Vitamin D and Atopic Dermatitis: A Systematic Review and Meta-Analysis

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Running Head: Meta-Analysis of Vitamin D and Atopic Dermatitis

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Abstract

**Objectives:** Despite the evidence supporting the use of vitamin D supplements for managing atopic dermatitis (AD), no meta-analysis providing definite conclusions in this field has been reported. The purpose of the current study was to conduct a systematic review and meta-analysis of all controlled studies of vitamin D for treating AD to elucidate the efficacy of vitamin D for alleviating the symptoms of AD.

**Methods:** Literature searches were conducted using Ovid-MEDLINE, EMBASE, Web of Science, Cochrane Library, Korean databases, and Chinese database. Search terms used were: “vitamin D”, “atopic dermatitis”, “randomized”, “controlled trial”, and “clinical trial”.

Random effects models were used to calculate the mean difference (MD), with 95% confidence intervals (CI) to analyze the effects of vitamin D supplementation for severity of AD.

**Results:** Initial searches yielded 266 citations. Of these original results, nine met specific selection criteria. Four of the randomized controlled trials (RCTs) compared the efficacy of vitamin D with a placebo on severity of AD and were included in the meta-analysis. The vitamin D supplementation interventions showed a higher mean difference in severity of AD symptoms (MD = -5.81, 95% CI: -9.03, -2.59, p = 0.0004, I² = 50%).

**Conclusions:** Vitamin D has a potentially significant role for improving the symptoms of AD. The results from this study suggest that vitamin D supplementation may help ameliorate the severity of AD, and can be considered as a safe and tolerable therapy. However, larger-scale studies over a longer duration of treatment are needed to confirm this conclusion.
**Keywords:** Vitamin D; Atopic dermatitis; Systematic review; Meta-analysis; SCORAD index
Introduction

The prevalence of atopic dermatitis (AD) has been increasing worldwide over the last few decades among children and adults, particularly in industrialized countries. AD is a chronic inflammatory skin disorder characterized by dry, itchy skin, and immunological hypersensitivity to allergens [1]. The development of AD is closely associated with environmental and dietary factors such as pollen, house dust, mites, certain foods and food additives [2]. Nutritional studies indicate that supplementation with omega-3 fatty acids, vitamin D, and vitamin E are beneficial for reducing AD symptoms, and growing evidence from epidemiological and clinical studies shows that vitamin D deficiency may be involved in the etiology of AD [3-5]. Imbalances in T helper cell subsets (Th1/Th2) in cellular immunity contribute to the development of AD, and more frequent bacterial skin infections are associated with AD.

Vitamin D is a liposoluble vitamin known to act as a pleiotropic hormone. Vitamin D, which comes in two forms: D$_2$ (ergocalciferol) and D$_3$ (cholecalciferol), can be synthesized in the skin by ultraviolet-B (UVB) radiation, as well as absorbed from foods or supplements. The most common dietary sources of vitamin D$_3$ are halibut, mackerel, eel, salmon, beef liver, and egg yolks, and vitamin D$_2$ is rich in mushrooms exposed to sunlight when growing [6]. The current dietary reference intake (DRI) of vitamin D is 600 IU per day between the ages 1 and 70, and 800 IU per day for adults over age 70 [7]. Geographic areas with lower UVB exposure have higher prevalence of AD, and oral vitamin D supplementation has had a favorable effect on AD symptoms in children during the winter months [8]. Byremo et al. suggested that climate influences the prevalence of AD, and AD is exacerbated in adults and
children during the winter when vitamin D is under-produced. Sunrays have also been reported to have an antibacterial effect against *S. aureus* colonized in the skin [9].

Vitamin D intake results from a combination of dietary consumption and sunlight exposure, and the most biologically active form of vitamin D, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂-D₃), is produced by hydroxylation of 25-OH-D₃ in the kidney. A study of serum 25-OH-D₃ levels and the risk of AD demonstrated that the cellular effects of vitamin D on innate and adaptive immunity were triggered by the enzymatic activation of vitamin D [10]. Vitamin D in the innate immune system improved antimicrobial defenses by inducing the expression of the antimicrobial peptide cathelicidin [11]. Laboratory studies have suggested that vitamin D₃ stimulates expression of antibacterial peptides such as cathelicidin and human β-defensin (HBD), which are responsible for the prevention of skin infections, and synthesis of proteins such as filaggrin, which is necessary for stratum corneum barrier formation on the skin [12]. Active vitamin D also modifies the function of cells associated with adaptive immunity by suppressing dendritic cell maturation and inhibiting Th₁ cell proliferation through decreased Th₁ cytokine secretion. Vitamin D also blocked proinflammatory Th₁₇ cytokine secretion and decreased IL-2 production from regulatory T (Treg) cells, thereby inducing hyporesponsiveness [10]. In addition, vitamin D inhibited B-lymphocyte function, resulting in diminished secretion of immunoglobulin (Ig) E [13, 14]. Mechanistic *in vitro* and animal studies have indicated that vitamin D modulates AD pathogenesis and may contribute to AD etiology by improving the epidermal barrier via increased filaggrin expression, strengthening innate immunity to *S. aureus*, and reducing Th₂ immunity [15, 16]. In the acute phase of AD, Th₂-associated cytokines such as interleukin (IL)-4, IL-5, and IL-13 are predominant, which leads to production of IgE. IL-4 and IL-13 suppress the induction of antimicrobial peptides (AMP) and, thereby, inhibit destruction of *S. aureus* in the skin.
Vitamin D plays a role in alleviating the inflammatory response by decreasing IL-4 production and increasing AMPs [13]. In the chronic phase, the Th1 cytokine interferon (IFN)-\(\gamma\) has been implicated in keratinocyte apoptosis, and eczema is predominantly produced in AD patients. Vitamin D inhibits Th1 cell proliferation and decreases the secretion of IFN-\(\gamma\) [16].

Despite the evidence supporting the use of vitamin D supplements for managing AD, no meta-analysis providing definite conclusions in this field has been reported. The purpose of the current study was to conduct a systematic review and meta-analysis of all controlled studies of vitamin D for treating AD to elucidate the efficacy of vitamin D for alleviating the symptoms of AD.
Methods

Search strategy and data sources

The following electronic databases were searched to identify clinical studies where patients with atopic dermatitis were treated with Vitamin D supplementation. These included Ovid-MEDLINE (1966 to July 2015), EMBASE (1988 to July 2015), Web of Science (up to July 2015), Cochrane Library (up to July 2015), Korean databases such as KoreaMed, the Research Information Service System (RISS), and the Korean Studies Information Service system (KISS), and the Chinese Scientific Journals Database, including the China Academic Journal (CAJ). To minimize publication bias, references cited in the text of selected articles were further searched. The keywords and Medical Subject Headings (MeSH) for the population and the intervention were: “vitamin D”, “atopic dermatitis”, “randomized”, “controlled trial”, and “clinical trial”. Boolean operators were also used. The search terms included [(atopic dermatitis) OR AD] AND [vitamin D OR calciferol* OR ergocalciferol*].

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [17] and the statement by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (PRISMA) [18].

Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) types of participants: atopic dermatitis patients; 2) types of interventions: vitamin D supplementation, without restrictions regarding dose, route of administration or dosage interval. The comparator was no vitamin D supplementation or placebo; 3) types of outcome measures: severity scores of
atopic dermatitis and vitamin D related side effects; 4) type of studies: randomized controlled trials or controlled studies. Although no language barriers were imposed, all studies included in the review were written in English. Animal experiments, chemistry, or cell-line studies and editorial pieces, commentaries, review articles and case reports were excluded. Two independent reviewers screened the papers. In the first screening the related papers were identified by the titles, abstracts, and text, and the full text of relevant articles was retrieved for validation before final inclusion in the systematic review. A flow diagram of the article selection process is shown in Fig. 1.

Methodological quality assessment

The selected studies were critically appraised using RoB and RoBANS based on the study designs. According to recommendations outlined in the Cochrane Handbook, the following criteria were included [19]: “Random sequence generation”, “Allocation concealment”, “Blinding of participants”, “Incomplete outcome data”, “Selective outcome reporting”, and “Other bias”. We assigned a judgment relating to the risk of bias by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgment of “-” indicates low risk of bias, “+” indicates high risk of bias, and “?” indicates unclear or unknown risk of bias. Two of the authors independently assessed bias; any disagreement or misunderstandings were resolved by discussion until they reached a consensus.

Data extraction

The data were extracted in duplicate from all reports and independently recorded on a piloted form by the two of the authors. There was no blinding of authorship. The following
data were extracted for each study: authors; year of publication; inclusion and exclusion
criteria; study characteristics; description of interventions; mean or median duration of
vitamin D supplementation; number randomized and analyzed; number of withdrawals; and
outcomes. The outcome measures included effects and changes in atopic status, as well as
vitamin D-related adverse effects. Differences among reviewers related to data extraction
were resolved by discussion and consensus was reached.

Statistical analyses

Random effects models were used to calculate the mean difference (MD), with 95%
confidence intervals (CI) to analyze the effects of vitamin D supplementation for severity of
AD using Cochrane Collaboration’s software (RevMan Version 5.3.3 The Cochrane
Collaboration, 2014. Nordic Cochrane Center, Copenhagen, Denmark). Variance was
calculated using a correlation factor of 0.5, as suggested by the Cochrane Collaboration.
Heterogeneity of the included studies was tested using the Higgins $I^2$ statistic and meaningful
heterogeneity was determined by 50% of the $I^2$ value [17]. Based on the heterogeneity of the
included studies, fixed or random effects models were selected to calculate the pooled effect
measures. The $\chi^2$ test was included in the forest plots. To assess potential publication bias,
funnel plots for each outcome were also examined.
Results

General characteristics of the selected studies

Our initial literature search yielded 266 citations, of which 25 were duplicate studies. Following the screening process, a total of 232 studies were excluded based on the selection criteria, of which 9 studies were ultimately identified as relevant to our review. Therefore, we analyzed 9 studies [3, 8, 9, 12, 13, 20-23] and 576 patients (Table 1). A detailed flow chart of the literature search and the study selection is presented in Fig. 1. In this review, 7 RCTs [3, 8, 9, 20-23] and 2 controlled trials [12, 13] were included. The sample sizes ranged from 11 to 164. The years of publication for the studies ranged from 2006 to 2015. Four studies [8, 9, 13, 20] were conducted with AD children as the subjects, and one study [23] was conducted with mothers and their breast-fed infants with facial eczema, where the mean age for the mothers was 31.0 ± 5.13. Generally, the subjects were those who had their atopic symptom severity ranked from moderate to severe [8, 9, 12, 20-22], and two studies [8, 20] were conducted with subjects who had seasonal-related atopic dermatitis. In eight studies [3, 8, 12, 13, 20-23], vitamin D was supplemented orally. One study [9] categorized the subjects into two groups: a sun exposure group from a subtropical climate and a sun exposure group from a temperate environment. One of the studies used 800 IU/day [23], and the others applied 1,000 IU/day [8, 13, 20] and 1,600 IU/day [3, 22]. Though most studies used less than 2,500 IU/day, there were two studies [12, 21] that used 4,000 IU/day. Both of the studies [12, 21] were conducted with subjects who were ranked from moderate to severe AD, and in cases of subjects who had an average Rajka-Langeland score of 6, cholecalciferol was given for 3 weeks.

Seven studies [3, 12, 13, 20-23] used cholecalciferol, one study [8] used ergocalciferol...
and one study [9] looked at the effects of sun exposure. Based on the clinical information in the study, the patients were randomized into an experimental group and a control group. The experimental group stayed for 4 weeks in Gran Canar y, which is a Canary Island belonging to Spain, whereas the control group spent the time in their usual surroundings, at home, in Trondheim, a city of Norway. For the 28 days stay at Grand Canary in autumn, under the sun, 8 of these days were without rain, while the group in the spring had 23 sunny days with the remaining days slightly cloudy. In Trondheim, 13 of 28 days were without rain in the same period. The control group had the same shape, capacity, and method of administration, or were healthy controls. The main outcome variables were SCORAD, EASI, IGA, TIS and such indicators relating to the atopic symptom severity and 25(OH)D₃ which is the serum vitamin D level, and serum cathelicidin [12] as regulators of inflammatory response.

Methodological quality and risk of bias in the included studies

The quality and risk of bias assessment for the included studies is presented in Fig. 2. In terms of random sequence generation (risk of bias to selection), seven studies [3, 9, 13, 20-23] reported adequate methods, while this was unclear in two studies [8, 12]. Of the seven RCT studies, five studies had reports about allocation concealment but the other two studies [9, 21] were unclear. Patient and practitioner blinding or performance bias possibilities were low in six studies [3, 9, 20, 22, 23], unclear in two studies [8, 21] and unreported in one study [12]. As for assessor blinding, the risk of bias was low in four studies [3, 9, 22, 23] and unclear in five studies [8, 12, 13, 20, 21]. Most studies reported number of participants with missing data; only one study [13] had relatively high numbers of missing data (28.8%). Overall, most of the RCTs and controlled trials included in the review were classified as low
risk of bias, indicating high-quality studies.

**Outcomes**

Seven trials [3, 8, 9, 13, 20, 22, 23] reported on severity of AD symptoms, but in one study [23] the pre-intervention value was not reported. Another study [8] did not present the standard deviation, while another [13] presented the results from the experimental group, making it impossible to compare with the control group. Therefore, the meta-analysis included four trials [3, 9, 20, 22] and the results are as follows: The vitamin D supplementation interventions showed a higher mean difference in severity of AD symptoms (MD = -5.81, 95% CI: -9.03, -2.59, p = 0.0004, I² = 50%). It can be seen that the experimental group's intervention pre-post mean change value, compared to that of the control group, represented a statistically significant decrease (Fig. 3). SCORAD or EASI were reported in seven studies [3, 8, 9, 13, 20-23] and compared to the mean changes of the control group (-1.8 ± 4.8 – -9.4 ± 10.9), and were significantly different from the experimental group (-6.5 ± 8.8 – -23.56 ± 15.48). The EASI score was reported in two studies [8, 20] with the mean changes of the experimental group (-4.6 – -6.5 ± 8.8), compared to that of the control group (-2.2 – -3.3 ± 7.6), showing a statistically significant difference. IGA was reported in two studies [8, 20] where a comparison with the "before" and "after" intervention symptom improvement rate of the experimental group (56 – 80%) with that of the control group (17 – 43%) was significantly higher. TIS was reported in one study [3], and the mean changes of the experimental group (-1.6 ± 0.46) were significantly decreased, as compared to that of the control group (0.22 ± 0.46). The serum vitamin D level, 25(OH)D₃, was reported in two studies [3, 13], and the mean changes of the experimental group (9.4 ± 11.23 – 13.1 ±
3.8) were significantly higher, as compared to that of the control group (-0.4 ± 2.0 – 9.4 ± 
12.43). Serum levels of the inflammatory mediator cathelicidin were reported in one study 
[12], where there was a significant increase before and after intervention in the experimental 
group (20.38 RCU), as compared to that of the control group (0.78 RCU).

Publication bias

A symmetrical funnel plot was produced by these meta-analyses, which indicated no 
publication bias (hollow circles in Fig. 4).

Adverse events

Vitamin D supplementation-related adverse events or side effects were either not 
reported or presented as being without serious or minor adverse events [20, 23]. One study 
[9] reported a temporary low grade sun burn, but no negative effects were observed among 
the participants.
**Discussion**

AD has tripled during the last three decades, and one method of treatment is ultraviolet (UV) phototherapy, which causes production of vitamin D and alleviation of symptoms through immune suppression [24]. These systematic meta-analyses of controlled studies suggest that vitamin D is inversely associated with the severity of AD.

Clinical trials show that 25-OH-D$_3$ levels correlate inversely with the development and severity of AD, suggesting that vitamin D may play a protective role in the pathogenesis of the disease. Patients with vitamin D deficiency were more likely to have AD, and to develop a more severe form of the disease, as compared to those with vitamin D sufficiency [25, 26]. However, a recent study by Chiu et al. showed no association between vitamin D and disease severity in children with AD [27]. Several observational and human studies have shown associations between the effect of vitamin D and AD in children and adults, but the results of these trials were not consistent [3, 8, 20, 22, 28, 29]. The randomized controlled study (RCT) by Javanbakht et al.[22], which evaluated the effect of vitamin D on AD, showed no significant difference in the SCORing Atopic Dermatitis (SCORAD) index after vitamin D intervention, compared to placebo. Nonetheless, the RCT study by Sidbury et al. [8] reported a significant improvement in the Investigator Global Assessment (IGA) score in children with AD during the winter. A recent RCT study by Amestejani et al. [3] reported a significant reduction in SCORAD in the vitamin D treatment group only, but no difference in the control group. In Hata et al’s first RCT study (2008), they administered an oral dose of 4,000 IU of vitamin D$_3$ daily for 3 weeks to patients and healthy control subjects, and the patients with AD produced more than a 6-fold increase in cathelicidin levels, suggesting that oral supplementation of vitamin D dramatically induced cathelicidin production [12]. However, in
their second 2014 study, although vitamin D₃ intervention significantly increased serum 25-
OH-D₃ levels in AD subjects and non-atopic controls, there was no statistically significant
correlation between vitamin D and cathelicidin and HBD, and a weak trend was observed for
decreasing IL-13 with increasing change of serum 25-OH-D₃, requiring further investigation
of an association between Th₂ cytokines and vitamin D. These results were due to the small
sample size, varying seasonality, locales, skin types and short duration of treatment [21].
There is controversy with regard to how to obtain adequate vitamin D, as well as the total
amount necessary for health. This study is the first to address the efficacy of vitamin D on the
severity of AD by meta-analyses of controlled studies. However, there could be some bias
due to genetic background, environment, and other confounding factors. The type of vitamin
D administered in this study differed in the forms of vitamin D₂ and vitamin D₃. Parathyroid
hormone (PTH), which will increase the vitamin D level, may also confound the
interpretation of vitamin D efficacy on AD. There were different doses and durations of the
vitamin D intervention among studies, and a relatively low dose of vitamin D (1,000 IU of
ergocalciferol) and short duration of the intervention (one month) was administered in a study
by Sidbury et al. [8] In addition, enrolled patients had differing AD severity and the
frequency of emollient use was not controlled. In future studies, the impact of vitamin D on
similar severities of AD, as well as on all types of AD, will need to be examined. Most
studies in this meta-analysis were performed with younger patients, and future trials may
want to expand to examine the association of the benefit of vitamin D to the older adult
population with AD. In addition, RCTs with larger sample sizes are needed to provide more
meaningful results.

Exercise is an aggravating factor for AD because it causes heat and sweating, although
moderate exercises under the sun could provide some benefit [30]. In Norway, where summer
sunlight is scarce, UVA and UVB light are effective for AD treatment [31]. Sunlight not only regulates the cutaneous production of vitamin D, but also has anti-septic properties, which has led to the use of phototherapy with UVA-1 or UVB 311 nm as an adjuvant therapy for the treatment of severe AD. A typical feature in patients with AD is abnormally superinfected skin by *S. aureus*. The increased adherence of *S. aureus* to keratinocytes along with exotoxins produced by the bacteria cause T-cell activation and inflammatory cytokine release leading to aggravation of this inflammatory skin disease. Maisch et al. demonstrated an anti-staphylococcal effect after UV therapy [32]. Amestejani et al. [3] reported significant differences in vitamin D treated groups; however, their study did not control the patients’ travel to temperate climates during the trial or exercise, so could not exclude possibilities of UV-light synthesis of vitamin D. Furthermore, their patients were allowed to continue previously prescribed AD therapies including emollients, topical corticosteroids, and oral anti-histamines, which are co-interventions that could have caused difficulty in interpreting the effect of vitamin D on AD.

Dietary factors should have remained stable throughout the included studies. Specific nutritional components have been identified as exacerbating factors in AD, and the elimination of these components from the diet has shown to attenuate symptoms [33, 34]. The food additives used in processed foods have been considered to act as allergens that trigger the development of AD [35]. Consumption of organic dairy products has also been reported to be associated with lower eczema risk in infants [36]. In addition, the use of probiotics that are primarily used in fermented foods have been reported to be effective for treating AD in young children as well as adults. *L. paracasei, L. acidophilus, L. salivaris, B. animalis, B. lactis,* and *B. breve* were effective in the treatment of patients with AD by modulating gut microbial translocation, Th$_1$/Th$_{reg}$, and Th$_1$/Th$_2$ cytokine profiles [37, 38].
According to a meta-analysis of six RCTs of infants, the combined risk ratio of the prevalence of AD associated with probiotics was lower compared with the placebo control [39]. However, with the exception of the study by Camargo et al [20], no study controlled for differences in the diet of the vitamin D-treated group and the placebo group.

Furthermore, recent studies suggest psycho-neuro-immunologic factors and emotional stress are involved in AD flares. Stress impairs the skin barrier function and normal hypothalamic-pituitary-adrenal axis function, leading to increased neurogenic inflammation and Th2 allergic responses [40-42]. No studies included in this meta-analysis have considered the role of psychiatric diagnosis in the exclusion criteria of their RCT studies.

The benefit of baseline levels of serum 25-OH-D$_3$ in participants should have been examined since there were significant vitamin D differences in baselines among studies, which may have further confounded the results. Only the studies of Amestejani et al [3] and Hata et al [21] measured baseline levels. In addition, the seasons in which AD subjects were recruited were different, which could have caused different vitamin D starting levels and might have caused short-term supplementation of vitamin D to be ineffective in its ability to treat AD. These methodological limitations and lack of controls in the identified studies could be one of the reasons why the studies in this meta-analysis appear to be moderately heterogeneous. Therefore, further studies that are more appropriately controlled and sufficiently designed may be required to definitively examine the effect of vitamin D on AD.

**Limitations**

The study has several limitations. First, the total number of RCTs included in the analysis and the total sample size were too low to draw definitive conclusions. Thus, more rigorously designed RCTs are necessary to examine the effect of vitamin D on AD in greater detail. Second, while we have provided evidence supporting the role of vitamin D in AD
pathogenesis, we can not conclude that vitamin D plays a role in disease modulation after
disease onset. In the future study, the principles of Mendelian randomization and genome-
wide significant single nucleotide polymorphisms study upon 25-OH-D$_3$ can be applied to
strengthen the causality of vitamin D in AD etiology. However, in this study the main
findings remained robust in the role of vitamin D on the pathogenesis of AD

In conclusion, vitamin D has a potentially significant role for improving the symptoms of
AD. The results from this study suggest that vitamin D supplementation may help ameliorate
the severity of AD, and can be considered as a safe and tolerable therapy. However, larger-
scale studies over a longer duration of treatment are needed to confirm this conclusion.
Future studies for assessing adequate amounts of vitamin D intake for the treatment and
prevention of AD are also warranted.
Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

Author G.K. and author J.H.B. contributed equally to this study, and the final manuscript has been read and approved by all authors.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

http://www.textcheck.com/certificate/ggedxw
References


[35] Lee JM, Jin HJ, Noh G, Lee SS. Effect of processed foods on serum levels of


Figure Legends

Fig. 1 – Flowchart of the process for selecting studies for the systematic review.

Fig. 2 – Assessment of risk of bias in included studies

Fig. 3 – Forest plot of the meta-analysis for vitamin D on atopic dermatitis. Each study is identified by first author and year. The individual effect sizes are identified as “Mean Difference” with lower and upper limits (95% confidence intervals), Z value, and P values provided for each study. The overall summary effect size of the meta-analysis is noted as a diamond on the bottom line.

Fig. 4 – Funnel plot of the meta-analysis for vitamin D on atopic dermatitis. The hollow circles represent the studies in the meta-analysis. Y-axis represents standard error of study with X-axis showing effect size in each study.
### Table 1. Main characteristics and outcomes of included studies

<table>
<thead>
<tr>
<th>First author, year, [Ref. no.]</th>
<th>Study design</th>
<th>No. of Subjects I vs. C</th>
<th>Drop out %, Gender (M:F), Mean Age of Subjects (±SD)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention (Dose, Type, Duration, Source)</th>
<th>Control</th>
<th>Main Outcome</th>
<th>Mean change [Experimental, Control]</th>
<th>P-value</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amestejani, 2012 [03]</td>
<td>RCT</td>
<td>30 vs. 30 → 29 vs. 24, 11.7 %, NR, 23.34 ± 2.1</td>
<td>≥14 years, AD patients, no systemic diseases, concomitant systemic pyrctic or inflammatory processes</td>
<td>Pregnant or nursing mothers, systemic inflammatory disorder, vitamin, mineral, fatty acid supplement, oral contraceptive pills, steroid hormones, anti-epileptic, anti-coagulant drugs</td>
<td>1600 IU, Cholecalciferol, 8 weeks, Oral</td>
<td>Placebo filled with starch, same size and color with Vit D capsules</td>
<td>SCORAD</td>
<td>[-9.5 ± 3.7, -1.8 ± 4.8]</td>
<td>[0.01, 0.15]</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Byremo, 2006 [09]</td>
<td>RCT</td>
<td>32 vs. 29 → 30 vs. 26, 8 %, 26:30, 7.88 (range 3–13)</td>
<td>4-13 years old children with moderate to severe atopic eczema</td>
<td>Health travels to subtropical climate during the preceding 2 years, other serious diseases</td>
<td>Sun exposure in subtropical climate stay, 23 sunny days out of 28 days (spring), 28 sunny days out of 28 days (autumn)</td>
<td>Usual surroundings at home, 13 sunny days out of 28 days (spring), 8 sunny days out of 28 days (autumn)</td>
<td>SCORAD</td>
<td>[-16.0 ± 18.5, -6.2 ± 17.4]</td>
<td>[&lt;0.0005, 0.049]</td>
<td>Temporarily low grade sun burn</td>
<td></td>
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<tr>
<td>Camargo, 2014 [20]</td>
<td>RCT</td>
<td>58 vs. 49 → 57 vs. 47, 2.8 %, 63:44, 9 ± 5</td>
<td>2–17 years, Mongolian children with winter related AD, EASI score 10-72</td>
<td>Children with active skin infection, given antibiotic therapy</td>
<td>1,000 IU, Cholecalciferol, 4 weeks, Oral</td>
<td>Placebo drops, odorless, colorless, and tasteless</td>
<td>EASI</td>
<td>[-6.5±8.8, -3.3±7.6]</td>
<td>[0.04, NS]</td>
<td>No major or minor adverse events</td>
<td></td>
</tr>
<tr>
<td>Hata, 2014 [21]</td>
<td>RCT</td>
<td>30 vs. 30, 27.33, 31.6 ± 10.67</td>
<td>Moderate to severe AD with an average Rajka-Langeland score 6, no topical corticosteroids, no oral or topical antibiotics, no antivirals, immune enhancers, or topical calcineurin inhibitors for one week prior to enrollment</td>
<td>Systemic immunosuppressive, chemotherapeutic agents, light therapy, anti-inflammatory biologics or oral calcineurin inhibitors with 30 days, kidney disease, hyperparathyroidism, sarcoidosis, tuberculosis, lymphoma</td>
<td>4,000 IU, Cholecalciferol, 3weeks, Oral</td>
<td>Placebo clear gelatin capsule</td>
<td>25(OH)D$_3$</td>
<td>[9.4 ± 11.23, 9.4 ± 12.43]</td>
<td>[&lt;0.01, &lt;0.01]</td>
<td>NR</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>N intervention vs. N control</td>
<td>Comparison</td>
<td>Age</td>
<td>AD patients</td>
<td>Intervention</td>
<td>SCORAD</td>
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<tr>
<td>Javanbakht, 2011 [22]</td>
<td>RCT</td>
<td>13 vs. 13 → 12 vs. 11, 11.5%, 4:19, 23.7 ± 2.43</td>
<td>13-45 years old, AD patients, SCORAD 10-70, normal hepatic and renal function</td>
<td>Taking vitamin, mineral, fatty acid supplements, oral contraceptive pills, steroid hormone, anti-epileptic, anti-coagulant agents, pregnant or nursing mothers</td>
<td>1,600 IU, Cholecalciferol, 8 weeks, Oral</td>
<td>placebo capsule filled with starch</td>
<td>[−12.7 ± 11.6, -9.4 ± 10.9]</td>
<td>NR, NR</td>
<td>NR</td>
<td></td>
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<tr>
<td>Norizoe, 2014 [23]</td>
<td>RCT</td>
<td>82 vs. 82 → 72 vs. 74, 10.9%, NR, 31.0 ± 5.13</td>
<td>Mothers and their breast-fed infants, infants with facial eczema</td>
<td>Vit D supplement already being taken, history of urinary tract stone or disease related to calcium or bone in the mothers, allergy to food additives</td>
<td>800 IU, Cholecalciferol, 6 weeks, Oral</td>
<td>Identical looking placebo once daily</td>
<td>[4.75 ± 7.49, 3.95 ± 5.36]</td>
<td>* 0.62**</td>
<td>No serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sidbury, 2008 [08]</td>
<td>RCT</td>
<td>5 vs. 6, 6.5, median 7 (range 2–13)</td>
<td>Winter related AD w/o exposure to harmful UV radiation, EASI score 10-18.6</td>
<td>Travel to temperate climate during the trial</td>
<td>1,000 IU, Ergocalciferol, 4 weeks, Oral</td>
<td>Identical looking placebo once daily</td>
<td>[−4.6 ± NR, -2.2 ± NR]</td>
<td>0.4 **</td>
<td>NR</td>
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<tr>
<td>Di Filippo, 2015 [13]</td>
<td>Controlled study</td>
<td>39 vs. 20 → 22 vs. 20, 28.8%, NR, 4 ± 3.15</td>
<td>AD children</td>
<td>Systemic, anti-inflammatory therapy or Vit D supplement in the previous 6 months, calcineurin inhibitor in the previous 2 weeks</td>
<td>1,000 IU, Cholecalciferol, 2 weeks, Oral</td>
<td>Healthy control group</td>
<td>[-4 [-1 [4[80%], 1[17%]] [-23.56 ± 15.48, NR] [-0.001, NR]</td>
<td>NR</td>
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<tr>
<td>Hata, 2008 [12]</td>
<td>Controlled study</td>
<td>14 vs. 14, NR, NR</td>
<td>Moderate to severe AD, Rajka-Langeland score of 6</td>
<td>4,000 IU, Cholecalciferol, 3 weeks, Oral</td>
<td>Healthy control group</td>
<td>Cathelicidin</td>
<td>[20.38 RCU, 0.78RCU]</td>
<td>[&lt;0.01,0.05]</td>
<td>NR</td>
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</table>

C, Control; EASI, Eczema Area and Severity Index; I, intervention; IGA, Investigator’s Global Assessment; NR, not reported; RCU, Relative Copy Units; SCORAD, SCORing Atopic Dermatitis; TIS, Three Item Severity score, +1 (worse), 0 (same), -1 (better), *; post intervention, ** between interventional and control group.
Records identified through database searching (n = 265)

Records after duplicates removed (n = 241)

Records screened (n = 241)

Records excluded (n = 198)

Full-text articles assessed for eligibility (n = 43)

Studies included in analysis (n = 9)

Full-text articles excluded, with reasons (n = 34)
- Did not answer research question (n = 19)
- No original data (n = 7)
- Observational studies (n = 8)
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<th>Allocation concealment</th>
<th>Blinding of participants &amp; personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
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<td>12</td>
<td>-9.4</td>
<td>10.9</td>
<td>11</td>
<td>10.1%</td>
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</table>

Total (95% CI) 128 108 100.0% -5.81 [-9.03, -2.59]

Heterogeneity: $\tau^2 = 4.76; \chi^2 = 5.99, df = 3 (P = 0.11); I^2 = 50$
Test for overall effect: $Z = 3.54 (P = 0.0004)$
Highlights

● We have evaluated current evidence for the effectiveness of vitamin D for atopic dermatitis.

● The meta-analysis of these data indicate that vitamin D supplementation may help ameliorate the severity of AD, and can be considered as a safe and tolerable therapy.

● Vitamin D has a potentially significant role for improving the symptoms of AD. However, larger-scale studies over a longer duration of treatment are needed to confirm this conclusion.

● Future studies for assessing adequate amounts of vitamin D intake for the treatment and prevention of AD are also warranted.