Evaluation of Association of Vitamin D in Alopecia Areata: A Case–control Study of 100 Patients in a Tertiary Rural Hospital of Southern India

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Abstract

Background: Alopecia areata is a common autoimmune disorder which is characterized by non-scarring hair loss. Vitamin D plays an important role in immune regulation, cell growth, differentiation, and maintenance of hair cycle. **Aims and Objectives:** (1) To evaluate serum vitamin D levels in alopecia areata. (2) To compare serum vitamin D levels in new versus old cases and with respect to severity of alopecia areata. **Materials and Methods:** A retrospective case–control study with 100 cases of alopecia areata and 100 age- and sex-matched healthy controls was conducted from December 2014 to November 2015. All subjects underwent complete clinical evaluation and serum vitamin D levels. **Results:** The mean serum vitamin D level was significantly lower in patients with alopecia areata (18.90 ± 8.32 ng/mL) (64%) as compared to healthy controls (28.21 ± 18.32 ng/mL) (38%) ($P < 0.001$). The mean serum vitamin D levels was significantly lower in old cases (15.11 ± 4.75 ng/mL) as compared to new cases (20.85 ± 9.09 ng/mL) ($P < 0.001$). The proportion of subects with vitamin D deficiency was significantly higher among old cases (84.3%) as compared to new cases (53.1%) ($P < 0.05$). There was a significant inverse correlation between Severity of Alopecia Tool scores and serum vitamin D levels ($r = -0.298$, $P < 0.05$). **Conclusion:** Decreased vitamin D levels were observed in patients with alopecia areata and significant inverse correlation exists between vitamin D levels and duration/severity of the disease. These findings may suggest a causal role of vitamin D deficiency in the pathogenesis and therapeutic role of vitamin D supplementation in the management of alopecia areata.

Keywords: *Eosinophils, granuloma annulare, plasma cells, vasculitis*

Introduction

Alopecia areata is a type of non-scarring alopecia involving the hairs of scalp and/or body.[1] It is a common condition, accounting for around 0.7% of new dermatology cases in India.[2] Alopecia areata can be associated with significant psychosocial implications in the patient owing to the cosmetic disfigurement associated with it. It is an autoimmune disease characterized by T-cell (CD4+ and CD8+) infiltrates and cytokine production specifically targeting anagen-stage hair follicles.[3]

Vitamin D functions as a pro-hormone, primarily synthesized in epidermal keratinocytes under the influence of ultraviolet radiation or acquired from diet.[4,5] It acts as a modulator of immune functions of T lymphocytes and B lymphocytes.[6]

It has been demonstrated that vitamin D receptors are strongly expressed in the key structures of hair follicles and its expression is necessary for the maintenance of normal hair cycle.[7] Hence, we hypothesized that vitamin D deficiency may be a risk factor for development of alopecia areata.j

Materials and Methods

The study was a retrospective case–control study involving 100 cases of alopecia areata and 100 healthy controls conducted from December 2014 to November 2015. The cases and controls were recruited from the outpatient department of dermatology, venereology, and leprology of a medical college and hospital located in rural part of Bengaluru district of Southern India. Ethical clearance for the study was taken from the Institutional Ethics Committee.

All cases and controls were enrolled from February to July, during the months of spring and summer in India. The amount of sun radiations reaching the surface is almost the same in these months.[8]

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How to cite this article: Siddappa H, Kumar YH, Vivekananda N. Evaluation of association of vitamin D in alopecia areata: A case–control study of 100 patients in a tertiary rural hospital of Southern India. Indian Dermatol Online J 2019;10:45-9.

Received: March, 2018. **Accepted:** July, 2018.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_84_18

Quick Response Code:

Patients with alopecia areata belonging to any age group or gender were included. Patients with other types of alopecia (such as tinea capitis, androgenetic alopecia, trichotillomania, scarring alopecia, traction alopecia, telogen effluvium), other coexisting chronic dermatological disease (such as psoriasis, vitiligo), autoimmune or systemic diseases (such as diabetes mellitus, anemia, hypo/hyperthyroidism, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, chronic renal disease, chronic liver disease), and patients who have recieved systemic corticosteroids, immunosuppressive drugs , calcium or vitamin D supplements in the past 4 weeks or phototherapy in the past 3 months were excluded.

Diagnosis of alopecia areata was based on clinical findings. In doubtful cases, histopathological examination (perifollicular lymphocytic infiltration)[1] and trichoscopy (to look for exclamation mark hairs, coudability, yellow dots, black dots, short vellus hairs)[1] were performed. Severity of Alopecia Tool (SALT) score was calculated by dividing the entire scalp into four parts based on the surface area, top (40% – 0.4), posterior (24% – 0.24), right side (18% – 0.18), and left side of scalp (18% – 0.18). The percentage of hair loss in each area was determined independently and was multiplied by the factor mentioned above for each of the four areas and summing the products of each area will give the SALT score and they were divided as S0 (no hair loss), S1 (<25%), S2 (25%–49%), S3 (50%–74%), S4 (75%–99%), and S5 (100%).[9]

Patients were categorized into two subgroups – new cases and old cases. New cases were defined as patients presenting with first episode of alopecia areata and a disease duration lasting less than 6 months. Old cases were defined as patients with first episode of alopecia areata lasting more than 6 months or patients with multiple episodes of alopecia areata.

Clinical photographs of cutaneous lesions were taken for assessment of severity of lesions after taking informed patient consent. The healthy control group consisted of 100 age- and sex-matched individuals without any history of alopecia areata or other autoimmune/systemic diseases. Serum vitamin D was measured through chemiluminescence immunoassay method and graded as follows: deficiency <20 ng/mL; insufficiency 20–29.99 ng/mL; normal >30 ng/mL.

Statistical analysis

The statistical software SPSS 15.0 was used for the analysis of data. Student's (two-tailed, independent) *t*-test was used to compare the quantitative parameters between two or more groups of patients. Chi-square/Fisher's exact test has been used to compare the categorical variables between two or more groups. Correlation was assessed using Spearman's correlation. *P* value <0.05 was considered to be significant and *P* value <0.001 as highly significant.

Results

A total of 100 cases and 100 controls satisfying the inclusion and exclusion criteria were included in the study. Baseline clinical characteristics of cases and controls have been illustrated in Table 1. There were 72 males and 28 females (M:F -2.57:1) in the cases and 58 males and 42 females (1.38:1) in the control group. The age ranged from from 5 to 60 years in cases. The majority of the cases and controls (48) belonged–age group of 21-30 years. The mean age of the cases was 24.52 ± 10.06 years and controls was 28.96 ± 11.49 years. The most commonly involved site was scalp [Table 1].

The mean serum vitamin D levels of male cases and female cases were 18.38 ± 8.41 and 20.23 ± 8.07 ng/mL, respectively. There was no significant statistical difference in the mean serum vitamin D levels between males and females ($P > 0.05$). Positive family history was present in 4% of cases.

The mean serum vitamin D level was significantly lower in cases as compared to controls (18.90 ± 8.32 vs 28.21 ± 18.32 ng/mL; $P < 0.001$). The number of patients with serum vitamin D deficiency was significantly higher among cases than in controls (64 cases vs 38 controls; $P < 0.001$).

Table 1: Demographic and clinical data of cases and controls

	Cases (100)	Controls (100)	
Sex, *n* (%) – male	72 (72%)	58 (58%)	
Female	28 (28%)	42 (42%)	
Male:female	2.57:1	1.38:1	
Age (in years), mean age	24.52 ± 10.06	28.96 ± 11.49	
Range	5–60	3–72	
New cases, *n* (%)	66 (66%)	-	
Old cases, *n* (%)	34 (34%)	-	
Sites – scalp	63	-	
Beard	24	-	
Scalp + beard	8	-	
Scalp + eyebrow	4	-	
Saclp + beard + eyebrow	1	-	
SALT subclasses, *n* (%) – S1	75 (99%)	-	
S2	-	-	
S3	1 (1%)	-	
S4	-	-	
S5	-	-	
Mean serum vitamin D (in mg/mL)	18.90 ± 8.32	28.21 ± 18.32	
Serum vitamin D (%) – normal	10	36	
Insufficiency	26	26	
Deficiency	64	38	$P < 0.001$

SALT, Severity of Alopecia Tool

The cases were further divided into new and old cases – 66 new cases and 34 old cases. The mean serum vitamin D level in old cases was significantly lower than that of new cases (15.11 ± 4.75 vs 20.85 ± 9.09 ng/mL; $P < 0.001$). The number of patients with vitamin D deficiency was significantly higher among old cases ascompared to new cases (29/34 old cases vs 35/66 new cases; $P < 0.05$).

A total of 76 cases presented with alopecia involving scalp and they were further subclassified from S1 to S5 based on their SALT scores. Almost all the scalp alopecia cases, that is, 75 cases, belonged to subclass 1 (S1). Only one case belonged to subclass 3 (S3). When the serum vitamin D levels were plotted against their SALT score, there was a significant inverse correlation between the two. ($r = -0.298$; $P < 0.05$) [Figure 1].

Discussion

Alopecia areata is an autoimmune disease which is characterized by non-scarring hair loss and can affect any hair-bearing area of the body. It is caused by CD4+ and CD8+ T cells targeting the hair follicles as an autoimmune-mediated skin.[10]

Vitamin D is a pro-hormone which is synthesized in the skin and regulates the immune response by controlling T and B lymphocytes. Its deficiency has been established as a risk factor for autoimmune diseases such as systemic lupus erythematosus, psoriasis, vitiligo, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease.[11,12]

It is hypothesized that the development of hair follicle depends on vitamin D receptor expression which correlates with increased differentiation of follicle keratinocytes.[13] A recent study demonstrated that decreased expression of vitamin D receptor in alopecia areata lesions is related to decreased expression of Wnt signaling pathway, which inhibits proliferation and differentiation of hair follicles and epidermal cells,[14] although the exact mechanism which links serum vitamin D deficiency with alopecia areata is unknown.

Few recent studies have found decreased serum vitamin D levels in patients with alopecia areata.[6,13,15-18] Hence, this study was planned to find out the association between serum vitamin D levels and alopecia areata in South Indian population.

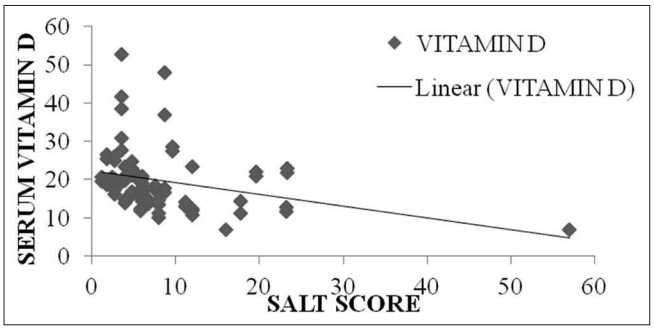

Figure 1: Correlation between serum vitamin D and SALT score

The majority of the cases were males 72%. The male: female ratio of cases in our study was 2.57:1. Similar male predominance ratio was also found by Yilmaz N *et al*.[13] (2:1), Cerman AA *et al*.[6] (1.87:1), Attawa EM *et al*.,[16] (1.87:1) and Nassiri S *et al*.[19] (2.1:1).

There was no significant difference between mean serum vitamin D levels of male cases and female cases (18.38 ± 8.41 vs 20.23 ± 8.07 ng/mL; $P > 0.05$). Even Nassiri S *et al*.[19] and Attawa EM *et al*.[16] did not find any significant difference between male and females cases.

We found a positive family history of alopecia areata in about 4% cases. However, there was no significant difference in serum vitamin D levels of patients with positive family history as compared to those without any family history of alopecia areata. El-Mongy NN *et al*.[17] and Attawa EM *et al*.[16] saw positive family history in 8.6% and 8.7%, respectively, in the cases. Even they did not find any significant difference in serum vitamin D between those with and without family history of alopecia areata.

In our study, the mean serum vitamin D level was significantly lower in cases as compared controls (18.90 ± 8.32 vs 28.21 ± 18.32 ng/mL; $P < 0.001$). Even Yilmaz N *et al*.,[13] Cerman AA *et al*.,[6] Mahamid M *et al*.,[15] Attawa EM *et al*.,[16] El-Mongy NN *et al*.,[17] and Bhat YJ *et al*.[18] found similar significant lower levels of serum vitamin D in cases as compared to controls. However, the mean serum vitamin D levels of cases in Yilmaz N *et al*.,[13] Cerman AA *et al*.,[6] Mahamid M *et al*.,[15] and Attawa EM *et al*.[16] were comparatively less when compared to our study. These variations could be due to the studies being conducted in different geographical locations. The amount of radiation reaching the surface of the earth will depend on the latitude of each geographical location which may lead to variation in the amount of serum vitamin D synthesis in the body thus affecting the average serum vitamin D level of the population [Table 2].

An analysis of the distribution of serum vitamin D deficiency among cases and controls showed a statistically significant higher percentage of vitamin D deficiency among cases than in controls (64% vs 38%; $P < 0.001$). The percentage of vitamin D deficiency in southern India was estimated to be about 40%–70%.[20] It is worthwhile to mention that various studies which have estimated vitamin D deficiency in general population have used different cut-offs to define vitamin D deficiency. Some studies have defined values less thn 35 ng/mL as deficiency.[21] Mahamid M *et al*.,[15] Cerman AA *et al*.,[6] and Yilmaz N *et al*.[13] also found that the percentage of vitamin D deficiency was significantly more among alopecia areata cases ascompared to controls.

We found that the mean serum vitamin D level was significantly lower in the old cases as compared to new

Table 2: Comparison of mean serum vitamin D levels and percentage of deficiency of vitamin D to other similar studies

Study	Mean serum vitamin D level (in ng/mL)		Deficiency of vitamin D (in %)	
	Cases	Controls	Cases	Controls
Our study	18.90 ± 8.32	28.21 ± 18.32	64	38
Yilmaz N *et al*.[15]	13.38 ± 7.09	20.51 ± 8.45	85	-
El-Mongy NN *et al*.[19]	26.6 ± 13.1	33.7 ± 22.3	-	-
Cerman AA *et al*.[8]	11.84 ± 6.18	23.57 ± 9.03	91	33
Mahamid M *et al*.[17]	11.32 ± 10.18	21.55 ± 13.62	69	25
Attawa EM *et al*.[18]	14.13 ± 8.72	22.43 ± 10.94	21.7	13
Bhat YJ *et al*.[19]	16.6 ± 5.9	25.49 ± 1.02		

cases (15.11 ± 4.75 vs 20.85 ± 9.09 ng/mL; $P < 0.001$). There was significantly higher percentage of patients with vitamin D deficiency among old cases as compared to new cases (85% in old cases vs 53% in new cases; $P < 0.05$). d'Ovidio R *et al*.[22] also found lower levels of serum vitamin D in chronic relapsing alopecia areata cases as compared to healthy controls although the difference was not statistically significant.

In addition, we found a statistically significant inverse correlation between SALT score and serum vitamin D levels ($P < 0.05$). Similarly, Cerman AA *et al*.,[6] Attawa EM *et al*.,[16] and Bhat YJ *et al*.[18] found a significant inverse correlation between SALT scores and serum vitamin D levels.

To our knowledge, this is the first case–control study among South Indian population which has evaluated the role of serum vitamin D in alopecia areata. In addition, our study was unique as we have also investigated the correlation between serum vitamin D levels and duration and severity of disease (SALT score). This association of serum vitamin D levels with respect to alopecia areata, its duration, and severity may suggest a possible role of serum vitamin D deficiency in pathogenesis of alopecia areata. and vitamin D levels as a potential marker for disease duration and severity of alopecia areata. Further studies are required to evaluate the role of supplementing vitamin D in the treatment of alopecia areata.

Some of the limitations of the study were that there was lack of severe cases of alopecia areata and the fact that degree of sunlight exposure and dietary intake of vitamin D can also lead to variation in serum vitamin D levels.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

References

1. Seetharam KA. Alopecia areata: An update. Indian J Dermatol Venereol Leprol 2013;79:563-75.
2. Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. Int J Dermatol 1996;35:22-7.
3. McElwee KJ, Tobin DJ, Bystryn JC, King Jr LE, Sundberg JP. Alopecia areata: An autoimmune disease? Exp Dermatol 1999;8:371-9.
4. Saleh HM, Abdel Fattah NS, Hamza HT. Evaluation of serum 25- hydroxyvitamin D in vitiligo patients with and without autoimmune diseases. Photodermatol Photoimmunol Photomed 2013;29:34-40.
5. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80:1678-88.
6. Cerman AA, Solak SS and Altunay IK. Vitamin D deficiency in alopecia areata. Br J Dermatol 2014;170:1299-1304.
7. Bikle DD. Vitamin D metabolism and function in the skin. Mol Cell Endocrinol 2011;347:80-9.
8. Heidari B, Haji Mirghassemi MB. Seasonal variations in serum vitamin D according to age and sex. Caspian J Int Med 2012;3:535-40.
9. Olsen EA, Hordinsky MK, Price VH, Roberts JL, Shapiro J, Canfield D, *et al*. National Alopecia Areata Foundation. Alopecia areata investigational assessment guidelines. Part II. National Alopecia Areata Foundatin. J Am Acad Dermatol 2004;51:440-7.
10. Abdel Hafez HZ, Mahran AM, Hofny EM, Attallah DA, Sayed DS, *et al*. Alopecia areata is not associated with *Helicobacter pylori*. Indian J Dermatol 2009;54:17-9.
11. Hewison M. An update on vitamin D and human immunity. Clin Endocrinol 2012;76:315-25.
12. Ersoy-Evans S. Commentary: Vitamin D and autoimmunity: Is there an association? J Am Acad Dermatol 2010;62:942-4.
13. Yilmaz N, Serarslan G, Gokce C. Vitamin D concentrations are decreased in patients with alopecia areata. Vitam Trace Elem 2012;1:105-9.
14. Lim YY, Kim SY, Kim HM, Li KS, Kim MN, Park KC, *et al*. Potential relationship between the canonical Wnt signaling pathway and expression of the vitamin D receptor in alopecia. Clin Exp Dermatol 2014;39:368-75.
15. Mahamid M, Abu-Elhija O, Samamra M, Mahamid A, Nseir W. Association between Vitamin D levels and Alopecia Areata. Isr Med Assoc J 2014;16:367-70.
16. Attawa EM, Kandil AH, Elbalaat W, Samy AM. Assessment of vitamin D level in patients of alopecia areata. J Clin Investigat Dermatol 2016;4:1-4.
17. El-Mongy NN, El-Nabarawy E, Hassaan SA, Younis ER, Shaker O. Serum 25-hydroxy vitamin D3 level in Egyptian patients with alopecia areata. J Egypt Dermatol Soc 2013;10:37-41.
18. Bhat YJ, Latif I, Malik R, Hassan I, Sheikh G, Lone KS, *et al*. Vitamin D level in alopecia areata. Indian J Dermatol 2017;62:407-10.

19. Nassiri S, Saffarian Z and Younespour S. Association of vitamin D level with alopecia areata. Iran J Dermatol 2013;16:1-5.
20. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, *et al*. High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians. Am J Clin Nutr 2007;85:1062-7.
21. Rosen AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al*. The 2011 Report on dietary reference intakes for calcium and vitamin d from the institute of medicine: What clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.
22. d'Ovidio R, Vessio M, d'Ovidio FD. Reduced level of 25-hydroxyvitamin D in chronic/relapsing alopecia areata. Dermatoendocrinol 2013; 5:271-3.