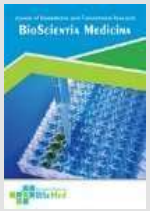
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Effectiveness of Vitamin D Supplementation in Reducing Atopic Dermatitis Severity in Children: A Meta-Analysis

Ni Putu Junika Putri[1*], I Wayan Gede Sutadarma[2]

[1]General Practitioner, Famili Husada Hospital, Gianyar, Indonesia

[2]Department of Clinical Nutrition, Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

ARTICLE INFO

Keywords:
Atopic dermatitis
Children
EASI
SCORAD
Vitamin D

***Corresponding author:**
Ni Putu Junika Putri

E-mail address:
junikaputri77@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i2.1193

A B S T R A C T

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease that commonly affects children, with increasing prevalence worldwide. Vitamin D has demonstrated immunomodulatory effects, suggesting a potential role in AD management. This meta-analysis aimed to evaluate the effectiveness of vitamin D supplementation in reducing AD severity in children. **Methods:** A systematic search of PubMed, Science Direct, and Cochrane databases was conducted for randomized controlled trials (RCTs) published between 2012 and 2024, investigating the effects of vitamin D supplementation on AD in children. The primary outcome was the change in SCORAD (SCORing Atopic Dermatitis) or EASI (Eczema Area and Severity Index) scores. Meta-analysis was performed using Review Manager (RevMan 5.4) software. **Results:** Four RCTs met the inclusion criteria, comprising a total of 234 participants. The meta-analysis revealed a significant reduction in SCORAD scores (-2.83; 95% CI: -4.9, -0.76) and EASI scores (-0.41; 95% CI: -0.70, -0.13) in the vitamin D supplementation groups compared to the control groups. A combined analysis of both scoring systems further confirmed the overall significant effect of vitamin D in reducing AD severity (-1.57; 95% CI: -2.78, -0.36). **Conclusion:** Vitamin D supplementation is effective in improving AD symptoms in children. Further large-scale RCTs are warranted to determine the optimal dosage and duration of vitamin D supplementation for AD management in children.

1. Introduction

Atopic dermatitis (AD), also known as eczema, is a chronic inflammatory skin disease characterized by dry skin, intense itching, and recurrent eczematous lesions. It is one of the most common skin disorders in children, affecting an estimated 15-20% of children worldwide. The prevalence of AD has been steadily increasing over the past few decades, particularly in industrialized countries, posing a significant public health concern. This rise is attributed to a complex interplay of genetic and environmental factors, including changes in lifestyle, diet, and exposure to allergens and pollutants. AD typically manifests in early childhood, with the majority of cases developing before the age of 5 years. The clinical presentation of AD varies depending on the age of the individual and the severity of the disease. In infants, AD often presents as red, weeping, and crusted lesions on the face, scalp, and extensor surfaces of the limbs. In older children and adults, AD tends to involve the flexural surfaces of the limbs, such as the antecubital and popliteal fossae, as well as the neck and wrists. The chronic and relapsing nature of AD can significantly impact the quality of life of affected individuals and their families. The intense itching associated with AD can lead to sleep disturbances, irritability, and difficulty concentrating, affecting a child's performance in school and social interactions. The

pathogenesis of AD is complex and multifactorial, involving an interplay of genetic susceptibility, immune dysregulation, and skin barrier dysfunction. Genetic factors play a crucial role, with a family history of AD being a strong risk factor. Several genes have been identified as being associated with AD, including those involved in skin barrier function, immune regulation, and inflammatory responses. Immune dysregulation is another key feature of AD, characterized by an imbalance between T helper type 1 (Th1) and T helper type 2 (Th2) immune responses. In AD, there is a predominance of Th2 responses, leading to the production of inflammatory cytokines that contribute to the development of skin inflammation and itching. Skin barrier dysfunction is also a major contributor to AD, as it allows irritants, allergens, and microbes to penetrate the skin, triggering inflammation and exacerbating the disease.[1-4]

The management of AD typically involves a multifaceted approach aimed at reducing symptoms, preventing flares, and maintaining skin hydration. These strategies include gentle skincare practices, such as using lukewarm water for bathing, avoiding harsh soaps and detergents, and regularly moisturizing the skin with emollients. Identifying and avoiding triggers that can exacerbate AD is also crucial. Common triggers include allergens such as dust mites, pollen, and pet dander, as well as irritants such as wool, synthetic fabrics, and certain chemicals. Topical medications, such as corticosteroids and calcineurin inhibitors, are often used to reduce inflammation and itching during flares. In severe cases, systemic medications, including corticosteroids and immunosuppressants, may be necessary. Other management strategies include wet wraps, which involve applying wet bandages to the affected skin after applying topical medications, and phototherapy, which involves exposure to ultraviolet (UV) light. Despite the availability of these management strategies, AD can be a challenging condition to control, and many individuals continue to experience significant symptoms and impairment in their quality of life. Therefore, there is a need for additional therapeutic options for AD management. Vitamin D is a fat-soluble vitamin that is essential for calcium absorption and bone health. In recent years, vitamin D has also gained recognition for its immunomodulatory effects. Vitamin D receptors are expressed on various immune cells, including T cells, macrophages, and dendritic cells. Vitamin D can modulate the function of these cells, influencing both innate and adaptive immune responses. Studies have shown that vitamin D can suppress the production of pro-inflammatory cytokines, promote the production of anti-inflammatory cytokines, and enhance the function of regulatory T cells, which help to suppress immune responses and maintain immune tolerance.[5-7]

Given its immunomodulatory effects, vitamin D has been investigated as a potential therapeutic agent for various inflammatory diseases, including AD. Several observational studies have reported an association between vitamin D deficiency and an increased risk of AD, as well as increased disease severity. Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D [25(OH)D] level of less than 20 ng/ml. Optimal vitamin D levels are considered to be between 30 and 60 ng/ml. A number of randomized controlled trials (RCTs) have investigated the effects of vitamin D supplementation on AD in children. However, the results of these trials have been inconsistent. Some trials have shown significant improvements in AD symptoms with vitamin D supplementation, while others have not. The reasons for these inconsistencies may include differences in study design, participant characteristics, vitamin D dosages, and treatment durations. To provide a more comprehensive understanding of the role of vitamin D in AD management, we conducted a meta-analysis of RCTs to evaluate the effectiveness of vitamin D supplementation in reducing AD severity in children.[8-10] This meta-analysis aimed to synthesize the available evidence and provide a more definitive answer to the question of whether vitamin D supplementation is beneficial for children with AD.

2. Methods

A comprehensive and systematic search of three prominent electronic databases, namely PubMed, Science Direct, and Cochrane Library, was undertaken. The search encompassed all relevant articles published from January 1st, 2012, to October 31st, 2024. The following search string was adapted for each database, ensuring consistency and comprehensiveness; ("vitamin D"OR"cholecalciferol" AND ("dermatitis, atopic" OR "eczema") AND ("child" OR "pediatric") AND ("randomized controlled trial "OR "clinical trial"). The search results from each database were compiled and de-duplicated. The titles and abstracts of the remaining articles were screened independently by two reviewers. Any discrepancies were resolved through discussion and consensus, or by consulting a third reviewer if necessary.

Studies were considered eligible for inclusion based on the following criteria; Study design: Randomized controlled trials (RCTs) were exclusively included, as they provide the highest level of evidence for evaluating the effectiveness of interventions; Population: Studies focusing on children (age < 18 years) diagnosed with atopic dermatitis were included; Intervention: The intervention of interest was vitamin D supplementation in any form (e.g., vitamin D3, vitamin D2) and any dosage regimen; Comparator: The comparator group could be a placebo, no treatment, or standard care for atopic dermatitis; Outcomes: Studies were required to report at least one of the following primary outcome measures; SCORAD (SCORing Atopic Dermatitis) index: A validated tool for assessing the severity of atopic dermatitis, encompassing objective measures (e.g., extent of lesions, intensity of erythema) and subjective symptoms (e.g., pruritus, sleep loss); EASI (Eczema Area and Severity Index): Another validated tool for measuring the severity of atopic dermatitis, evaluating the extent and severity of erythema, induration/papulation, excoriation, and lichenification across different body regions; Language: Studies published in English were included to ensure accurate interpretation and analysis; Publication type: Full-text articles were required for inclusion, excluding abstracts, conference proceedings, and unpublished data. Studies were excluded from the meta-analysis if they met any of the following criteria; Study design: Non-randomized studies, observational studies, case reports, reviews, and editorials were excluded; Population: Studies involving adults or mixed populations of children and adults were excluded; Intervention: Studies evaluating interventions other than vitamin D supplementation (e.g., topical corticosteroids, phototherapy) were excluded; Outcomes: Studies not reporting SCORAD or EASI scores as outcome measures were excluded; Language: Studies not published in English were excluded; Publication type: Studies not available as full-text articles were excluded.

Data from the included studies were extracted independently by two reviewers using a standardized data extraction form. This form was piloted on a subset of studies to ensure clarity and consistency. The following data elements were extracted; Study characteristics: First author's last name, year of publication, study design, country of study, sample size (total number of participants), number of participants in each intervention group; Participant characteristics: Mean age of participants, sex distribution (percentage of males and females), the severity of atopic dermatitis (e.g., mild, moderate, severe), baseline vitamin D levels (if reported); Intervention characteristics: Type of vitamin D supplementation (e.g., vitamin D3, vitamin D2), the dosage of vitamin D supplementation, frequency of administration, duration of supplementation; Outcome data: Mean change in SCORAD index from baseline to endpoint, standard deviation (SD) of the change in SCORAD index, mean change in EASI score from baseline to endpoint, standard deviation (SD) of the change in EASI score.

The methodological quality of the included RCTs was assessed independently by two reviewers using the Cochrane Risk of Bias tool. This tool evaluates the risk of bias across several domains, including; Random sequence generation: Assesses the adequacy

of the method used to generate the allocation sequence (e.g., random number table, computer-generated randomization); Allocation concealment: Assesses whether the allocation sequence was concealed from those enrolling participants, preventing selection bias; Blinding of participants and personnel: Assesses whether participants and personnel administering the interventions were blinded to the treatment assignment; Blinding of outcome assessment: Assesses whether those assessing the outcomes were blinded to the treatment assignment; Incomplete outcome data: Assesses the extent of missing outcome data and whether it was addressed appropriately in the analysis; Selective reporting: Assesses whether the study protocol was available and whether all pre-specified outcomes were reported; Other bias: Assesses any other potential sources of bias (e.g., funding source, conflicts of interest). Each domain was rated as "low risk," "high risk," or "unclear risk" of bias. Disagreements between reviewers were resolved through discussion and consensus, or by consulting a third reviewer if necessary.

The meta-analysis was performed using Review Manager (RevMan 5.4) software, a widely used software package for conducting systematic reviews and meta-analyses. The primary outcome measures were the mean change in the SCORAD index and EASI score from baseline to endpoint. The mean difference (MD) and 95% confidence interval (CI) were calculated for each study and pooled across studies using a random-effects model. This model assumes that the true effect size varies between studies, providing a more conservative estimate of the overall effect. Heterogeneity between studies was assessed using the I2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. An I2 value of 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, and 75% indicates high heterogeneity. Publication bias was assessed visually using a funnel plot, which plots the effect size of each study against its standard error. Asymmetry in the funnel plot may suggest publication bias, where smaller studies with non-significant results are less likely to be published.

Sensitivity analyses were planned to assess the robustness of the findings to various factors, including; Risk of bias: Excluding studies with a high risk of bias in any domain; Dosage of vitamin D: Analyzing studies with different dosages separately; Duration of supplementation: Analyzing studies with different durations separately. Subgroup analyses were planned to explore potential sources of heterogeneity, including; Age of participants: Analyzing studies with different age groups separately; Severity of atopic dermatitis: Analyzing studies with different severities separately. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical approval was not required for this study, as it involved the analysis of published data.

3. Results

Table 1 provides a summary of the four randomized controlled trials (RCTs) included in the meta-analysis evaluating the effectiveness of vitamin D supplementation in reducing atopic dermatitis (AD) severity in children. The table lists four studies from various locations (Iran, Mexico, Mongolia, and Egypt) published between 2012 and 2020. This suggests a global interest in exploring vitamin D's role in managing childhood AD. All included studies are RCTs, the gold standard for evaluating treatment effectiveness. This strengthens the reliability of the meta-analysis findings. The studies involved children with AD, with average ages ranging from 9 to 12.9 years. The sample sizes varied from 53 to 107 participants. All studies investigated vitamin D3 supplementation at different dosages (1000 IU/day to 5000 IU/day) and durations (1 month to 3 months). This variation allows for exploring potential dose-response relationships. Two common scoring systems were used to measure AD severity: SCORAD (SCORing Atopic Dermatitis) and EASI (Eczema Area and Severity Index). These are validated tools that provide objective and subjective measures of AD severity. All

four studies reported significant improvements in AD symptoms in the vitamin D groups compared to the control groups. This provides preliminary evidence supporting the beneficial effects of vitamin D supplementation in children with AD.

Table 1. Characteristics of included studies.

Study	Year	Design	Country	Population and number of subjects	Dosage	Duration of administration	AD assessment	Results
Amestajani et al	2012	RCT	Iran	Children > 14 years E = 29 K = 24	Vitamin D3 1600 IU	2 months	SCORAD	Based on the SCORAD value index, the vitamin D group showed significant improvement in patients with mild, moderate, and severe AD (P<0.05).
Armendariz, et al		RCT	Mexico	Children average 12.9 years E=33K=32	Vitamin D3 5000 IU 1 time/day	3 months	SCORAD	At week 12, patients who had serum 25(OH)D levels ≥20 ng/ml showed lower SCORAD compared to patients who had levels <20 ng/ml (P <0.001).
Camargo, et al	2014	RCT	Mongolia	Children, average 9 years E = 58K = 49	Vitamin D3 1000IU 1 time/day	1 month	EASI	The average difference in EASI scores for the vitamin D supplementation group vs placebo was significant = -6.5 (8.8) vs -3.3(7.6); -3.2 (95% CI= -0.9 – -5.5) p=0.001.
Mansour, et al	2020	RCT	Egypt	Children average 12 years E = 47K = 45	Vitamin D31600 IU 1 time/ day	3 months	EASI	The average EASI score in the group given vitamin D vs placebo at the end of the study was significant= 20.42(14.6) vs 27.47 (10.1), p = 0.035.

Figure 1 illustrates the process of identifying and selecting studies for inclusion in the meta-analysis on the effectiveness of vitamin D supplementation in reducing atopic dermatitis (AD) severity in children; Identification: The researchers began by searching three databases (PubMed, Science Direct, and Cochrane) and identified a total of 273 records. This indicates a comprehensive search strategy. 24 duplicate records were identified and removed, leaving 249 unique records. This ensures that each study is considered only once. Further screening using automated tools (likely filters within the databases) removed 25 ineligible records, possibly those not related to the topic or not meeting basic inclusion criteria (e.g., not RCTs); Screening: The remaining 224 records were screened based on their titles and abstracts. This initial screening excluded 107 records that were not in English (5) or were not relevant to the research question (102). 97 full-text reports were assessed for eligibility based on pre-defined inclusion

and exclusion criteria; Included: After careful evaluation of the full-text reports, 93 studies were excluded because they were not RCTs (80) or the full-text was not available (4). This rigorous selection process ensures that only high-quality studies are included in the meta-analysis. Ultimately, 4 studies met all the inclusion criteria and were included in the meta-analysis.

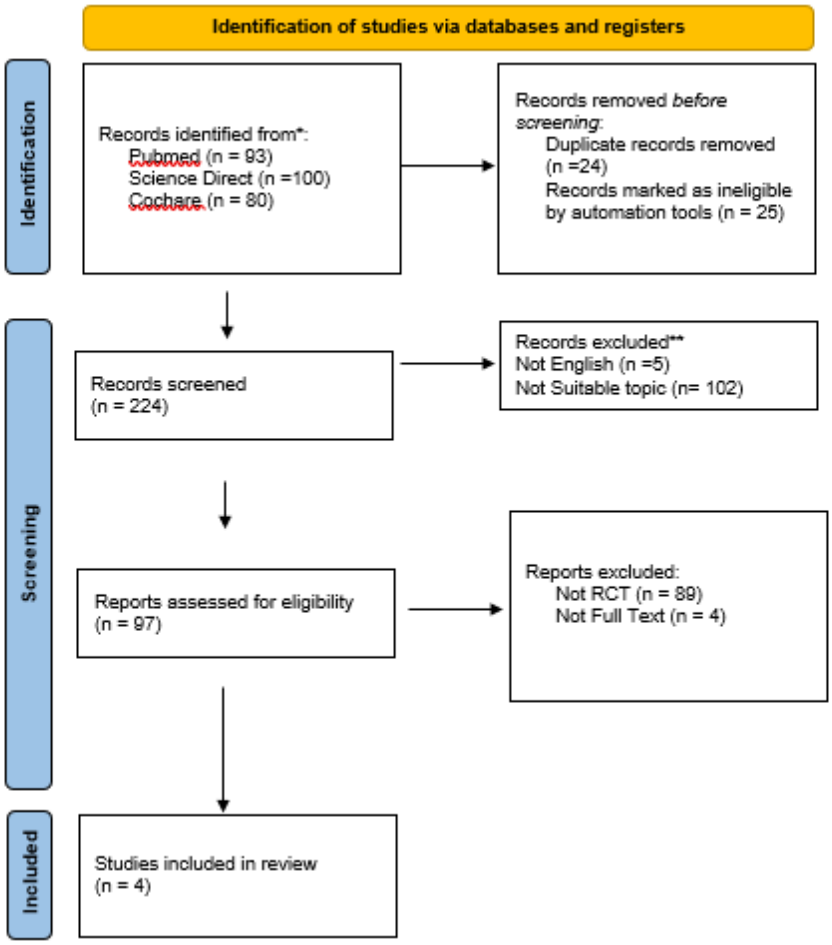


Figure 1. Study flow diagram.

Figure 2 provides a visual summary of the risk of bias assessment for each of the four studies included in the meta-analysis. The assessment uses the Cochrane Risk of Bias tool, which evaluates various aspects of study design and conduct that could introduce bias into the results. All four studies consistently show green circles across all domains, suggesting a low risk of bias across all assessed areas. This is a positive finding, increasing confidence in the reliability of the results from these studies. This indicates that the studies likely employed robust methods for randomizing participants, concealing allocation, blinding participants and assessors, and handling missing data, minimizing potential biases. While the figure suggests a low risk of bias, it's important to remember that this is an assessment based on the information reported in the studies. There's always a possibility of some undetected bias.

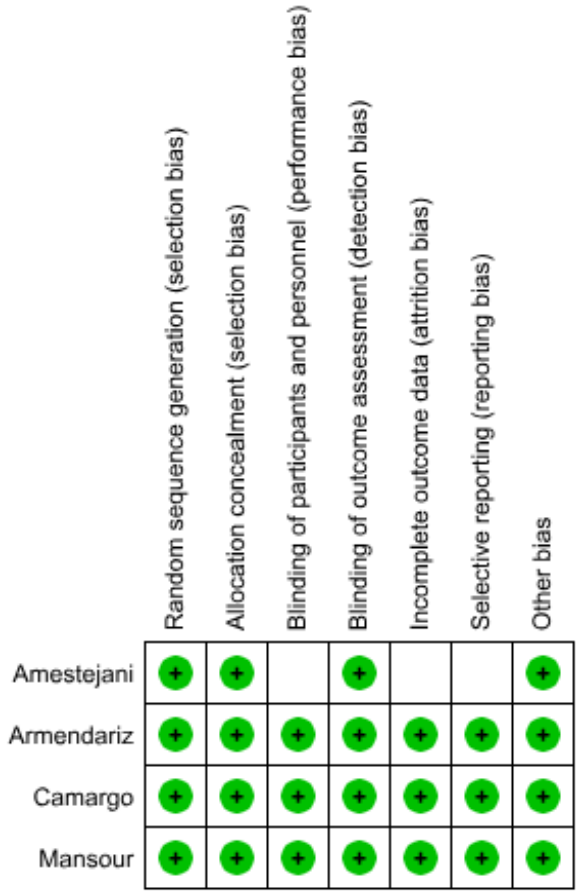


Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Green Positive: low risk; White: moderate risk.

Figure 1 summarizes the results of the meta-analysis on the effectiveness of vitamin D supplementation in reducing atopic dermatitis (AD) severity in children. It displays the findings of individual studies and the overall pooled effect; Studies and Subgroups: The plot is divided into two sections: 1.1.1 SCORAD and 1.1.2 EASI, representing the two scoring systems used to assess AD severity. Each study included in the meta-analysis is listed within its respective subgroup; Data for Each Study: For each study, the mean and standard deviation (SD) of the change in AD scores (SCORAD or EASI) are shown for both the vitamin D supplementation group and the control group. The weight assigned to each study reflects its contribution to the overall pooled effect. Larger studies with less variability typically receive higher weights; Effect Size and Confidence Intervals: The small squares represent the mean effect size (Std. Mean Difference) of vitamin D supplementation in each study. The size of the square corresponds to the study's weight. The horizontal lines extending from the squares represent the 95% confidence intervals (CI) for each study. A wider CI indicates greater uncertainty in the effect estimate; Pooled Effect: The diamonds at the bottom of each subgroup and the overall analysis represent the pooled effect size across all studies. The center of the diamond indicates the pooled mean difference, and its width represents the 95% CI; Heterogeneity: The I^2 statistic is reported for each subgroup and the overall analysis. This statistic measures the percentage of variability between studies that is due to heterogeneity rather than chance. High heterogeneity (I^2 = 93% for SCORAD, I^2 = 95% overall) suggests that the studies

are not all measuring the same effect, potentially due to differences in study design, populations, or interventions. Low heterogeneity (I^2 = 0% for EASI) indicates that the studies are more consistent in their findings; Overall Effect and Significance: The pooled effect for SCORAD shows a significant reduction in AD severity with vitamin D supplementation (Std. Mean Difference -2.83; 95% CI: -4.90, -0.76). The pooled effect for EASI also shows a significant reduction in AD severity (Std. Mean Difference -0.41; 95% CI: -0.70, -0.13). The combined analysis of both scoring systems confirms a significant overall effect of vitamin D in reducing AD severity (Std. Mean Difference -1.57; 95% CI: -2.78, -0.36).

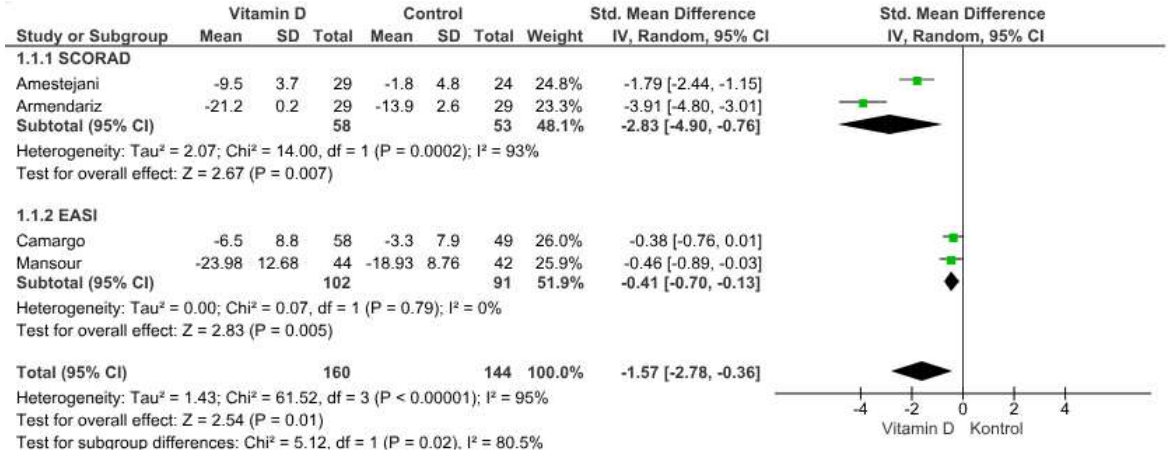


Figure 3. Forest plot of meta-analysis.

4. Discussion

Vitamin D, a fat-soluble vitamin, has long been recognized for its crucial role in calcium absorption and bone health. However, in recent decades, research has unveiled a far broader spectrum of biological activities attributed to vitamin D, extending its influence far beyond skeletal health. It is now understood that vitamin D plays a crucial role in regulating immune responses, influencing cell growth and differentiation, and modulating inflammatory processes. This expanded understanding of vitamin D's functions has sparked significant interest in its potential therapeutic applications for various health conditions, including atopic dermatitis (AD). While vitamin D's classical role in calcium homeostasis and bone health is well-established, its multifaceted involvement in immune regulation has garnered increasing attention in recent years. This immunomodulatory capacity of vitamin D is mediated through a complex interplay of molecular mechanisms, primarily involving the vitamin D receptor (VDR). The VDR, a nuclear receptor belonging to the steroid/thyroid hormone receptor superfamily, is expressed on a wide array of immune cells, including T cells, B cells, macrophages, and dendritic cells. This widespread expression underscores the pleiotropic effects of vitamin D on both innate and adaptive immune responses. The immunomodulatory actions of vitamin D are initiated by its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], which is produced in the kidneys through a tightly regulated process. 1,25(OH)2D enters the cell and binds to the VDR, inducing a conformational change that allows it to form a heterodimer with the retinoid X receptor (RXR). This VDR-RXR complex then translocates to the nucleus, where it binds to specific DNA sequences known as vitamin D response elements (VDREs) located in the promoter regions of target genes. This binding modulates the transcription of these genes, ultimately influencing the expression of proteins

involved in immune responses. Innate immunity, the body's first line of defense against invading pathogens, is significantly influenced by vitamin D. One of the key mechanisms by which vitamin D enhances innate immunity is through the induction of antimicrobial peptides (AMPs). AMPs are small proteins with broad-spectrum antimicrobial activity, playing a crucial role in eliminating pathogens and preventing infection. Cathelicidin, a potent AMP, is particularly responsive to vitamin D. Studies have shown that 1,25(OH)2D enhances the expression of cathelicidin in various cell types, including macrophages, keratinocytes, and epithelial cells. This increased cathelicidin production contributes to the killing of bacteria, fungi, and viruses, thereby strengthening the innate immune response. Beyond AMPs, vitamin D also modulates the function of key innate immune cells, such as macrophages and dendritic cells. Macrophages, phagocytic cells that engulf and destroy pathogens, are influenced by vitamin D in several ways. Vitamin D enhances macrophage chemotaxis, the process by which macrophages migrate to sites of infection. It also promotes phagocytosis, the engulfment and destruction of pathogens by macrophages. Furthermore, vitamin D modulates the production of cytokines by macrophages, influencing the inflammatory response. Dendritic cells, antigen-presenting cells that bridge the innate and adaptive immune systems, are also influenced by vitamin D. Vitamin D modulates the maturation and differentiation of dendritic cells, affecting their ability to present antigens to T cells and initiate adaptive immune responses. Adaptive immunity, the body's specific and targeted response to pathogens, is also profoundly influenced by vitamin D. Vitamin D exerts a significant impact on T cell differentiation and function, shaping the immune response to infection and inflammation. One of the most striking effects of vitamin D on adaptive immunity is its ability to promote the differentiation of regulatory T cells (Tregs). Tregs are a specialized subset of T cells that play a crucial role in maintaining immune tolerance and preventing excessive inflammation. They suppress the activity of other immune cells, preventing them from attacking the body's own tissues and maintaining immune homeostasis. Vitamin D enhances the differentiation of Tregs by increasing the expression of Foxp3, a transcription factor essential for Treg development and function. This increase in Tregs contributes to immune suppression and reduces inflammation, which is particularly relevant in the context of autoimmune and inflammatory diseases. Conversely, vitamin D suppresses the differentiation of pro-inflammatory Th1 and Th17 cells. Th1 cells produce interferon-gamma (IFN-γ), a cytokine that promotes cellular immunity and inflammation. Th17 cells produce IL-17, a cytokine implicated in the pathogenesis of various autoimmune and inflammatory diseases. By suppressing the differentiation of Th1 and Th17 cells, vitamin D can dampen the inflammatory response and promote immune tolerance. This effect is particularly important in conditions such as AD, where an imbalance in T helper cell responses contributes to the pathogenesis of the disease. In addition to its systemic immunomodulatory effects, vitamin D also exerts direct effects on the skin, which are particularly relevant in the context of AD. The skin is a major site of vitamin D synthesis, and it also expresses VDR, allowing it to respond directly to vitamin D. Vitamin D enhances the expression of filaggrin, a protein crucial for maintaining the skin's barrier function. Filaggrin helps to form a protective layer in the stratum corneum, the outermost layer of the skin, preventing water loss and the entry of allergens and irritants. Vitamin D regulates the proliferation and differentiation of keratinocytes, the predominant cell type in the epidermis. Vitamin D promotes the production of AMPs in the skin, contributing to the defense against pathogens. Vitamin D modulates the production of cytokines and chemokines in the skin, influencing the inflammatory response. In AD, the skin's barrier function is often compromised, leading to increased permeability to allergens and irritants. This increased permeability triggers inflammation and exacerbates the disease. Vitamin D, by enhancing skin

barrier function and modulating inflammation, may help to ameliorate AD symptoms. Atopic dermatitis (AD), commonly known as eczema, is a chronic inflammatory skin disease that affects millions of people worldwide, particularly children. It is characterized by a constellation of symptoms, including dry skin, intense itching, and recurrent eczematous lesions. The pathogenesis of AD is complex and multifactorial, involving an intricate interplay of genetic susceptibility, immune dysregulation, and skin barrier dysfunction. One of the hallmarks of AD is an imbalance in T helper (Th) cell responses, with a predominance of Th2 cytokines. Th cells are a type of white blood cell that play a central role in orchestrating the immune response. They can differentiate into various subsets, each with distinct functions and cytokine profiles. In AD, there is a shift towards a Th2-dominant immune response. Th2 cells produce cytokines such as interleukin-4 (IL-4), IL-5, and IL-13, which promote allergic inflammation and antibody production. Th2 cytokines recruit and activate inflammatory cells, leading to the redness, swelling, and heat associated with AD lesions. Th2 cytokines stimulate sensory nerves, causing the intense itching that is a hallmark of AD. Th2 cytokines can disrupt the skin's barrier function, making it more susceptible to allergens, irritants, and microbes. Vitamin D, with its diverse immunomodulatory properties, has emerged as a potential therapeutic agent for AD. Several lines of evidence suggest that vitamin D may play a beneficial role in AD by modulating the immune response and enhancing skin barrier function. Vitamin D has been shown to suppress the production of Th2 cytokines, including IL-4, IL-5, and IL-13. This suppression may help to reduce the inflammatory response in AD and alleviate symptoms such as itching and redness. The mechanisms by which vitamin D suppresses Th2 responses are complex and not fully understood. Vitamin D may directly inhibit the differentiation of Th2 cells and suppress their cytokine production. Dendritic cells are antigen-presenting cells that play a crucial role in initiating T cell responses. Vitamin D can modulate the function of dendritic cells, influencing their ability to promote Th2 differentiation. In addition to suppressing Th2 responses, vitamin D may also promote the differentiation of Th1 cells. Th1 cells produce cytokines such as interferon-gamma (IFN-γ), which promote cellular immunity and help to counterbalance Th2 responses. By promoting Th1 responses, vitamin D may help to restore immune balance in AD and reduce the dominance of Th2-driven inflammation. The skin's barrier function is crucial for maintaining skin health and preventing the entry of allergens, irritants, and microbes. In AD, the skin barrier is often compromised, contributing to the development and exacerbation of the disease. Filaggrin is a protein that plays a crucial role in the formation of the stratum corneum, the outermost layer of the skin. Vitamin D has been shown to increase filaggrin expression, which may help to strengthen the skin barrier and reduce its permeability. Lipids are essential components of the skin barrier, helping to maintain its integrity and prevent water loss. Vitamin D may promote lipid synthesis in the skin, further contributing to barrier function. The skin is colonized by a diverse community of microbes, which play a role in maintaining skin health. However, in AD, there is often an imbalance in the skin microbiome, with an overgrowth of certain bacteria, such as Staphylococcus aureus. This bacterial overgrowth can exacerbate AD symptoms by triggering inflammation and disrupting the skin barrier. Vitamin D has antimicrobial effects, which may help to control the growth of bacteria on the skin and reduce their contribution to AD flares. Vitamin D promotes the production of antimicrobial peptides (AMPs), such as cathelicidin, which have broad-spectrum antimicrobial activity. AMPs can directly kill bacteria and prevent their colonization of the skin. Vitamin D can modulate the immune response to bacteria, reducing inflammation and promoting the clearance of infection. The skin is not only a target organ for vitamin D but also a site of vitamin D synthesis. Keratinocytes, the predominant cell type in the epidermis, express the enzymes necessary to

convert 7-dehydrocholesterol to vitamin D3 upon exposure to ultraviolet B (UVB) radiation from sunlight. This locally produced vitamin D3 can then be converted to its active form, 1,25(OH)2D, by enzymes in the skin. The presence of VDR in keratinocytes and other skin cells allows the skin to respond directly to vitamin D. This local action of vitamin D is thought to be important for maintaining skin health and regulating various processes, including cell growth, differentiation, and immune responses. Vitamin D deficiency has been linked to impaired skin barrier function, which is a key feature of AD. Studies have shown that individuals with AD often have lower levels of vitamin D compared to healthy controls. Vitamin D deficiency may lead to reduced filaggrin expression, weakening the skin barrier and increasing its permeability. Vitamin D deficiency may impair lipid synthesis in the skin, further compromising barrier function. Vitamin D deficiency may alter the composition of the skin microbiome, favoring the growth of bacteria that can exacerbate AD. Given the evidence suggesting a role for vitamin D in AD pathogenesis, vitamin D supplementation has been investigated as a potential therapeutic strategy for AD. Several RCTs have evaluated the effects of vitamin D supplementation on AD symptoms, with promising results. Vitamin D supplementation has been associated with a reduction in SCORAD and EASI scores, indicating an improvement in AD symptoms. Vitamin D supplementation may reduce skin inflammation in AD, as evidenced by decreased levels of inflammatory markers. Vitamin D supplementation may improve skin barrier function in AD, as indicated by increased filaggrin expression and reduced transepidermal water loss.[11-16]

Vitamin D deficiency is a global health concern, affecting an estimated 1 billion people worldwide. This deficiency is particularly prevalent in individuals with limited sun exposure, those with darker skin pigmentation, and those with certain medical conditions or dietary habits that impair vitamin D absorption or metabolism. Numerous observational studies have consistently demonstrated a strong association between vitamin D deficiency and an increased risk of atopic dermatitis (AD), as well as greater disease severity. This association has been observed in various populations, including children and adults, across different ethnicities and geographic locations. Vitamin D plays a crucial role in regulating immune responses, as discussed in the previous section. Vitamin D deficiency can disrupt this delicate balance, leading to immune dysregulation that favors the development and exacerbation of AD. One of the key ways vitamin D deficiency contributes to AD is by promoting a Th2-dominant immune response. As mentioned earlier, Th2 cells produce cytokines that drive allergic inflammation and contribute to the characteristic features of AD. Vitamin D deficiency can lead to an overproduction of these Th2 cytokines, while simultaneously suppressing the Th1 response, further exacerbating the immune imbalance in AD. The Th2-dominant environment promotes the recruitment and activation of inflammatory cells in the skin, leading to increased redness, swelling, and itching. Th2 cytokines stimulate B cells to produce immunoglobulin E (IgE), an antibody involved in allergic reactions. Elevated IgE levels are a hallmark of AD and contribute to its pathogenesis. Vitamin D deficiency can impair the function of regulatory T cells (Tregs), which normally help to suppress immune responses and maintain immune tolerance. This impaired Treg function can further contribute to the uncontrolled inflammation in AD. The skin's barrier function is essential for maintaining skin health and preventing the entry of allergens, irritants, and microbes. In AD, this barrier is often compromised, leading to increased permeability and susceptibility to external triggers. Filaggrin is a crucial protein for skin barrier integrity. Vitamin D deficiency can lead to reduced filaggrin expression, weakening the skin barrier and increasing its permeability. Lipids are essential components of the skin barrier, helping to maintain its integrity and prevent water loss. Vitamin D deficiency can impair lipid synthesis in the skin, further compromising barrier function. This

compromised skin barrier allows allergens, irritants, and microbes to penetrate the skin more easily, triggering inflammation and exacerbating AD symptoms. The skin is home to a diverse community of microbes, collectively known as the skin microbiome. In healthy skin, these microbes play a beneficial role in maintaining skin health and preventing colonization by harmful pathogens. However, in AD, there is often an imbalance in the skin microbiome, with an overgrowth of certain bacteria, such as Staphylococcus aureus. Vitamin D promotes the production of antimicrobial peptides (AMPs), such as cathelicidin, which have broad-spectrum antimicrobial activity. Vitamin D deficiency can lead to reduced AMP production, making the skin more vulnerable to bacterial colonization and infection. Vitamin D deficiency can impair the immune system's ability to effectively respond to and eliminate microbes on the skin, further contributing to microbial dysbiosis and inflammation. Given the strong association between vitamin D deficiency and AD, and the understanding of vitamin D's immunomodulatory and skin barrier-enhancing properties, there has been growing interest in exploring vitamin D supplementation as a potential therapeutic strategy for AD. Several randomized controlled trials (RCTs) have investigated the effects of vitamin D supplementation on AD symptoms, with promising results. Vitamin D supplementation has been associated with a reduction in SCORAD and EASI scores, indicating an improvement in AD symptoms. Vitamin D supplementation may reduce skin inflammation in AD, as evidenced by decreased levels of inflammatory markers. Vitamin D supplementation may improve skin barrier function in AD, as indicated by increased filaggrin expression and reduced transepidermal water loss.[17-20]

5. Conclusion

This meta-analysis of four randomized controlled trials provides evidence that vitamin D supplementation is effective in reducing atopic dermatitis (AD) severity in children. The analysis demonstrated a statistically significant improvement in AD symptoms, measured by both SCORAD and EASI scores, in children receiving vitamin D supplementation compared to those in control groups. This finding supports the growing body of evidence suggesting a beneficial role for vitamin D in AD management, likely due to its immunomodulatory effects and its influence on skin barrier function. While promising, these findings should be interpreted with caution due to the limited number of included studies and the heterogeneity observed, particularly in terms of vitamin D dosages and treatment durations. Further large-scale, well-designed randomized controlled trials are warranted to confirm these findings, establish optimal treatment protocols (including dosage, duration, and target vitamin D levels), and explore the long-term effects and safety of vitamin D supplementation in children with AD. Despite these limitations, this meta-analysis contributes valuable evidence to the growing understanding of vitamin D's role in AD. It supports the consideration of vitamin D supplementation as an adjunctive therapy for children with AD, particularly those with documented vitamin D deficiency, in conjunction with established first-line treatments.

6. References

1. Amestejani M, Salehi BS, Vasigh M, Sobhkhiz A, Karami M, Alinia H, Kamrava SK, Shamspour N, Ghalehbaghi B, Behzadi AH. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. J. Drugs Dermatol. 2012; 11: 327–330.
2. Camargo CA, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J. Allergy Clin. Immunol. 2014; 134: 831.e1–835.e1.
3. Mansour NO, Mohamed AA, Hussein M, Eldemiry E, Daifalla A, Hassanin S, et al. The impact of vitamin D supplementation as an adjuvant therapy on clinical outcomes in

patients with severe atopic dermatitis: a randomized controlled trial. Pharmacol Res Perspect. 2020; 8: e00679.

4. Sánchez-Armendáriz K, García-Gil A, Romero CA, Contreras-Ruiz J, Karam-Orante M, Balcazar-Antonio D, et al. Oral vitamin D3 5000 IU/day as an adjuvant in the treatment of atopic dermatitis: a randomized control trial. Int J Dermatol. 2018; 57:1516-20.
5. Çiçek F, Köle MT. Evaluation of the impact of serum vitamin D levels on the Scoring Atopic Dermatitis index in pediatric atopic dermatitis. Children (Basel). 2023; 10(9).
6. Aycan ÖK, Özcanlı Çay Ö, Can D. Vitamin D level in children with atopic dermatitis. Journal of Controversies in Obstetrics & Gynecology and Pediatrics. 2024; 2(1): 16–8.
7. Özdemir Ö. Vitamin D, allergen sensitization, and atopic dermatitis. World Allergy Organ J. 2024; 17(11): 100978.
8. Shen C-H, Chen C-B, Chiang M-H, Kuo C-N, Chung W-H, Lin Y-K, et al. Vitamin D level is inversely related to allergen sensitization for risking atopic dermatitis in early childhood. World Allergy Organ J. 2024; 17(4): 100890.
9. Rodrigues I, Gonçalo M. Atopic dermatitis and vitamin D. Port J Dermatol Venereol. 2024; 82(2).
10. McCarthy RL, Tawfik SS, Theocharopoulos I, Atkar R, McDonald B, Dhoat S, et al. Vitamin D deficiency and atopic dermatitis severity in a Bangladeshi population living in East London: a cross-sectional study. Skin Health Dis. 2024; 4(3): e358.
11. Grieco T, Moliterni E, Paolino G, Chello C, Sernicola A, Egan CG, et al. Association between vitamin D receptor polymorphisms, tight junction proteins and clinical features of adult patients with atopic dermatitis. Dermatol Pract Concept. 2024; 14(3): e2024214.
12. Novsa RR, Andina. The Analysis study of effectiveness of vitamin D supplementation in atopic dermatitis: a comprehensive systematic review. J Adv Res Med Health Sci (ISSN 2208-2425). 2024; 10(7): 16–23.
13. Zhang Q, Yang D, Shen Q, Li W, Li R, Tang Y, et al. Correlation of maternal vitamin D status in early pregnancy and vitamin D supplementation during pregnancy with atopic dermatitis in infants: a prospective birth cohort study. Nutrients. 2024; 16(13): 2168.
14. Droitcourt C, Arellano J. Atopic dermatitis and vitamin D supplementation: The end of the story? J Eur Acad Dermatol Venereol. 2024; 38(9): 1677–8.
15. Borzutzky A, Iturriaga C, Pérez-Mateluna G, Cristi F, Cifuentes L, Silva-Valenzuela S, et al. Effect of weekly vitamin D supplementation on the severity of atopic dermatitis and type 2 immunity biomarkers in children: a randomized controlled trial. J Eur Acad Dermatol Venereol. 2024; 38(9): 1760–8.
16. Feily A, Namazi MR. Vitamin A + D ointment is not an appropriate emollient for atopic dermatitis. Dermatitis. 2010; 21(3): 174–5.
17. Bianchi L, Hansel K, Tramontana M, Assalve D, Stingeni L. Occupational allergic contact dermatitis with secondary spreading from vitamin k3 sodium bisulphite in a pig farmer. Dermatitis. 2015; 26(3): 150–1.
18. Dębińska A, Sikorska-Szaflik H, Urbanik M, Boznański A. The role of vitamin D in atopic dermatitis. Dermatitis. 2015; 26(4): 155–61.
19. Huber J, Hawkes JE, Powell DL. Cobalt-induced contact urticaria presenting as chronic urticaria due to intramuscular vitamin B12 injections. Dermatitis. 2016; 27(5): 313–4.
20. Huang Y-H, Yang T-H, Huang P-C, Chen Y-K, Huang L-T. Low vitamin D levels in breast milk may be a risk factor for atopic dermatitis flare-up during infancy. Dermatitis. 2021; 32(6): e124–5.