THE APPEAL OF VITAMIN D SUPPLEMENTATION IN ATOPIC DERMATITIS TREATMENT FOR CHILDREN : A LITERATURE REVIEW

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ABSTRAK

Dermatitis atopik (DA) adalah penyakit kulit yang umum terjadi pada anak-anak, yang menyebabkan kulit meradang, gatal, bersisik, dan kering. DA mempengaruhi 15-20% populasi anak di dunia. DA dapat menurunkan kualitas hidup, terutama pada kasus yang parah. Kulit gatal menyebabkan gangguan tidur, baik pada anak maupun orang tua, rasa malu, biaya pengobatan dan rendahnya produktivitas secara keseluruhan. Oleh karena itu, tinjauan literatur ini bertujuan untuk menyelidiki secara komprehensif daya tarik suplementasi vitamin D sebagai pilihan pengobatan tambahan terhadap DA. Tujuan dari tinjauan ini adalah untuk mengetahui peran vitamin D dalam pengobatan DA dengan mengumpulkan dan menganalisis temuan terkini dalam literatur ilmiah. Penelitian mengambil sumber database akademis dari Pubmed, Science Direct, dan Chocrane dengan menggunakan kata kunci yang relevan seperti "vitamin D", "kalsiferol", "dermatitis atopik", dan "anak-anak" yang setelah dilakukan screening diambil 11 artikel untuk dianalisis lebih lanjut. . Pasien DA umumnya memiliki kadar serum vitamin D yang lebih rendah dan pasien dengan kadar serum 25(OH)D yang lebih rendah lebih mungkin menderita DA sedang dan berat. Vitamin D oral (1000-1600 IU/hari) secara signifikan meningkatkan gejala klinis dan mengurangi keparahan penyakit berdasarkan indeks SCORAD. Pemahaman mendalam tentang manfaat suplementasi vitamin D dalam pengobatan DA pada anak-anak adalah penting untuk pengembangan strategi terapi DA, terutama dengan mempertimbangkan dosis, usia, wilayah geografis, karena pengobatan DA yang memadai pada anak-anak dapat mencegah perkembangan lebih lanjut. dari pawai atopik.

Kata kunci : anak-anak, dermatitis atopik, suplementasi, vitamin D

ABSTRACT

Atopic dermatitis (AD) is a common skin disease in children, that causes skin to be inflamed, itchy, flaky and dry. AD affects 15-20% children population in the world. AD may lower quality of life, especially the severe cases. Itchy skin lead to sleep disturbances, both children and parents, embarassment, treatment expense and low productivity overall. Therefore, this literature review aims to investigate comprehesively the appeal of vitamin D supplementation as an additional treatment option against AD. The purpose of this review is to determine the role of vitamin D in AD treatment by collecting and analyzing current findings in the scientific literature. The research took academic database sources from Pubmed, Science Direct, and Chocrane using relevant keywords such as "vitamin D", "calciferol", "atopic dermatitis", and "children" which after screening, 11 articles were taken for further analysis. AD patients generally have lower vitamin D serum levels and those with lower 25(OH)D serum levels are more likely to suffer moderate and severe AD. Oral vitamin D (1000-1600 IU/day) significantly increased clinical symptoms and reduced disease severity based on SCORAD index. A deep understanding of the appeal of vitamin D supplementation in AD treatment for children is important for the development of AD therapeutic strategies, especially with the consideration of dosage, age, geographical area, as adequate treatment of AD in children may prevent further progression of atopic march.

Keywords *: vitamin D, supplementation, atopic dermatitis, children*

INTRODUCTION

Atopic dermatitis (AD) is a chronic skin inflammation that typically appears during infancy or early childhood. AD affects around 1-3% adult and 15-20% children population in

the world. It primarily affect young children, aged six years old under. It happens increasingly common in developed countries especially urban locations (Bylund, et al., 2020). In Indonesia, the prevalence of AD increases significantly in the last decade. Latest evidence suggests that atopic dermatitis is a primary skin barrier defect that may promote the development of other allergic conditions, such as asthma or allergic rhinitis. It highlights the importance of preventing atopic dermatitis, which may precedes "atopic march" in children (Fuxench, et al., 2024). Atopic dermatitis may lower quality of life, especially the severe cases. Patients with AD suffer itch, flaked and dry skin. Itchy skin lead to sleep disturbances, both children and parents, embarassment, treatment expense and low productivity overall (Wollenberg, et al., 2023). Few additional supplementation have been found to minimize the severity of AD, including probiotic, gamma linolenic acid, omega-3 fatty acid, and vitamin D (Lim, et al., 2024).

Mean vitamin D levels were found lower in AD patients. Studies suggest that vitamin D may affect the natural course of disease in AD (Dogru, 2017). Vitamin D may play protective role in the pathogenesis of atopic dermatitis (Kim, 2016). Vitamin D has an important role not only in maintaining bone, but also supporting immune system function in inflammatory disorders, including AD (Kim, et al., 2019). Vitamin D has therapeutic effects such as stimulating the immune system by modulating B cells, dendritic cells, interleukin-10, and interleukin-17. Vitamin D also increases barrier function and skin barrier restoration (Limanda, et al., 2024). The primary treatment of AD typically uses corticosteroids and immunosuppresants, which cause considerable side effects (Lyons, et al., 2015). Therefore, the aim of this literature review is to further investigate comprehesively the appeal of vitamin D supplementation as an additional treatment option against AD.

METHOD

This research uses descriptive research model which is a literature review. Literature review is a research method to identify, evaluate and interpret all relevant research results related to a particular research question. The method of collecting data is by reading and managing writing materials from various sources, including journals, books, documentation, the internet and libraries. This literature review is grouping data that meets the inclusion criteria, which are then collected and a summary is made, including the name of the researcher, year of publication of the journal, research title, method and results. To further clarify the analysis, the abstract and full text of the journal are examined. The data that has been collected is then searched for similarities and differences and then discussed to draw conclusions.

The study uses inclusion criteria, includes articles that directly discuss the role of vitamin D on atopic dermatitis in children. The article selected are cross sectional, case control, cohort study, randomized controlled trial, systematic review, and meta-analysis published in a peer-reviewed journal within the last ten years to ensure the relevance and latest information. Meanwhile, exclusion criteria are unavailable full text articles, not written in English or Indonesian, publications that are not supported by empirical data are also excluded from the analysis. The articles were collected through the use of PubMed, Science Direct, and Chocrane databases using the keyword "vitamin D", "calciferol", "atopic dermatitis", and "children". The article analyzed were only articles with available full text that were written in English and Indonesian published from 2015 to 2024. Twelve articles that match the criteria were selected to be analyzed in this literature review.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) assessment diagram to determine the articles is as follows (Diagram 1).

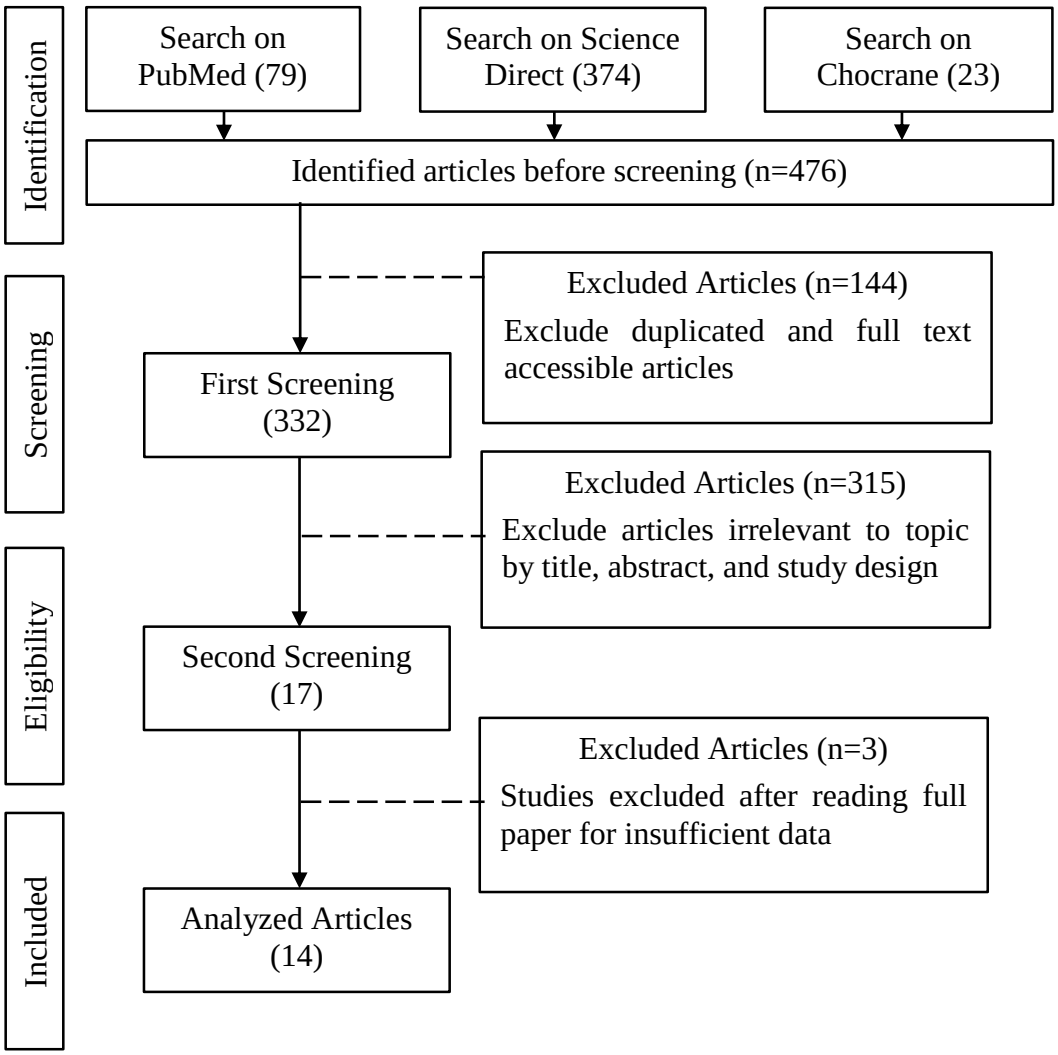

Diagram 1. Systematic Reviews and Meta-Analysis (PRISMA)

RESULTS

Table 1. Research Result Literature Review

Author (Year)	Title	Design, Respondent	Method	Result
Camargo, C.A. Jr, et al. (2014)	Randomized Trial of Vitamin D Supplementation on for Winter-Related Atopic Dermatitis In Children	Randomized double-blind placebo-controlled study, 107 children with winter-related atopic dermatitis	Subjects were randomly administered oral vitamin D (1000 IU/day) versus placebo for 1 month	Vitamin D supplementation over placebo for a month produced a clinically and statistically significant improvement in EASI score compared to placebo (adjusted mean change: -6.5 vs -3.3, respectively; P = .04). Increase in Investigator's Global Assessment showed better results in vitamin

				D compared to placebo (P = .03).
Aldaghi, M., et al. (2020)	The Effect of Multistrain Synbiotic and Vitamin D3 Supplements on The Severity of Atopic Dermatitis Among Infants Under 1 Year of Age: A Double-Blind, Randomized Clinical Trial Study	Randomized double-blind clinical trial study, 81 infants with atopic dermatitis	Subjects were randomly supplemented with five drops/day of synbiotic in addition to routine treatment, versus vitamin D3 1000 IU/day in addition to routine treatment, versus control group who received routine treatments only for 2 months.	The mean SCORAD scores were substantially decreased in the synbiotic (bxy: −13.90, 95% CI, −20.99, −6.81; p < .001) and vitamin D3 (bxy: −12.38, 95% CI, −19.33, −5.43; p = .001) groups as compared to control group.
Raj, K. A. P., et al. (2022)	Correlation of Serum Vitamin D Levels With Severity of Pediatric Atopic Dermatitis and The Impact of Vitamin D Supplementation on Treatment Outcomes	Prospective cohort study, 35 pediatric patients with atopic dermatitis and deficiency in vitamin D	Subjects were supplemented with 1000 IU/day of vitamin D for three months. Serum vitamin D levels and SCORAD scores were measured at the beginning and end of three months in all patients.	The baseline vitamin D levels in both groups did not have significant difference (p = .97). There was a significant (p = .02) inverse relationship between the atopic dermatitis severity and baseline serum vitamin D levels (r = −0.52). Maximum reduction in SCORAD (41.4 ± 12.7) after 3 months of vitamin D supplementation was seen in severe atopic dermatitis and the minimum (2.4 ± 13.2) in mild atopic dermatitis (p = .0003).
Borzutzky, A., et al. (2014)	Vitamin D deficiency rickets in an adolescent with severe atopic dermatitis	Case study, 14 year-old girl with severe atopic dermatitis	Subject was treated with vitamin D in accordance to rickets guideline	Treatment with Vitamin D increased her 25OHD level to 44 nmol/L, with normalization of alkaline phosphatase, parathyroid hormone, and calcium. Moreover, we observed a dramatic improvement in her AD severity with Vitamin D treatment.
Sanmartin, R., et al. (2020)	The Association Between Atopic Dermatitis and Serum 25-Hydroxyvitamin D in Children: Influence of Sun Exposure,	Cross sectional study, 134 patients with atopic dermatitis and 105 healthy controls, aged 0 to 14 years old	Subjects were assessed for these parameters: age, sex, body mass index (BMI), atopic dermatitis severity, atopic history, Fitzpatrick skin type, dietary vitamin D intake,	25(OH)D serum levels were significantly lower in moderate and severe atopic dermatitis than in mild atopic dermatitis, although the correlation was only significant in subjects with light Fitzpatrick skin type (mean(SD) 36.7 (11.9) ng/mL;

	Diet, and Atopy Features-A Cross-Sectional Study		sun-induced vitamin D production, sunscreen usage, serum 25(OH)D levels	moderate 28.8 [11.5] ng/mL; and severe 27.6 [12.1] ng/mL, P = .045).
Lee, Y.W., et al. (2019)	Serum 25-Hydroxyvitam in D Deficiency in Malaysian Children with Severe Atopic Dermatitis	Case control study, 135 children patient with atopic dermatitis and 65 children without atopic dermatitis	Subjects were examined for serum 25-hydroxyvitamin D [25(OH)D] levels and SCORAD index	The 25(OH)D serum levels measured in children with atopic dermatitis was not statistically different from children without. Meanwhile, 25(OH)D serum levels were significantly lower in children with severe atopic dermatitis compared to those with mild-to-moderate [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 atopic dermatitis was 3.82 times the children with non-severe atopic dermatitis (95% confidence level: 1.13, 12.87).
Kim, M.J., et al. (2016)	Vitamin D Status and Efficacy of Vitamin D Supplementati on in Atopic Dermatitis: A Systematic Review and Meta-Analysis.	Systematic review and meta-analysis study of seven observational studies and four clinical trials	Assessment of studies from MEDLINE, EMBASE, and Cochrane up to May 2015	Compared with control groups, the serum 25(OH)D levels were lower in the patients with atopic dermatitis of all ages, and primarily in the pediatric patients (mean = −3.03 ng/mL; 95% CI = −4.76 to −1.29). Additionally, the SCORAD index and EASI score reduced post vitamin D supplementation (mean = −5.85; 95% CI = −7.66 to −4.05).
Xiang, J., et al. (2019)	Comorbidity of Vitamin A and Vitamin D Deficiency Exacerbates the Severity of Atopic Dermatitis in Children	Cross sectional study, 81 patients with atopic dermatitis and 65 healthy controls, aged 2 to 12 years old	Parameters in subjects were examined as follows: SCORAD levels, total IgE levels, peripheral blood eosinophil counts, vitamin A levels, vitamin D levels	Serum vitamin D and vitamin A levels were significantly lower in children with AD than in normal children ($p < 0.001$, $p = 0.0423$). The SCORAD scores were significantly higher in atopic dermatitis patients with deficiency in vitamin D and

				vitamin A, than in other patients. Inverse correlations were found statistically significant between eosinophil counts and vitamin D and vitamin A levels.
Huang, C.M., et al. (2018)	Effects of Vitamin D Levels and Supplementation on Atopic Dermatitis: A Systematic Review	Systematic review, of four randomized control trial, five cohort, six case control and six cross sectional studies	Assessment of publications with children aged 0 to 18 years old with atopic dermatitis, from Ovid MEDLINE, EMBASE, and Cochrane databases up to May 2015	Significant inverse correlation was observed between serum vitamin D level and atopic dermatitis severity was described in 62.5% (10 of 16) publications. There were 67% (4 of 6) studies that reported a significant improvement in atopic dermatitis severity after vitamin D supplementation.
Mansour, N.O., et al. (2020)	The Impact of Vitamin D Supplementation as An Adjuvant Therapy on Clinical Outcomes in Patients with Severe Atopic Dermatitis: A Randomized Controlled Trial	Randomized controlled trial, 92 children aged 5 to 16 years old with severe atopic dermatitis	The patient groups were randomized to receive vitamin D3 1600 IU/day or placebo, along with routine therapy of topical 1% hydrocortisone cream twice daily for 12 weeks.	The vitamin D3 group achieved a significant higher level of 25(OH)D ($P < .001$) compared to control group. The mean EASI score was significantly lower in the vitamin D3 group compared to placebo ($P = .035$). The percent change in EASI score from baseline differed significantly between the vitamin D3 group (56.44 ± 29.33) and placebo group (42.09 ± 19.22) after intervention ($P = .039$).
Park, J.S., et al. (2023)	Effect of Vitamin D on the Treatment of Atopic Dermatitis With Consideration of Heterogeneities: Meta-Analysis of Randomized Controlled Trials	Meta-analysis study of five randomized controlled trial	Assessment of studies were identified in the PubMed, EMBASE, MEDLINE, and Cochrane Library databases up to June 30, 2021	Vitamin D supplementation did not decrease AD severity, even when AD was classified as severe vs non-severe. However, vitamin D supplementation was found to be effective in the treatment of AD in RCTs that included both children and adults, but not in those that included only children. Geographic location was associated with a significant difference in the therapeutic effect of vitamin D

				supplementation. Moreover, vitamin D supplementation of > 2,000 IU/day decreased AD severity, but supplementation ≤ 2,000 IU/day did not. Vitamin D supplementation, in general, was not effective for the treatment of AD. However, vitamin D supplementation might provide a therapeutic effect depending on the geographic location and dose of supplementation.
Hidayati, et al. (2022)	Efficacy of Vitamin D Supplementation on The Severity of Atopic Dermatitis in Children: A systematic review and meta-analysis	Systematic review, meta-analysis study of four articles	Assessment of literatures were identified in the PubMed, Cochrane Library, ProQuest, Google Scholar, and a clinical trial website, ClinicalTrials.gov	There was a meaningful difference of -0.93 (95%CI -1.76, to -0.11, p<0.001) of patient outcome, but there was no difference in cure rate (risk ratio 1.46 (95%CI 0.72, to 2.97, p=0.008) in vitamin D supplementation groups compared to placebo groups. Vitamin D supplementation in paediatric atopic dermatitis patients could offer improvement of disease severity but the recommended dose and duration of administration cannot be concluded yet.
Hattangdi-Haridas, et al. (2019)	Vitamin D Deficiency and Effects of Vitamin D Supplementation on Disease Severity in Patients with Atopic Dermatitis: A Systematic Review and Meta-Analysis in Adults and Children	Meta-analysis of fourteen studies	Assessment of publications with both children and adult with atopic dermatitis, from MEDLINE, EMBASE, and COCHRANE databases up to February 2018	The paediatric atopic dermatitis population are at high-risk of lower serum vitamin D. Supplementation of vitamin D around 1600 IU/daily results in a clinically significant AD severity reduction.
Li, et al. (2022)	Vitamin D Supplementation and Allergic	Systematic review, meta-analysis study of thirty two	Search of articles from MEDLINE, Embase, Web of Science, the	Vitamin D supplementation significantly reduces the severity of atopic

	Diseases during Childhood: A Systematic Review and Meta-Analysis	randomized controlled studies	Cochrane library, and three Chinese databases up to 15 August 2022	dermatitis in children, with reduced SCORAD or EASI scores in children with atopic dermatitis compared with placebo (standard mean difference = −0.5, 95% CI: −0.87 to −0.12, p = 0.009).

DISCUSSION

Table 1 presents the reviewed literatures, that contain several concepts around atopic dermatitis and vitamin D. It shows that vitamin D has inverse relationship with the severity level of atopic dermatitis in children. Paediatric patients with AD also relatively has lower vitamin D serum in their blood. Vitamin D supplementation significantly reduce clinical symptoms in moderate and severe atopic dermatitis, based on the SCORAD or EASI score.

Atopic dermatitis (AD), often reffered to as eczema, is a chronic cutaneous condition that causes inflammation, irritation, and redness of the skin. It is characterized by pruritus, eczematous plaques, dry skin, and impaired skin barrier (Wollenberg, et al., 2023). AD has the risk of causing significant distressed quality of life in both children and adults. AD mainly affects young children under the age of six years old with predilection areas in the face, scalp, and extensor surfaces (Aldaghi, et al., 2022). The causes of AD include both genetic and environmental factors. Patients with family history of atopic conditions, such as atopic dermatitis, asthma, and allergic rhinitis, often have impaired epidermal barrier function due to mutation of filaggrin (FLG) gene that affect decreased water retention and elevated susceptibility to allergens and irritants, which leads to further immune responses (Zhang, et al., 2024). The immune system in AD is deviated towards a Th2-dominant response, generating an increased production of pro-inflammatory cytokines (interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-31 (IL-31)), that instigate inflammation and pruritus. Exacerbation of AD is also caused by environmental factors such as limited exposure to sunlight, living in dry climate area, and consuming high sugars and polyunsaturated fatty acids diet (Özdemir, 2024).

Vitamin D supports immune system and reduces local and systemic inflammation by modulating cytokine production, inhibiting T-helper cell (Th-1 and Th-17) proliferation, and decreasing IL-2, IFN-y, and IL-4 secretion. AD is a condition where skin barrier function is compromised and cathelicidin levels are altered. An altered cytokine suppresses AMPs expression, specifically Th2 cytokines (IL-4 and IL-13) (Di Filippo, et al., 2015). Vitamin D promotes toll-like receptor and antimicrobial peptides (cathelicidin, B defensin), improves external susceptibility to pathogens by inducing LL-37 and reduces cytokine release and inflammation (Vestita, et al., 2015). Vitamin D also inhibitis pro-inflammatory cytokines (IL-12, IFN-y), suppresses IgE release, and increases IL-4, IL-5, IL-10 production in order to suppress dendritic cell activity and mast cell release (Kim et al., 2016; Hattangdi-Haridas et al., 2019).

The effect of vitamin D supplementation on AD shows a significant clinical improvement compared to placebo (Camargo, 2014; Mansour, et al., 2020; Hattangdi-Haridas et al., 2019). Vitamin D supplementation also reduces the severity based on SCORAD or EASI score (Aldaghi, et al., 2020; Raj, et al., 2022; Kim, et al., 2016; Huang, et al., 2018; Hidayati, et al., 2022). Study conducted by Borzutzky, et al. showed meaningful results, namely a decrease in the SCORAD index using oral vitamin D. However, other article showed significant results, only in patients with light Fitzpatrick skin type (Sanmartin, et al., 2020). Other study also shows vitamin D supplementation did not decrease AD severity (Park, et al., 2023). This can be

influenced by various factors, such as dosage, age, and geographic area. Therapeutic effect of vitamin D supplementation may be reduced in place with minimum ultraviolet light. AD patients generally measured lower vitamin D serum levels and a decrease in SCORAD index, that a study show AD children 3.82 times more likely to have vitamin D deficiency (Lee, et al., 2019; Kim, et al., 2016; Xiang, et al., 2019). Serum vitamin D levels in AD patients are influenced by various factors, namely age, severity, and race. Studies suggest causal relationship between vitamin D levels in blood and the risk of atopic dermatitis (Ren, et al., 2022). There was an inverse correlation between eosinophil counts and vitamin D levels, which means AD patients who in theory have higher eosinophil counts, also have decreased vitamin D levels. (Xiang, et al., 2019).

Compared to previous research, the findings suggest that vitamin D supplementation has its own upsides and downsides. While it results in better clinical symptoms and severity of AD, the benefits of vitamin D supplementation are more effective in particular situations, such as available UV-B light exposure, melanin composition in skin, and sunscreen usage (Park, 2023; Sanmartin, 2020). It should be taken into consideration in choosing vitamin D supplementation as therapy in AD regarding enough UV-B exposure and dosage depending on melanin skin composition. The shortcomings of this research are the recommended dose and duration of vitamin D have not been decided in any studies or guidelines, that may be applied to all population, which need to be researched further for easier clinical application.

CONCLUSION

From the results of the study, it can be concluded that a comprehensive understanding of vitamin D in maintaining immune system is important in alternate supplementation treatment in moderate and severe atopic dermatitis, assessed by SCORAD index. Analysis of the literatures show the trend of vitamin D deficiency in AD patients, which cause study trials using vitamin D to give satisfactory results. However, differences outcome of AD patients in vitamin D supplementation are also influenced by age, dosage, preparation, and geographic area. Therefore, this study might be developed by conducting further research to determine the proper dosage of vitamin D supplementation with the consideration of the patients age and geographic area.

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