ORIGINAL ARTICLE

A Prospective Case Control Study Comparing Serum Vitamin D Levels in Patients with and without Alopecia Areata

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Abstract

Background

Alopecia areata (AA) is the most common cause of non-scarring alopecia.[1] Many studies reported decreased serum vitamin D levels in patients with AA compared to healthy subjects.[1-8] This study aimed to assess the prevalence of vitamin D deficiency in patients with AA compared to patients without AA. The secondary objective was to determine the correlation between vitamin D deficiency with disease severity and the pattern of AA.

Methods

This research was a case control study involving patients with AA from the dermatology clinic in Hospital Raja Permaisuri Bainun. All the subjects and controls were age, sex and Fitzpatrick skin type matched. Serum vitamin D (25-hydroxyvitamin D) (25 OHD) levels were obtained and analysed by the chemiluminescence immunoassay method. AA severity was assessed by Severity of Alopecia Tool (SALT) score.

Results

A total of 50 subjects, out of which 25 patients with AA and 25 controls, were recruited. The median serum vitamin D level was 54.15 nmol/L (IQR 139) in the AA group and 53.79 nmol/L (IQR 64.47) in the control group. However, the difference was not statistically significant (*p=0.823*). The prevalence of vitamin D deficiency was higher in the AA group (12%) compared to the control group (4%), but it was not statistically significant (*p=0.304*). There was no statistical significance in serum vitamin D levels with disease severity (SALT score) (*p=0.171*) and pattern of AA (*p=0.657*).

Conclusion

There was no statistical difference in the prevalence of vitamin D deficiency between patients with and without AA. There was no correlation between serum vitamin D levels with disease severity and pattern of AA. Further studies using a larger sample size is needed to justify measuring serum vitamin D levels in patients with AA.

Key words: *Alopecia areata, Vitamin D, SALT score, Malaysia*

Introduction

Alopecia areata (AA) is a common form of non-scarring hair loss.[1] AA usually presents as patches of hair loss on the scalp, but it may also involve any areas of hair-bearing skin.[2] AA is an organ-specific autoimmune disease exemplified by T-cell infiltrate and cytokine production around anagen-stage hair follicles.[3] AA affects about 1-2% of the general

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population, with an estimated lifetime risk of 1.7%.[9] There is a higher prevalence in younger (21-40 years old) patients, but no significant difference in incidence exists between males and females.[10] AA can profoundly affect a patient's quality of life, resembling the degree seen in other diseases, such as psoriasis and atopic dermatitis.[11] Vitamin D is a secosteroid hormone that is vital for calcium homeostasis and bone health.[3] Vitamin D is also implicated in certain cancers, cardiovascular health and immune system.[12,13,14]

Literature data suggest that vitamin D may be involved in the pathogenesis of AA due to its immunomodulatory effects.[3,7] It has been shown that Vitamin D Receptors (VDRs) are strongly expressed in hair follicles. The lack of VDRs reduced epidermal differentiation and the growth of hair follicles.[4] Some studies reported decreased serum vitamin D levels in AA in comparison to healthy subjects.[1-8] A significant negative correlation between Severity of Alopecia Tool Score (SALT score) and serum vitamin D was found in several studies.[2,3,5,6,8] However, data concerning the correlation between vitamin D and clinical disease parameters were inconsistent.[2,15] A study by Ghafoor R *et al*.[16] showed that serum vitamin D levels were significantly lower in patients with AA than healthy controls. Yilmaz *et al.*[17], however, did not find any correlation between serum vitamin D concentrations in 42 patients with AA and the extent of hair loss, number of patches, disease duration and nail involvement. Erpolat *et al.*[18] conducted a case control study on 41 AA patients and found no statistically significant difference in the serum vitamin D levels between AA patients and healthy controls. Therefore, the vitamin D levels among patients in Malaysia with AA is not known.

The findings of our study may justify incorporating vitamin D supplements as adjunct therapy on top of the standard therapy. Our primary objective was to compare vitamin D deficiency in patients with or without AA. Secondary objectives were to assess the prevalence of vitamin D deficiency in patients with AA and determine the correlation of vitamin D deficiency with disease severity in patients with AA.

Materials and Methods

Study design and subject recruitment

This was a prospective case control study conducted at the dermatology clinic of Hospital Raja Permaisuri Bainun Ipoh, Perak, Malaysia, between the period of May 2020 and November 2020. AA patients aged 12 years old and above were recruited into the study by a convenient sampling method. Exclusion criteria included pregnancy/lactating females; patients on oral vitamin D supplementation/topical vitamin D analogues, patients with other types of alopecia (such as tinea capitis, androgenic alopecia, trichotillomania, scarring alopecia, traction alopecia, telogen effluvium), patients with BMI>25(as vitamin D deficiency was associated with obesity)[3] and patients with other systemic autoimmune diseases (e.g. vitiligo, rheumatoid arthritis, diabetes mellitus, thyroid disorder, lupus erythematosus etc.).

AA patients were interviewed to obtain demographic data, which consisted of their age, gender, ethnicity, Fitzpatrick skin phototype, education level, family history of AA, duration of the disease, presence of comorbidities, smoking and drinking habits, dietary restrictions and clothing practices.

Diagnosis of AA was based on clinical findings and dermatoscopy (to look for exclamation mark hairs, coudability, yellow dots, black dots, short vellus hair). Clinical data and clinical variables were documented. The duration of disease, site of involvement, severity assessment for scalp involvement (SALT score) and pattern of hair loss was recorded. Patients were asked to recall their 3-day diet history, which would subsequently be analysed for its vitamin D content using Nutritionist Pro™ Software of the United States Department of Agriculture (USDA) Standard Reference Database, First DataBank, Inc., San Bruno, California.

The sun exposure index (SEI) was calculated

using the formula: hours of sun exposure per week multiplied by the fraction of BSA (body surface area involvement using the Wallace Rule of Nines chart) exposed to sunlight. Subjects in the control group were selected randomly among patients and hospital staff without alopecia. The controls were matched to age, sex and Fitzpatrick skin type. Similar exclusion criteria were applied to the control group. Control subjects were assessed clinically with detailed history and thorough examination. A total of 50 subjects were recruited with 25 AA patients and 25 healthy controls into each arm, respectively.

Serum vitamin D sampling and analysis

Three millilitres (ml) of venous blood was obtained from all subjects and transferred to a Lithium Heparin tube. Samples were collected and sent to the biochemical pathology laboratory in Hospital Raja Permaisuri Bainun Ipoh. The samples were centrifuged and transported to the biochemical pathology laboratory in Hospital Putrajaya. The blood samples were analysed by chemiluminescence immunoassay method through Beckham DXI analyser to measure serum total Vitamin D (25 -hydroxyvitamin D) (25OHD) levels. Clinical decision values were defined as deficient (<25 nmol/L), insufficient (25-75 nmol/L), sufficient (76-250 nmol/L) and possible intoxication (>250 nmol/L).

Sample size calculations

The sample size of this study was calculated based on a systematic review and meta-analysis by Lee S *et al*.[15] This sample size was calculated using Power and Sample Size Calculation version 3.1.2 with alpha = 0.05 and power = 80%. The sample size calculated was 46 (i.e. 23 subjects with AA and 23 subjects in the control group).

Data analysis

The Statistical Package for Social Sciences for Windows version 22.0 (SPSS, Chicago, IL, USA) was used to perform the statistical analysis. The data normality was checked by the Shapiro-Wilk test. The computed significance levels for age, BMI, vitamin D level, vitamin D category and vitamin D intake are > 0.05). Therefore, normality cannot be assumed, and a non-parametric test was performed. The descriptive data were expressed as median and inter quarter range, or frequency and percentage. Mann- Whitney test was used for the analysis of the difference between two study group means. Because of the small sample size of SALT 4 and SALT 5, and Ophiasis, Totalis and Universalis, they were collapsed into one single group, respectively (Naidu &Baddireddy 2020).[19] Kruskal Wallis H test was used to determine the difference between the three study groups means; $p<0.05$ was considered statistically significant.

Ethical approval

This study was registered with the National Medical Research Registry (NMRR-20-41-52526). Ethical approval for the study was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

Results

Table 1 shows the demographic and clinical characteristics of subjects with AA and controls. A total of 50 subjects were recruited, with 25 AA patients and 25 healthy controls in each arm, respectively. There was no significant difference ($p>0.05$) between the two groups regarding age, sex, BMI, race, education, comorbidities, smoking habits, alcohol intake, diet, Fitzpatrick skin type, medications, family history with AA and family history of autoimmune diseases.

The median vitamin D level was slightly higher in the AA group compared to the control group, although the difference was not statistically significant (54.15 nmol/L vs 53.79 nmol/L, $p=0.823$). The median vitamin D intake was higher in the control group (7.86 mcg; IQR 34.9) compared to the AA group (6.65 mcg; IQR:44), but the difference was not statistically significant ($p=0.503$). The median SEI was higher in the AA group (220.5; IQR: 209.8) compared to the control group (146.16; IQR: 863.7) even though the difference was not statistically significant ($p=0.823$). Vitamin D deficiency was higher in the AA group (12%) compared to the control

group (4%), while vitamin D insufficiency was found in 76% of AA patients and 92% in the control group. However, the results were not statistically significant (*p=0.304*). *(Table 2)*

Table 1. Demographic characteristics and clinical characteristics of subjects with and without alopecia areata (n = 50)

Demographic	**Subject (AA) n = 25**	**Control n = 25**	*p value*
Median (IQR) or n (%) **Age (in years)**	29 (25)	29 (22)	*0.938[c]*
Sex			
Male	11 (44 %)	9 (36 %)	*0.773[b]*
Female	14 (56 %)	16 (64 %)	
BMI	23 (5.1)	22 (5.1)	*0.839[c]*
Race			
Malay	7 (28 %)	7 (28 %)	*1.000[a]*
Chinese	9 (36 %)	9 (36 %)	
Indian	9 (18 %)	9 (18 %)	
Education			
Primary	1 (4 %)	0 (0 %)	*0.456[a]*
Secondary	15 (60 %)	13 (52 %)	
Tertiary	9 (36 %)	12 (48 %)	
Comorbid			
Yes	7 (28 %)	3 (12 %)	*0.289[b]*
No	18 (72 %)	22 (88 %)	
Smoker			
Yes	4 (16 %)	4 (16 %)	*1.000[a]*
No	20 (80 %)	20 (80 %)	
Ex-smoker	1 (4 %)	1 (4 %)	
Alcohol			
Yes	7 (28 %)	3 (12 %)	*0.289[b]*
No	18 (72 %)	22 (88 %)	
Diet			
Vegetarian	2 (8 %)	0 (0 %)	*0.490[b]*
Non- vegetarian	23 (92 %)	25 (100 %)	
Fitzpatrick			
Type III	9 (36 %)	9 (36 %)	*1.000[a]*
Type IV	7 (28 %)	7 (28 %)	
Type V	9 (36 %)	9 (36 %)	
Medications			
Yes	8 (32 %)	12 (48 %)	*0.387[b]*
No	17 (68 %)	13 (52 %)	
Family history AA			
Yes	1 (4 %)	0 (0 %)	*1.000[b]*
No	24 (96 %)	25 (100 %)	
Family history Autoimmune			
Yes	2 (8 %)	2 (8 %)	*1.000[b]*
No	23 (92 %)	23 (92 %)	

[a]Chi-Square test; [b]Fisher's exact test; [c]Mann-Whitney test

Table 2. Vitamin D level and deficiency in case and control group

	Subject (AA) n =25 Median (IQR)	**Control n =25 Median (IQR)**	***p value***
Vitamin D level (nmol/L)	54.15 (139.0)	53.79 (64.47)	*0.823a*
Vitamin D intake (*mcgmcg*)	6.65 (44)	7.86 (34.9)	*0.503[a]*
Sun Exposure index (SEI)	220.50 (209.8)	146.16 (863.7)	*0.823[a]*
Vitamin D categories	n (%)	n (%)	
Deficient < 25	3 (12 %)	1 (4 %)	*0.304[b]*
Insufficient 25-75	19 (76 %)	23 (92 %)	
Sufficient 76-250	3 (12 %)	1 (4 %)	

[a]Mann-Whitney test; [b]Chi-Square test

The association of SALT score with vitamin D level was obtained by Kruskal-Wallis statistic and was interpreted as a chi-square value. There was no statistically significant association between SALT score and vitamin D levels (*p=0.171*). *(Table 3*)

Table 3. Association of SALT scores with vitamin D level

SALT subclass (n=25)	**n (%)**	**Median (IQR)**	***p* value**
S1	18 (72 %)	54.56 (32.5)	0.171a
S2	2 (8 %)	34.42 (0)	
S3-S5	5 (20 %)	42.78 (43.13)	

[a]Kruskal-Wallis test

A similar analysis was performed for the association of AA patterns with vitamin D levels. The result showed no statistically significant difference between the pattern of AA with vitamin D levels (*p=0.657*). *(Table 4)*

Table 4. Association of pattern scores with vitamin D level

Pattern subclass (n=25)	**n (%)**	**Median (IQR)**	***p* value**
P1 (patchy: single)	6 (24 %)	44.62 (37.29)	0.657 [a]
P2 (patchy: multiple)	15 (60 %)	54.16 (30.65)	
P3 (ophiasis, totalis and universalis)	4 (16 %)	43.49 (35.66)	

[a]Kruskal-Wallis test

Discussion

Vitamin D can be obtained from 3 sources: endogenous synthesis in the skin induced

by ultraviolet B (UVB) radiation, dietary intake, and vitamin D supplementation.[3,13,14] 7-dehydrocholesterol is the precursor molecule in the skin which absorbs UVB light and converts to vitamin D3(cholecalciferol). Vitamin D3 binds to vitamin D3 binding protein and is transported to the liver where it is hydroxylated to 25-hydroxyvitamin D (calcidiol) (25(OH)D). Calcidiol is then converted to 1,25-dihydroxy-vitamin D3 (calcitriol) in the kidney by 1-α hydroxylase.[13,14] The optimal level for 25-hydroxyvitamin D (25OHD), the most stable and reliable parameter to evaluate vitamin D status, starts at 30 ng/ml, although the level of 25OHD required to maintain optimum immune system homeostasis has yet to be established.[20]

The active form of vitamin D (1,25-hydroxyvitamin D) acts by binding to specific vitamin D receptors found in the nucleus of target cells.[7] Vitamin D Receptor (VDR) is highly expressed in the key structures of hair follicles, and it is vital for the maintenance of the normal hair cycle. It has been demonstrated that a lack of VDRs reduces the growth of hair follicles. Therefore, with the role of vitamin D and VDR in the hair cycle, it is hypothesised that vitamin D deficiency may have a role in AA.[1,2]

A study conducted in Malaysia on vitamin D status in Malaysian men found that the prevalence of vitamin D deficiency was 0.5% and insufficiency was 22.7%, respectively.[21] Numerous studies have shown that vitamin D insufficiency was common in tropical countries, including Vietnam, Malaysia, and Indonesia.[21] The prevalence of vitamin D deficiency among Malaysian adolescents aged 13 years was 78.8%.[22]

In our study, there was no significant difference in terms of the median vitamin D level between the AA and control group, even though the level was slightly higher in the AA group. A study by Nassiri *et al.*[24] found no statistically significant difference in serum vitamin D levels between AA cases and controls (ordinal odds ratio:0.49 (0.18-1.34 and 95%CI, $p=0.16$). Erpolat *et al.*[18] also reported similar findings with mean serum vitamin D levels of 8.1 ng/ml in AA patients compared to 9.8 ng/ml in healthy controls, which was not statistically significant ($p>0.05$). In contrast, numerous studies reported high statistically significant lower vitamin D levels in cases compared to control. Aksu Cerman *et al*.[3] reported significantly lower mean serum vitamin D levels in AA patients (11.84±6.18 ng/ml) than healthy controls (23.57±9.03 ng/ml) ($p<0.001$). A study conducted by Bhat *et al*.[4] found a statistically significant difference in the mean serum vitamin D levels of AA patients (16.6±5.9 ng/ml) as compared to the control group (40.5±5.7 ng/ml) ($p<0.001$).[4] Similar findings of high statistically significant lower vitamin D levels in AA cases compared to control was also reported in studies conducted by Sidappa *et al*.[5], Mahamid *et al*.[7], Rehman *et al*.[8], and Yilmaz *et al*.[17]

Our study revealed that Vitamin D deficiency and insufficiency was high in both AA (12%, 76%) and control group (4%, 92%). This finding was consistent with recent studies, which showed vitamin D insufficiency was commonly found in tropical countries such as Vietnam, Malaysia and Indonesia.[21] A study conducted by Kok-Yong Chin *et al*.[21] found that the prevalence of vitamin D deficiency (<30 nmol/L) was 0.5% and insufficiency (30-50 nmol/L) was 22.7% among Malaysian men. The result of higher vitamin D deficiency and insufficiency in both groups in our study compared to Kok-Yong Chin *et al*.[21] The discrepancy might be due to different definitions of vitamin D deficiency and insufficiency used in the study. Another study conducted in Malaysia by Moy *et al*.[23]found that vitamin D insufficiency was observed in 67.9% of participants among Malay adults in Malaysia. Another study conducted by Rahman et al.[24] in Malaysia also showed a high prevalence of inadequate serum vitamin D levels among postmenopausal Malaysian women. A total of 73.3% of Malay postmenopausal women and 12.2% of Chinese postmenopausal women had insufficient serum vitamin D levels (<50 nmol/L).[24]

In our study, there was no statistical difference in the prevalence of vitamin D deficiency between AA and the control group even though vitamin

D deficiency was higher in the AA group than the control group (12% vs 4%, *p>0.05*). This observation could be due to a small sample size leading to insignificant results. Erpolat *et al*.[18]also reported higher vitamin D deficiency in the AA group compared to control (93.8% vs 85.3%), but the difference was not statistically significant (*p>0.05*). Numerous studies reported a significantly higher prevalence of vitamin D deficiency in AA compared to the control group. Suchana *et al*.[1] reported 83.3% of vitamin D deficiency in the AA group compared to the control group (53.3%; *p=0.01*). Bakry *et al*.[2] found that 83.3% in the AA group versus 23.3% in the control group had deficient serum vitamin D levels (*p<0.001*). Similar findings were reported by Aksu Cerman *et al*.[3] and Naidu *et al*.[19]

Our study did not find any statistically significant correlation between serum vitamin D levels and SALT scores. Suchana *et al*.[1] found that patients with more severe SALT scores tend to have lower serum vitamin D levels, with an inverse correlation (r=-.026, *p=0.89*); however, the results were not statistically significant. Naidu *et al*.[19] also showed slightly lower serum vitamin D levels as the SALT score progressed, but the difference was not statistically significant (*p=0.06*). Various studies, as reported by Yilmaz *et al*.[17], d'Ovidio *et al*.[20], El-Mongy *et al*.[25] and Darwish *et al*.[26] found no significant correlation between serum vitamin D levels with disease severity. However, this contradicts numerous other studies that found that serum vitamin D levels showed a significant negative correlation with disease severity.[2,3,4,5,6,8] Aksu Cerman *et al*.[3] found a significant inverse correlation between disease severity and serum vitamin D levels in AA patients (r =-0.730; *p<0.001*). Bhat *et al*.[4] also reported a significant negative correlation between SALT sore and vitamin D levels (r=-0.730; *p<0.001*).[4] Similar findings of significant inverse correlation between SALT score and vitamin D levels were reported by Sidappa *et al*.[5], Gade *et al*.[6], and Rehman *et al*.[8]

Regarding the correlation of serum vitamin D levels with the pattern of disease, our study did not find any correlation between different patterns of AA with serum vitamin D levels. This finding was similar to a study conducted by El-Mongy *et al*.[25], which reported no statistical significance between serum vitamin D levels and disease pattern (*p=0.14*). Similar findings were reported in studies conducted by Yilmaz *et al*.[17],d'Ovidio *et al*.[20] and Nassiri *et al*.[27] In contrast, a study conducted by Bakry *et al*.[2] showed a gradual decline of serum vitamin D levels from patchy AA to Alopecia totalis/universalis. Serum vitamin D levels of alopecia totalis/universalis patients were significantly lower when compared to patchy AA (*p<0.001*) and ophiasis (*p<0.05*). Rehman *et al*.[8] also reported similar findings where serum vitamin D levels negatively correlated with the pattern of AA (r=-0.273, *p=0.004*).

The median SEI in the AA group was higher than the control group, although the result was not statistically significant (SEI: 220.50 vs 146.16, *p>0.05*). A study conducted by Bingley *et al*.[28] among 93 adults in Hawaii showed low serum vitamin D levels despite adequate sun exposure, suggesting variable responsiveness to UVB radiation among individuals.[28] A study conducted on 167 Malaysians by Wong *et al*.[29] on sun exposure among healthy adults in a health facility showed a mean SEI of 160±144, lower than the median SEI of 220.5 in the AA group from our study.[29] Although Malaysia is a tropical country with adequate sunlight throughout the year, a low SEI among Malaysians can be attributed to sun avoidance to achieve a fairer skin tone, which is deemed more desirable, and escape the tropical heat. Other factors include the choice of clothing, with most Asians dresses modestly due to influence by tradition, culture, or religion, which limits the amount of sunlight that reaches the skin.[29] The primary cause of vitamin D deficiency is inadequate exposure to sunlight.[30]

The median vitamin D intake was lower in the AA group compared to the control group, although it was not statistically significant. Vitamin D intake was low in both groups, which correlates to low serum vitamin D levels in both groups.

The finding could be attributed by very few foods that naturally contain or are adequately fortified with vitamin D. As examples, food sources that are naturally high in vitamin D include cod liver oil, salmon, sardines, tuna, shitake mushrooms and egg yolks. The recommended vitamin D intake is 600 IU/day (15 mcg) for adults aged 19-50 years old, and at least 600-800 IU/day (15-20 mcg) for adults aged 50-70 years old and above 70 years old, respectively. However, for serum vitamin D level to rise above 30 ng/ml (75 nmol/L), one may require 1500-2000 IU/day (38 mcg-50 mcg) of supplemental vitamin D.[30]

Limitations

The limitations of this study include a relatively limited sample size. As this study was conducted from a single centre in Malaysia, larger studies involving multiple centres may be more representative of the population in Malaysia. In addition, as the patients were not followed up with vitamin D supplementation and repeated serum vitamin D levels, it was hard to conclude if vitamin D supplementation may be beneficial as an adjunctive treatment for patients with AA.

Conclusion

There is no significant statistical difference in vitamin D levels between patients with AA and without. However, the prevalence of vitamin D insufficiency was high in both AA and control groups. There is also no correlation between serum vitamin D levels with severity and pattern of disease.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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