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SYSTEMATIC REVIEW ARTICLE

Impact of Vitamin D and Iron in the Treatment of Non-Scarring Alopecia: A Systematic Review

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ABSTRACT

Alopecia is a common dermatological complaint. Affected people are frequently upset and attempt to stop hair loss by taking a variety of over-the-counter vitamin and mineral supplements. However, the evidence for their effectiveness is limited. Nutrients are thought to play a major role in non-scaring alopecia. We reviewed the literature about the most common micronutrients, vitamin D and iron as well as their significance in the hair follicle cycle and hair loss treatment. 2 independent researchers reviewed peer reviewed papers published in the English language. In the present study, we sought to evaluate the possible roles of vitamin D and iron in non-scarring alopecia. A thorough literature search of the PubMed, Google Scholar and Research Gate databases was conducted to assemble published studies on the association between alopecia, blood vitamin D, iron, and ferritin levels. In this review we have found that a substantial link between vitamin D, iron and non-scarring alopecia. However, vitamin D and iron administration in correcting hair loss and managing these conditions are lacking. Hence, further studies are needed with larger number of subjects to know the role of these nutrients before vitamin D and iron can be routinely recommended as a treatment modality in these conditions.

Keywords: vitamin D, Iron, non-scarring alopecia, hair loss, ferritin.

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INTRODUCTION

Alopecia by definition is the absence of hair from the normally hairy area and affects more than 25% of women in developed countries.[1] Like other parts of the body, hair also needs adequate nutrition for its growth and development, and hair is affected by various nutritional deficiencies.[2,3] Despite the fact that the significance of macro and micronutrients in normal hair follicle development is still unknown.[4] Hair loss can range in severity from a single coin-sized patch to widespread alopecia affecting the entire scalp and the rest of the body. The illness is very unpredictable; spontaneous hair regrowth can occur at any point during its course, with the chance of relapse. Alopecia areata (AA) is a particularly difficult condition to treat, and the majority of the existing treatments are ineffective. Because it is a psychologically stressful disease, clinicians should give patients honest information regarding treatments and their efficacy. Hair loss occurs in patches over portions of the body but can ccasionally become severe and affect the entire body. Indeed, the clinical manifestations of AA are varied, ranging from

well-defined patches of hair loss on the scalp to complete hair loss on the scalp (alopecia areata totalis), or even the whole scalp and body (alopecia areata universalis).[5] Scarring and non-scarring alopecia are the two basic types of alopecia.[6] The hair follicles are irreparably damaged in scarring alopecia, resulting in permanent hair loss. The capillary cycle is disrupted in non-scarring alopecia, but the hair follicles are intact, allowing hair to regenerate. Certain diseases including alopecia areata, tinea capitis, and trichotillomania, which are characterised by unequal hair loss in specific areas, can be distinguished from diffuse hair loss produced by telogen or anagen effluvium in this category. Androgenic alopecia, on the other hand, can be diffuse or show a pattern.[7,8] Despite its great prevalence, the pathobiology of this chronic hair loss problem is unknown, and the present treatments are only symptomatic and do not prevent the disease from relapsing.[9] This condition can be caused by defective or malfunctioning hair follicles (primary alopecia) or by inflammation and hypertrophy of the epidermis, with hair follicle involvement as a result (secondary alopecia). There are roughly 100,000 hair follicles on the human scalp. 90% of them are in the anagen phase, which means they don't have alopecia and need important nutrients like proteins, vitamins and minerals to build healthy hair.[10,11] Alopecia is divided into several kinds, the most frequent of which are androgenic alopecia (common baldness), alopecia areata, and chemotherapy-induced alopecia. Although many different explanations have been proposed, determining the actual underlying aetiology of alopecia areata remains a challenge. The most powerful explanations, however, are immunological, environmental, psychological, and genetic variables.[12] Micronutrients in the diet, like as vitamins and minerals, are increasingly being used to treat androgenic alopecia. These minerals are essential for a healthy hair follicle cycle. Micronutrient deficiency is a modifiable risk factor connected with alopecia development, prevention, and treatment. Vitamins and minerals are essential for optimal cell growth and function, and a lack of these can lead to hair loss. The regular hair follicle cycle relies heavily on micronutrients, particularly vitamin D and iron. The treatment of non-scarring alopecia and answering patients' questions about the role of these nutrients in hair loss control is a dynamic and expanding field of study. As a result, we attempted to analyse the association between alopecia and vitamin D and iron in our community in this study.

MATERIALS AND METHODS

Because there is little information on the link between alopecia and low serum vitamin D and iron levels, our review will look for and present pertinent studies. The PubMed, Google Scholar and Research gate databases were specifically searched for pertinent literature on alopecia, blood vitamin D levels, and iron levels. References in the included articles were also examined and, if appropriate, incorporated into the study. Articles considered for inclusion were peer-reviewed and published within the last 30 years, having full-text or abstracts in English and primary data.

Vitamin D

Vitamin D is a steroid hormone that largely governs calcium metabolism; it is generated from cholesterol in keratinocytes of the skin under the influence of UV light, and then converted to an active form in the kidney and liver. Calcitriol, also known as 1,25(OH)2D3, is the active form of vitamin D that binds to VDR (Vitamin D Receptor), a nuclear transcription factor that belongs to the steroid-thyroid-retinoid receptor gene superfamily, and affects the expression of numerous genes.[13] In hair follicle biology, 1, 25(OH) 2 D3 plays a crucial function.

Vitamin D receptors are found in macrophages, T cells, and natural killer cells, all of which are important participants in sustaining immunological privilege.[14,15] Vitamin D receptors are found

in the outer root sheath and mesodermal papilla of the hair follicle, where they are hypothesised to trigger anagen.[16] As a result, vitamin D is thought to play a role in Alopecia areata (AA). The relationship between Vitamin D insufficiency and AA is still unknown. Vitamin D plays a role in both the innate and acquired immune systems, and the presence of VDRs and their activating enzyme 1-hydroxylase on immune cells such as macrophages, dendritic cells, and T cells implies that it plays a role. VDR is a member of nuclear hormone receptor family and acts as a ligand-inducible transcription factor that regulates Vitamin D responsive genes.[17] Vitamin D is obtained from two sources: cutaneous production from sunlight exposure and oral intake, which includes both food and supplemental.[18]

Patients with AA have low serum 25(OH) D levels, which are inversely related to disease severity. As a result, evaluating patients with alopecia areata for vitamin D deficiencyappears to be beneficial in terms of the likelihood of vitamin D supplementation.[19] Vitamin D is involved in a number of signalling pathways that control hair follicle growth and differentiation. In most investigations, serum vitamin D levels were found to be inversely related to non-scarring alopecias such as telogen effluvium, androgenetic alopecia, alopecia areata, and trichotillomania. Scarring alopecia is also linked to a vitamin D deficit.[20] According to Sanke et al, there is a link between vitamin D insufficiency and the severity of androgenetic alopecia. Vitamin D, according to the scientists, may play a role in the early onset of androgenetic alopecia. More research on a bigger population and the effect of vitamin D supplementation on the advancement of androgenetic alopecia are needed, according to the scientists, to corroborate their findings.[21] A substantial link between alopecia areata and vitamin D insufficiency was discovered in another study. Vitamin D insufficiency was found to be a significant risk factor for the development of alopecia areata in this investigation.[22]

One study found a trend toward an increased percentage of vitamin D-deficient persons among alopecia areata patients, which shed light on the vitamin D-alopecia areata link (AA) [23]. Marahatta et al reported that The prevalence of serum 25(OH) D deficiency was substantially higher in the alopecia areata group than in the control group, with an inverse relationship between its level and the severity of the condition.[24] A study by Erpolat et al looked into the link between serum 25(OH)D levels and alopecia areata. However, given Turkey's high prevalence of vitamin D insufficiency, no differences between alopecia areata patients and controls were found.[25] One paediatric study included 20 paediatric patients with alopecia areata and 34 paediatric healthy controls and the serum vitamin D levels were evaluated in both diseased and control ones showed that Vitamin D deficiency is not the only etiologic factor in AA pathogenesis, but in the presence of other etiological factors, this deficiency can aggravate alopecia areata severity, and thus, the authors suggested vitamin D supplementation may be beneficial in treatment of pediatric AA.[26]

In one study, serum vitamin D levels were correlated with the degree, pattern, and duration of alopecia areata (AA), as well as the density of vitamin D receptor (VDR) expression across hair follicles in AA patients. The participants in this study were 30 AA sufferers and 30 healthy controls. At baseline and after 6 months of AA treatment, clinical data, serum Vit. D measurement, and scalp biopsy for histopathology and VDR expression were done in patients and controls. According to the authors, vitamin D insufficiency in AA is inversely related toillness severity and duration. VDR expression was lower in AA and negatively linked with inflammation histologically, but not with serum Vit.D levels, disease severity, pattern, or duration.[27] A retrospective case-control research was undertaken with 100 alopecia areata cases and 100 healthy controls who were age and sex matched. The authors looked examined AA's

serum Vitamin D levels. Vitamin D levels were found to be lower in patients with alopecia areata, and there was a strong inverse relationship between vitamin D levels and the duration/severity of the condition, according to the findings. These findings suggested that vitamin D deficiency plays a causal function in the aetiology of alopecia areata and that vitamin D supplementation plays a therapeutic role in the treatment of alopecia areata.[28] Thirty cases of alopecia areata (AA) and thirty age-gender-matched controls were studied in a case-control study. The authors measured serum Vitamin D levels in both groups and compared them. Patients with alopecia areata had considerably lower serum Vitamin D levels than healthy controls, according to the findings.[29] In a separate study, researchers looked at serum Vitamin D levels in 135 people with alopecia areata (AA) and 135 age and sex matched controls. When compared to controls, the case group had a higher percentage of patients with deficient and insufficient Vitamin D levels. Vitamin D insufficiency may be one of the elements involved in the etiopathogenesis or worsening of AA, according to the findings. Vitamin D supplementation as a therapy strategy may help to enhance the clinical result of AA.[30] Detailed characteristics of clinical studies of alopecia and Vitamin D are presented in **Table 1.**

Iron

Iron is required for important physiological and developmental activities such as oxygen transport, energy synthesis, and cell proliferation in nearly all forms of life. Only a small number of microbes appear to be able to survive without using iron's electron-exchange apacity.[31] Iron (Fe), a trace element, is necessary for oxygen metabolism, oxygen uptake, and electron transport in mitochondria, as well as energy metabolism, muscular function, and hematopoiesis. Iron is consequently necessary for physical function and well-being, but free bivalent iron is quickly oxidised to trivalent iron, which, when present in its free form, can cause tissue damage by causing the generation of free oxygen radicals.[32]

Although there is insufficient evidence to recommend universal screening for iron deficiency in patients with hair loss, iron deficiency is a frequent cause of alopecia. Zinc and iron levels in serum and hair were lower in female androgenic alopecia (FAGA) compared to that of normal individuals indicating that trace elements might play an important role in the etiopathogenesis of FAGA. Another likely mechanism for the possible effect of iron on hair growth stems from its requirement as a cofactor for ribonucleotide reductase, the rate-limiting enzyme for DNA synthesis. Iron depletion could prevent proper function of this enzyme, resulting in inhibition of proliferation.[33]

Anemia from iron deficiency is the most common anemia type[34] and may derived from inadequate intake (e.g., poor diet quality), malabsorption (e.g., gastritis, celiac disease, gastritis, gastrointestinal resection, iron refractory iron deficiency anemia), increased physiological requirement (e.g., growth, menses, pregnancy), or pathological blood loss (e.g.,internal bleedings, menorrhagia, intravascular hemolysis). The nutritional iron deficiency is the most common cause of iron deficiencies and is mainly triggered by increased needs not fully guaranteed by dietary intakes.[35]

In 2022, Leiva-Salinas et al, was conducted a retrospective and prospective observational cross-sectional studies as well as an intervention to automatically register and measured ferritin when not requested by the general practitioner. The results showed that there were 343 and 1032 primary care laboratory requests prompted by alopecia in the retrospective and prospective studies. Hemoglobin was requested in almost every patient and ferritin in 88%.5% of the cohort had anemia, and 25% had iron deficiency. The intervention registered and measured that 123 ferritin and 24 iron deficiencies were detected. The authors concluded that primary care patients

with alopecia and laboratory tests request were mainly young female and intervention added ferritin when not requested, detecting iron deficiency in 27.9% of women, potentially avoided the adverse effects of iron deficiency on hair loss.[36] 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.[37]

In one study, the authors tried to investigate the relationship between Alopecia aearata (AA) and iron, zinc, and copper levels of serum and hair. The study enrolled sixteen female patients with AA (14–40 years old) and 27 healthy female controls. Serum and hair level of iron, zinc, and copper were measured by flame emission spectroscopy. They did not detect a significant difference in the serum and hair level of iron, zinc, and copper between patients and controls. There was a significant correlation between serum and hair level of iron (r =0.504, P = 0.001), zinc (r = 0.684, P = 0.0001), and copper (r = 0.759, P = 0.0001) in patients and controls. The authors suggested that there was no statistically significant difference between trace elements among AA patients and controls as well as the trace elements level in hair and serum may not be relevant to the immunologic dysfunction that exists in AA patients.[38]

Tamer et al aimed to compare the serum levels of ferritin, folate, vitamin B12, zinc, thyroid stimulating hormone and vitamin D in patients complaining of diffuse hair loss and in healthy individuals. Here in this study included fifty-four patients with hair loss (47 females, 7 males) and 55 healthy individuals within the control group (47 females, 8 males). Serum levels of ferritin, folate, vitamin B12, zinc, thyroid stimulating hormone and 25-hydroxyvitamin D were evaluated in all participants retrospectively. The results showed that serum concentrations of folate, vitamin B12, zinc and thyroid stimulating hormone were similar in the two groups. However, the mean serum ferritin and 25-hydroxyvitamin D levels were significantly lower in patients with hair loss than in healthy individuals. This study revealed that serum ferritin and 25-hydroxyvitamin D levels are generally low in patients complaining of hair loss. Therefore, the authors suggested that serum ferritin and vitamin D levels should be evaluated and supplemented prior to treatment in all patients complaining of diffuse hair loss.[39]

In an analytical cross-sectional study evaluated whether common types of alopecia in women are associated with decreased tissue iron stores, as measured by serum ferritin. They studied patients with telogen effluvium (n = 30), androgenetic alopecia (n = 52), alopecia areata (n = 17), and alopecia areata totalis/universalis (n = 7). The study reported that the mean ferritin level in patients with androgenetic alopecia and alopecia areata were statistically significantly lower than in normals without hair loss. Whereas, the mean ferritin levels in patients with telogen effluvium and alopecia areata totalis/universalis were not significantly lower than in normal.[40]

Ali and Nighat were conducted one study to evaluate serum iron and ferritin levels in patients with AA. Fifty patients of AA and 50 age and sex matched control subjects without any hair loss was included. This study reported there was no significant difference found in mean hemoglobin, ferritin, and iron levels in two groups.[41] Dhaher et al, 2018 aimed to evaluate serum and hair zinc and iron levels in patients with FAGA and to compare the findings with normal controls (27 women with FAGA and the second was age-matched 28 healthy women control group). Serum iron level in FAGA group was lower than in the control, but it was not significant statistically.[45,46] Telogen effluvium (TE) is common alopecia in women, characterized by

diffuse hair loss. Cheng et al, 2021, tested the serum ferritin levels among TE, female and rogenetic alopecia (FAGA) patients, and healthy controls. The authors showed serum ferritin could be used as a diagnostic indicator to distinguish TE patients from FAGA patients or healthy people. 15–40 years old females (264 TE and 124 female androgenetic alopecia patients and 183 healthy women). They reported that the serum ferritin in telogen effluvium patients were significantly lower than that in the healthy control group (P = 0.000) or female androgenetic alopecia patients (P =0.000).[47] Another prospective case control study carried out in 50 females with AGA (androgenetic alopecia) and 50 health groups as controls to evaluate the level ferritin and Vitamin D3 in both groups. They reported that Serum Vit D3 and Ferritin concentrations were significantly decrease in female with androgenic alopecia [48]. Another cross-sectional study conducted by Devaraj et al, 2021 showed that with increase in severity of alopecia areata, there was a decrease in mean serum ferritin both in males and females. This implies that the severity of AA is influenced by serum ferritin levels. Their study did not include controls; no postulates can be made in this regard. Detailed characteristics of clinical studies of alopecia and iron. Status is presented in Table 2.

RESULTS

Table 1: Characteristics of the clinical studies: Alopecia and Vitamin D status

Authors	Type of study	Subject	Control	parameters measurement	Findings
Cerman Aksu et al, 2014	Cross sectional study	Cases 86AA Vitiligo 40	56	serum 25(OH) D level	The prevalence of 25(OH) D deficiency was significantly higher in patients AA compared with patients with vitiligo and healthy controls (33%) (P =0·003 and P < 0·001, respectively). A significant inverse correlation was found between disease severity and serum 25(OH) D level in patients with AA (r = -0·409; P < 0·001).
Saini et al, 2021	Case control study	50AA	50	serum vitamin D	significantly decreased Level of Vitamin D in cases, compared to controls 20.10 vs. 29.34 ng/mL (P ≤ 0.001). Cases (86%) had deficiency of Vitamin D and Cases (14%) had insufficient vitamin D levels. A positive correlation between vitamin D deficiency and severity of androgenetic alopecia (AGA), statistically significant (P ≤0.5).
Lizarondo et al,2021	Cross sectional Study s	29	29		A significant difference between cases (24.41 ± 6.87 ng/mL) compared to control (24.68 ± 6.68 ng/mL) (*P* = .88).
Marahatta et al, 2019	Case Control Study	30	30	25-hydroxyvitamin D [25(OH) D]	Prevalence of 25-hydroxyvitamin D [25(OH)D] deficiency was significantly higher in AA group (83.3%) compared to the control group (53.3%)(P=0.01). Serum 25(OH) D level was reduced more in Alopecia areata group (P=0.06) than the control group

Erpolat et al,2017	Case Control Study	41	32	serum vitamin D	No statistically significant difference in the serum vitamin D level between AA patients and healthy controls ($p > 0.05$). Serum 25(OH) D levels in patients with AA ranged from 5.0 to 38.6 ng/ml with a mean of 8.1 ng/ml. Serum 25(OH) D levels in healthy controls ranged from 3.6 to 38.5 ng/ml with a mean of 9.

Authors	Type of study	Subject		parameters measurement	Findings
		Cases	Control		
Unal et al, study2017	Case control	20	34	serum vitamin D	serum 25(OH) D concentration of patients was 15.47±7.66 ng/mL,and of control group was 11.09±10.53 ng/mL. No statistically Significant difference between two groups (*P*: 084).
Daroach studyet al, 2017	Case control	30	34	serum vitamin D	Mean serum Vit.D levels was 7.65 ± 4.50 ng/ml and 15.8 ± 11.47 ng/ml in patients and controls, respectively Vit.D deficiency in AA correlates inverselywith disease severity and duration
Siddappa et al, study 2019	Case control	100	100	serum vitamin D	Significantly lower serum Vitamin D in patients with alopecia areata (18.90 ± 8.32 ng/mL) (64%) as compared to healthy controls (28.21 ± 18.32 ng/mL) (38%) ($P < 0.001$).
Ghafoor et al, study 2017	Case control	30	30	serum vitamin D	Median (IQR) vitamin D level of cases was 13.5 (18.6) ng/dL and healthy controls was 22.5 (16.25) (p=0.001). Serum Vitamin D levels were significantly lower inpatients with alopecia areata compared to healthy controls
Rehman et al, study 2019	Case control	135	135	serum vitamin D	Statistically significant difference is seen in case groups compared to controls ($P = 0.01$). Case group had deficient and insufficient levels of Vitamin D.
Bhat et al, study 2017	Case control	50	35	serum vitamin D	Significantly lower level of serum 25(OH)D of AA patients (16.6 ± 5.9 ng/ml) compared to control group (40.5 ± 57) ($P < 0.001$).

Alopecia areata (AA)

Table 2: Characteristics of clinical studies: Alopecia and Iron status

Authors	Type of study	Subject		parameters measurement	Findings
		Cases	Control		
Dastgheib et al, 2014	case control study	16 (F)	27 (F)	Serum and hair level of iron, zinc	significant difference in the serum and hair level of iron, zinc and copper between patients and controls
Tamer et al, 2020	Retrospective study	54 (47 F+7M)	55 (47 F+8M)	ferritin, folate, vitamin B12, zinc thyroid stimulating hormone and 25-hydroxy vitamin D	mean serum ferritin and 25-hydroxyvitamin D levels were significantly lower in patients with hair loss than in healthy individuals
Kantor	case control study	TE-30 AA-17 AAT/U-7	17	Serum ferritin	significantly lower concentration of ferritin level in patients with androgeneticet al, 2003 alopecia and alopecia areata than normals without hair loss. No significant difference seen in ferritin levels of patients with TE and AAT/U
Ali and Nighat, 2021	case control study	50 AA	50	Serum Iron and ferritin	no significant difference in mean hemoglobin, ferritin, and iron levels in two groups
Pradhan et al, 2018	case control study	60 (F)	60 (F)	Various parameters of iron status	Significantly lower serum ferritin levels in cases compared to controls (p=0.018) Patients with alopecia areata (p=0.008) and androgenetic alopecia (p=0.021) had significantly lower serum ferritin, no statistically significant difference in telogen effluvium and controls (p=0.857).
Dhaher et al, 2018	case control study	27-FAGA 28		serum and hair zinc and iron	Serum iron level in FAGA group was lower than in the control no statistically significance (88.9±22.3 µg/dl vs. 100.9±18.9 µg/dl).

Authors	Type of study	Subject		parameters measurement	Findings
		Cases	Control		
Cheng et al, 2021	Case Control Study	104 FAGA 193 TE	183	Serum ferritin	significantly lower levels of serum ferritin in telogen effluvium patients than that in the healthy control (P = 0.000) or female androgenetic alopecia(P =0.000).
Jasim et al, 2021	Prospective Case Control study	50 AA	50	Serum ferritin and Vitamin D3	Significant decrease in vit D and ferritin level in case (AGA) group than that in control (healthy) group (P < 0.001)

F: Female, M: Male, Alopecia Areata Totalis/Universalis AAT/U, Telogen effluvium (TE), Alopecia Areata (AA), Female Androgenetic Alopecia (FAGA).

CONCLUSION

The majority of the papers we considered in this review dealt with vitamin D and alopecia areata, whereas studies on iron and alopecia areata were scarce. According to our research, there have only been a few studies on iron status and alopecia. This comprehensive review summarises the available data on the global incidence, prevalence, and burden of alopecia. The results of this study will assist researchers better understand the profile of alopecia patients, as well as the role of Vitamin D and iron body storage as a risk factor. Thus, help to plan for laboratory parameters like vitamin D and iron levels and treatment strategy. We think that Vitamin D and iron deficiency anaemia are the two important risk factors for alopecia and screening for these two nutrients in patients with alopecia is an effective tool for the further treatment. However, further

clinical and experimental studies with a larger number of participants and a wider range of potentially influential parameters are required to establish the connection between these two nutrients and alopecia. Because of this disparity, as well as the fact that most studies on alopecia and iron only included female subjects, researchers concluded that there was insufficient evidence to recommend iron deficiency screening in hair loss patients. When comparing alopecia and vitamin D studies, solid studies to indicate the efficacy of alopecia and iron administration in treating hair loss and controlling these conditions are lacking, according to a literature search in PubMed, google and Research gate search.

Future plans

Our findings should serve as a foundation for future epidemiologic research, including clinical trials of Vitamin D and iron therapy and an evaluation of the role of iron in alopecia in males, might be initiated. Moreover, the research understanding the role of vitamin D and iron as factors in hair loss could be useful in developing novel treatments as well as in generating hypotheses to better elucidate the molecular reasons of these disorders.

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