REVIEW

An overview of the genetic aspects of hair loss and its connection with nutrition

NURIYE GOKCE[1], NESLIHAN BASGOZ[1], SERCAN KENANOGLU[1], HILAL AKALIN[1], YUSUF OZKUL[1], MAHMUT CERKEZ ERGOREN[2,3], TOMMASO BECCARI[4], MATTEO BERTELLI[5,6,7], MUNIS DUNDAR[1,*]
[1] Department of Medical Genetics, Faculty of Medicine, Erciyes University, Kayseri, Turkey; [2] Department of Medical Genetics, Faculty of Medicine, Near East University, Nicosia, Cyprus; [3] DESAM Institute, Near East University, Nicosia, Cyprus; [4] Department of Pharmaceutical Science, University of Perugia, Perugia, Italy; [5] MAGISNAT, Peachtree Corners (GA), USA; [6] MAGI Euregio, Bolzano, Italy; [7] MAGI'S LAB, Rovereto (TN), Italy

Keywords

Androgenetic alopecia • Hair loss • Mediterranean Diet • Nutrition

Summary

Hair loss is a widespread concern in dermatology clinics, affecting both men's and women's quality of life. Hair loss can have many different causes, which are critical to identify in order to provide appropriate treatment. Hair loss can happen due to many variables, such as genetic factors or predisposition, vitamin and mineral deficiencies, skin problems, hair growth disorders, poor diet, hormonal problems, certain internal diseases, drug use, stress and depression, cosmetic factors, childbirth, and the chemotherapy process. Treatment for hair loss varies depending on the type of alopecia, deficiency, or excess of structures such as vitamins and minerals, and also on hair and skin structure.
The Mediterranean diet is characterized by low amounts of saturated fat, animal protein, and high amounts of unsaturated fat, fiber, polyphenols, and antioxidants. The main nutrients found in the Mediterranean Diet are rich in antioxidant, anti-inflammatory components. It also has an important place in hair loss treatment, since recently treatment strategies have included polyphenols and unsaturated oils more and more frequently. The goal of this work was to review published articles examining alopecia and its types, the many micronutrients that affect alopecia, and the role of the Mediterranean diet in alopecia. The literature shows that little is known about hair loss, nutritional factors, and diet, and that the data collected are conflicting. Given these differences, research into the function of diet and nutrition in the treatment of baldness is a dynamic and growing topic.

Introduction

Hair loss or alopecia, a clinical condition that is frequently seen in dermatology clinics, can be caused by many etiological factors and it significantly affects the patients' quality of life [1]. This group of diseases is basically divided in two subgroups: cicatricial alopecias and non-cicatricial alopecias. While cicatricial alopecia may progress with loss of follicles, thus causing irreversible hair loss, this condition is usually reversible in non-cicatricial ones. Many causes are known to have a role in non-cicatricial alopecia, including emotional issues, chronic disorders, dietary inadequacies, trace elements, and vitamin deficiencies [2]. Other factors can be stress, drug use, immune system, endocrine disorders, and genetic and epigenetic changes [3].
A balanced and regular diet is very important for healthy hair: sudden weight loss, low-caloric diets, unbalanced diet, obesity, and excessive intake of vitamin and mineral supplements can cause hair loss. Micronutrients, which are the main elements of the hair follicle cycle, are very important in alopecia, which is why dietary supplements (mostly vitamin and mineral) are among the preferred methods to prevent hair loss. Given the frequency of hair loss in current times and its impact on the patients' social lives, finding effective alopecia treatments impacts a huge portion of the population [2].
The role of diet in the development and treatment of alopecia has recently been a hot topic of research. It has been found that plant-rich diets – such as the Mediterranean Diet (MD), whose main nutrients are rich in antioxidants, anti-inflammatory, and estrogenic components – include chemicals that stimulate hair growth and reduce hair loss. These diets contain phytochemicals that promote hair development by lowering the generation of reactive oxygen species in the dermal papilla cells, causing growth hormones to be secreted [4].
This is why dietary practices characterized by a large intake of anti-inflammatory, antioxidant and estrogenic activities are emphasized as additional treatments for alopecia. This review aims to explain the general background of alopecia, to emphasize the role of nutritional and dietary supplements in the treatment of alopecia, and to consider the effects of herbal treatment methods on alopecia patients.

Alopecia and types of alopecia

Alopecia is the partial or complete loss of hair, which can be caused by a disruption in the hair development

https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.26

cycle or by damage to the hair follicles as a result of systemic or local factors such as genetics, hormone imbalances, and infection [5-7].
The hair growth cycle consists of four stages: the anagen phase (the growth phase, which is also the longest, lasting 2-7 years); the catagen phase (the transitional phase, lasting up to 2 weeks, which includes hair follicle involution due to apoptosis); the telogen phase (the resting phase, lasting up to 12 weeks); and the exogenous phase (the release phase of telogen hair) [8].
The fact that alopecia is affected by many factors causes the existence of a wide number of types of alopecia. Androgenic alopecia, alopecia areata, chemotherapy-induced alopecia, anagen effluvium, telogen effluvium, traction alopecia, and trichotillomania are some of the most common kinds. The clinical classification system of Rook and Dawber divides all types of alopecia into two categories: cicatricial alopecia and non-cicatricial alopecia [6, 7].

Cicatricial alopecias

Cicatricial alopecias (CAs) are clinical pathological conditions that describe permanent hair loss caused by the replacement of damaged hair follicles with fibrotic scar tissue. They are classified into two groups, primary cicatricial alopecia (PCA) and secondary cicatricial alopecia (SCA) [9, 10].
The PCA group includes multiple inflammatory diseases with distinct clinical and histopathological features and unknown and irreversible causes, primarily affecting and destroying hair follicles. It is responsible for 7% of all hair loss cases. PCA is subdivided into lymphocytic, neutrophilic, or mixed subtypes [11, 12]. Chronic cutaneous lupus erythematosus, lichen planopilaris, classic Brocq pseudopelade, folliculitis decalvans, and dissection folliculitis are some of the diseases with clinical conditions [13].
The SCA group includes inflammatory and neoplastic conditions and physical traumas that usually affect primarily the dermis and cause secondary follicular destruction [9]. While in PCAs the disease directly affects hair follicles, in SCAs they disappear due to secondary reasons. Factors affecting SCA formation include genodermatoses, permanent alopecia due to developmental defects, physical and chemical injuries, infections, inflammatory dermatoses, drug uses, and neoplastic conditions [14]. The classification of cicatricial alopecias is summarized in Table I.

Non-cicatricial alopecias

Non-cicatricial alopecia is reversible alopecia, characterized by an altered hair cycle and by the fact that hair follicles are preserved [5].
Non-cicatricial alopecias are divided in local alopecias and diffuse alopecias [17]. Local alopecias include alopecia areata, tinea capitis, and trichotillomania. Diffuse alopecias include alopecia totalis or universalis, telogen or anagen effluvium. The classification of non-cicatricial alopecias is summarized in Table II. The most common alopecia in this group is androgenic alopecia.

Androgenic alopecia, caused by the miniaturization of hair follicles, is the most common type of progressive hair loss, affecting 30-50% of men and approximately 30% of middle-aged women. Alopecia areata, the second most common type of non-cicatricial alopecia, is known to be associated with autoimmune problems [5].

Common causes of hair loss

As previously stated, the hair growth cycle consists of four phases: anagen, catagen, telogen, and exogen. Hair loss differs according to the affected stage. Although there are many different reasons for hair loss, androgen and stress-related causes are usually underlying. Other systemic causes of hair loss include telogen effluvium, nutrition, endocrine imbalances, drugs, infections, special diseases, malignancies, problems with the immune system, environmental factors, age, and genetic factors [3].

Androgen-related alopecia

The most common type of hair loss is androgenetic alopecia, which affects 80% of men and 50% of women. In this kind of alopecia, genetic factors and age-related causes affect the androgen mechanism, which is the one allowing vellus hair to turn into longer, thicker, and darker terminal hair: the defect in this mechanism makes it function differently by stimulating the regression of hair follicles to turn into vellus hairs. Androgenetic alopecia is a dynamic and continuous hair loss problem, in which mast cells and lymphocytes are defined around the miniaturized follicle, rich in stem cells [18-20].
Although androgens play an important role in androgenetic alopecia, genetic predisposition is also important: genetic background plays an important role, with a rate of 0.81 in twin studies, thus showing familial clustering. Having a polygenic feature, its genetic background is complex. However, changes in the androgen receptor (AR) gene and 5-alpha reductase gene were found to be effective in androgenetic alopecia. In addition, triple repeat polymorphisms have been associated with single nucleotide polymorphisms. It has been stated that the AR gene on the X chromosome and the ectodysplasin A2 receptor (EDAR2) gene are related and that polymorphisms in this gene are associated with androgenic alopecia, but its exact role has not been fully defined. Androgenetic alopecia is associated with genetic alterations in the WNT signaling pathway, which regulates dermal papilla cells and androgen metabolism. Expression studies and epigenetic studies are limited, as scalp biopsy is difficult to obtain. Overexpression of prostaglandin synthase (PGDS) and the PGDS product prostaglandin D2 (PGD2) restrict hair development by generating an early catagen phase, according to the limited study [8, 21].

Stress-induced alopecia

Stress is one of the most common reasons of hair growth disorders and hair loss, since it leads to an increase in the level of cortisol released into the body. It has been proven

Tab. I. Classification of cicatricial alopecias [9, 14-16].

Primary Cicatricial Alopecia (working classification of PCA by North American Hair Research Society)	Secondary Cicatricial Alopecia		
Lymphocytic	Chronic cutaneous lupus erythematosus, Lichen planopilaris, Frontal fibrosing alopecia, Graham Little syndrome, Classic pseudopelade (Brocq), Central centrifugal cicatricial alopecia, Alopecia mucinosa, Keratosis follicularis spinulosa decalvans	Physical or chemical trauma	Burns, Toxic/corrosive substances (e.g. acid or alkali burns), Ischemia/pressure, Traction/ trichotillomania (end stage)
		Ionizing radiation	Radiation
		Infections	Bacterial infections, Viral infections, Fungal infections (tinea capitis, in particular, deep trichophytosis caused by zoophilic pathogens)
Neutrophilic	Folliculitis decalvans, Dissecting cellulitis/folliculitis	Malignant and benign tumors	Primary tumors, Metastases, Lymphoproliferative diseases, Epidermal and organoid nevi
		Genodermatoses	Aplasia cutis congenita, Ectodermal dysplasia, Ichthyosis, Epidermolysis bullosa, Darier's disease, Incontinentia pigmenti, Hyalinosis cutis et mucosae
		Granulomatous diseases	Sarcoidosis, Necrobiosis lipoidica
Mixed	Folliculitis (acne) keloidalis, Folliculitis (acne) necrotica, Erosive pustular dermatosis	Autoimmune diseases	Graft–versus–host disease, Scleroderma (en coup de sabre), Lichen sclerosus, Blistering dermatoses (cicatricial pemphigoid)
Non-Specific	Idiopathic scarring alopecia with inconclusive clinical and histopathological findings, End stage of various inflammatory scarring alopecias	"Deposition" dermatoses	Amyloidosis, Mucinosis
		Inflammatory diseases	Psoriasis, Pityriasis amiantacea

that cortisol has a negative effect on the formation mechanism of the hair follicle by breaking down hyaluronan and proteoglycans, which are integrating substances in the extracellular matrix and skin. Acute and chronic stress is known as the main cause of telogen effluvium. Stress also can aggravate the types of alopecia that are primarily caused by endocrine imbalances, immunological responses, and toxic causes. In addition, the stress that occurs in response to hair loss causes hair loss to continue. In animal studies, chronic stress has been associated with hair growth arrest, increased granulation of mast cells, and perifollicular inflammation. Further studies have also shown that certain stress mediators, such as substance P, adrenocorticotropic hormone, prolactin, and cortisol, inhibit hair growth [22].

Telogen effluvium

Telogen effluvium is a scarless hair loss condition caused by physiological stress (such as delivery, rapid weight loss, mental stress, long-term drug usage), medical conditions like hypo/hyperthyroidism, post-diet effects, and prolonged fasting. Although it is generally reversible, it affects the psychosocial status of the patients, and its mechanism has not been discovered yet. Telogen effluvium is difficult to diagnose and treat because there are many factors at play in the etiology of the disease [23, 24].

Endocrine imbalances

The formation of hair follicles occurs as a result of a molecular genetic process regulated before birth. Many hormones and their receptors play important roles in the healthy progression of this process: thyroid hormones, glucocorticoids, insulin-like growth factor-I, and prolactin are all hormones that influence hair development, although androgens are the most important ones. In addition, vitamin D receptors and retinoid X receptors are also effective in postpartum hair growth [21, 25].

Immune System

Alopecia areata and primary cicatricial alopecia are two common forms of immune-mediated alopecia. Alopecia areata is a T-cell-mediated autoimmune illness that affects hair follicles in the anagen stage. The JAK-STAT (Janus kinase-signal converter and transcription activator) signaling pathway is involved in its development [26].

The concept of immune privilege is the phenomenon of protection of organs or tissues that can be seen in the corneal tissue, testis, placenta, liver, intestine, brain, hair follicle, and mucosal tissues from autoimmune threats developed by the host's immune system [27].

Hair follicles in the anagen stage are protected from unwanted immune responses by exhibiting immune privilege from the protrusion level to the bulb. The key mechanisms are the lack or reduction of MHC class I and MHC class II expression, signaling that there is no risk with the CD200 signal, and the absence of antigen presentation. In the development of alopecia areata, collapse is observed in the anagen hair bulb. While NK-G2D+ T cells and natural killer (NK) cells rapidly increase in the medium, perifollicular mast cells exhibit proinflammatory properties and interact with CD8+ T cells that recognize autoantigens [26-28].

The intense presence of CD8+CD3+ cytotoxic T cells in anagen stage hair follicles and the more targeting of pigmented hair suggest that the targets of cytotoxic T cells are melanocytes and melanogenesis-related autoantigens. The fact that over 100 single nucleotide polymorphisms are associated in studies indicates the importance of the genetic background [26, 28].

Studies have shown that in primary cicatricial alopecia there is a loss of immune privilege in the protrusion region. Although it is not exactly known what causes the loss of immune privilege, it is thought that among the causes might be perifollicular/intrafollicular increase in skin microtrauma, infectious or psycho-emotional stressors, bacterial superantigens, mast cell degranulation, and ectopic interferon γ (IFN-γ) secretion [26].

Other causes of alopecia

Drug-induced alopecia is a type of non-scarring alopecia involving the scalp, which occurs when one of the two main mechanisms of the normal hair growth cycle, anagen effluvium or telogen effluvium, is stopped. When the drug is stopped, the hair loss improves. Other body hairs are rarely affected by drugs [29]. Anti-hypertensives, anti-arrhythmics, statins, anti-metabolites, psychotropic agents, anti-convulsants, anti-coagulants, antiretrovirals, and H2 blockers are among the drugs that cause hair loss [3].

Hair loss is also known to be caused by agents such as bacterial infection Treponema pallidum, viral infection Epstein-Barr virus, HIV, hepatitis C, varicella-zoster virus, and cytomegalovirus [3].

Hair loss and subsequent alopecia are seen as a result of diseases such as liver and kidney failure, rheumatological disorders, discoid lupus erythematosus, connective tissue disorders, amyloidosis, cutaneous sarcoidosis, systemic sarcoidosis [3]. Alopecia can also be seen in systemic and cutaneous hematological malignancies. Although it is usually associated with mycosis fungoides, hair loss is common in cutaneous T-Cell lymphoma [3, 30].

Nutrition and hair loss

The integrity of the normal function of healthy skin and hair depends largely on an adequate and balanced diet. Whether a nutritional imbalance is a general or specific deficiency, an excessiveness of one component over another can compromise the organism's balance. When looking at the studies published in the literature, it is apparent that the nutritional elements that cause hair loss in healthy adults are still to be thoroughly determined.

In the first published reports in this domain, that are animal studies carried out in the first half of the XX century to explain the relationship between nutritional factors and hair loss, Cunningham identified iron deficiency in rats in 1932, Sullivan and Nicholls found riboflavin deficiency in 1941, and Day studies reported that zinc deficiency causes hair loss in both rats and mice [31-35]. The discovery and identification of vitamins related to dietary deficits have had a profound impact on the evolution of nutrient medicine since the first clinical trials. People frequently look for information on vitamin and mineral supplements and diets to prevent or treat many skin disorders, including hair loss. Hair loss greatly affects a person's appearance and personality in physical and social aspects. As a result, hair loss has a negative impact on the standard of living of men and women alike, therefore making the treatment of alopecia essential [36, 37]. Among the about 100,000 hair follicles on the human scalp, 90% of them are in the anagen phase without alopecia, requiring critical nutrients including proteins, vitamins, and minerals to create healthy hair [38]. As a result, trace elements, such as vitamins, are crucial dietary components [39]. Vitamins and trace elements are micronutrients that are critical elements of the diet, even though they are only required in minute amounts. The normal cycle of hair follicles is dependent on micronutrients as they play a role in cell renewal, which is common in rapidly dividing hair follicles [40]. Furthermore, several micronutrients are suggested to minimize oxidative stress because they play a role in alopecia pathogenesis [41]. As a result, a detailed understanding of the significance of these micronutrients could aid research into alopecia prevention and therapy [40].

Micronutrients

Vitamin A, which is made up of a set of unsaturated chemical compounds such as retinol, retinal, and retinoic acid, is an essential nutrient that humans cannot generate and thus it must be taken from diet [42]. Vitamin A and its compounds are required for a variety of functions throughout life, including immune function, cell differentiation and proliferation, reproduction, growth, maintenance of epithelial cell integrity, vision, and em-

bryogenesis [43, 44]. Generally, excessive vitamin A consumption can lead to hair loss in most people [45].
In one study, dietary vitamin A activates follicle stem cells by activating the hair cycle developmental and growth phases in a dose-dependent manner (anagen) [46, 47]. For healthy hair, it is important to maintain homeostasis and, accordingly, to maintain an appropriate concentration of the active metabolite [48]. A sufficient level of vitamin A may usually be obtained via a well-balanced diet. One case reported of a 60-year-old man who took too much vitamin A and had non-scarring fronto-central alopecia and a decrease in pubic and axillary hair. These changes were accompanied by drug toxicity associated with excessive intake of vitamin A by the patient [49]. In conclusion, these studies show that there are some optimal levels of vitamin A that are suitable, but very little or too much of this molecule contributes to the formation, maintenance, or advancement of alopecia [40].
The only vitamin B produced by the body is B7 (biotin). The recommended daily amounts of the vitamin B complex, which are pantothenic acid, riboflavin, thiamine, niacin, B6, B12, and folate, can be taken through a balanced diet. Lack of biotin is extremely uncommon in people who eat a healthy, well-balanced diet, and biotin supplements are not necessary [50]. Hair loss has only been linked to B2 (riboflavin), B7 (biotin), B12, and folate deficits. Biotin (vitamin H or B7) is a vitamin B complex with five carboxylases (acetyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, pyruvate carboxylase, and propionyl-CoA carboxylase) [50]. In addition, biotin is effective in cell signaling, histone modifications, and gene regulation [51]. Biotin lack is a condition that can be inherited or acquired; the inheritance pattern is autosomal recessive and there can be neonatal and infantile forms. It is caused by a lack of the enzyme holocarboxylase synthetase and appears from the first six weeks of life; it can be a potentially fatal disease in newborns. Diffuse dermatitis and alopecia are common among survivors. The scalp may be devoid of vellus and terminal follicles, and may also lack lanugo hairs, eyebrows, and eyelashes. Hair on the scalp, eyebrows, and eyelashes may be present but sparse or completely lost [52, 53].
Despite the popularity of biotin, there is still insufficient evidence in randomized controlled trials to support that supplementing this micronutrient prevents or treats hair loss. There are no clinical studies showing that biotin supplements are effective in treating hair loss unless people are deficient [54]. Hair loss, rashes on the skin, and fragile nails are all signs of biotin deficiency. In one study, 38% of women suffering from hair loss had low levels of biotin [55].
Humans cannot produce folate. Folate is essential for cell division and maintenance, and for synthesis of the nucleotide (thymidine), which is required for DNA repair. Folate also plays an important role in the 'site-specific' methylation of the cytosine base in gene expression. Remethylation of plasma homocysteine to methionine is another action of folate/folic acid. This water-soluble vitamin's demand is satisfied in part by dietary folate and in part with the use of synthetic folic acid [56]. Hair, skin, and nail changes may indicate a lack of folate [38].
Vitamin B12 (also known as cobalamin) is needed to activate folate, which is essential for DNA synthesis. Inadequate nutrition causes impaired nerve transmission and insufficient erythrocyte and other hematological cell production. B12 is an essential nutrient in the transfer of a methyl group in a reaction that requires methionine synthase, which converts homocysteine to methionine. This reaction activates folate, which can be used in DNA synthesis. Myelin production, and thus the preservation and repair of nerve axons, both require B12. In addition, B12 is required for energy synthesis in mitochondria and erythropoiesis in the bone marrow [57].
Due to the effect of B12 and folate on nucleic acid, it has been highlighted that they could play a role in the proliferation of hair follicles [38]. Additionally, a case-control review of dietary research on alopecia areata found no changes in vitamin B12 values in patients with and without alopecia areata. Although vitamin B12 appears to not affect hair growth and repair, research on the subject is scarce [53].
Ascorbic acid, often known as vitamin C, is a water-soluble vitamin produced as a product of glucose metabolism. Vitamin C has a chelating and reducing effect. This effect helps intestinal absorption and mobilization of iron [58, 59]. Accordingly, vitamin C supplementation is critical for patients suffering from hair loss due to iron deficiency [38]. The enzyme l-gulonolactone oxidase, which is necessary for the production of vitamin C, is evolutionarily deficient in humans, which is why vitamin C must be received from diet [60]. The pathophysiological role of vitamin C in the hair cycle is poorly known [53]. Citrus juices contain large amounts of vitamin C, and patients with iron deficiency are recommended to take oral supplements such as orange juice [61]. While vitamin C insufficiency has been linked to anomalies in body hair [59], there's still no evidence of a link between vitamin C values and hair loss.
Vitamin D is a steroid hormone that is fat-soluble. Vitamin D plays a regulatory role in various pathways, such as calcium absorption, bone mineralization, immune system, and DNA transcription [62, 63]. Vitamin D, whether obtained from diet or through the skin, is inactive and must be activated by enzymes [38]. Vitamin D insufficiency is a typical occurrence [64]. It was observed that vitamin D has an effect on the hair cycle in animal research. By attaching to the nuclear vitamin D receptor (VDR), vitamin D regulates keratinocyte development and differentiation. VDR immunoreactivity

Tab. II. Classification of Non-Cicatricial Alopecias [17].

Diffuse Alopecia	Local Alopecia
Female pattern hair loss	Alopecia areata
Male pattern hair loss	Tinea capitis
Diffuse alopecia areata	Traction alopecia
Alopecia totalis or universalis	Trichotillomania
Telogen effluvium	
Anagen effluvium	

is highest in the anagen phase in murine hair follicle keratinocytes [38, 53]. Vitamin D thus plays a function in alopecia and may be the cause of hair loss in vitamin D-deficient rickets patients [65]. Alopecia, hypocalcemia, rickets, hyperparathyroidism, and osteomalacia develop in mice lacking the vitamin D receptor (VDR). Normalizing mineral ion homeostasis prevents all these abnormalities, except alopecia. Hair regeneration experiments in athymic nude mice demonstrate that the lack of VDR in keratinocytes results in a defect in anagen initiation, similar to the one observed in mice without VDR. Although these studies show that expression of the VDR in keratinocytes is necessary, they do not prove that it is sufficient to maintain the normal hair cycle [66]. Patients with VDR mutations who develop vitamin D resistance also suffer from severe alopecia of the body and scalp [53, 65]. In two patients with inherited vitamin D-resistant rickets and baldness, Forghani et al. discovered novel nonsense mutations in the VDR gene [67, 68]. Daroach et al. compared patients with alopecia areata to healthy controls in a prospective study to correlate VDR expression in alopecia areata patients, finding higher vitamin D deficiency levels in the alopecia group [69]. To better understand the effects of vitamin D in alopecia, more large-scale research is required [68].

Iron is vital for all cellular functions because of its role in electron transport, oxygen delivery, and enzyme activity. It includes a wide range of enzymes, from hydroxylases – regulating cellular metabolism – to demethylases – changing DNA chromatin and consequently gene expression [70]. Iron is vital in rapidly proliferating cells, such as those in the hair follicle matrix, since it is a cofactor for ribonucleotide reductase, the rate-limiting enzyme in DNA synthesis. Some studies have demonstrated that various genes in the hair follicle are regulated by iron [71]. Iron deficiency, which also causes telogen effluvium, is the most frequent dietary deficiency worldwide [72, 73]. The level of serum ferritin, also known as iron-binding protein, is an important correlate of total body iron stores and is utilized in hair loss research as an indicator. Iron deficiency is frequent in women who are experiencing hair loss [31]. A mutation in the *TMPRSS6* gene caused the "mask mouse" to lose body hair and develop iron deficiency anemia, according to a study conducted by Du et al. A mutation in *TMPRSS6* was linked to an inability to downregulate *HAMP* expression in mice, and elevated hepcidin levels were linked to reduced dietary iron absorption and, as a result, iron insufficiency. Iron treatment, interestingly, corrected iron deficiency and stimulated hair growth in these animals [74]. Further research is needed to develop iron supplementation guidelines, therapy markers, and cures for patients suffering from hair loss due to iron deficiency.

Selenium (Se) is primarily involved in thyroid hormone metabolism, redox homeostasis, and enzymatic activity like glutathione peroxidases (GPx) as an important microelement. The antioxidant potential of other selenoproteins is thought to have a significant impact on human health [75]. Hair loss has been observed in selenium-deficient rats [76] and in knock-out mice lacking a selenium cofactor protein [77]. Although these findings suggest a link between selenium deficiency and hair loss, the role of selenium in human hair follicles is still not fully understood. Hair loss can be caused by selenium toxicity [53]. Among people who have been diagnosed with selenium toxicity, 72 percent was affected by hair loss affected, losing 10 percent to 100 percent of their hair [78]. After starting daily selenium therapy in 6 infants with pseudoalbinism alopecia-like findings, alopecia and pseudoalbinism improved when serum selenium levels reverted to normal [79]. Another clinical study showed that there was a significant reduction in hair loss and other gastrointestinal symptoms in ovarian cancer patients who received selenium supplements during chemotherapy as compared to controls. This result shows that selenium has a beneficial effect during chemotherapy [80]. Selenium is thought to play a role in the hair cycle, and healthy people can obtain enough through their diet. Supplementation is not suggested unless there are known deficits, particularly given the risk of hair loss due to toxicity.

Zinc is a trace element that is essential for a variety of cellular functions through proteins, enzymes, and zinc fingers, and also acts as a multitude of transcription factors important in gene regulation [81, 82]. Zinc deficiency can cause telogen effluvium, thin white and brittle hair, as well as many dermatological problems [83]. Superoxide dismutase is one of the zinc-dependent enzymes, which is thought to be one of the contributing factors to alopecia areata [84]. The function of antioxidant processes in alopecia areata is a popular issue in the scientific community. Zinc has also been linked to the Hedgehog signaling pathway, which has been linked to hair follicle morphogenesis [53]. Although zinc homeostasis impairment has been linked to a number of issues, its diabetic effects and function in metabolic syndrome are still being researched [85]. Zinc is a cofactor for enzymes involved in dopamine transport [86], cell membrane stabilization [87], and prostaglandin metabolism. Data relating zinc levels to telogen effluvium and androgenetic alopecia are not homogeneous. In another study comparing 312 people with hair loss with 32 controls, patients with alopecia areata and telogen effluvium showed low zinc levels [88].

In summary, nutritional supplement can damage the hair, when taken without a cause: a surplus dosage of micronutrients, including vitamins A and E, as well as selenium, has been linked to hair loss [83]. Hypervitaminosis A can cause hair loss, and findings on the effects of isotretinoin on hair loss back up this theory. Even though the connection between vitamin D values and telogen effluvium or androgenetic alopecia is still contested, most researchers concur that patients having alopecia and vitamin D insufficiency should take vitamin D supplements. On the other hand, people with iron-deficient alopecia need vitamin C. There is no evidence that vitamin E has a function in androgenetic alopecia or telogen effluvium. Women with hair loss are more likely to be lacking iron. In individuals with iron insufficiency and/

or low ferritin, many researchers deem that iron supplementation is necessary. Data on zinc concentrations in telogen effluvium and androgenetic alopecia are not yet clear and zinc screening is not advisable. It can be also a cause of hair loss, selenium toxicity, and riboflavin deficiency. Nevertheless, there are still no comprehensive studies to make any recommendations about screening for riboflavin or selenium. Hair loss can be caused by a lack of biotin. However, there is no proof that biotin supplementation increases hair growth. Exogenous biotin may also interfere with several laboratory tests, resulting in erroneous negative or positive results. Although some research has been carried out on the link between hair loss and B12 or folate/folic acid, currently there is not enough data on these dietary supplements.

Mediterranean diet and hair loss treatment

The Mediterranean Diet (MD), among the healthiest nutrition models accepted by the whole world, was put forward by Prof. Ancel Keys and his friends from examining the typical diet in Southern Italy and Greece. The MD is characterized by a low intake of saturated fat and animal protein, by a high intake of unsaturated fats, fiber, and antioxidants, and by appropriate intake of omega-6/omega-3 fatty acids. It is generally rich in vegetables, fruits, legumes, nuts, grains, fish, and unsaturated fats, with small amounts of meat and dairy products [89-91]. In the Seven Country Study, the MD has been linked to a lower risk of coronary artery disease. In addition, several studies support its effectiveness in preventing diabetes, obesity, and even various types of cancer [89, 91]. This is thought to be related to an adequate intake of polyphenols, which play a critical role in the MD. Polyphenols have genomic effects that play a part in the inactivation and activation of regulatory genes. They also exert epigenetic effects by modulating the expression of microRNAs, regulating mechanisms such as DNA methylation and histone modification, and chromatin rearrangement [91, 92]. The genetic and epigenetic effects of polyphenols, one of the main components of the MD, on the genome have recently been the focus of attention for researchers.

In addition, polyphenols protect the body against harsh climatic conditions and oxidative stress, which are involved in the defense against ultraviolet radiation and pathogen attacks in plants. Diets rich in these secondary metabolites found in fruits, vegetables, fiber foods, cereals, and beverages protect against the development of chronic and neurodegenerative diseases, diabetes, cancer, cardiovascular diseases, aging, and hypertension in humans [93]. Polyphenols can act as antioxidants, stimulate cell signaling pathways, and reduce inflammation by blocking gene activity. Studies have proven that the MD plays an important role in reducing inflammation [94]. The presence of over 8,000 polyphenols identified so far and the differences between the regions of the MD are considered limiting factors in the study of the effects of this diet. However, the protective effect of polyphenols has been proven by many studies [91, 93]. Plants containing flavonoids are promising in terms of reducing hair loss or stimulating hair growth [95].

The effects of the main components of the foods consumed in the MD are examined in hair loss and in many other diseases. Studies have shown that the polyphenolic compounds in tea significantly increase hair growth. In addition, it has been reported that epigallocatechin-3-gallate, the main component of tea polyphenols, can reduce the risk of androgenetic alopecia by inhibiting 5α-reductase, which increases hair growth in humans [96].

Essential fatty acids (linolenic, linoleic, oleic, myristoleic, palmitoleic, and stearic acids) found in olive oil, which has an important place in the MD, have inhibitory effects on 5α-reductase (5AR) that provide hair regrowth [4, 18, 97]. It has been reported that hair loss and depigmentation are seen in hair and eyebrows in people affected by linoleic acid and alpha-linolenic acid deficiency [83]. Mice with testosterone-induced alopecia showed a significant increase in hair growth after day 16 of topical applications of hydroalcoholic extracts of rosemary, which is a polyphenol. In vitro tests showed strong inhibition of the 5AR enzyme binding to the dihydrotestosterone (DHT) receptor [98, 99]. Although not fully proven, topical applications of coconut oil for hair loss treatment continue to be used [100].

Polyunsaturated fatty acids are thought to be absorbed into mast cell membranes, altering membrane-associated enzymes such phospholipases, which affect mast cell exocytosis. In a monkey study, it was shown that supplementing polyunsaturated fatty acids reduced hair loss in slightly alopecic monkeys; however, the cause of the hair loss was unknown [101].

A plant nanoparticle of safflower oil body loaded with human fibroblast growth factor 10 (hFGF10) in mice with androgenetic alopecia was found to accelerate hair regeneration by targeting hair follicles and reducing inflammation without any toxicity It has also been found to reduce hair follicle inflammation by inhibiting the overproduction of TNF-α, IL-1β, and IL-6 in macrophages and increasing the proliferation of dermal papilla cells. In this respect, it can be seen as a viable treatment option in androgenetic alopecia [102]. The standardized para rubber seed oil has been proven to be a safe and efficient bio-oil to stimulate hair growth or reduce/suppress hair loss [103].

Although there are many products for the treatment of alopecia, their effectiveness is controversial; research thus focuses on more effective pharmaceutical product development. As a result, the bioactivity of oligomeric procyanidin, a dimeric derivative from apples that can stimulate hair epithelial cell proliferation and induce anagen phase in vitro and in humans, is a popular application [104].

In one study, it was observed that resveratrol, an antioxidant, anti-inflammatory, and anti-apoptotic agent, when applied to mice, stimulated the transition of the hair cycle from the telogen phase to the anagen phase, delayed the transition to the catagen phase, and protected the hair

follicle from oxidative damage. Resveratrol is considered to be a potential candidate drug for the treatment of alopecia [105]. In addition, a topical lotion containing Redensyl and Sepicontrol A5 polyphenols is used as an alternative treatment for androgenetic alopecia, as it is very safe and provides patient satisfaction [106]. When given to rabbits, *Ficus benghalensis* leaf extracts were found to be effective in increasing hair follicle development by lowering the action of 5-reductase II [107].

As a result, a lack of certain nutrients, such as vitamins, minerals, vital fatty acids, and proteins, can cause hair loss, structural anomalies, and color changes, albeit the exact causes remain unknown [83]. Hair loss is prevalently treated by dermatologists, and it has a significant psychological and emotional impact on patients. Micronutrients like vitamins and minerals have a vital, though not completely understood, role in hair follicle formation and in immune cell activity. A lack of these micronutrients could be a modifiable risk factor for the development, prevention, and treatment of alopecia.

It has been proven by studies that those who follow the MD have less risk of alopecia. As the use of polyphenol-based phytochemicals – frequently used in the MD– increases, the effect of polyphenols in the treatment of alopecia is taken into consideration. In addition, in several studies essential oils were used in the treatment of alopecia, leading to positive results [4, 91].

Considering all the data, more research is needed soon on the role of nutrients in the hair cycle, its association with known alopecia diseases, and effective supplementation regimens. The fact that the incidence of alopecia is low in those fed the MD is promising for the development of the most appropriate preventive and supportive treatments by further researching the active ingredients frequently used in the MD.

Acknowledgements

None.

Conflicts of interest statement

The authors declare no conflict of interest.

Author's contributions

MD, MB, and TB developed the study design and conceptualization of the research methodology. NG, NB, and SK contributed to the manuscript's writing. MD, YO, HA, and MCE contributed to manuscript reviewing and editing processes. All authors have read and approved the final manuscript

References

[1] Mounsey AL, Reed SW. Diagnosing and treating hair loss. Am Fam Physician 2009;80:356-62.

[2] Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The role of vitamins and minerals in hair loss: a review. Dermatol Ther (Heidelb) 2019;9:51-70. https://doi.org/10.1007/s13555-018-0278-6

[3] Lin RL, Garibyan L, Kimball AB, Drake LA. Systemic causes of hair loss. Ann Med 2016;48:393-402. https://doi.org/10.1080/07853890.2016.1180426

[4] Pham CT, Romero K, Almohanna HM, Griggs J, Ahmed A, Tosti A. The role of diet as an adjuvant treatment in scarring and nonscarring alopecia. Ski Appendage Disord 2020;6:88-96. https://doi.org/10.1159/000504786

[5] Cardoso CO, Tolentino S, Gratieri T, Cunha-Filho M, Lopez RFV, Gelfuso GM. Topical treatment for scarring and non-scarring alopecia: An overview of the current evidence. Clin Cosmet Investig Dermatol 2021;14:485-99. https://doi.org/10.2147/CCID.S284435

[6] Rambwawasvika H, Dzomba P, Gwatidzo L. Alopecia types, current and future treatment. J Dermat Cosmetol 2021;5:93-99. https://doi.org/10.15406/jdc.2021.05.00190

[7] Cotsarelis G, Millar SE. Towards a molecular understanding of hair loss and its treatment. Trends Mol Med 2001;7:293-301. https://doi.org/10.1016/S1471-4914(01)02027-5

[8] Martinez-Jacobo L, Villarreal-Villarreal CD, Ortiz-López R, Ocampo-Candiani J, Rojas-Martínez A. Genetic and molecular aspects of androgenetic alopecia. Indian J Dermatol Venereol Leprol 2018;84:263-8. https://doi.org/10.4103/ijdvl.IJDVL_262_17

[9] Fanti PA, Baraldi C, Misciali C, Piraccini BM. Cicatricial alopecia. G Ital Dermatologia Venereol 2018;153:230-42. https://doi.org/10.23736/S0392-0488.18.05889-3

[10] Karakuzu A. Primary cicatricial alopecia. Turkderm 2014;48:56-9. https://doi.org/10.4274/turkderm.48.s13

[11] Civaş E, Aykan A, Aksoy B, Eski M. Surgical correction of primary cicatricial alopecia: Experience with nine patients. TURKDERM 2018;52:85-90. https://doi.org/10.4274/turkderm.20270

[12] Filbrandt R, Rufaut N, Jones L, Sinclair R. Primary cicatricial alopecia: Diagnosis and treatment. Cmaj 2013;185:1579-85. https://doi.org/10.1503/cmaj.111570

[13] Villablanca S, Fischer C, García-García SC, Mascaró-Galy JM, Ferrando J. Primary Scarring Alopecia: Clinical-Pathological Review of 72 Cases and Review of the Literature. Skin Appendage Disord 2017;3:132-43. https://doi.org/10.1159/000467395

[14] Finner AM, Otberg N, Shapiro J. Secondary cicatricial and other permanent alopecias. Dermatol Ther 2008;21:279-94. https://doi.org/10.1111/J.1529-8019.2008.00210.X

[15] Olsen EA, Bergfeld WF, Cotsarelis G, Price VH, Shapiro J, Sinclair R, Solomon A, Sperling L, Stenn K, Whiting DA, Bernardo O, Bettencourt M, Bolduc C, Callendar V, Elston D, Hickman J, Ioffreda M, King L, Linzon C, McMichael A, Miller J, Mulinari F, Trancik R. Summary of North American Hair Research Society (NAHRS)-sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001. J Am Acad Dermatol 2003;48:103-10. https://doi.org/10.1067/MJD.2003.68

[16] Kanti V, Röwert-Huber J, Vogt A, Blume-Peytavi U. Cicatricial alopecia. JDDG 2018;16:435-61. https://doi.org/10.1111/DDG.13498

[17] Mounsey AL, Reed SW. Diagnosing and treating hair loss. Am Fam Physician. 2009;80:356-62.

[18] Lourith N, Kanlayavattanakul M. Hair loss and herbs for treatment. J Cosmet Dermatol 2013;12:210-22. https://doi.org/10.1111/JOCD.12051

[19] Gentile P, Garcovich S. Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: wnt pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. Cells 2019;8:466. https://doi.org/10.3390/cells8050466

[20] Alessandrini A, Bruni F, Piraccini BM, Starace M. Common

causes of hair loss- clinical manifestations, trichoscopy and therapy. J Eur Acad Dermatol Venereol 2021;35:629-40. https://doi.org/10.1111/jdv.17079

[21] Batrinos ML. The endocrinology of baldness. Hormones 2014;13:197-212. https://doi.org/10.1007/BF03401334

[22] Thom E. Stress and the hair growth cycle: Cortisol-induced hair growth disruption. J Drugs Dermatology 2016;15:1001-4.

[23] Chien Yin GO, Siong-See JL, Wang ECE. Telogen Effluvium – a review of the science and current obstacles. J Dermatol Sci 2021;101:156-63. https://doi.org/10.1016/J.JDERMSCI.2021.01.007

[24] Asghar F, Shamim N, Farooque U, Sheikh H, Aqeel R. Telogen Effluvium: A Review of the Literature. Cureus 2020;12:e8320. https://doi.org/10.7759/cureus.8320

[25] Alonso LC, Rosenfield RL. Molecular genetic and endocrine mechanisms of hair growth. Horm Res 2003;60:1-13. https://doi.org/10.1159/000070821

[26] Anzai A, Hsi E, Wang C, Lee EY, Aoki V, Christiano AM. Pathomechanisms of immune-mediated alopecia. Int Immunol 2019;31:439-47. https://doi.org/10.1093/intimm/dxz039

[27] Bertolini M, McElwee K, Gilhar A, Bulfone-Paus S, Paus R. Hair follicle immune privilege and its collapse in alopecia areata. Exp Dermatol 2020;29:703-25. https://doi.org/10.1111/EXD.14155

[28] Rahmani W, Sinha S, Biernaskie J. Immune modulation of hair follicle regeneration. npj Regen Med 2020;5. https://doi.org/10.1038/s41536-020-0095-2

[29] Patel M, Harrison S, Sinclair R. Drugs and Hair Loss. Dermatol Clin 2013;31:67-73. https://doi.org/10.1016/j.det.2012.08.002

[30] Bi MY, Curry JL, Christiano AM, Hordinsky MK, Norris DA, Price VH, Duvic M. The spectrum of hair loss in patients with mycosis fungoides and Sézary syndrome. J Am Acad Dermatol 2011;64:53-63. https://doi.org/10.1016/j.jaad.2009.12.056

[31] Rushton DH. Nutritional factors and hair loss. Clin Exp Dermatol 2002;27:396-404. https://doi.org/10.1046/j.1365-2230.2002.01076.x

[32] Cunningham IJ. Influence of dietary iron on hair and wool growth. https://www.cabdirect.org/cabdirect/abstract/19321401596 (accessed on: April 26, 2022).

[33] Sullivan M, Nicholls J. Nutritional dermatosis in the rat. IV. Riboflavin deficiency. J Invest Dermatol 1941;4:181-91. https://doi.org/10.1038/jid.1941.17

[34] Day HG. The effects of zinc deficiency in the mouse. https://www.cabdirect.org/cabdirect/abstract/19421402451 (accessed on: April 26, 2022).

[35] Day HG, McCollum EV. Effects of Acute Dietary Zinc Deficiency in the Rat. Proc Soc Exp Biol Med 1940;45:282-4. https://doi.org/10.3181/00379727-45-11653P

[36] Lohia K, Doshi BR, Manjunathswamy B. Hair loss severity and its impact on quality of life in patients suffering from androgenic alopecia: A one-year cross-sectional study. Clin Dermatology Rev 2022;5:59. https://doi.org/10.4103/CDR.CDR_52_20

[37] Adamowicz R, Załe P, Dukiel A, Nowicka D. Association between androgenetic alopecia and psychosocial disease burden: a cross-sectional survey among polish men. 2022;2022:1845044. https://doi.org/10.1155/2022/1845044

[38] Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The role of vitamins and minerals in hair loss: a review. Dermatol Ther (Heidelb) 2019;9:51-70. https://doi.org/10.1007/S13555-018-0278-6

[39] Mason JB. Vitamins, Trace Minerals, and Other Micronutrients. Twenty Fourth edition. Elsevier Inc. 2012. https://doi.org/10.1016/b978-1-4377-1604-7.00558-3

[40] Thompson JM, Mirza MA, Park MK, Qureshi AA, Cho E. The role of micronutrients in alopecia areata: a review. Am J Clin Dermatol 2017;18:663-79. https://doi.org/10.1007/S40257-017-0285-X

[41] Prie BE, Voiculescu VM, Ionescu-Bozdog OB, Petrutescu B, Iosif L, Gaman LE, Clatici VG, Stoian I, Giurcaneanu C. Oxidative stress and alopecia areata. J Med Life 2015;8:43. https://doi.org/10.1016/j.jaad.2009.10.0

[42] Tanumihardjo SA, Russell RM, Stephensen CB, Gannon BM, Craft NE, Haskell MJ, Lietz G, Schulze K, Raiten DJ. Biomarkers of Nutrition for Development (BOND) – Vitamin A Review. J Nutr 2016;146:1816S. https://doi.org/10.3945/JN.115.229708

[43] Duester G. Retinoic acid synthesis and signaling during early organogenesis. Cell 2008;134:921-31. https://doi.org/10.1016/J.CELL.2008.09.002

[44] Stephensen CB. Vitamin A, infection, and immune function. Annu Rev Nutr 2001;21167-92. https://doi.org/10.1146/ANNUREV.NUTR.21.1.167

[45] Yamamoto K, Sadahito K, Yoshikawa M, Nobuyuki O, Mikami O, Yamada M, Nakamura K, Yasuyuki N. Hyena disease (premature physeal closure) in calves due to overdose of vitamins A, D3, E. Vet Hum Toxicol 2003;45:85-7.

[46] Suo L, Sundberg JP, Everts HB. Dietary vitamin A regulates wingless-related MMTV integration site signaling to alter the hair cycle. Exp Biol Med 2015;240:618. https://doi.org/10.1177/1535370214557220

[47] Duncan FJ, Silva KA, Johnson CJ, King BL, Szatkiewicz JP, Kamdar SP, Ong DE, Napoli JL, Wang J, King LE, Whiting DA, McElwee KJ, Sundberg JP, Everts HB. Endogenous retinoids in the pathogenesis of alopecia areata. J Invest Dermatol 2013;133:334. https://doi.org/10.1038/JID.2012.344

[48] Everts, H.B. Endogenous retinoids in the hair follicle and sebaceous gland. Biochim Biophys Acta 2012;1821:222-9. https://doi.org/10.1016/j.bbalip.2011.08.017

[49] Cheruvattath R, Orrego M, Gautam M, Byrne T, Alam S, Voltchenok M, Edwin M, Wilkens J, Williams JW, Vargas HE. Published online in Wiley InterScience (www.interscience.wiley.com). LIVER Transplant 2006;121888-91. https://doi.org/10.1002/lt.21007

[50] Saleem F, Soos MP. Biotin Deficiency. J Nutr Educ 2021;13:96. https://doi.org/10.1016/S0022-3182(81)80040-4

[51] Zempleni J, Kuroishi T. Biotin. Adv Nutr 2012;3:213. https://doi.org/10.3945/AN.111.001305

[52] Goldberg LJ, Lenzy Y. Nutrition and hair. Clin Dermatol 2010;28:412-9. https://doi.org/10.1016/J.CLINDERMATOL.2010.03.038

[53] O'Connor K, Goldberg LJ. Nutrition and hair. Clin Dermatol 2021;39:809-18. https://doi.org/10.1016/J.CLINDERMATOL.2021.05.008

[54] Guo EL, Katta R. Diet and hair loss: effects of nutrient deficiency and supplement use. Dermatol Pract Concept 2017;7:1-10. https://doi.org/10.5826/dpc.0701a01

[55] Trüeb RM. Serum Biotin Levels in Women Complaining of Hair Loss. Int J Trichology 2016;8:73-7. https://doi.org/10.4103/0974-7753.188040

[56] Czeizel AE, Dudás I, Vereczkey A, Bánhidy F. Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. Nutrients 2013;5:4760. https://doi.org/10.3390/NU5114760

[57] Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D. How prevalent is vitamin B(12) deficiency among vegetarians? Nutr Rev 2013;71:110-7. https://doi.org/10.1111/NURE.12001

[58] Valdés F. Vitamin C. Actas Dermosifiliogr 2006;97:557-68. https://doi.org/10.1016/S0001-7310(06)73466-4

[59] Fleming JD, Martin B, Card DJ, Mellerio JE. Pain, purpura and curly hairs. Clin Exp Dermatol 2013;38:940-2. https://doi.org/10.1111/CED.12118

[60] Chhabra N, Chhabra S. A case oriented approach towards biochemistry. First edition. New Delhi: Jaypee Brothers Medical Publishers 2013.

[61] Gropper S, Smith J. Advanced human nutrition and metabolism, 6th ed. Belmont: Wadsworth, Cengage Learning 2012.

[62] D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? Autoimmun Rev 2015;14:363-9. https://doi.org/10.1016/J.AUTREV.2014.10.008

[63] Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev 2012;12:127-36. https://doi.org/10.1016/J.AUTREV.2012.07.007

[64] Parva NR, Tadepalli S, Singh P, Qian A, Joshi R, Kandala H, Nookala VK, Cheriyath P. Prevalence of vitamin D deficiency and associated risk factors in the US population (2011-2012). Cureus 2018;10:e2741. https://doi.org/10.7759/CUREUS.2741

[65] Vupperla D, Lunge S, Elaprolu P. Vitamin D-dependent rickets type ii with alopecia: a rare case report. Indian J Dermatol 2018;63:176-9. https://doi.org/ 10.4103/IJD.IJD_434_17

[66] Chen CH, Sakai Y, Demay MB. Targeting expression of the human vitamin D receptor to the keratinocytes of vitamin D receptor null mice prevents alopecia. Endocrinology 2001;142:5386-9. https://doi.org/10.1210/ENDO.142.12.8650

[67] Forghani N, Lum C, Krishnan S, Wang J, Wilson DM, Blackett PR, Malloy PJ, Feldman D. Two new unrelated cases of hereditary 1,25-dihydroxyvitamin D-resistant rickets with alopecia resulting from the same novel nonsense mutation in the vitamin D receptor gene. J Pediatr Endocrinol Metab 2010;23:843-50. https://doi.org/10.1515/JPEM.2010.136

[68] Gerkowicz A, Chyl-Surdacka K, Krasowska D, Chodorowska G. The role of vitamin D in non-scarring alopecia. Int J Mol Sci 2017;18:2653. https://doi.org/10.3390/IJMS18122653

[69] Daroach M, Narang T, Saikia UN, Sachdeva N, Sendhil Kumaran M. Correlation of vitamin D and vitamin D receptor expression in patients with alopecia areata: a clinical paradigm. Int J Dermatol 2018;57:217-22. https://doi.org/10.1111/IJD.13851

[70] Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol 2020;223:516-24. https://doi.org/10.1016/J.AJOG.2020.03.006

[71] Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. J Invest Dermatol 2003;121:985-8. https://doi.org/10.1046/J.1523-1747.2003.12540.X

[72] Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. J Am Acad Dermatol 2006;54:824-44. https://doi.org/10.1016/J.JAAD.2005.11.1104

[73] Shrivastava S. Diffuse hair loss in an adult female: approach to diagnosis and management. Indian J Dermatol Venereol Leprol 2009;75:20-8. https://doi.org/10.4103/0378-6323.45215

[74] Du X, She E, Gelbart T, Truksa J, Lee P, Xia Y, Khovananth K, Mudd S, Mann N, Moresco EMY, Beutler E, Beutler B. The serine protease TMPRSS6 is required to sense iron deficiency. Science 2008;320:1088-92. https://doi.org/10.1126/SCIENCE.1157121

[75] Ju W, Ji M, Li X, Li Z, Wu G, Fu X, Yang X, Gao X. Relationship between higher serum selenium level and adverse blood lipid profile. Clin Nutr 2018;37:1512-7. https://doi.org/10.1016/J.CLNU.2017.08.025

[76] Bates JM, Spate VL, Steven Morris J, St Germain DL, Galton VA. Effects of Selenium Deficiency on Tissue Selenium Content, Deiodinase Activity, and Thyroid Hormone Economy in the Rat during Development. Endocrinology 2000;141:2490-500. https://doi.org/10.1210/ENDO.141.7.7571

[77] Sengupta A, Lichti UF, Carlson BA, Ryscavage AO, Gladyshev VN, Yuspa SH, Hatfield DL. Selenoproteins Are Essential for Proper Keratinocyte Function and Skin Development. PLoS One 2010;5:e12249. https://doi.org/10.1371/JOURNAL.PONE.0012249

[78] MacFarquhar JK, Broussard DL, Melstrom P, Hutchinson R, Wolkin A, Martin C, Burk RF, Dunn JR, Green AL, Hammond R, Schaffner W, Jones TF. Acute selenium toxicity associated with a dietary supplement. Arch Intern Med 2010;170:256. https://doi.org/10.1001/ARCHINTERNMED.2009.495

[79] Masumoto K, Nagata K, Higashi M, Nakatsuji T, Uesugi T, Takahashi Y, Nishimoto Y, Kitajima J, Hikino S, Hara T, Nakashima K, Nakashima K, Oishi R, Taguchi T. Clinical features of selenium deficiency in infants receiving long-term nutritional support. Nutrition 2007;23:782-7. https://doi.org/10.1016/J.NUT.2007.08.001

[80] Petru E, Petru C, Benedicic C, Sieja K, Talerczyk M. Re: "Selenium as an element in the treatment of ovarian cancer in women receiving chemotherapy." Gynecol Oncol 2005;96:559-60. https://doi.org/10.1016/J.YGYNO.2004.09.060

[81] Uwitonze AM, Ojeh N, Murererehe J, Atfi A, Razzaque MS. Zinc Adequacy Is Essential for the Maintenance of Optimal Oral Health. Nutrients 2020;12:949. https://doi.org/10.3390/NU12040949

[82] Ogawa Y, Kawamura T, Shimada S. Zinc and skin biology. Arch Biochem Biophys 2016;611113-9. https://doi.org/10.1016/J.ABB.2016.06.003

[83] Finner AM. Nutrition and Hair. Deficiencies and Supplements. Dermatol Clin 2013;31:167-72. https://doi.org/10.1016/j.det.2012.08.015

[84] Abdel Fattah NSA, Atef MM, Al-Qaradaghi SMQ. Evaluation of serum zinc level in patients with newly diagnosed and resistant alopecia areata. Int J Dermatol 2016;55:24-9. https://doi.org/10.1111/IJD.12769

[85] Dubey P, Thakur V, Chattopadhyay M. Role of minerals and trace elements in diabetes and insulin resistance. Nutrients 2020;12:1-17. https://doi.org/10.3390/NU12061864

[86] Robberecht H, Verlaet AAJ, Breynaert A, de Bruyne T, Hermans N. Magnesium, Iron, Zinc, Copper and Selenium Status in Attention-Deficit/Hyperactivity Disorder (ADHD). Molecules 2020;25:4440. https://doi.org/10.3390/MOLECULES25194440

[87] Dodig-Curković K, Dovhanj J, Curković M, Dodig-Radić J, Degmecić D. Uloga cinka u lijecenju hiperaktivnog poremećaja u djece. The role of zinc in the treatment of hyperactivity disorder in children. Acta Med Croatica 2009;63:307-13.

[88] Kil MS, Kim CW, Kim SS. Analysis of serum zinc and copper concentrations in hair loss. Ann Dermatol 2013;25:405-9. https://doi.org/10.5021/AD.2013.25.4.405

[89] Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; A Literature Review. Nutrients 2015:7:9139-53. https://doi.org/10.3390/nu7115459

[90] Ventriglio A, Sancassiani F, Contu MP, Latorre M, Di Salvatore M, Fornaro M, Bhugra D. Mediterranean Diet and its Benefits on Health and Mental Health: A Literature Review. Clin Pract Epidemiol Ment Health 2020;16:156-64. https://doi.org/10.2174/1745017902016010156

[91] Cannataro R, Fazio A, La Torre C, Cristina Caroleo M, Cione E, Albertini C. Antioxidants Polyphenols in the Mediterranean Diet: From Dietary Sources to microRNA Modulation. Antioxidants 2021;10:328. https://doi.org/10.3390/antiox10020328

[92] Amleh A, Sharif J, Jeronimo C, López-Camarillo C, Á C-R, Carlos-Reyes Á, Sullivan López-González J, Meneses-Flores M, Gallardo-Rincón D, Ruíz-García E, Marchat LA, Astudillo-de la Vega H, Hernández de la Cruz ON. Dietary Compounds as Epigenetic Modulating Agents in Cancer. Front Genet 2019;10:79. https://doi.org/10.3389/fgene.2019.00079

[93] Ganesan K, Xu B. A critical review on polyphenols and health benefits of black soybeans. Nutrients 2017;9:455. https://doi.org/10.3390/nu9050455

[94] Bonaccio M, Pounis G, Cerletti C, Donati MB, Iacoviello L, de Gaetano G. Mediterranean diet, dietary polyphenols and low grade inflammation: results from the MOLI-SANI study. Br J Clin Pharmacol 2017;83:107-13. https://doi.org/10.1111/BCP.12924

[95] Bassino E, Gasparri F, Munaron L. Protective role of nutritional plants containing flavonoids in hair follicle disruption: a review. Int J Mol Sci 2020;21:523. https://doi.org/10.3390/IJMS21020523

[96] Bassino E, Gasparri F, Munaron L. Protective role of nutritional plants containing flavonoids in hair follicle disruption: a review. Int J Mol Sci 2020;21:523. https://doi.org/10.3390/IJMS21020523

[97] Fortes C, Mastroeni S, Mannooranparampil T, Abeni D, Panebianco A. Mediterranean diet: fresh herbs and fresh vegetables decrease the risk of Androgenetic Alopecia in males. Arch Dermatol Res 2018;31071-6. https://doi.org/10.1007/s00403-017-1799-z

[98] Murata K, Noguchi K, Kondo M, Onishi M, Watanabe N, Okamura K, Matsuda H. Promotion of hair growth by Rosmarinus officinalis leaf extract. Phytother Res 2013;27:212-7. https://doi.org/10.1002/PTR.4712

[99] Malvezzi De Macedo L, Mendes Dos Santos É, Militão L, Tundisi LL, Ataide JA, Barbosa Souto E, Gava Mazzola P. Plants Rosemary (Rosmarinus officinalis L., syn Salvia rosmarinus Spenn.) and Its Topical Applications: A Review. Plants (Basel) 2020;9:651. https://doi.org/10.3390/plants9050651

[100] Wallace TC. Health effects of coconut oil-a narrative review of current evidence. J Am Coll Nutr 2019;38:97-107. https://doi.org/10.1080/07315724.2018.1497562

[101] Hamel AF, Menard MT, Novak MA. Fatty Acid supplements improve hair coat condition in rhesus macaques. J Med Primatol 2017;46:248-51. https://doi.org/10.1111/jmp.12271

[102] Kong J, Qiang W, Jiang J, Hu X, Chen Y, Guo YX, Liu H, Sun S, Gao H, Zhang Y, Gao Y, Liu X, Liu X, Li H. Safflower oil body nanoparticles deliver hFGF10 to hair follicles and reduce microinflammation to accelerate hair regeneration in androgenetic alopecia. Int J Pharm 2022;616121537. https://doi.org/10.1016/J.IJPHARM.2022.121537

[103] Lourith N, Kanlayavattanakul M, Chaikul P. Para rubber seed oil: The safe and efficient bio-material for hair loss treatment. J Cosmet Dermatol 2021;20:2160-7. https://doi.org/10.1111/JOCD.13843

[104] Tenore GC, Caruso D, Buonomo G, D'Avino M, Santamaria R, Irace C, Piccolo M, Maisto M, Novellino E. Annurca apple nutraceutical formulation enhances keratin expression in a human model of skin and promotes hair growth and tropism in a randomized clinical trial. J Med Food 2018;21:90-103. https://doi.org/10.1089/jmf.2017.0016

[105] Zhang Y, Ni C, Huang Y, Tang Y, Yang K, Shi X, Zhang Y, Li Z, Wang J', Zhu Y, Li H, Ma Y, Lin J, Wang J, Liu Q, Wu W. Hair growth-promoting effect of resveratrol in mice, human hair follicles and dermal papilla cells. Clin Cosmet Investig Dermatol 2021;14:1805-14. https://doi.org/ 10.2147/CCID.S335963

[106] Katoulis AC, Liakou AI, Koumaki D, Vakirlis E, Tsantes AG, Mortaki D, Bozi E, Ioannides D. A randomized, single-blinded, vehicle-controlled study of a topical active blend in the treatment of androgenetic alopecia. Dermatol Ther 2020;33:E13734. https://doi.org/10.1111/DTH.13734

[107] Iltaf J, Noreen S, Rehman MFU, Ghumman SA, Batool F, Mehdi M, Hasan S, Ijaz B, Akram MS, Butt H. Ficus benghalensis as Potential Inhibitor of 5α-Reductase for Hair Growth Promotion: In Vitro, In Silico, and In Vivo Evaluation. Front Pharmacol 2021;12:774583. https://doi.org10.3389/fphar.2021.774583

Correspondence: Munis Dundar, Department of Medical Genetics, Faculty of Medicine, Erciyes University, 38039, Kayseri, Turkey. E-mail: dundar@erciyes.edu.tr

How to cite this article: Gokce N, Basgoz N, Kenanoglu S, Akalin H, Ozkul Y, Ergoren MC, Beccari T, Bertelli M, Dundar M. An overview of the genetic aspects of hair loss and its connection with nutrition. J Prev Med Hyg 2022;63(suppl.3):E228-E238. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.26