Similar findings, including alopecia with pseudoalbinism, were found in 6 infants receiving nutritional support. In these six infants, after starting daily selenium therapy (5 μg/kg/day), selenium serum levels returned to the normal range of 5–15 μg/dL, and alopecia and pseudoalbinism improved [118].

A clinical trial in patients with ovarian cancer undergoing chemotherapy showed a significant decrease in hair loss and other gastrointestinal symptoms in patients receiving selenium supplementation, as compared with

controls. The authors concluded that ingesting selenium is a supportive element in chemotherapy [119].

The recommended dietary allowance for selenium is 55 μg daily for individuals aged ≥ 14 years in U.S. populations. The availability of selenium in a variety of foods, such as meat, vegetables, and nuts, are sufficient to meet the daily requirement [120]. Selenium ingestion in an amount exceeding 400 μg daily may cause toxicity. Symptoms of acute or chronic selenium toxicity include nausea, vomiting, nail brittleness and discolorations, hair loss, fatigability, irritability, and foul breath odor [120]. An outbreak of selenium toxicity from a liquid dietary supplement that contained 200-fold the labeled concentration of selenium resulted in severe hair loss in most patients [121].

ZINC

Zinc is an essential trace element, which means that the body cannot generate it on its own; it must be supplied through the diet. The main dietary sources of zinc are fish and meat. Zinc deficiency can occur in patients consuming large amounts of cereal grain (which contains a phytate considered to be chelating agent of zinc), in those with poor meat consumption or TPN, and in infants on milk formula. Other causes of zinc deficiency include anorexia nervosa (secondary to inadequate intake, increased zinc excretion, and malabsorption due to laxative abuse), inflammatory bowel disease, jejunal bypass surgery, and cystic fibrosis. Alcoholism, malignancy, burns, infection, and pregnancy may all cause increased metabolism and excretion of zinc.

Alopecia is a well-known sign of established zinc deficiency with hair regrowth occurring with zinc supplementation [122], [123]. Data correlating zinc levels with TE and AGA are, on the other hand, not homogeneous. A retrospective cross-sectional study of 115 subjects diagnosed with TE (acute and chronic) found that 9.6% of subjects had zinc deficiency [48]. Another study comparing 312 subjects with hair loss (including AA, MPHL, FPHL, and TE) with 32 controls showed low levels of zinc in patients with AA and TE. These authors recommended zinc replacement if levels were < 70 μg/dL [124]. However, this finding was not confirmed by a recent study of 40 patients with CTE, with 30 healthy subjects as controls, with the authors finding no difference in zinc levels between the affected and control patients. [125].

A review article on zinc in patients with AA showed that four of the six case–control studies found low zinc levels in patients with AA as compared to healthy control groups [55]. One of these case–control studies was conducted by Kil et al. and included patients with MPHL, FPHL, and TE. The results of this study showed a strong correlation between zinc deficiency (< 70 μg/dL) and hair loss [124]. Another study found a strong association between zinc deficiency and AA severity and chronicity [126]. However, in contrast to these studies, there are two case–control studies carried out in Iran [111] and Finland [113] that showed no significant correlation between zinc level and AA compared to the controls.

The role of zinc supplementation is also open to debate. In a double-blinded placebo-controlled trial published in 1981, where the investigators administered 220 mg zinc gluconate twice per day for 3 months to AA subjects, there was no improvement of AA after zinc supplementation [127]. On the other hand, another study involving 15 patients with AA who took 50 mg zinc gluconate for 12 weeks showed good results in nine of the 15 subjects [128].

ROLE OF MICRONUTRIENTS IN SCALP SCALING CONDITIONS

Passi et al. noticed a significant deficiency of serum vitamin E in patients with seborrheic dermatitis (both human immunodeficiency virus [HIV] seropositive or HIV seronegative) ($p < 0.001$) as compared with a control group [129]. Of note, zinc therapy was found to significantly increase both the size of the sebaceous glands and cell proliferation in the sebaceous glands in an animal study [130].

A possible relationship between vitamin D level and psoriasis, including scalp psoriasis, is

controversial. The authors of an observational case–control study investigated 561 subjects, of whom 170 had psoriasis (6 with scalp psoriasis), 51 had autoimmune bullous diseases, and 340 were healthy controls. The 25-hydroxyvitamin D [25(OH)D] blood level in each group was measured and found to be significantly different in all three groups, with psoriatic patients having significantly lower vitamin D levels (21.8 ng/mL) than healthy controls (34.3 ng/mL) (p = 0.0007). The authors of this study concluded that vitamin D level may correlate with psoriasis duration [131].

RESTRICTIVE DIETARY PRACTICE AND TE

The matrix cells in the follicle bulb have a very high turnover. A caloric deficiency or deprivation of several elements, including vitamins, minerals, essential fatty acids, and proteins, caused by decreased uptake can lead to hair loss, structural abnormalities, and pigment changes, although the exact mechanism(s) are not well known [132]. Goette et al. described nine patients who developed TE after 2–5 months of starting a vigorous weight reduction program and losing 11.7–24 kg. It was thought that rigorous caloric restriction with subsequent inadequate energy supply of the hair matrix might be the cause for the precipitation of TE of the crash dieter [133]. In addition, a few case reports have been published relating TE with crash diet [134–136].

SUMMARY

Hair loss is considered to be a common problem in the dermatological community and has a profound negative psychological and emotional impact on patients. Micronutrients, such as vitamins and minerals, play an important, but not entirely clear role in normal hair follicle development and immune cell function. Deficiency of such micronutrients may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia. These effects are summarized in Table 1.

Telogen Effluvium/Androgenetic Alopecia

Although a relationship between vitamin D levels and AGA or TE is still being debated, most authors agree in supplementing vitamin D in patients with hair loss and vitamin D deficiency. Vitamin C intake is crucial in patients with hair loss associated with iron deficiency. There are no data to support the role of vitamin E in AGA or TE.

Iron deficiency is common in females with hair loss, and most authors agree in supplementing iron in patients with iron deficiency and/or low ferritin levels. However, there is no consensus on “normal ferritin” levels, and most authors prescribe supplements to the patient when the ferritin level is < 40 ng/dL. L-lysine supplementation is recommended for vegan individuals with iron deficiency.

Data correlating TE and AGA with zinc level are not homogenous, and screening for zinc is not recommended. Selenium toxicity and riboflavin deficiency can cause hair loss. However, comprehensive studies are lacking, which preclude any recommendation for screening of selenium or riboflavin.

Biotin deficiency causes hair loss, but there are no evidence-based data that supplementing biotin promotes hair growth. Moreover, exogenous biotin interferes with some laboratory tests, creating false negative or false positive results. There are a few studies addressing the relationship between hair loss and folic acid or vitamin B12, but the lack of extensive studies precludes any recommendation for vitamin B12 or folate screening or supplementation. Hypervitaminosis A causes hair loss, and data on the effects of isotretinoin in hair loss support this association.

Alopecia Areata

Several studies show an association between AA and low vitamin D levels. Patients should be checked and given supplementation if vitamin D levels are low.

Table 1 The role of micronutrients in non-scarring alopecia and premature graying of hair

Micronutrients	TE/AGA	AA	Premature hair graying	ACP outcome study grading
Vitamin D	Study results are conflicting, but most authors agree on supplementing vitamin D in patients with hair loss and vitamin D deficiency	Several studies showed an association between AA and low vitamin D levels Correction of vitamin D deficiency improves AA outcome and enhances response to treatment	Screening for deficiency and supplementation are recommended	Moderate in all studies
Vitamin C	Crucial in patients with hair loss associated with iron deficiency	Few studies, thereby precluding recommendations	Data are not available	Very low in AA studies
Vitamin E	Data not available	Conflicting data, thereby precluding recommendations	Data are not available	Moderate in AA studies
Iron/Ferritin	Most authors agree on iron supplementation in patients with iron or ferritin deficiency and hair loss	Iron deficiency reported in female patients, likely coincidental	Screening for deficiency and supplementation are recommended	Moderate in all studies
Zinc	Data are not homogenous and findings are too inconsistent to recommend screening	Most studies revealed low serum levels in AA Evidence-based information on efficacy of zinc supplementation in AA is lacking	Data are not available	Moderate in TE/AGA and AA studies
Selenium	Toxicity can cause hair loss. There are no data to recommend screening	No data to provide recommendations	Screening for deficiency and supplementation are recommended	Low in TE/AGA and premature graying of hair studies
Riboflavin	Deficiency can cause hair loss. Data are too scarce to recommend screening	Data are not available	Data are not available	Very low in TE/AGA studies

Table 1 continued

Micronutrients	TE/AGA	AA	Premature hair graying	ACP outcome study grading
Biotin	Biotin levels can be low in patients complaining of hair shedding Efficacy of supplementation not supported by evidence-based trials Exogenous biotin interferes with some laboratory tests, creating false negative or false positive results	No studies on biotin as monotherapy	Data are not available	Low and very low in TE/AGA studies
Folic acid/ Vitamin B12	Data are not sufficient to recommend screening and supplementation	A few studies suggest that the levels of folate or vitamin B12 might modify progression of AA Data are scarce for recommending supplementation	Screening for deficiency and supplementation are recommended	-Low in TE/AGA studies -Moderate in AA and in premature graying of hair studies
Vitamin A	Hypervitaminosis A causes hair loss Screening is recommended in selected cases	Data are not available	Data are not available	Low and very low in TE/AGA studies

AA alopecia areata, *AGA* androgenetic alopecia, *TE* telogen effluvium, *ACP* american college of physicians

Studies on the role of iron in AA have shown a discrepancy in the results between females and males. There is a need for placebo-controlled clinical trials evaluating iron supplementation in the treatment of AA. Most studies on zinc have revealed lower serum levels in AA patients than in controls. However, double-blind trials investigating zinc supplementation in AA are lacking, and studies on selenium serum level in AA patients are very rare, which precludes any conclusion on the role of selenium in AA.

The authors of a few studies suggest that the levels of folate or vitamin B12 might modify the progression of AA, but data are still too limited to recommend screening or supplementation of B vitamins. Biotin supplementation has been successful in the treatment of brittle nails [137]. There are no studies of biotin as monotherapy for AA.

Premature Hair Graying

Deficiency in a few micronutrients has been implicated in the pigment loss of hair, including ferritin, vitamin D, folate, vitamin B12, and selenium deficiencies. We recommend screening for these vitamins and minerals in patients presenting with premature graying of hair and

subsequent supplementation of the deficient micronutrients [114].

CONCLUSION

Given the role of vitamins and minerals in normal hair follicle development and in immune cell function, large double-blind placebo-controlled trials are required to determine the effect of micronutrient supplementation on hair growth in those patients with both micronutrient deficiency and non-scarring alopecia to establish any association between hair loss and micronutrient deficiency. Each study conducted to data has its own specific limitation, and the constraint of cost and lack of motivated funders for this research are significant limitations.

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