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ORIGINAL ARTICLE

Deficiency Pattern and Responsiveness in Clinical Settings in Discovering the Correlation between Vitamin D Analogues and Hair Growth in Alopecia Areata

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ABSTRACT

Background: Alopecia areata (AA) is an autoimmune disorder characterized by patchy hair loss, often linked to vitamin D deficiency, which plays a crucial role in the regulation of hair follicle cycling.

Objective: To evaluate the level of serum vitamin D in Alopecia areata (AA) patients, as well as the relationship between the condition's severity and the effectiveness of vitamin D analogues in these individuals.

Methods: A randomized control study was conducted using non-probability consecutive sampling, including 143 patients. The AA was diagnosed through clinical and dermoscopic features, along with the SALT score calculation. Serum vitamin D levels and baseline demographics were recorded for each patient. For one year, 0.005% calcipotriol was applied topically twice daily. Patients were followed up with every month, and a concluding SALT score was assessed at the termination of the study to evaluate treatment effectiveness. A p-value of less than 0.05 was considered significant.

Results: The mean age of the participants was 31.2 ± 8.9 years, with 58% female and 42% male. After six months, the mean SALT score dropped from 21.2 ± 5.8 at baseline to 9.7 ± 3.2. Serum vitamin D levels were low in 99 out of 143 individuals (69.2%). Using SALT50 as a metric of effectiveness, topical calcipotriol was found to be beneficial in 101 patients (70.6%) overall.

Conclusion: AA patients have considerably lower serum vitamin D levels, and its analogues can help grow more hair, significantly reducing the severity of AA.

Keywords: Alopecia areata; Calcipotriol; SALT score; Vitamin D deficiency.

INTRODUCTION

Alopecia areata (AA) is a disorder of the immune system that results in non-scarring cases of hair loss[1]. The prevalence of AA is 0.1-0.2% worldwide[2]. It can affect any portion of the body; however, the scalp is most frequently affected. Although people of all ages and genders can contract this illness, young girls are disproportionately afflicted. The most prevalent pattern is patchy alopecia; additional patterns include AA totalis, AA universalis, ophiasis, etc[3,4].

Previous investigations have indicated an association with other autoimmune illnesses, such as vitiligo, pernicious anemia, and lichen planus. Five different pathogenetic mechanisms, including those relating to genetics, immunity, and hormones, have been described. HLA linkage is suggested by a history of AA and concord in the monozygot twins [5,6]. The histologic hallmark of AA is the peribulbar lymphocytic infiltration, which is primarily made up of TH1 cells with a high CD4 to CD8 ratio. Hair follicle-derived autoantigens are infiltrated by autoreactive T lymphocytes, primarily of the CD8 and CD4 T type cells, sparing the stem cell compartment. This prevents scarring and preserves the potential for hair regeneration[7]. Due to this inflammatory milieu, hair follicles prematurely transition from the anagen phase into the telogen phase, repeating similar cycles over time[8].

Alopecia areata and other autoimmune disorders with varied prevalence have been linked to vitamin D deficiency. Lack of it results in a decrease in self-tolerance and makes a person more susceptible to autoimmune illnesses[9]. Apart from preserving calcium equilibrium, it functions as an immunomodulator by stimulating certain genes linked to immunological pathways and inhibiting others. VDR(s) (vitamin D receptor(s)), which are highly expressed in hair follicles involved in hair development and cell differentiation process, mediate the immunomodulatory activity of this hormone[10]. Alpha 1ahydroxylase, an enzyme required for the synthesis of the active form of vitamin D (vit.D3), was expressed in the matrix cells of hair follicles, indicating a potential involvement for the vitamin in hair growth[11]. The significance of vitamin D in immunological regulation, cellular differentiation, and hair formation is strengthened in alopecia associated with vitamin D-resistant rickets type 2 [12].

There are numerous ways to treat AA, such as immunosuppressive medications, cyclosporin, minoxidil, and steroids. Vitamin D analogues in different formulations have been investigated in the therapy of AA, with varying degrees of success, while taking into account the immunological and hormone-induced pathogenetic pathways. The use of more recent immunomodulators, such as vitamin D, makes sense given the same side effect profiles of steroids and other immunosuppressive medications. Since calcipotriol is frequently accessible in our setup, among other vitamin D derivatives, it was selected for evaluation in this investigation. The current study is aimed at exploring the deficiency pattern of vitamin D and the responsiveness of the vitamin D analogue (0.005% calcipotriol) and its correlation with hair growth in alopecia areata patients[13].

METHODOLOGY

In this randomized control study, patients were chosen using a non-probability sampling technique after receiving approval from the Institutional review board the study was conducted considering all ethical considerations. The study duration was August 2021 to July 2022 and took place at Niazi Medical and Dental College, Sargodha and burns and plastic surgery centre, Hayatabad, Peshawar, Pakistan. The sample size for this study was calculated based on the expected prevalence and effect size for the primary outcome of interest. Using a power of 80% ($\beta = 0.20$) and a significance level of 5% ($\alpha = 0.05$), the minimum required sample size was determined to detect a statistically significant difference. Based on these parameters, the calculated sample size for this study was 143 participants. Clinical diagnosis and dermoscopic confirmation of the AA diagnosis were made. Written consent was obtained from each patient, detailing the study's concept, cost, and potential side effects related to the understudy medications. Basic demographic information was gathered, including baseline SALT score, age, gender, disease duration, family history, and autoimmune conditions. A baseline limit of ≤20ng/dl was chosen to

indicate a deficiency in the serum vitamin D status, which was determined by taking venous blood [14]. Every patient had twice-daily topical calcipotriol (0.005%) treatment. Following them every month, the last SALT score was measured at the termination of the study (1 year), with a p-value of less than 0.05 considered significant. The number of patients who achieved SALT50, or a 50% decrease in SALT score from the baseline, was used to determine efficacy.

A tool for assessing scalp hair loss that is both subjective and quantitative is the SALT (severity of alopecia areata assessment tool). Based on surface area, the entire scalp is split into four quadrants: left temporal (18%-0.18), right temporal (18%-0.18), occipital region (24%-0.24), and vertex (40%-0.4). Each location's percentage of hair loss is recorded separately, multiplying with the proportion of scalp covering that part, and the results are added up, resembling the PASI score [15]. The participants with AA, regardless of duration, sex, and <50% scalp involvement, between the ages of 18 and 60, were included in the study.

Exclusion criteria consist of patient's age group less than 18 and more than 60, involvement of other body areas affected by AA, involvement of more than 50% of their scalp, the presence of A. totalis or A. universalis, clinical pattern suggesting a poor prognosis, such as ophiaisis, or recurrent disease, and history of using immunosuppressive or immunomodulator drugs within the previous three months are all excluded from consideration. Patients with autoimmune diseases and those who were nursing or pregnant were also not allowed.

Statistical software for social science was used to enter, classify, and analyse the data (SPSS Version 24). Age, illness duration, vitamin D status, and SALT score at the reference point and twelve months post-treatment were all computed as mean ± SD. For efficacy and gender, frequencies and percentages were computed. Patients were grouped according to their age, gender, SALT score, serum vitamin D levels, and length of illness. To determine the impact of these on the outcome, stratification was performed using a two-sided chi-square test, with P ≤0.05 serving as the threshold for statistical significance. Groups of ≤30 and >30, ≤20 and >20, ≤6 months and >6 months, and ≤20 and >20 were created based on age, serum vitamin D levels period, and SALT scores, respectively. Tables are used to summarize the results.

RESULTS

This study included n=143 instances of AA. Table 1 displays the fundamental clinical and demographic characteristics of the research cohort. The average age of the patients was 31.2±8.9 years, and the average duration of the disease was 6.3±3.7 months. Among the participants, 60 (42%) were men, and 83 (58%) were women. The baseline mean SALT score was 21.2±5.8. After six months of treatment, this score significantly decreased to 9.7±3.2 (p-value <0.0001), indicating a notable improvement in the severity of AA. The mean serum vitamin D level was 23.1±9.9 ng/dl, and 99 (69.2%) patients were found to have a vitamin D deficiency (Table 1).

Table 2 presents the efficacy of calcipotriol treatment concerning various variables. The overall efficacy of the treatment was observed in 101 (70.6%) patients, and patients with higher baseline SALT scores showed more improvement in hair growth (p-value = 0.0400). Age, gender, and the duration of the illness did not have a significant impact on hair growth. In patients aged ≤30 years, 70 (49.0%) showed efficacy compared to 32 (22.4%) patients aged >30 years. Similarly, 50 (35.0%) males and 52 (36.4%) females responded to the treatment. In terms of disease duration, patients with ≤6 months showed efficacy in 72 (50.3%) cases compared to 30 (21.0%) in those with >6 months. Additionally, the efficacy was higher in patients with vitamin D deficiency (73.7%) but was not significantly different from those with normal vitamin D levels (p-value = 0.3300) (Table 2).

The distribution of vitamin D levels among the patients is detailed in Table 3. Of the 143 patients, 99 (69.2%) had vitamin D levels <20 ng/dl, indicating a deficiency, while 44 (30.8%) had vitamin D levels ≥20 ng/dl.

Table 4 presents the severity of AA and its correlation with vitamin D levels. In patients with a SALT score ≤20, 34 (23.8%) had vitamin D deficiency, and 16 (11.2%) had sufficient vitamin D levels. For those with a SALT score >20, 65 (45.5%) were vitamin D deficient, and 28 (19.6%) had sufficient vitamin D levels, suggesting a possible correlation between higher severity of AA and vitamin D deficiency.

Table 1: Demographic Characteristics and Relevant Data

Parameter	n (%)
Number of participants	143 (100%)
Age distribution	
≤30 years	85 (59.4%)
>30 years	58 (40.6%)
Duration distribution	
≤6 months	91 (63.6%)
>6 months	52 (36.4%)
Gender	
Male	60 (42.0%)
Female	83 (58.0%)
Mean SALT score distribution	
≤20	50 (35.0%)
>20	93 (65.0%)
Vitamin D distribution	
<20 ng/dl	99 (69.2%)
≥20 ng/dl	44 (30.8%)

Table 2: Effectiveness of vitamin D analog to different Variables

Group	Effectiveness Yes n(%)	Effectiveness No n(%)	p-value
Age (years)			0.3500
≤30	70 (49.0%)	15 (10.5%)	
>30	32 (22.4%)	26 (18.1%)	
Gender			0.9500
Male	50 (35.0%)	10 (7.0%)	
Female	52 (36.4%)	33 (23.1%)	
Duration in months			0.8000
≤6	72 (50.3%)	19 (13.3%)	
>6	30 (21.0%)	24 (16.8%)	
Baseline SALT score			0.0400
≤20	36 (25.2%)	14 (9.8%)	
>20	66 (46.2%)	29 (20.3%)	
Vitamin D levels			0.3300
<20 ng/dl	73 (51.0%)	26 (18.2%)	
≥20 ng/dl	29 (20.3%)	17 (11.9%)	
Patients achieving SALT50 after 12 months	101 (70.6%)	42 (29.4%)	

Table 3: Percentage of Patients with Vitamin D Deficiency

Vitamin D Level (ng/dl)	Number of Patients n (%)
<20	99 (69.2%)
≥20	44 (30.8%)

Table 4: Severity of AA) and Correlation with Vitamin D Levels

SALT Score	Vitamin D Deficiency	Number of Patients n (%)
≤20	Deficient (<20 ng/dl)	34 (23.8%)
	Sufficient (≥20 ng/dl)	16 (11.2%)
>20	Deficient (<20 ng/dl)	65 (45.5%)
	Sufficient (≥20 ng/dl)	28 (19.6%)

Table 5: Efficacy of Calcipotriol in Patients with Different Vitamin D Levels

Vitamin D Level (ng/dl)	Patients Showing Efficacy n (%)
Deficient (<20 ng/dl)	73 (73.7%)
Sufficient (≥20 ng/dl)	29 (65.9%)

The efficacy of calcipotriol in patients with varying vitamin D levels is summarized in Table 5. Among the patients with vitamin D deficiency (<20 ng/dl), 73 (73.7%) showed improvement with calcipotriol treatment. Meanwhile, among patients with sufficient vitamin D levels (≥20 ng/dl), 29 (65.9%) showed efficacy. Although the efficacy was higher in the vitamin D-deficient group, the difference was not statistically significant (p-value = 0.3300). Only

3% of patients experienced side effects such as erythema, irritation, and a burning sensation in the treated areas, indicating that the treatment was generally well-tolerated.

DISCUSSION

Alopecia areata (AA) is an inflammatory disease that typically has an erratic course and results in hair loss without scarring[16]. Typically, young girls are involved. Hormone imbalances, immunological dysregulation, and genetics are the fundamental pathogenetic pathways[17].

There have been reports of vitamin D insufficiency in AA and other autoimmune illnesses. It makes sense to treat AA with vitamin D3 analogues because one of vitamin D's major biological actions is to regulate cellular turnover, which maintains follicular growth[18].

In this study, 69.2% of the 143 patients were vitamin D deficient, and 65.0% of them had a SALT score of 20 or higher (p-value = 0.0400). Comparably, the total efficacy of calcipotriol was 70.6%, primarily among vitamin D-deficient individuals (73.7%), although the difference was not statistically significant when compared to individuals with normal vitamin D levels (p-value = 0.3300). The higher proportion of female patients (58%) may be attributed to the fact that women seek medical attention more frequently and are more aware of cosmetic concerns. On the other hand, some research has revealed that AA was predominantly male[19].

A case-control study conducted in Istanbul with 86 patients with AA and 58 healthy people supports our findings. Most of them had the multi-patch type of alopecia. The average age was 32.21±9.60 years. Serum vitamin D levels in AA patients were lower than in healthy controls (p-value <0.001), and they correlated negatively with the SALT score (p ≤0.001)[20].

Significantly decreased serum vitamin D levels were seen in AA patients compared to controls in another study conducted by Ghafoor R et al. (p≤0.001). Out of all AA patients, at 23.77±8.86 ng/dl, 40% of the participants were male, and 60% were female. In line with our study, half of the patients had an illness duration of three to twelve months at presentation. Similarly, the results of this investigation indicated a negative relationship between the SALT score and serum vitamin D levels[21].

In India, 100 AA patients and 100 matched controls were the subjects of a retrospective investigation. With a mean age of 24.52±10.06 years, the patients were mostly male. In general, older individuals were more often involved, with the mean value of vitamin D levels in serum in 64% of AA patients being lower than in controls (p-value <0.001). The SALT score and vitamin D levels showed a similar correlation (p <0.05) to our study[22].

The majority of patients in the prospective analysis of 22 AA patients by Narang et al.. had low vitamin D levels. For three months, the patients were administered calcipotriol lotion twice a day. In 59% of patients, hair growth returned to normal, and efficacy was inversely correlated with serum vitamin D levels (p≤ 0.009)[23].

El Taieb, MA, and others included 60 patients in a randomized control experiment and split them into four groups: placebo, calcipotriol, narrowband UVB, and a combination of both. After three months, the SALT scores of all patients—aside from the placebo group—showed a significant decline (p≤0.026, 0.005, 0.004, and 0.140, respectively). However, combination therapy did not outperform individual treatment options[24].

Molinelli et al. studied 35 patients, of whom 46% were male and 54% were female. The patient's scalp was separated into the left and right hemispheres. One side of the patient received a 0.005% calcitriol ointment, while the other received a twice-daily 0.05% clobetasol propionate ointment for three months. While hair regrowth was seen on both sides, it was more pronounced in the areas treated with calcipotriol (p-value = 0.814), and the adverse effect profile was also reduced. Similarly, patients were monitored for a full year; however, although not statistically significant, relapse rates were reduced in the calcipotriol group (p-value = 0.306) [25].

An Indian study assessed the effectiveness of a combination of clobetasol and calcipotriol in individuals with AA. Two groups of sixty patients in total were randomly assigned. In both groups, the baseline SALT score, age, and gender were similar. While one group employed a mixture of 0.005% calcipotriol and 0.05% clobetasol, the other group utilized clobetasol by itself with comparable results. All patients showed significant improvement at the 6-month mark, with the combination side showing the greatest improvement (p = 0.05). In a similar vein, the vitamin D levels of every patient were lower. Although the vitamin D shortage in AA patients was validated by our investigation, no long-term follow-up was conducted to determine whether correcting blood vitamin D levels affected reversing hair growth. In this aspect, more research is required[26].

CONCLUSION

Our study revealed a correlation between vitamin D insufficiency and AA, with the degree of the correlation being inversely related to serum vitamin D levels. Vitamin D analogues are also more successful in helping people with vitamin D deficiency achieve hair regrowth.

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Conflict of Interest: The authors declare that they have no competing interests relevant to this study.

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Authors' Contributions:

- AA conceptualized the study, supervised the project, and drafted the manuscript.
- NK contributed to the study design, data acquisition, and statistical analysis.
- AJ provided critical revisions and expert insights in dermatology.
- MI was involved in patient recruitment and data collection.
- SA contributed to pharmacological assessments and literature review.
- NL assisted in data interpretation and final manuscript preparation.

All authors reviewed and approved the final version of the manuscript.

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