Serum vitamin D levels in alopecia areata: a case-control study

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Background and Aim: Alopecia areata (AA) is a chronic, autoimmune disease that causes non-scarring hair loss. Recently, serum vitamin D has been implicated in the etiopathogenesis of AA due to its immunoregulatory effects. Its deficiency can cause a loss of self-tolerance and predispose individuals to autoimmune diseases. This study compared the serum vitamin D levels between AA cases and controls. We aimed to compare the serum levels of vitamin D between AA patients and age and sex-matched healthy controls and to elucidate any correlation between AA and vitamin D serum levels in terms of disease pattern, severity, and extent.

Methods: A case group comprising 25 AA patients and a second group of 25 healthy controls of 10 years of age or older were involved in the study. A detailed history was taken, along with a complete clinical examination. Serum vitamin D levels were measured and compared between the groups.

Results: The mean level of vitamin D in cases (17.15 ± 5.01 ng/ml) was significantly lower as compared to controls (34.58 ± 20.83 ng/ml) ($P < 0.001$). The duration, pattern, and severity of AA had no significant relationship with patients' serum vitamin D levels.

Conclusion: We demonstrated a statistically significant variation in serum vitamin D between controls and cases, with lower values in patients. Our findings indicate a possible cause-and-effect relationship between low serum vitamin D and AA, which needs further exploration.

Keywords: alopecia areata, vitamin D, non-cicatricial alopecia

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INTRODUCTION

Alopecia areata (AA) is a non-cicatricial alopecia of autoimmune etiology. Various factors have been implicated in the etiopathogenesis of AA. Due to its immunomodulatory properties, vitamin D has been associated with AA and other autoimmune disorders. The current literature shows that vitamin D receptors are present in hair follicles. These receptors and their expression are responsible for maintaining a normal hair cycle [1]. The human body acquires vitamin D from dietary sources or direct synthesis by epidermal keratinocytes on exposure to UV rays [2]. It acts as a pro-hormone modulating the immune responses of B as well as T lymphocytes [3],

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so its role in the etiopathogenesis of AA has been emphasized repeatedly in recent studies [4-6]. Due to the scarcity of related data among Indian residents, we conducted this study to determine patients' serum vitamin D levels and compared them with the corresponding levels in controls.

METHODS

We carried out a case-control study, including patients suffering from AA attending the Dermatology Outpatient Department at Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, India, from June 2018 to April 2019. The study population comprised 50 patients (25 cases of AA and 25 healthy sex and age-matched controls) after assessing their eligibility according to specific selection criteria.

Our inclusion criteria deemed eligible patients ranging from 10 to 60 years of age diagnosed with AA of different severity and duration based on clinical features and dermoscopic examination. Controls were the attendants of patients visiting the hospital, matched in terms of age and sex before enrollment into the study. Excluded were patients with other dermatological disorders; known cases of anemia, atopy, diabetes mellitus, chronic liver or renal disease, thyroid disorders, or any known autoimmune disorder; patients presenting with other causes of hair loss like telogen effluvium, androgenic alopecia, female pattern hair loss, and scarring alopecia; patients on any oral or topical medications during the past month like vitamin D supplements, immunosuppressants, or topical vitamin D analogs; females who were pregnant or lactating; and individuals with a body mass index (BMI) > 25 kg/m^2.

Data collection

First, proper well-explained consent was taken from all study subjects. Then, a detailed history was obtained, including the present illness, the duration, site, and number of patches, personal history, and treatment history. Family history with respect to AA or other skin or systemic disorders affecting serum vitamin D levels was also taken.

A physical and dermatological examination and a dermoscopy were done to diagnose AA. The Severity of Alopecia Tool (SALT) score, ranging from 0 to 100, was calculated and classified for the clinical assessment of the degree of AA [7]. Cases were classified into five subclasses: S1 to S5 [8]:

- S1- Mild: patients with less than 25% hair loss.
- S2- Moderate: patients having 25-49% involved area.
- S3, S4 and S5- Severe: patients with > 50% hair loss.

Depending on the pattern of disease, AA patients were classified into:

- Patchy AA: single or multiple patches.
- Alopecia totalis: complete scalp hair loss.
- Alopecia universalis: complete hair loss on the whole body (including the scalp).

Analysis of serum vitamin D (25-hydroxyvitamin D) levels

After overnight fasting, 5 ml of venous blood was withdrawn from both cases and controls, followed by immediate processing of samples by centrifugation (at 4000 rpm at room temperature). A chemiluminescence kit (Siemens USA) was used to analyze plasma levels of 25-hydroxyvitamin D as per the manufacturer's protocol using a Siemens ADVIA Centaur Analyzer. The interpretation of the results was as follows:

- < 10 ng/ml: deficient
- 10-30 ng/ml: insufficient
- > 30 ng/ml: sufficient

Statistical analysis

Microsoft Excel and SPSS version 25.0 were used to tabulate and analyze data. The unpaired *t*-test was applied to measure the statistical difference in mean values among cases and controls. Spearman's correlation was used to measure any correlations between serum vitamin D levels and the disease severity or pattern. P values of less than 0.001 and 0.05 were considered highly significant and significant, respectively.

Ethical consideration

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

The violation of the Ethical Statement rules may result in severe consequences.

I agree with the above statements and declare that this submission follows the policies outlined in the Guide for Authors and in the Ethical Statement (Ethics code- IEC-997).

RESULTS

The mean age of presentation of AA was 27.64 years. Notably, 68% of the study population comprised males, while only 32% were females (sex ratio-2.125:1). Most patients were in the 21 to 30 age group. The most common clinical presentation was patchy AA in 88% of cases. Most (52%) AA patients had 1 to 2 patches, with the scalp being the most commonly affected site in 68%. The mean duration of the disease was 9.5 months. The majority of patients (56%) had AA for six months or less (Tables 1 and 2).

The mean serum vitamin D level of cases (17.15 ± 5.01 ng/ml) was markedly lower as compared to the controls (34.58 ± 20.83 ng/ml; $P < 0.001$), with the majority of cases (92%) having insufficient levels of vitamin D. Males had relatively higher serum values of vitamin D compared to females in both case and control groups, but only the case group had statistically significant results ($P < 0.001$). Serum Vitamin D levels negatively correlated with the disease duration, pattern, severity, and nail changes, but the results were not statistically significant (Table 3).

Table 2. Medical history of patients

Disease Characteristic	Value
Duration	
Mean	9.51 ± 8.89 m
Range	7 d to 36 m
Severity	Number of cases (n)
S1 (mild)	20 (80%)
S2 (moderate)	2 (8%)
S3+S4+S5 (severe)	3 (12%)
Pattern	
1-2 patches	13 (52%)
3- 4 patches	4 (16%)
5-10 patches	5 (20%)
AT	1 (4%)
AU	2 (8%)
Recurrence	
Present	17 (68%)
Absent	8 (32%)
Nail Changes	
Present	8 (32%)
Absent	17 (68%)

Abbreviations: AT, alopecia totalis, AU, alopecia universalis; d, days; m, months; n, number;

DISCUSSION

Alopecia areata (AA) is a chronic inflammatory disorder commonly encountered by dermatologists. The frequency of AA patients in the dermatology outpatient department ranges from 0.7–3.8% [9]. A variety of clinical patterns ranging from reversible patchy hair loss to complete scalp and body hair loss are seen at our hospital (and its clinics), which is a tertiary care center for dermatological disorders.

Several hypotheses have been proposed to explain the etiology of AA, which remains unclear. Episodic breakouts of AA have been reported in schools and orphanages, which points to an infectious cause. Initially, the etiology was considered viral, but further research could not corroborate it. A genetic or inherited cause of AA is supported by an increased incidence of disease in monozygotic twins or the presence of family history in cases of AA across multiple generations. Along with genetic susceptibility, various other triggering factors may be implicated in the disease pathogenesis, like infections, stress, diet, hormones, and vaccinations. Current data suggests an autoimmune etiology; the coexistence of AA with

Table 1. Demographic data of the case and control groups

Group	Age range	Mean age	Gender distribution	Average BMI (kg/m^2)
Case	12–48	27.64 ± 9.83	M: 17, F: 8	22.63 ± 1.35
Control	17–47	28.56 ± 7.95	M: 17, F: 8	22.45 ± 1.56
P-value		0.718	1.000	0.671
Significance		Not significant	Not significant	Not significant

Abbreviations: BMI, body mass index; F, females; M, males

Table 3. Serum vitamin D levels and other factors

Variable	Mean value (ng/ml)	*P*-value and correlation	Significance
Mean serum vitamin D level			
Cases	17.15 ± 5.01	$P < 0.001$	Highly significant
Controls	34.58 ± 20.83		
Serum vitamin D and gender			
Cases			
Male	19.78 ± 3.47	$P < 0.001$	Highly significant
Female	11.55 ± 2.41		
Controls			
Male	38.87 ± 22.18	$P = 0.136$	Not significant
Female	25.47 ± 14.95		
Mean serum vitamin D and disease duration			
0-6 months	16.98 ± 5.40		
6-12 months	19.33 ± 5.08	$P = 0.709$, $\rho = -0.078$	Not significant
12-40 months	15.33 ± 3.85		
Mean serum vitamin D and disease pattern			
Patchy AA	17.63 ± 4.92		
AT	16.17	$P = 0.075$, $\rho = -0.362$	Not significant
AU	12.30 ± 6.31		
Mean serum vitamin D and disease severity			
Mild	17.78 ± 5.14		
Moderate	16.18 ± 1.50	$P = 0.230$, $\rho = -0.249$	Not significant
Severe	13.59 ± 5.01		
Mean serum vitamin D and nail changes			
Present	15.89 ± 4.67	$P = 0.400$	Not significant
Absent	17.74 ± 5.19		

Abbreviations: AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis

other autoimmune disorders like psoriasis, vitiligo, anemia, thyroid disease, and diabetes mellitus supports this hypothesis [10].

Recent studies have demonstrated the immunomodulatory effects of vitamin D. It was reported that 1,25(OH)2D3 plays an essential role in the biology of the hair follicle [11]. Expression of the vitamin D receptor (VDR) is required for the normal development of hair follicles as it is necessary for hair follicle cycling, and its deficiency can also inhibit the differentiation of keratinocytes [12]. Therefore, in our study, we sought to assess the serum levels of vitamin D in AA patients and healthy controls. The mean serum vitamin D in cases (17.15 ng/ml) was markedly lower than in controls (34.58 ng/ml). Statistically, the difference was highly significant ($P < 0.001$). The results are similar to those of Bhat *et al.* [13] and Cerman *et al.* [6], in which the mean serum levels of vitamin D were significantly lower in cases compared with controls. However, Erpolat *et al.* [14] found contrasting results.

We found a statistically significant variation in Serum vitamin D levels according to gender in cases ($P < 0.001$) but not in patients in the control group ($P = 0.136$). Males had relatively higher serum values of vitamin D than females. This may be because most female participants were housewives, while most males were farmers who were highly exposed to sunlight. These findings are in accordance with the study by Cerman *et al.* [6], in which lower serum vitamin D levels were observed in females of both cases and controls. Contrasting results were reported by Bhat *et al.* [13], where no significant difference in serum vitamin D levels of males and females with AA was found.

We found no significant correlation between serum vitamin D levels and AA duration ($P = 0.709$). This finding agrees with the study of Rehman *et al.* [15], though Daroach *et al.* [16] reported an inverse correlation between serum vitamin D levels and disease duration.

There was an insignificant variation in serum vitamin D along with the clinical pattern of the disease (Table 3). The levels showed a gradual decline as the disease pattern progressed from patchy AA to alopecia universalis, with mean values of 17.63

ng/ml and 12.305 ng/ml, respectively. However, no significant correlation was found between vitamin D levels and the AA pattern ($P = 0.075$), which may be attributed to the small sample size. Similar findings were reported by D'Ovidio *et al.* [17] and Mahamid *et al.* [18]. However, Bakry *et al.* [19] found a significant correlation between vitamin D levels and AA patterns.

We compared the variation of vitamin D with AA severity (Table 3). The severity of alopecia was determined according to the SALT score. Serum vitamin D levels showed no significant correlation with the severity of AA ($P = 0.230$). Nonetheless, maximum serum levels of vitamin D (17.78 ng/ml) were present in patients with mild disease, while minimum levels (13.59 ng/ml) were seen in patients with severe disease. Our results are in accordance with the study conducted by Yilmaz *et al.* [11], which elucidated no significant correlation between vitamin D levels and AA severity. However, differing results were reported by Cerman *et al.* [6] and Ghafoor *et al.* [5].

CONCLUSION

We selected 25 cases of AA and 25 healthy controls (sex and age-matched) and compared the serum vitamin D levels of the two groups. Vitamin D levels were markedly lower in cases than in controls. However, no significant correlation existed between serum vitamin D and AA pattern, duration, or severity. These findings indicate a possible cause-and-effect relationship between vitamin D and AA, which needs further exploration. Our study emphasizes the need for a more comprehensive approach to understanding the relationship between vitamin D and AA and exploring the possibility of the therapeutic role of vitamin D in AA.

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Authors' contributions

All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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