Chapter 7
Role of Oral Supplements: When and How to Choose

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Introduction

People commonly inquire about vitamin and mineral supplementation and diet as a means to prevent or manage hair loss. Answering these queries is frequently challenging, given the enormous and conflicting evidence that exists on this subject.

Vitamin A

In most cases, a balanced diet will supply a healthy amount of vitamin A [1]. The recommended dietary allowance of vitamin A for adults 19 years or older is 1300 μg/day (4300 units) for US populations. While there is no upper intake level for provitamin A carotenoids, preformed vitamin A can be toxic. For adults 19 years or older, the tolerable upper intake level is 10,000 IU [2]. It is important to consider what form of vitamin A is contained in supplements (provitamin A carotenoids or preformed vitamin A) and in what proportion.

In general, consuming too much or over-supplementing vitamin A can cause hair loss [3–6].

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A. Tosti et al. (eds.), *Hair and Scalp Treatments*,
https://doi.org/10.1007/978-3-030-21555-2_7

The same advice generally applies to vitamin A derivatives because isotretinoin is a well-known cause of hair loss, causing a decrease in hair count, density, and percentage of anagen hairs [7].

When treating patients with a personal or family history of androgenetic alopecia (AGA) with isotretinoin, always prescribe a treatment to prevent hair loss.

Vitamin B

Only riboflavin, biotin, folate, and vitamin B 12 deficiencies have been associated with hair loss, but data are not very strong. Vitamin B2 (riboflavin) is a component of two important coenzymes: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) [8]. FMN and FAD represent 90% of dietary riboflavin and play roles in cellular development and function, metabolism of fats, and energy production [9]. The body stores only small amounts of riboflavin in the liver, heart, and kidneys. Riboflavin deficiency—while extremely rare in the United States—can cause hair loss [10].

Biotin (vitamin B7 or vitamin H) is a common ingredient of hair loss supplements. Adequate intake of biotin for adults is 30 μg/day in US populations. The average dietary intake of biotin in Western countries is adequate, and biotin deficiency in healthy individuals eating a normal diet has never been reported [11, 12]. However, a deficiency can occur in patients with inflammatory bowel diseases, malabsorption, alcoholism, after treatment with broad-spectrum antibiotics, valproic acid or isotretinoin, in parenteral nutrition, after partial gastrectomy, in elderly individuals, pregnant women, and athletes. Many supplements for hair, skin, and nails far exceed the recommended daily intake of biotin. While there is no evidence for biotin toxicity, high biotin intake can cause falsely high or falsely low lab test results [13].

Biotin can in fact interfere with tests that use biotin-streptavidin technology. Streptavidin which is a biotin-based immunoassay is vulnerable to interference when it is 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 [14]. Biotin interference with 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 [14–17].

Biotin interference caused a falsely low result in a troponin test that led to a missed diagnosis of a heart attack and a patient's death [13]. Some hCG devices are subject to biotin interference, and clinicians should suggest quantitative serum hCG measurement in patients taking biotin. The latter is not subject to biotin interference [18].

While signs of biotin deficiency include hair loss, skin rashes, and brittle nails, efficacy of biotin in supplements for hair, skin, and nails has not been

assessed in large-scale studies [11, 19]. However 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 daily could improve hair health after 3–4 months in children with uncombable hair syndrome [20–23].

The recommended dietary allowance of food folate is 400 μg daily for adults, which is supported by required fortification of some foods in the United States [8]. The tolerable upper intake level of folate is 1000 μg [24]. While most people in the United States obtain adequate 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 [8].

The recommended dietary allowance of vitamin B12 is 2.4 μg for adult US populations. There is no established upper limit for vitamin B12 intake, as it has low potential for toxicity [8]. The role of folate and vitamin B12 in nucleic acid production suggest they might play a role in the highly proliferative hair follicle [25]. There are not many studies addressing the relationship between B vitamins and hair loss. The effects of low folate and vitamin B12 levels in inducing TE are not supported by high-quality studies [26]. However, we recommend testing levels of folate and vitamin B12 and supplement when low.

Vitamin C

Vitamin C plays an essential role in the intestinal absorption of iron, because of its chelating and reducing effect, assisting iron mobilization and intestinal absorption [27]. Therefore, vitamin C intake is important in patients with hair loss associated with iron deficiency. Although vitamin C deficiency is typically associated with body hair abnormalities [28], there are no data correlating vitamin C levels and hair loss.

Vitamin D

Low vitamin D levels have been reported in several autoimmune diseases [29–34]. 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 producing vitamin D resistance, sparse body hair, and alopecia that frequently involves the whole scalp and body [35–37].

Alopecia Areata

Literature data suggests that vitamin D, due to its immunomodulatory effect, may be involved in alopecia areata (AA) [38, 39]. The mean serum 25-hydroxyvitamin D levels in patients with AA were significantly lower than that in the non-AA subjects [40–42]. The level of vitamin D showed a significant inverse correlation with

disease severity [41, 42]. Therefore, vitamin D level has to be measured and patient should receive supplementation when vitamin D levels are low.

Female Pattern Hair Loss and Telogen Effluvium

Data on vitamin D in female pattern hair loss (FPHL) and telogen effluvium (TE) are contradicting with 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 [43–47]. However, we recommend checking vitamin D levels and supplementing vitamin D in patients who have low levels (below 30 nmol/L).

Vitamin E

Vitamin E is involved in the oxidant/antioxidant balance and helps to protect against free-radical damage [48].

Iron

The most common nutritional deficiency in the world is iron deficiency, which contributes to TE [49, 50]. Serum ferritin (iron-binding protein) is considered a good indicator of body iron stores and is relied upon in hair loss studies. Serum ferritin concentration is used to measure a patient's total iron storage [51]. However, serum ferritin levels may be raised in patients with inflammatory, infectious and neoplastic conditions, and liver disorders.

Iron deficiency is common in women with hair loss [52]. Nevertheless, the association of hair loss and low serum ferritin level has been debated over the years [53]. Using serum ferritin levels as a marker for iron-storage deficiency, the definition of iron deficiency (but not specifically iron deficiency anemia) ranges from levels of less than or equal to 15 μg/L to levels of less than 70 μg/L [54–59]. A cut-off of 30 μg/L has a sensitivity and specificity in detecting iron deficiency of 92% and 98%, respectively. We usually prescribe ferritin supplementation in women with iron levels below 30 ng/dL. Of note, L-lysine supplementation (1.5–2 g/day) is recommended for vegetarian/vegan individuals with iron deficiency [52].

Selenium, Copper, Magnesium

Selenium is an essential trace element required for synthesis of more than 35 proteins. Glutathione peroxidase (antioxidant enzyme) depends on selenium as a cofactor. Selenium deficiency occurs in low birth weight infants and in patients

requiring total parenteral nutrition (TPN). It can also occur in a location where the soil lacks selenium [60].

Loss of pigmentation of the hair has been described in patients receiving TPN without selenium supplementation. Hair started to re-pigment after 6–12 months of therapy with intravenous selenium [61]. Similar findings including alopecia with pseudoalbinism were found in infants receiving nutritional support. 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 [62].

Selenium supplementation is a supportive element in chemotherapy as it may significantly decrease hair loss and other gastrointestinal symptoms [63]. The recommended dietary allowance is 55 μg daily for individuals 14 years or older in US populations. The availability of selenium in a variety of foods, e.g., meat, vegetables, and nuts, is sufficient for the daily requirement [64]. 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 [64, 65].

Copper acts with zinc in the antioxidant enzyme copper/zinc superoxide dismutase [66]. Magnesium acts as a cofactor for over 300 enzymes and plays a critical role in nucleotide synthesis, a frequent process in the rapidly dividing hair follicle [67]. Evidence are conflicting and insufficient to suggest to dose levels of copper and magnesium in AA [34].

Zinc

Zinc is an essential trace element, which means that the body cannot generate it by its own, and it must be supplied through the diet. Dietary sources include fish and meat. Zinc deficiency can occur in patients consuming large amounts of cereal grain (which contain a phytate considered a chelating agent of zinc), with poor meat consumption, total parenteral nutrition, and milk formula for infants. 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 [68, 69]. Data correlating zinc levels with TE and AGA are not homogeneous and role of zinc supplementation is debated [70]. Zinc supplementation has been utilized in AA with conflicting results [34].

Premature Graying of Hair

The process of gray hair seems to be associated with the progressive loss of pigment-producing cells. Premature graying of hair is considered when it occurs before the age of 20 in whites, 25 in Asians, and 30 in Africans [71]. Premature graying or

canities is associated with several autoimmune disorders such as vitiligo, thyroid disease, pernicious anemia, and Werner's syndrome. Moreover, data suggest a role for external factors such as climate, ultraviolet light, drugs, smoking, minerals, and nutritional deficiencies in the development of premature graying [72].

Patients should be checked for levels of calcium, ferritin, vitamin D, biotin, vitamin B12, folic acid, copper, and selenium and supplemented when deficient [70].

Plants with Medical Properties

Several botanically derived compounds have showed the ability to inhibit hormonal pathways associated with AGA. Notably, these botanical products have not been linked with adverse reactions or teratogenicity associated with the therapeutic drugs [73]. Recently, a few studies have reported the efficacy of botanical substances in the treatment of AGA. Lists of medical plants used to regrow hairs are summarized in Tables 7.1, 7.2, and 7.3. Additional information on nutritional supplements investigated for treatment of TE or hair thinning are summarized in Chap. 10, Table 10.7.

Summary

Telogen Effluvium/Androgenetic Alopecia

Although the relationship between vitamin D levels and AGA or TE are still debated, most authors agree about 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.

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; we recommend to supplement patient when ferritin is below 30 μg/L. Data correlating TE and AGA with zinc level are not homogenous, and screening for zinc is not recommended. The same applies for selenium and 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. We recommend screening patients for these vitamins. Hypervitaminosis A causes hair loss and dosing vitamin A can be important in patients taking multivitamins and food rich in vitamin A in their diet.

Table 7.1 Plants with inhibitory effect of 5α-reductase enzymes

Plant name	Study design in humans	Dose	Results
Serenoa repens saw palmetto	A randomized, double-blind, placebo-controlled trial [74]	Liposterolic extracts of *Serenoa repens* (LSESr) and its glycoside sitosterol, 50 mg, and saw palmetto extract (standardized to 85–95% liposterolic content) 200 mg	60% of participants showed improvement of AGA relative to baseline and compared to 11% in the placebo group
	Prospective open-label 2-year study comparing *Serenoa repens* to finasteride [75]	Serenoa repens (320 mg daily) vs. finasteride (1 mg daily)	Finasteride was more effective in 66% of subjects; however, 60% of patients who received *Serenoa repens* noticed stabilization of AGA after 2 yeas
Red ginseng	Topical application is effective in vitro/ in vivo studies [76] with no evidence of efficacy in humans		
Puerariae flos	Topical application is effective in animal studies [77] with no evidence of efficacy in humans		
Carthamus tinctorius	Topical application is effective in animal studies [78] with no evidence of efficacy in humans		
Camelia sinensis	Topical application is effective in animal studies [79] with no evidence of efficacy in humans		
Boehmeria nipononivea	Topical application is effective in animal studies [80] with no evidence of efficacy in humans		
Thuja occidentalis	Topical application is effective in animal studies [81] with no evidence of efficacy in humans		
Rosmarinus officinalis	Topical application is effective in animal studies [82] with no evidence of efficacy in humans		

Table 7.2 Plants with anti-inflammatory effects

Plant name	Key ingredient	Evidence of efficacy
Ginkgo biloba	Rich in quercetin, a bioflavonoid with anti-inflammatory properties [83]	Quercetin provided effective treatment as well as prevention of relapse of AA in mice [83]. No evidence of efficacy in humans
Ashwagandha	Its naturally occurring steroidal content is much higher than that of hydrocortisone [84]	Tested for its anti-aging properties at a dosage of 3 g daily for 1 year. The participants experienced significant improvement in hemoglobin, red blood cell count, and hair melanin [85]

Table 7.3 Plants with stimulant effects on hair regrowth

Plant name	Key ingredient(s)	Potential effect(s)	Evidence of efficacy
Malus domestica	Procyanidin B-2 is a compound identified in apple (*Malus domestica*)	Protective action on transforming growth factor beta-induced apoptosis that is supposed to trigger catagen induction in the hair cycle [86]	In vitro studies [87] and effective in humans by topical applications [88, 89] and oral administration [90]
Crataegus pinnatifida	Polyphenol of gallic acid extract and proanthocyanidin of cyaniding chloride extract	Induces hair growth by promoting anagen phase, which might be mediated by the activation of B-cell lymphoma-2 which has anti-apoptotic properties and enhancing cell survival [91]	Topical application is effective in animal studies [91] with no evidence of efficacy in humans
Cercidiphyllum japonicum	Methanol, quercetin, taxifolin, gallic acid, myricetin, and dihydromyricetin [86]	The methanol extract of heartwood of Cercidiphyllum japonicum stimulated proliferation of mouse hair epithelial cells, similar to minoxidil and procyanidin B-2	Topical application is effective in animal studies [86] with no evidence of efficacy in humans
Citrus bergamia risso/ lycium	The extract from bergamot and boxthorn	Plays an active role in skin and the promotion of hair growth	Topical application is effective in animal studies [92] with no evidence of efficacy in humans
Citrullus colocynthis	Petroleum ether extract	Anti-inflammatory	Topical application is effective in animal studies [93, 94] with no evidence of efficacy in humans
Cuscuta reflexa	Cuscutin, amarbelin, β-sitosterol, stigmasterol, kaempferol, dulcitol, myricetin, quercetin, coumarin, and oleanolic acid [95]	Switching of hair follicle from telogen phase to anagen phase and retention of the late anagenic hair follicles [94]	Topical application is effective in animal studies [94] with no evidence of efficacy in humans
Marine derivative products	AminoMar™ C marine complex, equisetum arvense (a naturally occurring form of silica), malpighia glabra (acerola cherry providing vitamin C), zinc, and biotin	Promoting hair growth, improvements in the appearance of skin, nails, eyelashes, and eyebrows in women, and nail and skin quality in men [96]	Promote hair growth and decrease hair shedding in women and men with thinning hair as shown by an initial pilot study and five randomized, double-blind studies [96, 97]

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. Also, we recommend iron supplementation if ferritin levels are below 30 μg/L.

Most studies on zinc revealed lower serum levels in AA patients compared to controls. However, double-blind trials investigating zinc supplementation in AA is lacking.

A few studies suggest that the levels of folate or vitamin B12 might modify progression of AA, but data are still too small to recommend screening or supplementation of B vitamins. Biotin supplementation has been successful in the treatment of brittle nails [98]. There are no studies of biotin as monotherapy for AA.

Premature Canities

There are a few micronutrients implicated in the pigment loss of the hair; they include ferritin, vitamin D, folate, vitamin B12, biotin, calcium, copper, and selenium deficiency. We recommend screening for these vitamins and minerals in patients presenting with premature graying of hair and supplementation of deficient micronutrients.

Medical Plants Used for Hair Loss Treatment

There are some botanicals that inhibit 5α-reductase enzymes, have anti-inflammatory effects, or may stimulate hair growth. Among these botanicals, studies showed that *Serenoa repens*, saw palmetto, *Malus domestica*, and marine derivative products were the most used plants for hair loss.

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