# Serum 25-Hydroxyvitamin D deficiency in Malaysian children with severe atopic dermatitis

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**ABSTRACT**

**Background: Vitamin D deficiency has been shown to be a determinant of disease severity in patients with atopic dermatitis (AD). There is a lack of information on the prevalence of vitamin D deficiency in Malaysian children with AD. The objective of this study was to determine the association of vitamin D deficiency with AD severity, to compare vitamin D deficiency between children with and without AD and to determine prevalence of vitamin D deficiency in children with AD.**

**Methods: A case-control study to examine serum 25-hydroxyvitamin D [25(OH)D] levels in children with and without AD was done. Serum 25-hydroxyvitamin D [25(OH)D] level was measured by immunoassay. AD severity was evaluated using the SCORing Atopic Dermatitis (SCORAD) index.**

**Results: The serum levels of 25(OH)D, measured in 135 children with AD was not statistically different from 65 children without AD [median (IQR): 25.2ng/mL (15.45) vs 25.9ng/mL (15.87), p=0.616]. However, serum vitamin D levels were significantly lower in children with severe AD compared to those with mild-to-moderate AD [median (IQR): 16.0ng/mL (19.32) vs 26.3ng/mL (15.56), p=0.021]. The odds of having vitamin D deficiency in children with severe AD was 3.82 times that of children with non-severe AD (95% confidence level: 1.13, 12.87).**

**Conclusion: This study suggests that there is an inverse association between vitamin D level and the severity of AD in Malaysian children.**

**KEY WORDS:**
*atopic dermatitis, adolescent, children, vitamin D, 25-hydroxyvitamin D, Malaysia*

## INTRODUCTION

Atopic dermatitis (AD) is a common chronic, disabling, recurrent inflammatory skin disease occurring primarily in infants and children. Xerosis and severe pruritus are the cardinal signs as well as prerequisite for the diagnosis of AD. The clinical presentation of AD is highly variable, depending on the age of the patient and disease activity. AD occurs in 10% to 20% of children and may persist into adolescence or adulthood in up to 10% of the patients.[1,2] Previous studies have indicated that severe AD significantly impacts families of children with AD and the children themselves.[3,4] Consequently, clinicians are studying conditions that may be associated with AD, such as vitamin D deficiency and exploring it as a potential therapeutic uses apart from the usual conventional treatment.

Topical agents are the mainstay treatment of AD, with emollients and moisturisers as the principal maintenance therapy. Topical corticosteroids are the first-line treatment for AD flare-ups and are used for both active disease and prevention of relapses. However, their long term use is associated with local and systemic adverse effects. Systemic immunomodulating medications are indicated and recommended in severe cases of AD. Nevertheless, systemic immunosuppression can potentially cause severe adverse effects including life-threatening infections and malignancy.

Ultraviolet (UV) phototherapy is one of the treatment options with fewer adverse effects in the treatment of AD. Recent studies have suggested that ultraviolet B (UVB)-induced vitamin D can be used as a possible mediator in the alleviation of severity and symptoms of AD.[5] Vitamin D also inhibits the adverse effects of UV on the skin.[6,7]

Vitamin D is acquired in two forms: VD2 (ergocalciferol) and VD3 (cholecalciferol). VD3 is mainly synthesized from cholesterol precursors in the skin in response to UVB radiation. Some types of fish are a good source of VD3. VD2 comes from plant sources and is used to produce VD2 supplements. Both VD2 and VD3 are metabolised by the liver into 25-hydroxyvitamin D/calcifediol [25(OH)D] which is the circulating prohormone that is commonly measured to determine vitamin D sufficiency status. 25(OH)D is then hydroxylated in the kidney by the enzyme 25-hydroxyvitamin D-1α hydroxylase to the active form 1,25-dihydroxyvitamin D/calcitriol [1,25(OH)$_2$D3].

Recent epidemiologic studies have linked the rise in allergic diseases such as AD, food allergy/anaphylaxis with factors such as latitude, sunlight and vitamin D deficiency.[8-10] Data reported from several countries that are geographically far from the equator have shown that the prevalence of these allergic diseases increase at higher latitude.[8,11,12] Levels of 25(OH)D has been inversely correlated with levels of IgE sensitisation in children and adults.[10] The 2007 National

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Survey of Children's Health in the United States of America among 91,462 children found that exposure to high UV levels was significantly correlated with a lower prevalence of AD.[13]

Clinical data show that 25(OH)D levels correlate with the development of AD and its severity. Oren et al., found that vitamin D deficient patients were more likely to report AD than vitamin D sufficient patients.[9] A prospective cohort study measuring cord blood vitamin D levels has shown that vitamin D deficiency during pregnancy increases the risk of AD in the first year of life.[14] A systematic review and meta-analysis from 15 observational studies and five randomised controlled trials which looked into the association between 25(OH)D and AD suggested that lower level of vitamin D is associated with increased risk and greater severity of AD.[15] Improvement of AD after oral supplementation with vitamin D has also been reported.[16-18]

There is lack of information regarding the serum level of vitamin D in Malaysian children with AD and its association with the severity of the disease. In this study, we aim to determine the relationship between vitamin D levels and the severity of AD and compare the prevalence of vitamin D deficiency between children with and without AD.

## MATERIALS AND METHODS

*Study design and population*

This is a case-control study to compare the serum levels of 25-hydroxyvitamin D in children with and without AD. Cases were children below 18-years of age with dermatologist-diagnosed AD based on the UK Working Party's Diagnostic Criteria of AD.[19] Control comprised of children without AD or any other inflammatory skin condition. Subjects who had chronic systemic disease other than asthma, allergic rhinitis or hyperimmunoglobulin E syndrome, prior phototherapy, ongoing or prior treatment for known vitamin D deficiency or any medication known to interact with calcium were excluded.

All children with AD and eligible controls who attended the Dermatology Clinic, Hospital Sultanah Aminah Johor Bahru were recruited consecutively between the 1st December 2016 and 31st May 2017. This study was approved by the Malaysian Ministry of Health Institutional Review Board and Medical Research Ethics Committee. Written consents were given by all parents/legal guardians and written assents were obtained from children aged 12-years and above. A standard study questionnaire was used to record the demographics, height and weight, Fitzpatrick skin types, characteristics of AD (assessment of disease severity and treatment modality), personal and family history of atopy, dressing habits and 3-day dietary recall. Body mass index (BMI) was calculated as weight in kilogram (kg) divided by height in metre squared ($m^2$). Anthropometric status of all subjects were categorised based on the World Health Organization (WHO) growth standards using the BMI-for-age indicators.[39] Fitzpatrick skin phototype of Chinese, Malay and Indian subjects were categorised to phototype III, phototype IV and phototype V respectively. If the skin colour of a subject was a shade fairer or darker than those of the same race, questions regarding reaction of their skin to sun exposure, e.g., tanning, erythema were asked instead. Subjects from those other than the three major races in Malaysia were also asked similar questions. Children who wore a full set of attire comprising headscarf, long sleeved shirt/blouse and long pants/skirt daily were considered as fully covered. Dietary recalls were obtained from the parents or guardians of the children or from the children themselves. Dietary levels of vitamin D were subsequently computed using Nutritionist Pro™ (version 4.0; Axxya Systems).

*Determination of disease severity*

The severity of AD disease was graded using the Severity Scoring of Atopic Dermatitis (SCORAD) index.[20] The SCORAD index consists of the interpretation of the extent of the disorder which is composed of six items (erythema, oedema/papulation, oozing/crust, excoriation, lichenification, dryness) and two subjective symptoms (itch and sleeplessness). The maximum score was 103 points with mild <25 points, moderate 25-50 points and severe >50 points.[21] The scoring was completed by the same investigator for all subjects.

*Analysis of serum 25-Hydroxyvitamin D [25(OH)D]*

A single measurement of serum concentration of vitamin D [measured as 25(OH)D] was obtained for all subjects on the day of their recruitment. Two millilitres of venous blood was drawn from all subjects and analysed using electrochemiluminescence immunoassay (ECLIA) on the Cobas 601 analyser. The values obtained were used as continuous variables and also categorised into deficient <20ng/mL, insufficient 20-30ng/mL and sufficient >30ng/mL.[22,23] The serum 25(OH)D levels of the AD cohort were compared with the controls and correlated with parameters as shown in the results.

*Statistical analysis*

Descriptive statistics was presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which was not normally distributed. Depending on the distribution of datas, we used chi-squared test, Fisher's exact test, Mann-Whitney test or Kruskal-Wallis test for bivariate analysis. Statistical significance was set at $p<0.05$. Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) (version 15; SPSS Inc., Chicago, IL. USA).

## RESULTS

Table I shows the demographic and clinical characteristics of children with AD and controls. There were no significant differences between the cases and controls in terms of age, gender, ethnicity, body mass index and serum vitamin D level. Cases had significantly lower dietary vitamin D in their diet and were more likely to wear fully covered clothing as compared to controls.

Age and gender were shown to be significantly associated with the serum level of vitamin D in children with AD as well as non-AD children (Table II). Preschoolers, who were defined as children below seven years of age, had the highest serum vitamin D levels. On the other hand, children aged ≥13 years

**Table I: Demographic and clinical characteristics of atopic (cases) and non-atopic (control) children (n=200)**

| Demographic | Atopic Dermatitis n=135 | | Non-Atopic Dermatitis n=65 | | P value |
|---|---|---|---|---|---|
| | Median (IQR) | n (%) | Median (IQR) | n (%) | |
| Age | 8.6 (4.93)d | 8.2 (4.42)[d] | | | 0.657[a] |
| Preschooler | | 55 (40.7) | | 25 (38.5) | |
| Primary | | 46 (34.1) | | 28 (43.0) | |
| Secondary | | 34 (25.2) | | 12 (18.5) | |
| Gender | | | | | |
| Male | | 60 (44.4) | | 34 (52.3) | 0.297[b] |
| Female | | 75 (55.6) | | 31 (47.7) | |
| Ethnicity | | | | | |
| Malay | | 88 (65.2) | | 44 (67.7) | 0.093[b] |
| Chinese | | 38 (28.2) | | 11 (16.9) | |
| Indian | | 6 (4.4) | | 5 (7.7) | |
| Others | | 3 (2.2) | | 5 (7.7) | |
| BMI-for-age | 16.8 (5.03) | | 16.8 (5.32) | | 0.819[c] |
| Normal | | 94 (69.6) | | 45 (69.2) | |
| Overweight | | 32 (23.7) | | 17 (26.2) | |
| Underweight | | 9 (6.7) | | 3 (4.6) | |
| Family history of atopic diathesis | | | | | |
| Yes | 112 (83.0) | | 29 (44.6) | < 0.001b | |
| No | 23 (17.0) | | 36 (55.4) | | |
| Serum 25(OH)D (ng/mL) | 25.2 (15.45) | | 25.9 (15.87) | | 0.616[c] |
| Categories of vitamin D level | | | | | |
| Deficient | | 40 (29.6) | | 19 (29.2) | 0.915[b] |
| Insufficient | | 49 (36.3) | | 22 (33.9) | |
| Sufficient | | 46 (34.1) | | 24 (36.9) | |
| Total n (%) | | | | | |
| Deficient | 59 (29.5) | | | | |
| Insufficient | 71 (35.5) | | | | |
| Sufficient | 70 (35.0) | | | | |
| Dietary vitamin D intake (µg) | 0.217 (0.47) | | 0.333 (0.49) | | 0.005[c] |
| Clothing | | | | | |
| Fully-covered | | 20 (14.8) | | 3 (4.6) | 0.034[b] |
| Not fully-covered | | 115 (85.2) | | 62 (95.4) | |

[a] Independent t-test
[b] Chi-square test
[c] Mann-Whitney test
[d] Mean (SD)

**Table II: Association between socio-demographic factors and levels of serum vitamin D among atopic (cases) and non-atopic (control) children (n=200)**

| Factor | Level of serum Vitamin D | | | | | |
|---|---|---|---|---|---|---|
| | Atopic Dermatitis n=135 | | | Non-Atopic Dermatitis | | |
| | n | Median (IQR) ng/mL | P value | n | Median (IQR) ng/mL | P value |
| Age | | | | | | |
| Preschooler | 55 | 32.6 (20.60) | < 0.001[a] | 25 | 33.3 (15.60) | < 0.001[a] |
| Primary | 46 | 23.3 (9.42) | | 28 | 24.7 (9.96) | |
| Secondary | 34 | 21.7 (16.08) | | 12 | 17.3 (5.57) | |
| Gender | | | | | | |
| Male | 60 | 28.9 (15.40) | 0.006b | 34 | 23.9 (13.70) | 0.042[b] |
| Female | 75 | 22.2 (13.66) | | 31 | 29.7 (19.74) | |
| Ethnicity | | | | | | |
| Malay | 88 | 24.5 (19.40) | 0.295[a] | 44 | 26.8 (14.28) | 0.991[a] |
| Chinese | 38 | 26.8 (9.49) | | 11 | 25.8 (23.16) | |
| Indian | 6 | 18.4 (20.27) | | 5 | 22.7 (30.92) | |
| Others | 3 | 24.6 (-) | | 5 | 23.1 (13.12) | |
| BMI-for-age | | | | | | |
| Normal | 94 | 26.6 (15.70) | 0.570[a] | 45 | 28.6 (14.31) | 0.003[a] |
| Overweight | 32 | 24.0 (15.71) | | 17 | 20.5 (9.70) | |
| Underweight | 9 | 26.6 (20.58) | | 3 | 16.4 (-) | |
| Skin phototype | | | | | | |
| Phototype III | 38 | 26.0 (9.66) | 0.69[7a] | 10 | 32.6 (22.76) | 0.507[a] |
| Phototype IV | 88 | 24.7 (19.13) | | 49 | 25.9 (13.57) | |
| Phototype V | 9 | 18.7 (25.91) | | 6 | 22.4 (29.11) | |

[a]Kruskal-Wallis test
[b]Mann-Whitney test

**Table III: Association between serum vitamin D levels and severity of atopic dermatitis (n=135)**

| [b]Severity of AD (SCORAD score) | Serum vitamin D level | | | | | |
|---|---|---|---|---|---|---|
| | Median (IQR) | n (%) | P value | Deficient | Non deficient | P value |
| Non-severe (≤50) | 26.3 (15.56) | 123 (91.1) | 0.021[a] | 33 (26.8) | 90 (73.2) | 0.023[c] |
| Severe (>50) | 16.0 (19.32) | 12 (8.9) | | 7 (58.3) | 5 (41.7) | |
| Mild (<25) | 27.2 (14.80) | 60 (44.4) | 0.072[a] | 11 (18.3) | 49 (81.7) | 0.010[c] |
| Moderate-Severe (≥25) | 23.1 (17.01) | 75 (55.6) | | 29 (38.7) | 46 (61.3) | |

[a]Mann-Whitney test
[b]SCORAD index
[c]Chi-square test

**Table IV: Serum vitamin D levels between various categories of Atopic Dermatitis severity as compared to non-atopic among children with vitamin D deficient (n=59)**

| Severity of AD | Serum vitamin D level | |
|---|---|---|
| | Median (IQR) ng/mL | P value |
| Atopic vs. non-atopic | 14.97 (7.11) vs. 16.38 (4.74) | 0.192[a] |
| AD severity vs. non-atopic | | |
| Non-severe vs. non-atopic | 15.41 (5.38) vs. 16.38 (4.74) | 0.482[a] |
| Severe vs. non-atopic | 10.53 (6.44) vs. 16.38 (4.74) | 0.010a |
| Mild vs. non-atopic | 15.47 (5.07) vs. 16.38 (4.74) | 0.767[a] |
| Moderate vs. non-atopic | 15.34 (5.94) vs. 16.38 (4.74) | 0.433[a] |
| Moderate-severe vs. non-atopic | 14.93 (7.36) vs. 16.38 (4.74) | 0.121[a] |

[a]Mann-Whitney test

**Table V: Association between severity of Atopic Dermatitis and socio-demographic factors (n=135)**

| Factor | Severity of Atopic Dermatitis | | | | P valuea |
|---|---|---|---|---|---|
| | Not Severe | | Severe | | |
| | n | % | n | % | |
| Age | | | | | 0.101[a] |
| Preschooler | 49 | 89.1 | 6 | 10.9 | |
| Primary | 45 | 97.8 | 1 | 2.2 | |
| Secondary | 29 | 85.3 | 5 | 14.7 | |
| Gender | | | | | 0.310[b] |
| Male | 53 | 88.3 | 7 | 11.7 | |
| Female | 70 | 93.3 | 5 | 6.7 | |
| Ethnicity | | | | | 0.896[a] |
| Malay | 80 | 90.9 | 8 | 9.1 | |
| Chinese | 34 | 89.5 | 4 | 10.5 | |
| Indian | 6 | 100.0 | 0 | 0.0 | |
| Others | 3 | 100.0 | 0 | 0.0 | |
| BMI | 16.8 (4.95)[d] | | 17.1 (5.51)[d] | | 0.850[c] |
| Normal | 83 | 88.3 | 11 | 11.7 | 0.364[a] |
| Overweight | 31 | 96.9 | 1 | 3.1 | |
| Underweight | 9 | 100.0 | 0 | 0.0 | |
| Skin phototype | | | | | |
| Phototype III | 34 | 89.5 | 4 | 10.5 | 0.790[a] |
| Phototype IV | 80 | 90.9 | 8 | 9.1 | |
| Phototype V | 9 | 100.0 | 0 | 0.0 | |
| Dietary Vitamin D (µg) | 0.147 (0.443)[d] | | 0.340 (0.329)[d] | | 0.037[c] |
| Clothing | | | | | |
| Fully-covered | 18 | 90.0 | 2 | 10.0 | 0.692[a] |
| Not fully-covered | 105 | 91.3 | 10 | 8.7 | |

[a]Fisher's Exact test
[b]Chi-square test
[c]Mann-Whitney test
[d]Median (IQR)

were found to have the lowest level of serum vitamin D. Among the cases, males had significantly higher serum vitamin D level. Interestingly, females had significantly higher serum vitamin D level among the controls. The controls with normal BMI-for-age had significant higher serum vitamin D level. Both ethnicity and skin phototypes were not associated with the vitamin D level in both cases and controls. As shown in Tables III and IV, children with severe AD were found to have significantly lower serum vitamin D levels. The odds of having vitamin D deficiency in children with severe AD was 3.82 that of children with non-severe AD (95% Confidence Interval (CI): 1.13, 12.87). Comparison between mild AD with moderate to severe AD did not yield significant association between the two categories.

Table V shows that there is no statistical differences between the non-severe AD and the severe AD children regarding the demographic factors. Surprisingly, dietary vitamin D intake was found to be significantly higher in the children with severe AD.

## DISCUSSION

Increasing epidemiological and clinical evidence suggest that vitamin D deficiency may be involved as the aetiology and pathogenesis of AD and other allergic diseases.[24] Vitamin D deficiency is currently a growing epidemic of the modern indoor lifestyle which is associated with reduced sun exposure and this partly explains the rising incidence of AD and other allergic diseases.[24,25] Recent data shows that vitamin D, through interaction with the vitamin D receptor, affects immune mechanisms, epidermal differentiation and skin barrier function.[6,27] In our study, around 30% of the children had serum 25(OH)D concentrations indicative of vitamin D deficiency. This finding was comparable to the study by Khor et al., conducted among 402 primary school children in Kuala Lumpur, Malaysia, which found that 35.3 % of their subjects had deficient level of vitamin D.28 A recent published data by Quah et al.,[29] also reported that the prevalence of vitamin D deficiency among Malaysian adolescents was 33 %. Their study was conducted among 1061 fifteen-year-old students from 15 urban and rural secondary schools in the state of Selangor, Perak and Kuala Lumpur, Malaysia.

As vitamin D plays a role in the development of AD, we expected our AD subjects to have a lower vitamin D level as compared to children without AD. Contradicting findings had been reported in the literature. Wang et al.,[30] Farajzadeh et al.,[31] and Cheon et al.,[32] found that the level of vitamin D was significantly lower in patients with AD than in the controls. Samochocki et. al.,[33] and Su et. al.,[34] both reported no statistically significant differences in the level of serum vitamin D in their patients with AD when compared with controls. We also did not find any significant difference in the serum vitamin D levels between our AD and non-AD children. We believed that this finding was not by chance as despite the significant difference in the attire of subjects and their dietary vitamin D intake between both groups, the serum vitamin D level among AD children was no different from normal children. This finding may be explained by the high prevalence of low levels of vitamin D in our general population as revealed by Ramalingam, who noted that two thirds of his vitiligo subjects and controls had deficient and insufficient vitamin D level, with no significant difference in the serum vitamin D levels between both cohorts.[35]

In our study the higher levels of vitamin D among pre-schoolers in both AD and non-AD groups may be due to them consuming food and beverages fortified with vitamin D, such as formula milk and cereals. Most of the older children in our study had stopped consuming such food when they began their primary schooling. We noted that our secondary school children in both cohorts had the lowest vitamin D levels. They may have spent more time indoors than outdoors when they became older. This could be because the secondary school children had much more homework and revision to complete resulting in indulging in sedentary indoor activities such as watching television and playing with modern technology gadgets. A study by Aniza, showed that more than half of adolescents preferred to indulge in indoor activities.[40] Female AD children in our study had lower vitamin D level compared with male AD children. All 20 of our AD children who always wore fully covered attires were females. This may be explained as the girls may have been embarrassed with their physical appearance and would have worn clothing to cover areas where AD is easily visible on the skin.

In our study, we demonstrated that severe AD children had significantly lower serum vitamin D levels. This finding is similar to the recent results of Su et al., [34] who reported significantly lower vitamin D levels in severe and moderate AD. Peroni et al.,[36] and Wang et. al.,[30] both reported inverse correlation between the serum vitamin D and severity of AD. In Peroni et al.'s study of 37 AD children, the mean serum levels of vitamin D were significantly higher in patients with mild AD as compared with moderate or severe AD.[36] Wang et al., study among 498 Chinese children with AD and adolescents in Hong Kong also showed serum 25(OH)D to be lowest in severe AD and highest in mild disease.[30]

In contrast, Chiu et al., found no significant correlations between vitamin D and the severity of AD in 94 children.[37] However, they found that subjects who were three years and older, black race and winter season were significantly associated with lower serum vitamin D level. Samochocki et al. and Javanbakht et al., also found no association between serum 25(OH)D and the severity of AD.[33,17] Instead, there was significant improvement in the SCORAD with supplementation of vitamin D in the two studies. The finding of improvement in disease severity with vitamin D treatment in AD patients was also supported by a randomised, placebo-controlled, double-blinded trial by Amestejani et al.[18] In their study, AD patients who were given 1600IU cholecalciferol (vitamin D) showed significant improvement in the SCORAD score across all categories of severity. In contrast to Amestejani et al., study, a randomised controlled double blinded study done by Hata et al.,[38] did not find any significant improvement in the severity scores of 30 AD subjects who randomly received 4000IU supplementation of vitamin D. Their study also showed no association between serum 25(OH)D with AD severity.

## LIMITATIONS

Our study is limited by the unmatched cohort of the cases and the controls. There is also a possibility of recall bias of caregivers during administration of the questionnaire. The three-day dietary recalls were obtained either from parents of young children or from well-articulating children during their clinic visits. Detailed entries of dietary intake were lacking with the use of Nutritionist Pro™ software. We also did not address socioeconomic status, cultural practices such as diet restrictions and psychosocial issues such as avoidance of physical activities and exposure to sunlight. These factors may arise as consequences to the AD itself or may influence the vitamin D levels as well as the severity of AD.

## CONCLUSION

In summary, our findings suggested an inverse association between the vitamin D levels and the severity of AD. In view of the results of other studies showing improvement in the severity of AD with supplementation of oral vitamin D, vitamin D may be useful as an adjunct in the treatment of AD especially in those with severe disease. However, due to conflicting results from various studies, the use of vitamin D supplementation as a routine treatment is perhaps controversial. Larger trials are necessary to validate our observation of vitamin D deficiency in severe AD as well as to clarify the advantages of vitamin D supplementation on AD prevention and outcomes.

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## CONFLICT OF INTEREST

The authors hereby certify that the work which is reported herein has not received financial support from any pharmaceutical company or other commercial source and neither the authors nor any first degree relatives have any special financial interest in the subject matter discussed in our manuscript.

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