

Correlation of low vitamin D status with atopic dermatitis severity in children

Habibah Hasyim Lubis^{1*}, Kristo Alberto Nababan², Deryne Anggia Paramita²

¹Postgraduate Master of Clinical Medicine Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Universitas Sumatera Utara Hospital, Medan, Indonesia

²Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Universitas Sumatera Utara Hospital, Medan, Indonesia Medan, Indonesia

*Corresponding to:

Habibah Hasyim Lubis; Postgraduate Master of Clinical Medicine Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Universitas Sumatera Utara Hospital, Medan, Indonesia;
drhabibahasyim@gmail.com

Received: 2021-01-20
Accepted: 2021-04-22
Published: 2021-04-30

ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder. Vitamin D has some roles in immunologic mechanisms. Vitamin D may influence the severity of AD. Previous studies of vitamin D correlation in children with atopic dermatitis have revealed conflicting results. This study determines the correlation between low vitamin D status with the severity of atopic dermatitis in children.

Methods: This is a cross-sectional analytical study with a cross-sectional approach that involved DA subjects aged ≤ 17 years with low vitamin D status. The recording of basics data and examination of subjects included assessing the scoring atopic dermatitis (SCORAD) score and measuring 25-hydroxyvitamin D (25(OH)D) level for all subjects. Statistical analyses were performed using Pearson's correlation coefficients, with $P < 0.05$ was considered statistically significant.

Result: A total of 30 subjects with AD with the most extensive distribution was in the age group of 11–17 years (53.33%), sex proportions were equal both male (50%) and female (50%), all subjects have an atopic family history (100%). The mean vitamin D level was $18,02 \pm 4,56$ ng/ml (deficiency), and the mean SCORAD score was $20,03 \pm 5,80$ (mild). There was a significantly strong negative correlation between low serum vitamin D level and severity of AD in children ($r = -0.666$, $p = 0.001$).

Conclusion: Lower vitamin D status is inversely associated with the severity of AD in children.

Keywords: atopic dermatitis, SCORAD, vitamin D, 25-hydroxy-vitamin D

Cite This Article: Lubis, H.H., Nababan, K.A., Paramita, D.A . 2021. Correlation of low vitamin D status with atopic dermatitis severity in children. *Bali Medical Journal* 10(1): 291-295. DOI: 10.15562/bmj.v10i1.2203

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease primarily beginning in childhood with a variable natural course. The itch hallmark symptom of the disease, often unrelenting in severe cases, leading to sleep disturbance and excoriated infection-prone skin.¹ In the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of AD in children varies significantly from 0.3% to 20,5% among 56 countries. However, there are consistent trends of increasing disease prevalence over time.² Atopic dermatitis has a complex etiology, whereby genetic and immune mechanisms act in concert with environmental factors to influence

manifestations of the disease.³

Vitamin D is a secosteroid, which was initially known for its skeletal role. However, in recent years, its functions in different organs have been increasingly recognized. Also, vitamin D functions in skin physiology, focusing on its role in certain inflammatory skin conditions such as psoriasis and atopic dermatitis.⁴

A study by Umar et al. in Qatar reported that vitamin D has various functions on the skin, including a role in the keratinocyte proliferation process, differentiation, apoptosis, skin barrier function, and immune system regulation. Vitamin D has been considered the therapy of choice for various skin diseases, including psoriasis and cutaneous lupus erythematosus.⁵ The results of studies

investigating vitamin D levels in patients with AD are contradictory.^{6,7}

The effect of vitamin D levels on disease resistance has not been thoroughly evaluated in children with AD. Effective therapy to control complaints in AD patients is still a challenge. Research is needed to assess the correlation between low vitamin D status and severity in AD patients hence support the finding of adjuvant therapy in the form of vitamin D supplements that can provide better clinical cures with fewer side effects.

METHODS

Sample Selection

This cross-sectional study was conducted from December 2019 to October 2020

in the Polyclinic of the Immunodermatology Division in Dermatology and Venereology Department of H. Adam Malik General Hospital Medan and Polyclinic Dermatology and Venereology of the Universitas Sumatera Utara Hospital Medan. Including 30 cases of children with atopic dermatitis and low vitamin D status. Samples obtained through basic data recording and examination included diagnosis using the Hanifin Rajka criteria, assessing AD severity with SCORAD index, and measuring 25-hydroxyvitamin D serum levels using a DiaSorin Liaison® analyzer with Chemiluminescence Immunoassay (CLIA) method.

The inclusion criteria are children aged ≤ 17 years old with AD and low vitamin D status who willing to participate and signing informed consent. Detailed clinical data obtained were patient's data recording consisting of age, sex, familial atopic history, SCORAD score, and serum vitamin D levels.

Low vitamin D status

Twenty-five-hydroxyvitamin D is the active form of vitamin D in the body, often used to measure serum vitamin D levels in a person.⁸ Based on Hollick in

2011 the reference values for 25(OH)D were reported as: deficiency < 20 ng/ml, insufficiency 20-29 ng/ml, normal 30-100 ng/ml, toxic > 100 ng/ml.⁹

SCORAD

The SCORAD index was developed by the European Task Force Atopic Dermatitis (ETFAD) in 1993. SCORAD index consists of the interpretation of the level of disturbance (A: according to the rule of nine - 20% of the score), the intensity consists of 6 items (B: erythema, edema/papules, scratching effect, scaling, lichenification, and dryness - 60% of the score; each item has four scores: 0, 1, 2, 3) and subjective symptoms (C: itching, difficulty sleeping - 20% of the score).⁴ In the SCORAD Index, a visual analog scale is used for the evaluation of subjective symptoms. The score distribution is achieved using the formula $A / 5 + 7B / 2 + C$. The maximum score is achieved when it is 103. The evaluation filled in 7-10 minutes depends on the approaching experience.^{10,11}

Ethical Approval

The protocol has approval by The Health Research, Ethical Committee, University

of Sumatera Utara, Medan, Indonesia (No: 223/TGL/KEPK FK USU-RSUP HAM/2020).

Statistical Analysis

Statistical analysis was performed using Pearson's or Spearman's correlation coefficients to assess significant correlations when the data had a normal or not normal distribution. The p-values ≤ 0.05 were considered statistically significant

RESULTS

Patient's characteristics

Subjects were 30 children suffering from atopic dermatitis with low vitamin D status with an age range of 1-17. The mean age was 9.96 ± 4.23 years by the most age range at 11-17 years of 16 subjects (53.3%). Gender characteristics have the same proportion of men and women as 15 subjects (50%) and women as 15 subjects (50%). Familial history of atopy obtained in all study subjects, namely 30 subjects (100%). Characteristics of the research subject seen in Table 1.

Characteristics of vitamin D levels and the severity of atopic dermatitis

The overall mean value of vitamin D levels in the study subjects was 18.02 ± 4.56 ng/ml hence classified as a deficiency. Deficiency levels of vitamin D were in 20 subjects (66.7%) with a mean value of 15.51 ± 3.01 ng/ml while insufficiency was in 10 subjects (33.3%) with the mean value of 23.06 ± 2.41 ng/ml. The mean value of SCORAD was 20.03 ± 5.80 , where 26 subjects (86.7%) classified as mild and 4 (13.3%) classified as moderate. Characteristics of vitamin D serum levels and the severity of atopic dermatitis seen in Table 2. Data presented in the form of mean and standard deviation (normally distributed data).

Correlation between low vitamin D status and severity in atopic dermatitis

Based on the Pearson correlation test, there was a significant correlation between vitamin D levels and the severity of AD based on SCORAD with a negative correlation direction and a strong correlation ($p < 0.001$; $r = -0.666$). In other words, if the serum vitamin D level

Table 1. Description of the Characteristics Research Subjects

Characteristics	Category	n (30)	Percentage (%)	Mean \pm SD*
Age (y.o)	0 -5	5	16,66	$9,96 \pm 4,23^*$
	6-10	9	30,00	
	11-17	16	53,34	
Sex	Male	15	50	
	Female	15	50	
Family history	Yes	30	100	
	No			

Note: SD: Standard of deviation; data presented in the form of mean and standard deviation (normally distributed data)

Table 2. Characteristics of vitamin D levels and the degree of severity of atopic dermatitis

Characteristics	Category	n (30)	Percentage (%)	Mean \pm SD*
Vitamin D	Deficiency	20	66,7	$18,02 \pm 4,56^*$ ng/ mL
	Insufficiency	10	33,3	
SCORAD	Mild	26	86,7	$20,03 \pm 5,80^*$ ng/ mL
	Moderate	4	13,3	
	Severe	0	0	

decreases, the atopic dermatitis severity will increase, and vice versa.

DISCUSSION

Atopic dermatitis is a chronic and itchy residual inflammatory skin disease that generally affects children, and to a lesser extent, it can affect adults. DA is a complex condition involving interactions between various gene products requiring environmental factors and immune response, leading to a late clinical phenotype with the varying initial course.¹

This present study reported a total of children suffering from atopic dermatitis with low vitamin D status with an age range of 1-17. The mean age was 9.96 ± 4.23 years by the most age range at 11-17 years of 16 subjects (53.3%). In line with Wang et al., who reported that the mean age of children with AD was 9.5 ± 4.27 with the most age range at the age of 1-16.⁹ Meanwhile, a study conducted by Akan et al. reported a mean age of 2 years with the most age range of 5 months-17 years.¹⁰

The diagnosis of AD is continually increasing by 10% to 20% incidences among the pediatric population. This condition essentially develops at an early age (45%) in children; infrequently, the symptoms begin to appear under the first six months. In 60% of patients, symptoms appear before the first year, and in 30% of children, new symptoms appear before the age of 5. Whereas 10% of AD diagnosed in the population aged 6 to 20 years.^{12,13}

The results of previous studies of ISAAC in 56 countries observed female preponderance for AD, with an overall female-to-male ratio of 1,3 to 1,0.¹ However, in the research of Halim et al., in Jakarta, there was no difference in the proportion of boys and girls in AD in the case group.¹³ In this study, the proportion of sexes is balanced based on the distribution of available data.

A familial history of atopy was obtained in all study subjects, namely 30 subjects. The results of this study supported by previous studies, in which the increased risk of AD in infants born to parents with a history of atopy originating from the mother was predictive (93 people, 23%) than a history of paternal atopy (53 people, 17%). AD is an inherited familial disease with a strong maternal influence.¹

A history of atopy in first-degree relatives is one of the diagnostic criteria for atopic dermatitis in infancy.¹⁴ The highest risk was babies born to mothers with a history of eczema.¹⁴ In line with Budiastuti's study, AD children with a maternal history were 42 (52,3%) and 42 (47,7%) paternal history.¹⁵

This study found that the overall average value of vitamin D levels in the study subjects was classified as a deficiency. In line with the research conducted by Baek et al. and D'Auria et al., which found that the majority of AD patients had vitamin D deficiency with mean levels of 18,3 ng/dl and 19,4 ng/dl.^{16,17} Slightly different results were found in the study conducted by Farajzadeh et al., where the mean value of vitamin D levels in AD patients was 24,62 ng/dl, also below normal levels but in the category of insufficiency.¹⁸ While Galli et al. obtained the average value of vitamin D levels classified normal in AD patients was 48,5 ng/dl.¹⁹

Twenty-five-hydroxyvitamin D is the active form of vitamin D in the body, used to measure serum vitamin D levels in a person. Vitamin D produced in the skin or obtained with food is biologically inactive and requires two subsequent hydroxylations to obtain full hormonal activity.²⁰ Apart from sun exposure, several studies suggest dietary vitamin D intake is related to serum vitamin D levels. Serum vitamin D levels do not correlate with total calorie intake, but the diet composition is more important for improving vitamin D status in infants. The main source of vitamin D in infancy is vitamin D dietary supplements. In infants and children, low levels of vitamin D may be because the baby spends more indoors, and parents tend to keep children away from exposure to direct sunlight, resulting in low production of vitamin D in the skin.²⁰⁻²²

In this study, the average SCORAD value was classified as mild. This result was following the research conducted by Kim et al. and Galli et al., wherefrom these two studies, the mean SCORAD value of AD patients were classified as mild (17,5). This result was different from the results of the research of Baek et al. and Chiu et al.^{23,19}

In this study, it was found there was a significant and strong negative correlation

between vitamin D levels and the severity of AD based on SCORAD. The result was in line with the results of previous, who also reported an inverse relationship between vitamin D levels and AD severity.²⁴⁻²⁹

The pathogenesis of AD is not fully understood. However, it results from a complex interaction between impaired skin barrier function, abnormalities of the immune system and the environment and infectious agents, decreased levels of ceramide, increased activity of endogenous proteolytic enzymes, and increased transepidermal water loss.¹

Vitamin D is a hormone with various physiological actions and influences the regulation of the immune system.^{20,22,23} It has been reported that vitamin D status is associated with the development of allergic diseases, including asthma in children and atopic dermatitis. Vitamin D deficiency is considered a significant risk factor for food allergies, and increased vitamin D intake in pregnant women reduces allergic sensitization in offspring.²

Vitamin D is produced endogenously in the skin. It showed that keratinocytes produce abundant amounts of $1\alpha, 25$ (OH) $2D_3$ of 25-OH D_3 under exogenous regulation of $1\alpha, 25$ (OH) $2D_3$. The production of biologically active vitamin D_3 varies with the degree of differentiation of keratinocytes. Moreover, because keratinocytes express vitamin D receptors (VDR), they can respond to the fully active form of vitamin D_3 - $1\alpha, 25$ (OH) $2D_3$. Together with calcium is one of the best regulators of epidermal differentiation. One point two five dihydroxy vitamin D_3 increases the expression of involucrin, transglutaminase, loricrin, and filaggrin. They increase the potential for calcium-induced differentiation of keratinocytes at the level of gene expression and mRNA stability. It also enhances the formation of a cornified envelope. Filaggrin will be degraded into NMF, which is essential for maintaining skin moisture content, low pH, or maintaining the barrier function of the stratum corneum.³⁰

Although the immunological effects of vitamin D still require further research, vitamin D is known to modulate phenotypes and induce tolerogenic function of dendritic cells. Besides, vitamin D decreases the expression of

proinflammatory cytokines such as IL-12 and increases the expression of the regulatory cytokines IL-10, which leads to decreased T cell activation.^{31,32} Vitamin D is a proposed modulator of the immune system response, which influences the development of atopic susceptibility.³³⁻³⁵

CONCLUSION

In conclusion, we found a relationship between low vitamin D status with atopic dermatitis severity in children. These results indicated that the low vitamin D status interfered with the SCORAD for atopic dermatitis patients. The limitations of this study were no observation of factors that may affect vitamin D levels, such as diet and sun exposure that could increase the severity of atopic dermatitis. Thus, additional studies are needed further to investigate the vitamin D level in atopic dermatitis patients.

ACKNOWLEDGEMENT

We want to express our greatest gratitude to the head of the master and specialist study program of the Dermatology and Venereology Department, Universitas Sumatera Utara.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

ABBREVIATIONS

AD, atopic dermatitis; y.o, years old; SCORAD, scoring atopic dermatitis; (25(OH)D), 25-hydroxyvitamin D.

AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering, and analysis, drafting, and approval for publication of this manuscript.

FUNDING

The authors are responsible for all of the study funding without grant or any external source of funding.

REFERENCES

- Simpson EL, Leung DYM, Eichenfield LF, Boguniewicz M. Atopic Dermatitis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, editors. Fitzpatrick's dermatology in general medicine. 9th ed. New York: McGraw Hill Education; 2019. p. 363-81.
- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet*. 1998;351:1225-1232.
- Nutten S. Atopic Dermatitis: Global Epidemiology and Risk Factors. *Ann Nutr Metab*. 2015; 66 (1): 8-16.
- Umar M, Sastry KS, Ali FA, Al-Khulaifi M, Wang E, Chouchane AI. Vitamin D and pathophysiology of inflammatory skin diseases. *Skin Pharmacol Physiol*. 2018;31:74-86. DOI: [10.1159/000485132](https://doi.org/10.1159/000485132)
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-132.
- Prielt B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients*. 2013 Jul 5;5(7):2502-21. doi: [10.3390/nu5072502](https://doi.org/10.3390/nu5072502).
- Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol*. 2008;122(2):261-266.
- Wang SS, Hon KL, Kong APS, Pong HNH, Wong GWK, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. *Pediatr Allergy Immunol*. 2014;25(1):30-35
- Holick ME. Photobiology of Vitamin D. *Biochemistry, Physiology and Diagnostics*. 4th ed. Vol 1. 2018; 45-55.
- Han TY, Kong TS, Kim MH, Chae JD, Lee JH, Son SJ. Vitamin D status and its association with the SCORAD score and serum LL-37 level in Korean adults and children with atopic dermatitis. *Ann Dermatol*. 2015;27(1):10-14
- Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1997;195(1):10-19.
- Akan A, Azkur D, Ginis T, et al. Vitamin D level in children is correlated with severity of atopic dermatitis but only in patients with allergic sensitizations. *Pediatr Dermatol*. 2013;30(3):359-363.
- Halim A, Munasir Z, Rohsiswatmo R. Manfaat Pemberian ASI Eksklusif dalam Pencegahan Kejadian Dermatitis Atopi pada Anak. *Sari Pediatri*. 2014;15(6):345-352 (13)
- Moore MM, Rifas-Shiman SL, Rich-Edwards JW, Kleinman KP, Camargo CA, Gold DR, Weiss ST, Gillman MW. Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics*. 2004 Mar 1;113(3):468-74.
- Budiastuti M, Wandita S, Sumandiono. Exclusive Breastfeeding and Risk of Atopic Dermatitis in High Risk Infant. *Berkala Ilmu Kedokteran*. 2007;39(4):192-198.
- Baek JH, Jung IH, Kim HY, et al. The link between serum vitamin D level sensitisation to food allergens and the severity of atopic dermatitis in infancy. *J Pediatr*. 2014;165:849-854.
- D'Auria E, Barberi S, Cerri A, et al. Vitamin D status and body mass index in children with atopic dermatitis: a pilot study in Italian children. *Immunol Lett*. 2017;181:31-35.
- Farajzadeh S, Reghabatpour L, Aflatoonian M, Mohammadi S, Amiri R. Assessment of serum level of 25-hydroxyvitamin D in Iranian children with atopic dermatitis, in Kerman city, an area with high sun exposure. *JPAD*. 2015;25(2):96-100.
- Galli E, Rocchi L, Carello R, Giampietro PG, Panei P, Meglio P. Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. *Eur Ann Allergy Clin Immunol*. 2015;47(2):41-47.
- Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, KronbergKippila C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr Allergy Immunol*. 2010;21:29-37.
- Kim SW, Sung SM. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in pediatrics. *Allergy*. 2013;68:439.
- Hovsepian S, Amini M, Aminorroaya A, Amini P, Iraj B. Prevalence of Vitamin D Deficiency among Adult Population of Isfahan City, Iran. *J Health Popul Nutr* [internet]. 2011;29(2):149-55. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21608424>
- Muehleisen B, Gallo RL. Vitamin D in allergic disease: shedding light on a complex problem. *J Allergy Clin Immunol*. 2013;131:324-9.
- Cheon BR, Shin JE, Kim YJ. Relationship between serum 25-hydroxyvitamin D and interleukin-31 levels, and the severity of atopic dermatitis in children. *Korean J Pediatr*. 2015;58(3):96-101.
- Thomsen SF. Atopic Dermatitis: Natural History, Diagnosis, and Treatment. *Hindawi Publishing- ISRN allergy*. 2014:1-7. Available from: <http://dx.doi.org/10.1155/2014/354250>
- Kim SW, Sung SM. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in pediatrics. *Allergy*. 2013;68:439.
- Galli E, Rocchi L, Carello R, Giampietro PG, Panei P, Meglio P. Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. *Eur Ann Allergy Clin Immunol*. 2015;47(2):41-47.
- Chiu YE, Havens PL, Siegel DH, Ali O, Wang T, Holland KE, et al. Serum 25-hydroxyvitamin D concentration does not correlate with atopic dermatitis severity. *J Am Acad Dermatol*. 2013;69:40-6.

29. Robl R, Uber M, Abagge KT, Lima MN, Carvalho VO. Serum vitamin D levels not associated with atopic dermatitis severity. *Pediatr Dermatol*. 2016;33(3):283-288.68
30. Nutten S. Atopic Dermatitis: Global Epidemiology and Risk Factors. *Ann Nutr Metab*. 2015;66(1):8-16.
31. Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J. Immunol*. 2000;164(5):2405–2411.
32. Piemonti L, Monti P, Sironi M et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *J. Immunol*. 2000;164(9):4443–4451.
33. Pyun BY. Natural History and Risk Factors of Atopic Dermatitis in Children. *Allergy Asthma Immunol Res*. 2015;7(2):101-105.
34. Piotrowska A, Wierzbicka J, dan Zmijewski A. Vitamin D in the Skin Physiology and Pathology. *Acta Biochimica Polonica*. 2016; 63 (1): 17-29.
35. Manousaki D, Paternoster L, Standi M, Moffatt MF, et al. Vitamin D Levels and Susceptibility to Asthma, Elevated Immunoglobulin E Levels, and Atopic Dermatitis: a Mendelian Randomization Study. *Plos Med*. 2017; 14 (5): 1-16.



This work is licensed under a Creative Commons Attribution