Section A -Research paper

Role of Vitamin D in Treatment of Alopecia Areata

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Article History: Received: 21.06.2023 **Revised:**04.07.2023 **Accepted:** 14.07.2023

Abstract:
Alopecia areata (AA) is a common non-scarring, inflammatory type of hair loss that affects people of all ages and genders. It has been shown that 1,25-dihydroxyvitamin D(3) receptors (VDRs) are highly expressed in the keratinocytes of human and murine hair follicles and the absence of expression of VDRs is associated with reduced hair follicle growth and epidermal differentiation. Reduced VDR expression in the hair follicles of affected areas has also been observed in studies of AA patients' scalps.

Keywords: Vitamin D, Alopecia Areata, AA.

Doi:-10.53555/ecb/2023.12.1197

Introduction:

Vitamin D (calciferol) is related to a group of fat-soluble vitamins with endocrine function. It has two major forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). It is a potent immunomodulator, regulates cell proliferation and differentiation, and cytokines production[(1)].

Vitamin D has been associated with various autoimmune diseases. Recently, vitamin D deficiency has been reported in AA[(2)]. Moreover, topical calcipotriol has been reported to be used successfully in treating AA[(3)].

Vitamin D sources, metabolism and functions

In the human body there are two major forms of vitamin D. More than 90% is vitamin D_3 (cholecalciferol), which is converted from 7-dehydrocholesterol by ultraviolet light B (UVB) exposure in the skin. About 10% is vitamin D2 (ergocalciferol), which comes from dietary sources. Both are biologically inactive[(4)].

In the liver, vitamin D is metabolically converted into 25-hydroxyvitamin D (25(OH)D) which is biologically inactive at physiological concentration. 25(OH)D has been considered as one of the most reliable indicators of Vitamin D levels in humans[(5)].

In the kidney, 25(OH)D is further converted to the biologically active metabolites 1, $25(OH)_2D_3$ (calcitriol) by 25(OH) 1α-hydroxy-D. The 1α-hydroxy enzyme is also widely expressed in non-kidney cells including immune cells and is able to convert the inactive 25(OH)D into the active 1, $25(OH)_2D$ in either an autocrine or paracrine manner[(6)].

Vitamin D functions by binding to the vitamin D receptor (VDR), a member of nuclear hormone receptors which is widely expressed in the kidney, immune cells, osteocytes and other types of cells. VDR activated by vitamin D forms a heterodimeric complex with retinoid X receptor. This complex is recruited to the vitamin D response elements in the target genes and interacts with additional co-regulators, influencing the expression of many genes. As such, vitamin D possesses multiple functions and target organs[7].

Table (1): Summary of Vitamin D function and biological effect[8].

Function	Effect
Calcium and phosphorus homeostasis	Bone health
Cell growth and regulation	Anti-proliferation, apoptosis, cancer
Immune function	Lowered risk for Multiple sclerosis, Irritable bowel syndrome, psoriasis, *Rheumatoid arthritis.*
Renin-angiotensin regulation	Lowered risk for HF, TIIDM, HTN
Neuromuscular regulation	Muscle strength, balance

Vitamin D status in AA

Despite the high prevalence of autoimmune diseases, their etiology and pathogenesis remain not fully understood. Current observations link vitamin D deficiency to many autoimmune diseases including Alopecia areata. This suggests that vitamin D might be an environmental factor that normally participates in the control of self-tolerance[9].

Early studies of vitamin D and the immune system demonstrated Vitamin D Receptor (VDR) expression in both T and B cells. VDR expression by these cells was only immunologically functional in active, proliferating cells, suggesting an antiproliferative role for 1, $25(OH)_2D$ on these cells[10].

VDR may play a vital role in the postnatal maintenance of the hair follicle, Mesodermal papilla cells and the outer root sheath (ORS). Epidermal keratinocytes express VDR in varied degrees in correlation with the stages of the hair cycle. In both the late anagen and catagen stages there is an increase in VDR, which is associated with decreased proliferation and increased differentiation of the keratinocytes. These changes are thought to promote the progression of the hair cycle[11].

The role of vitamin D in hair might be explained by the fact that an optimal concentration of vitamin D is needed to delay the hair aging phenomenon, including hair loss. As $1,25OH_2D$/VDR promotes the ability of β-catenin to stimulate hair follicle differentiation. And the VDR activation plays an important role in the hair follicle cycle, specifically anagen initiation. Also, VDR regulates directly or indirectly the expression of genes required for hair follicle cycling[12].

Several studies demonstrated significantly lower levels of vitamin D in the patients with AA than the control group[13]. Several studies showed significantly higher

prevalence of vitamin D insufficiency in patients with AA than the control group[14].

Studies shows inconsistent results. A Turkish study supports that patients with AA had a deficiency of 25(OH)D, but there was no statistically significant difference in the serum vitamin D levels between AA patients and healthy controls. Possible explanation for that might be due to their tendency towards lower values of 25(OH)D in geographical area, they also noted that the blood samples were collected only once during the late fall and winter months[15].

Another study including 55,929 women in the Nurses' Health Study, 133 patients of AA were followed-up over 12 years. The association between estimated vitamin D status and self-reported incident AA was evaluated. No significant correlation between serum 25(OH)D levels and risk of incident AA[16].

Two systemic reviews and meta-analyses published in 2018 demonstrated that, patients with AA have a higher prevalence of vitamin D deficiency and lower vitamin D levels than the control group[2].

Moreover, several studies revealed that serum vitamin D levels significantly and inversely correlate with the severity of AA[17].

Studies also showed that serum **Fawzi et al.**[18] and tissue **Daroach et al.**[14] VDR levels were lower in AA. One study found a negative correlation of tissue VDR and extent of AA.

Taken together, the above data show a substantial link between the levels of vitamin D and AA, suggesting an important role of vitamin D in the pathogenesis of the disease. However, the mechanism underlying this relationship still has to be deciphered[14,18].

Vitamin D for treatment of AA

We may consider the use of vitamin D as a treatment for AA, Since vitamin D plays a role in the pathogenesis of the disease. The systemic use of vitamin D in the treatment of human autoimmune diseases is still under investigation though The beneficial effects of 1, $25(OH)_2D_3$ supplementation have been observed in experimental autoimmune models[19]. In the experimental autoimmune models, animals are mostly supplemented with a high dose of 1, $25(OH)_2D_3$, but in humans, this strategy may lead to hypercalcemia[19] .

A case report of 7-year-old boy with AA and reduced VDR expression who did not respond to various treatments, including topical and intralesional corticosteroids. Recovery of whom was observed by topical application of calcipotriol[20].

Narang et al conducted a prospective study, in which 22 patients with AA were treated with calcipotriol lotion 0.005% twice daily for 3 months. After 12 weeks of treatment, hair regrowth was observed in 13 (59.1%) patients. Mean period for onset of disease stabilization and hair regrowth was 4 weeks and 4.21±2.13 weeks, respectively. Among these 13 patients, $SALT_{50}$ and $SALT_{100}$ was observed in 6 (46.2%) and 2 (9%) patients, respectively. Response to treatment was significantly better in patients with lower vitamin D levels. The authors concluded that topical calcipotriol can be an alternative treatment in AA[21].

Abd-ElRaheem et al. compared the efficacy of topical calcipotriol versus oral vitamin D in alopecia areata. Finding that

Topical calcipotriol (68% improvement) was better than oral vitamin D (52%) in the treatment of mild and moderate patchy alopecia areata not more than 40% of scalp distribution[22].

Oral vitamin D may be a main supplement in treatment of alopecia areata. There is no relation between serum vitamin D and efficacy of treatment, so it is not recommended to measure vitamin D before starting treatment[22] .

In clinical application of active vitamin D, the supra physiological doses needed to modulate immune responses may elicit concomitant calcemic side effects. To overcome this limitation, hypocalcemic analogs of active vitamin D with similar immunoregulatory activity are being exploited. Calcipotriol, a vitamin D_3 analogue, which is at least 100 times less calcemic than calcitriol, has been topically used in treating psoriasis with beneficial effects[23] .

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