

# Deficiency in alopecia areata and responsiveness to vitamin D analogues: A prospective trial

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## Abstract

**Objective** To assess serum Vitamin D status in patients with alopecia areata (AA), its correlation with AA severity and efficacy of vitamin D3 analogues in such patients.

**Methods** It was a randomized control trial. A total of 100 patients were selected using non-probability consecutive sampling technique. Diagnosis of alopecia areata was confirmed on clinical and dermoscopic features and severity of alopecia areata score (SALT) calculated. Serum Vitamin D levels were assessed in all patients along with basic demographic data. All patients received topical calcipotriol (0.005%) twice a day for 6 months. Patients were called for monthly follow-up and final SALT score was calculated at the end of 6 months to assess the efficacy. P-value <0.05 was taken as significant.

**Results** There were 100 cases of AA in total. The mean age was 30.5 ±8.4 with 42% male and 58% females. The mean SALT score at baseline was 20.7±5.4 and at the end of six months it decreased to 9.4±3.5s. Out of 100 patients 69 had low serum vit. D levels. Topical calcipotriol was effective in overall 71% patients using SALT<sub>50</sub> as a measure of efficacy.

**Conclusion:** It is concluded that Serum Vitamin D levels are lower significantly in patients with alopecia areata and vit. D3 analogues are effective in improving hair growth in such patients.

## Key words

Alopecia areata; Vit. D deficiency; Calcipotriol; SALT score.

## Introduction

Alopecia areata (AA) is an immune mediated disease causing non-scarring hair loss.<sup>1</sup> Worldwide its incidence is 0.1-0.2%.<sup>2</sup> All body parts can be involved, but scalp being the most common site. Both genders and all age groups

can suffer from this disease but young females are commonly affected.<sup>3</sup> Patchy alopecia is the most common pattern, other include AA totalis, AA univaersalis and ophiasis ect.<sup>4</sup> Association with other autoimmune diseases like lichen planus, vitiligo, pernicious anemia, has been reported in previous studies.<sup>5</sup> Various pathogenetic mechanism have been described including Genetic, immune related and hormonal. Positive family history and concordance in monozygotic twins' points towards HLA linkage.<sup>6</sup> Peribulbar lymphocytic infiltrate, being the histologic hallmark of AA, is predominantly composed of TH<sub>1</sub> cells with high CD4 to CD8 ratio. Autoreactive T lymphocytes

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mostly of CD8 and CD4 T type cells infiltrate hair follicle derived autoantigens while sparing the stem cell compartment, that's why no scarring occurs and the possibility of hair regrowth persists.<sup>7</sup> This inflammatory environment causes hair follicles to enter prematurely into telogen from anagen phase with similar cycles repeated over time.<sup>8</sup> Vitamin D deficiency has been reported in alopecia areata and other autoimmune diseases with variable prevalence. Its deficiency causes loss of self-tolerance and predispose individual to autoimmune diseases.<sup>9</sup> In addition to maintenance of calcium homeostasis, it acts as an immunomodulator, inducing some genes involved in immune pathways while suppressing other. The immunomodulatory action of this hormone is mediated via VDR (vitamin D receptors) that are strongly expressed in hair follicles involved in hair growth and cellular differentiation.<sup>10</sup> The matrix cells of hair follicles showed expression of alpha 1-hydroxylase, the enzyme necessary for synthesizing active form of vitamin D(vit.D3) suggesting its role in hair growth.<sup>11</sup> Alopecia in vit. D resistant rickets type 2 strengthens the role of vit. D in immune modulation, cellular differentiation and hair growth.<sup>12</sup>

Various treatment options are available for alopecia areata including steroids, minoxidil, cyclosporin and other immunosuppressives.<sup>13</sup> Looking at the hormonal and immune mediated pathogenetic mechanisms, vit. D analogues in various formulation have been evaluated in the treatment of alopecia areata that showed variable results. Similarly adverse effects profile of steroids and other immunosuppressive make the use of newer immunomodulators like vit. D logical. Among other vit. D derivatives calcipotriol is commonly available in our setup, so it was chosen to be evaluated in our study.

The purpose of this study was to evaluate vit. D deficiency in AA and its analogues efficacy in

the hair regrowth.

## Material and methods

After approval from Hospital administration, Patients were selected using was non-probability sampling technique. Diagnosis of AA was done clinically and confirmed dermoscopically. Written consent taken from all patients along with full explanation of the study design, investigation cost and possible adverse effects of under study drugs. Basic demographic data like age, gender, disease duration, family history, autoimmune diseases collected and baseline SALT score calculated. Venous blood was taken to assess serum vit. D status and a cutoff point of  $\leq 20\text{ng/dl}$  was used to define deficiency.<sup>14</sup> All patients received topical calcipotriol (0.005%) twice a day on regular basis. They were followed at monthly basis and final SALT score was calculated at the end of 6 months using p value  $< 0.05$  as significant. Efficacy was assessed based on number of patients achieving SALT<sub>50</sub> (50% reduction of SALT score from the baseline).

## SALT Score

SALT (severity of alopecia areata assessment tool) is a subjective and quantitative tool for assessment of scalp hair loss. The entire scalp is divided into 4 quadrants based on the surface area, vertex (40%-0.4), occipital region (24%-0.24), right temporal (18%-0.18), and left temporal (18%-0.18). Percentage of hair loss in each area is noted independently and is multiplied by the percentage of scalp covered in that area, and then summing the products of each area just like PASI score.<sup>15</sup>

**Inclusion Criteria** All patients with AA of any duration, between age 18 to 60 years, of both genders with  $< 50\%$  involvement of entire scalp).

**Exclusion Criteria** Patients of age group outside

the inclusion criteria, involvement of >50% of entire scalp, A. totalis, A. universalis, other body parts involved by the disease, clinical pattern suggesting bad prognosis like ophiasis, or recurrent disease, history of any immunosuppressive or immunomodulator use in the past three months. Pregnant/ breastfeeding patients and patients with autoimmune disease were also excluded.

**Data Collection** The data was entered, categorized and analyzed using statistical packages for social science (SPSS Version 24). Mean ± SD was calculated for age, duration of disease, vit. D levels and SALT score at baseline and 6 months after treatment. Frequencies and percentages were calculated for gender and efficacy. Patients were divided in groups by age, gender, duration of disease, serum vit. D levels and SALT score. Stratification was carried out by using two-sided chi-square test to see the impact of these on outcome with P ≤0.05 as criteria of statistical significance. Age, serum vit. D levels duration and SALT score were divided into groups of ≤30 and >30, ≤20 and >20, ≤6 months and >6months, and ≤20 and >20 respectively. Results are summarized in the form of tables and figures.

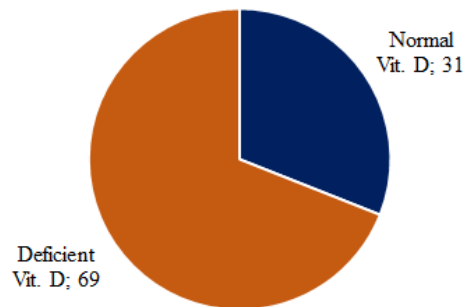
**Results**

There were 100 cases of AA in this study. The basic Demographic and clinical profile of the study population is shown in **Table 1**. The mean age and disease duration was 30.77±8.86 years and 6±3.8 months respectively. There were (42%) males and (58%) females. The baseline mean SALT was 20.7±5.4 and at the end of 6 months it was calculated to be 9.4±3.5 (p valve <0001). The mean serum vit. D level was 22.5±9.7ng/dl, with deficiency in overall 69% patients, **Figure 1**.

Among 65 patients having SALT score >20,

**Table 1** Basic demographic and relevant data.

Parameter	
Number of patients	100
Age (mean & SD)	30.5± 8.4
Age VIZ distribution	
≤30 years	59
>30 years	41
Duration (mean & SD)	6 ± 3.8
Duration viz distribution	
≤6 months	64
>6months	34
Gender	
Male	42
Female	58
SALT Score (Mean & SD)	p < 0.0001
Baseline	20.7 ± 5.4
After 6 months	9.4 ±3.5
Mean SALT score viz distribution	
≤20	35
>20	65
Mean Serum vit. D levels	22.5±9.7
Vit. D VIZ distribution	
<20ng/dl	69
>20ng/dl	31



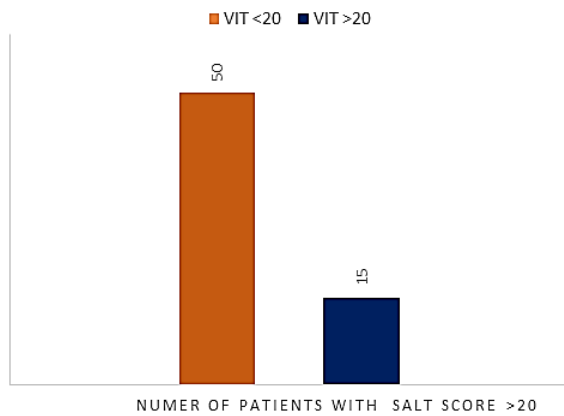
**Figure 1** Percentage of patients with vit. D deficiency levels.

76.9% were vit.D deficient (p value= 0.0198), **Figure 2**.

The overall efficacy of calcipotriol was 71%, more in vit. D deficient patients but compared to patients with normal vit.D levels, no significant difference was found (p value= 0.337), **Figure 3**. The age, diseased duration and gender had no significant effect on hair regrowth. On the other hand, greater improvement in hair growth was

**Table 2** Efficacy with respect to various variables and grouping.

Group	Efficacy		P value
	Yes	No	
Age in years	Mean & SD age 30.5± 8.4		0.3766
≤30	44	15	
>30	27	14	
Gender			1.0
Male	33	13	
Female	38	16	
Duration in months	Mean & SD 6 months±3.2		0.8144
≤6	49	19	
>6	22	10	
Baseline SALT score	Mean & SD 20.4±7.4		0.036948
≤20	20	15	
>20	51	14	
Vit. D levels	Mean & SD 22.5± 9.7		0.33707
≤20ng/dl	51	18	
>20ng/dl	20	11	
Patients achieving SALT <sub>50</sub>	Yes	No	
After 6 months	71	29	

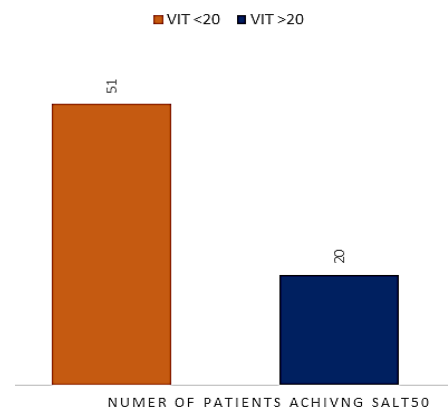


**Figure 2** Severity of AA inversely correlating with vit. D levels.

noted in patient with higher baseline SALT score (p value =0.036948). Only 3% had adverse effects like erythema, irritation and burning sensation in the treated areas.

### Discussion

Alopecia areata (AA) is an inflammatory condition causing hair loss without scarring and usually running an unpredictable course.<sup>16</sup> Young females are commonly involved. The basic pathogenetic mechanisms include genetics, immune dysregulation and hormonal disturbances.<sup>17</sup>



**Figure 3** Showing greater efficacy of calcipotriol in vit. D deficient patients.

Vit. D deficiency has been reported in AA and other autoimmune diseases. An important biological action of vitamin D is regulation of cellular turn over leading to maintenance of follicular growth, so the use of vitamin D<sub>3</sub> analogues seem logical in the treatment of AA.<sup>18</sup>

In this study 69% patients had vit. D deficiency, 65% had SALT score more than 20, most patients being in vit. D deficient category (p value=0.0198). Similarly overall efficacy of calcipotriol was 71%, mostly in vit. D deficient. The reason of greater number of female patients could be explained by the fact that females are

more conscious about their cosmetic issues and hence seek medical advice more frequently. Alternatively, some studies showed male predominance in AA.<sup>19</sup>

Our results are supported by a case control study of 86 patients of AA and 58 healthy patients carried out in Istanbul. Majority had multi patch alopecia. The mean age with SD was 32.21±9.60. As compared to healthy controls serum vit. D was deficient in AA patients (p value <0.001), with its levels correlating inversely with SALT score (p value<0.001).<sup>20</sup>

Another case control study conducted by Ghafoor R *et al.* also showed significantly lower serum vit. D levels in AA patients as compared to controls (p value=0.001).<sup>21</sup> Among all patients with AA 40% were men and 60% females with the mean age of 23.77±8.86 ng/d. Half of the patients presented with disease duration of 3-12 months comparable to our study. Similarly, this study also showed a negative correlation between serum vit. D levels and SALT score.

A retrospective study of 100 AA and 100 matched controls was conducted in India. Patients consisted predominantly of males with mean age 24.52±10.06 years. Overall, the mean serum vit. D levels were lower in 64% AA patients (P value<0.001) as compared to controls, older patients' beings frequently involved. Correlation between vit. D levels and SALT score was also comparable to our study (p value<0.05).<sup>22</sup>

A prospective study of 22 AA patients conducted by Narang *et al.* showed deficient vit. D levels in majority of patients. The patient received calcipotriol lotion twice daily for 3 months. At the end hair growth reverted to normal in 59% patients with efficacy inversely correlating to serum vit. D levels (< .009).<sup>23</sup>

El Taieb MA *et al.* Conducted a randomized control trial of 60 patients divided into 4 groups (calcipotriol, narrowband UVB, combination of both and placebo). At the end of 3 months all patients except placebo achieved significant decrease in SALT score (P=0.026, P=0.005, =0.004, P=0.140 respectively) but combination therapy was not superior to single treatment modality.<sup>24</sup>

A study of 35 patients consisting of 54 % male and 45 % females was conducted by Molinelli E *et al.* Patients scalp was divided into left and right hemispheres and Calcipotriol 0.005% ointment was applied on one side while on the other side clobetasol propionate 0.05% ointment applied applied twice daily for 3 months. Hair regrowth was observed on both sides but more in calcipotriol treated areas, although not statistically significant (p value=0.814) and with lower adverse effects profile. Similarly, patients were followed for 12 months but relapse rates were lower in calcipotriol group but not statistically significant (p value =0.306).<sup>25</sup>

An Indian study evaluated the efficacy of calcipotriol and clobetasol combination in AA patients. A total of 60 patients were randomized into 2 groups. The age, gender and baseline SALT score was comparable in both groups. One group applied 0.005% calcipotriol and 0.05% clobetasol in combination while other group used clobetasol alone with similar steingh. At the end of 6 months significant improvement was observed in all patients but more in combination side (p=0.05). Similarly, all the included patients had lower vit. D levels.<sup>26</sup>

## Conclusion

Our study showed an association between AA and vit. D deficiency, and its severity being inversely correlated with serum vit. D levels.

Similarly in achieving hair regrowth vit. D Analogues are more effective in vit. D deficient patients.

### Limitations of the study

Our study confirmed vit D deficiency in AA patients but there was no long-term follow-up to see the impact of serum vit D levels correction in reversal of hair growth. Further studies are needed in this regard.

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