SKIN

IN-DEPTH REVIEW

Alopecia Areata and Vitamin D_3 Deficiency: The Potential of Calcipotriol as a Treatment

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ABSTRACT

Background*:* Alopecia areata is a non-scarring form of hair loss associated with the loss of the hair follicle immune privilege with a prevalence of 2% in the population. It results in an accumulation of lymphocytes around the lower part of the hair bulb ultimately leading to hair loss.

Discussion*:* Vitamin D_3 deficiency is significantly more prevalent in patients with alopecia areata than in healthy populations and correlates with disease severity. The pathogenic involvement of vitamin D_3 in alopecia areata is attributed to its regulatory impact on immune and epidermal cells' function, particularly through modulation of the JAK/STAT pathway, T lymphocytes proliferation and hair follicle damage. The data on the effectiveness of vitamin D3 supplementation and topical calcipotriol in treating alopecia areata are inconsistent, and the evidence supporting their efficacy is primarily of low quality.

Conclusion*:* Screening patients with alopecia areata for vitamin D_3 deficiency could be beneficial, potentially allowing for supplementation. This article underscores the need for randomized, placebo-controlled studies with large patient cohorts to evaluate the efficacy of calcipotriol in the treatment of alopecia areata.

INTRODUCTION

Alopecia areata represents an autoimmune non-scarring alopecia affecting any region with hair follicles.[1] The prevalence reaches about 2% of the global population.[2] Manifestations of alopecia areata vary, typically initiating as patchy hair loss and possibly progressing to more extensive forms such as complete scalp loss (alopecia totalis) or total hair loss on the body (alopecia universalis).[3] The precise pathogenesis of alopecia areata remains partially elucidated. Genetic predisposition, immunological dysregulation, allergic responses, and alterations in the microbiome might be implicated. During the initial stages of the disease, interferon-gamma (IFN-γ) overproduction stimulates the upregulation of major histocompatibility complex (MHC) class I molecules in hair follicles, facilitated by increased expression of chemokines of the C-X-C motif (CXCL) and intracellular adhesion molecules (ICAM). This process leads to the immune recognition of hair follicle autoantigens by autoreactive cytotoxic CD8+NKG2D+ T cells, ultimately resulting in hair loss.[4] The Janus kinase/signal transducers and activators of transcription pathway is upregulated in alopecia areata. There is a clear increase in the activity of this signaling pathway observed in the tissues

affected by the disease, suggesting its significant role in the pathogenesis of the disease.[5] Alopecia areata has been associated with various disorders, such as atopic diseases, vitiligo, metabolic syndrome, *Helicobacter pylori* infection, systemic lupus erythematosus (SLE), and autoimmune thyroid diseases.[6] Treatment strategies for alopecia areata encompass topical, intralesional, and systemic glucocorticosteroids, Janus kinase inhibitors (JAKi), topical immunotherapy, cyclosporine, and methotrexate. Additionally, both topical and oral minoxidil are considered as adjunctive therapies.

Role of vitamin D3 has been linked to numerous autoimmune conditions such as rheumatoid arthritis, autoimmune thyroid diseases, coeliac disease, and autoimmune bullous diseases.[7] Its role has been also documented in scarring and non-scarring alopecias, particularly in alopecia areata.[8]

DISCUSSION

Metabolism and functions of vitamin D3

Vitamin D3 is a fat-soluble vitamin belonging to the group of secosteroids. The primary source of vitamin D3 is dietary intake. However, the most significant source of vitamin D3 is through cutaneous synthesis in response to exposure to ultraviolet B (UVB) radiation from sunlight. Sunlight triggers the conversion of 7-dehydrocholesterol in the skin to pre-vitamin D3, which undergoes isomerization to form vitamin D3, also known as cholecalciferol. Cholecalciferol is then transported to the liver, where it undergoes hydroxylation by the enzyme 25-hydroxylase to form 25-hydroxyvitamin D3 [25(OH)D3], the major circulating form of vitamin D3. Subsequent hydroxylation in the kidneys, catalyzed by the enzyme 1α-hydroxylase, converts 25(OH)D3 to the biologically active form, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], also known as calcitriol.

Calcitriol binds to the vitamin D receptor (VDR), which is a member of the nuclear receptor family, initiating genomic and non-genomic signaling pathways. Through genomic mechanisms, calcitriol regulates the expression of genes involved in calcium absorption in the intestines, bone mineralization, and renal reabsorption of calcium.[9] Non-genomic effects of vitamin D3 include the modulation of intracellular signaling cascades involved in immune functions and regulation of cell processes such as growth and differentiation, proliferation, and apoptosis. Vitamin D3 plays a role in reducing inflammation, and therefore its significance is examined not only in relation to autoimmune diseases but also in hypertension, diabetes, and cardiovascular diseases.[10]

Vitamin D deficiency prevalence in patients with alopecia areata

Numerous studies have reported significantly lower serum vitamin D3 levels among individuals diagnosed with alopecia areata compared to healthy controls.[11,12] Patients with alopecia areata also have a higher incidence of vitamin D3 deficiency (defined as serum 25(OH)D3 levels below 20 or 30 ng/mL depending on the study). According to a meta-analysis conducted by Lee et al., approximately 75.5% of patients with alopecia areata have vitamin D3 deficiency.[13] However, numerical data regarding the prevalence of vitamin D3 deficiency in patients with alopecia areata are quite inconsistent. For instance, d'Ovidio et al. found that only 42.4% of alopecia areata patients exhibited vitamin D3 deficiency.[14] These differences might stem from the studies being performed in various

geographic regions.[15] The latitude of each region affects the amount of radiation reaching the earth's surface, impacting vitamin D3 synthesis in the body and thereby influencing the average serum vitamin D3 levels in the population.[16] However, it is possible that the observed differences between studies are due to varying enrollment criteria, such as the severity of alopecia areata. Seasonal fluctuations in serum 25(OH)D3 levels might also explain these differences. Vitamin D3 deficiency is also observed in individuals with other forms of non-scarring alopecias, such as androgenetic alopecia, telogen effluvium, trichotillomania, and scarring alopecias.[17] Nevertheless, there is a stronger correlation between lower 25(OH)D3 levels and alopecia areata compared to androgenetic alopecia and other diseases with non-scarring or scarring alopecia.[18] Vitamin D3 levels in patients with alopecia areata are significantly lower than in patients with vitiligo ($p<0.001$).[19]

Role of vitamin D in pathogenesis of alopecia areata

Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway plays a crucial role in maintaining the cyclic transition during the initiation and regeneration of hair follicles.[20] The Wnt/β-catenin signaling pathway is a key regulator of various hair cells, including outer root sheath cells, hair matrix cells, and dermal papilla cells. This signaling pathway triggers the start of the anagen phase and controls the hair growth cycle.[21,22] The diminished expression of the vitamin D receptor in patients with alopecia areata correlates with reduced expression of Wnt/β-catenin signals. It leads to the inhibition of hair follicle and epidermal cells proliferation and differentiation through inhibition of involucrin, filaggrin, and proliferating cell nuclear antigen (PCNA) expression. Consequently, this disruption may result in hair follicle damage in alopecia areata.[23]

Collapse of hair follicle immune privilege, autoreactive effector T cells, and Treg cells

Hair follicles in the anagen stage demonstrate immune privilege from the bulge area down to the bulb. The breakdown of immune privilege in the anagen hair bulb is a critical factor for the development of alopecia areata.[24] Autoreactive Th1, Th2, and Th17 cells release IFN-γ, the crucial cytokine in alopecia areata, which impairs hair follicle function, disrupts the hair growth cycle, and inhibits hair growth.[25] Vitamin D3 significantly reduces IFN-γ production while enhancing IL-10 production in peripheral blood mononuclear cells.[26] Vitamin D3 deficiency results in excessive IFN-γ secretion and may contribute to the loss of immune privilege in the anagen hair bulb leading to alopecia areata.

1,25(OH)2D3 suppresses the secretion of proinflammatory cytokines such as IL-1, IL-2, IL-6, TNFα, and IL-12. IL-12 is an immunostimulatory cytokine crucial for directing the immune system towards the Th1 phenotype.[27] Vitamin D3 insufficiency causes the immune response to shift towards the Th1 and Th17 phenotype, leading to decreased secretion of Th2 cytokines (IL-4, IL-5, and IL-10). Zhou et al. suggest that vitamin D3 might aid in regulating the hyperactive self-effector T cells by enhancing the suppressive capabilities of Treg cells.[28] Consequently, Vitamin D3 deficiency may result in an increase of CD8+ T cell activation and hair follicles immune privilege collapse in patients with alopecia areata.[11]

JAK/STAT pathway

The pathogenesis of alopecia areata involves proinflammatory Th1 and Th17 cytokines, which are reliant on the Janus kinase and signal transducers and activators of transcription (JAK-STAT) pathway. The epidermis in skin biopsies from patients with alopecia areata shows a prominent JAK3 overexpression.[29] Targeting JAK/STAT pathways therapeutically with tofacitinib (a broad-spectrum JAK inhibitor) is highly effective for treating human alopecia areata and for preventing and reversing the condition in C3H/HeJ mouse models.[30] Vitamin D3 exerts an inhibitory influence on the JAK/STAT pathway and downregulation of gene expression in the NF-κB and JAK/STAT pathways in *Drosophila melanogaster* models and in human subjects.[31] Consequently, the inhibition of the JAK/STAT pathway by vitamin D3 could potentially counteract the effects of critical cytokines implicated in the pathogenesis of alopecia areata.[11]

Vitamin D3 deficiency in alopecia areata: cause or consequence?

Decreased serum 25(OH)D3 levels in patients with alopecia areata might suggest a causal role of this decrease in the pathogenesis of the disease.[32] Given the immunomodulatory role of vitamin D3, its deficiency may be an important factor in the pathogenesis of alopecia areata.[33] However, it cannot be excluded that low serum 25(OH)D3 levels in patients with alopecia areata may be secondary to the disease. Patients suffering from alopecia areata may experience more psychological stress and tend not to expose themselves to public and therefore open air, similar to patients with vitiligo.[34] Emotional distress stemming from significant hair loss could potentially lead patients to limit their outdoor activities compared to those unaffected by this condition. Consequently, their ability to synthesize vitamin D3 might be diminished.[16] Nevertheless, vitamin D3 deficiency is significantly more common in patients with alopecia areata compared to patients with vitiligo (90.7% vs. 70.5% *p=0.001* according to Cerman et al.).[19] This may suggest a possible higher intensity of stress factors in alopecia areata than vitiligo or the involvement of other additional factors contributing to greater vitamin D3 deficiency in patients with alopecia areata; however, these conclusions require further investigation.

Correlation of serum vitamin D3 level with clinical manifestation of alopecia areata

Serum 25(OH)D3 level correlates inversely with disease severity, duration, and number of patches in alopecia areata.[35,36] A significant negative correlation was observed between the Severity of Alopecia Tool (SALT) score and the serum level of 25(OH)D3.[37,38] Patients with patchy alopecia areata or ophiasis have lower vitamin D3 levels compared to patients diagnosed with alopecia universalis ($p<0.001$).[37] There is a significant negative correlation between the number of patches in alopecia areata and vitamin D3 levels ($p < 0.001$).[32]
There is no significant correlation between the 25(OH)D3 level and duration of the disease or nail affection in alopecia areata.[38]

According to a study conducted by Daroach et al., vitamin D3 deficiency does not correlate with the expression of vitamin D receptors (VDR) in hair follicle samples. VDR expression is diminished in patients with alopecia areata and inversely correlates with histological inflammation but does not correlate with the severity, pattern, or duration of the condition.[36]

Calcipotriol in the treatment of alopecia areata

Given the significance of vitamin D3 in the pathogenesis of alopecia areata, it could be considered a potential treatment for the condition. Calcipotriol is a vitamin D3 analogue with significantly lower calcemic effects compared to calcitriol.[39] Calcipotriol ointment has shown to be an effective and well-tolerated topical agent in patients with psoriasis.[40] Due to its capacity to decrease keratinocyte proliferation, promote keratinocyte differentiation, and exert immunomodulatory effects, it has been used also in the treatment of various skin conditions including atopic dermatitis, lichen planus, and vitiligo.[41] Several authors suggest that calcipotriol could be an effective and safe treatment option for mild-to-moderate alopecia areata, potentially serving as an alternative therapy, but there is not sufficient evidence of its efficacy in the treatment of alopecia areata.[42-47] While there are reports on the efficacy of calcipotriol in the treatment of alopecia areata, the lack of placebo-controlled double-blind trials limits conclusive evidence.

Research on the use of topical vitamin D3 in treating alopecia areata is inconsistent and often limited by small sample sizes or lack of coherence in study groups. Additionally, some studies lack appropriate controls or do not have a control group at all.[44-46]. Variations in inclusion criteria and sample collection during different seasons also represent limitations of these studies. Calcipotriol is not effective in severe cases of alopecia areata (alopecia totalis/universalis).[43] Kim et al. documented a case of a 7-year-old patient with a specific gene mutation causing reduced vitamin D receptor (VDR) expression and refractory alopecia areata despite prior use of topical and intralesional corticosteroids. After topical application of calcipotriol, complete hair regrowth was observed.[47]

A summary of the most important research on calcipotriol in the treatment of alopecia areata in various populations is shown (**Table 1**).

Positive findings have emerged regarding the efficacy of calcipotriol in combined therapy, especially when used with topical corticosteroids. According to a study conducted by Alam et al., adding topical calcipotriol 0.005% ointment to topical mometasone 0.1% cream yields significantly better outcomes than using mometasone alone for treating alopecia areata during a 6-month observation.[48] Nassar et al. support the notion that combining vitamin D3 analogues with topical potent steroids, like betamethasone dipropionate, offers a significantly more favorable treatment approach for alopecia areata compared to using topical superpotent steroids such as clobetasol dipropionate 0.05%. This combination results in fewer side effects while maintaining comparable efficacy.[49]

Due to the widespread prevalence of vitamin D3 deficiency in patients with alopecia areata, evaluation of vitamin D3 levels and supplementation, if necessary, can address the problem of its deficiency. There is no sufficient evidence regarding the effectiveness of vitamin D3 supplementation in the treatment of alopecia areata. Nevertheless, some authors suggest that it may be a therapeutic option for such patients.[17,35,37]

CONCLUSION

Vitamin D3 deficiency is significantly more prevalent in patients with alopecia areata. Serum 25(OH)D3 level inversely correlates with severity, duration, and number of

Table 1. The most significant research on calcipotriol in the treatment of alopecia areata in various populations.

Study (Year)	Patient Number	Study Design	Results	Main limitations	Country
El Taieb et al.[42] (2019)	15	Randomized controlled trial	A significant decrease in SALT score after treatment for 3 months (p=0.026). A significant difference in SALT score between the treated group and placebo (p=0.041).	Small sample size	Egypt
Berth-Jones et al.[43] (1991)	20	Randomized controlled trial	No evidence of a response in patients with alopecia totalis or universalis after treatment for 6 months.	Small sample size	United Kingdom
Çerman et al. [44] (2015)	48	Retrospective study	The total response in 69.2% of patients and complete hair regrowth in 27.1% of patients with mild-to-moderate patchy alopecia areata after treatment for 3 months.	Lack of control group	Turkey
Narang et al.[45] (2017)	22	Prospective study	The total response in 59.1% of patients and complete hair regrowth in 9% of patients after treatment for 3 months. A faster response and significant hair growth was better in patients with lower serum vitamin D_3 levels (p<0.009).	Small sample size and lack of control group	India
Molinelli et al.[46] (2020)	35	Prospective study	Hair regrowth of > 75% in 69% of patients treated with calcipotriol vs. 63% treated with clobetasol after treatment for 6 months (p=0.814).	Lack of appropriate control group (treated with placebo ointment)	Italy
Kim et al.[47] (2012)	1	Case report	Total recovery after topical application of calcipotriol in a patient with a VDR mutation.	-	South Korea

patches in alopecia areata. Screening patients with alopecia areata for vitamin D3 deficiency could be beneficial, as the occurrence of alopecia areata is a risk factor for vitamin D3 deficiency, potentially allowing for supplementation. Nevertheless, there is not substantial evidence supporting the effectiveness of vitamin D3 supplementation or topical calcipotriol in the treatment of alopecia areata. Further studies involving a large cohort are needed to evaluate their efficacy.

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