

The Role of Vitamin D in Atopic Dermatitis

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Vitamin D has been suggested to have an important impact on a much wider aspects on human health than calcium homeostasis and mineral metabolism, specifically in the field of human immunology. It has been reported that vitamin D influences the regulation of both innate and adaptive immune systems, which makes the association between vitamin D and allergic diseases a field of interest. Although many studies have sought to determine whether vitamin D has an influence on progression of allergic disease, the impact of vitamin D on atopic dermatitis development and severity remains unclear. In this review, we summarize recent studies relating vitamin D to atopic dermatitis and discuss its possible role in the pathogenesis of allergic skin diseases, emphasizing the need for well-designed, prospective trials on vitamin D supplementation in the context of prevention and treatment for allergic conditions.

Atopic dermatitis (AD), or eczema, is a multifactorial disorder with onset typically in early childhood and is the most common chronic inflammatory skin disease in industrialized countries.^{1,2} The worldwide cumulative prevalence of AD is approximately 10% to 20% in children and 2% to 10% in adults,^{2,3} and there has been a steady increase over the past few decades.^{4,5} Atopic dermatitis may result from complex interactions between genetic susceptibility genes resulting in an epidermal barrier dysfunction, abnormalities in the innate immune response, cutaneous inflammatory hypersensitivity, and an increased immunologic response to allergens and microbial agents.⁶ Although genetic predisposition is a fundamental factor of susceptibility to AD, the dramatic rise in the prevalence of AD during the last 2 generations cannot be explained by modifications of genes alone and points to environmental, lifestyle, or diet changes.⁷ Among other environmental factors, vitamin D has been suggested as playing a significant role in the development of allergic skin diseases and specifically in AD.⁸ Recent data have demonstrated that vitamin D affects both innate and adaptive immune mechanisms, influences cell differentiation, modulates proliferation and differentiation of keratinocytes, and is associated with keratinocyte production of antimicrobial peptides.^{9–11} Because these processes are involved in the pathogenesis of AD, the impact of vitamin D levels on this condition's risk and severity seems to be a biologically plausible hypothesis. A growing number of studies have attempted to prove

this hypothesis but with inconsistent findings.^{12–18} In 2013, Mutgi and Koo¹⁹ published an excellent review of the articles carefully extracted from those available up to January 2012, addressing the relationship between vitamin D levels and the risk or severity of AD and the therapeutic role of vitamin D replacement. The majority of reviewed observational studies demonstrated an inverse relationship between vitamin D levels and the prevalence and severity of AD in a dose-dependent manner. Furthermore, therapeutic trials suggested that repletion of vitamin D is associated with improvement in AD severity and corresponding serum vitamin D levels.¹⁹ Since then, the number of studies that have investigated the effect that vitamin D has on allergic diseases, and specifically allergic skin diseases, has increased significantly, and these studies have demonstrated more conflicting results.

In this review, we seek to highlight current knowledge of the impact of vitamin D on AD risk or severity and also summarize the studies of the effects of vitamin D supplementation on pregnant women's and newborns' AD. We searched PubMed for English-language original studies and considered articles published between January 2012 and January 2015 regarding studies conducted in children and adults.

THE RELATIONSHIP BETWEEN VITAMIN D LEVELS AND THE PREVALENCE OF ATOPIC DERMATITIS

Earlier studies demonstrate the importance of the role of vitamin D in AD risk and severity. Most of the studies determined if vitamin D deficiency is associated with the prevalence of AD. Although the results of the trials are conflicting, vitamin D remains a very important factor in the course of this disease. One of these studies found lower serum concentration of vitamin D in AD patients and showed that deficient patients were 5 times more likely to report AD as replete ones.¹²

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DOI: 10.1097/DER.0000000000000128

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Recently, Cheng et al²⁰ conducted a large cross-sectional study for which they collected data from 15,212 Korean adults. It was found that participants with AD had significantly lower vitamin D levels (18.27 ng/mL in patients without AD and 16.54 ng/mL in those with AD; $P < 0.001$) and that the risk of AD is higher among people with vitamin D deficiency. These results were not observed in patients with other allergic problems such as asthma, allergic rhinitis, or immunoglobulin E (IgE) sensitization.²⁰ Another study also found vitamin D deficiency to be strongly associated with childhood AD among the Chinese population of Hong Kong. A trial of 826 children (498 with AD and 328 nonatopic) demonstrated higher serum vitamin D levels in the control group than in AD patients (mean, 34.2 [SD, 14.5] nM vs 28.9 [SD, 15.3] nM; $P < 0.001$). It is worth mentioning that the proportion of participants with vitamin D levels of less than 50 nM was similar, but more patients with AD than control subjects had vitamin D deficiency (<25 nM).²¹

Samochocki et al²² also found low serum vitamin D levels in their study group (approximately 80% of participants with AD have a vitamin D deficit), but there was no statistically significant difference in vitamin D concentration between patients with AD and control subjects without AD. The same result of no difference between vitamin D levels in 30 patients with AD and 30 with no AD was reported by Hata et al²³ in a multicenter, case-control study. The whole study group had low serum vitamin D concentration—AD subjects had a level of 28.4 ng/mL, and control subjects had 30.1 ng/mL; however, the difference did not reach significance.²³

THE RELATIONSHIP BETWEEN VITAMIN D LEVELS AND THE SEVERITY OF ATOPIC DERMATITIS

Previously, there had been several reports that demonstrated the correlation between the vitamin D level and AD severity.¹⁹ Peroni et al¹³ revealed that in patients with mild symptoms the vitamin D level was much higher (36.9 ng/mL) than in people who were at a more advanced stage of the disease. At a vitamin D concentration of 27.5 ng/mL, moderate severity of symptoms was observed, and patients with a level of 20.5 ng/mL had a severe form of AD.¹³ Some recent studies have also found a correlation between vitamin D levels and AD severity, whereas others have not.

As mentioned above, Wang et al²¹ showed the correlation not only between vitamin D level and AD prevalence, but also between AD severities. The investigators also examined the short- and long-term severity of AD using, respectively, SCORing Atopic Dermatitis (SCORAD) in 306 cases and the Nottingham Eczema Severity Score in 290 children. Serum levels of vitamin D were inversely correlated with short- and long-term AD severity.²¹ In a cross-sectional study, Baek et al²⁴ examined 226 infants including 168 with AD and 58 with suspected food allergy without AD. They checked how vitamin D levels and food allergy influence AD severity and pointed to the conclusion that the severity of AD was independently influenced by serum vitamin D levels and by the degree of food allergen sensitization. They also examined to see if low vitamin D levels are

associated with a SCORAD index. Participants were divided into 3 groups by vitamin D levels: sufficiency (≥ 30.0 ng/mL), insufficiency (20.0–29.0 ng/mL), and deficiency (<20 ng/mL). The serum vitamin D levels were inversely correlated with the SCORAD index ($r = -0.196$, $P = 0.043$); the group with the lowest vitamin D levels had the highest SCORAD indices.²⁴

On the other hand, Lee et al²⁵ found no relationship between serum levels of vitamin D and AD severity in their 157 patients. However, when investigators took into consideration only a subgroup of 36 patients with food sensitization, the correlation was significant. It is probable that the food-sensitized group had a vitamin D deficiency due to avoiding certain foods including those rich in vitamin D.²⁵ Akan et al²⁶ also found that vitamin D may affect the severity of AD, especially in children with allergic sensitization. The authors examined 73 patients with AD, determined their SCORAD, performed skin-prick tests, measured specific IgE, and divided patients into 2 groups: one with sensitization and one without. Data analysis showed a negative correlation between SCORAD and vitamin D levels ($P = 0.02$) in the whole studied population, but when the 2 groups were assessed separately, the negative correlation was present only in the sensitized group ($P = 0.30$ vs $P = 0.047$). This study also discovered lower serum vitamin D levels in participants with AD.²⁶

In contrast to the already mentioned results, some studies did not find any relationship between vitamin D concentration and AD severity.^{23,27} In a cross-sectional study conducted in 97 children with AD, Chiu et al²⁷ found no correlation between levels of vitamin D and SCORAD ($P = 0.99$). More recently, Hata et al,²³ in a randomized, placebo-controlled, double-blind study conducted on 76 atopic, nonatopic, and psoriatic adult patients, also reported no vitamin D influence on the AD severity both before and after supplementation.

THE RELATIONSHIP BETWEEN VITAMIN D SUPPLEMENTATION AND THE AD SEVERITY

Based on the relationship between vitamin D deficiency and AD, trials of vitamin D supplementation in AD subjects were conducted.^{14,17–19}

In 2008, Sidbury et al¹⁴ hypothesized that the well-known therapeutic effect of UV radiation on children with winter-related AD is mainly because of the improved vitamin D status and may be achieved by vitamin D supplementation alone. That randomized controlled study confirmed that a 1-month oral vitamin D supplementation of 1000 IU lessens the AD severity according to the Investigator's Global Assessment in children who live at a high latitude with less UV exposure and AD worsening during the winter.¹⁴ Recently, Camargo et al²⁸ performed a randomized, double-blind, placebo-controlled trial of 104 Mongolian children with a specific subtype of AD (winter-related AD). For 1 month, 58 of them were administered a daily vitamin D supplementation of 1000 IU, and 49 of them were given a placebo. The connection between a 1-month follow-up vitamin D supplementation and a clinically meaningful improvement in the Eczema Area and Severity Index (EASI) was

observed. There were also changes in Investigator's Global Assessment that favored vitamin D over placebo. According to the authors, this study had some potential limitations. First, the initial vitamin D serum was not measured. The authors supposed that children with AD had low vitamin D levels, as in the outcome of the earlier study carried out with more than 500 Ulaanbaatar schoolchildren in Mongolia. Second, the duration of the intervention was short, and only 6 children with severe AD and none with very severe AD were enrolled.²⁸

In subsequent interventional studies, the therapeutic role of vitamin D supplementation was assessed not only in patients with winter-related AD. In a randomized, double-blind, placebo-controlled study, Amestajani et al²⁹ evaluated the benefits of 1600 IU vitamin D supplementation on AD severity. In this trial, 30 subjects were randomized to a daily dose of vitamin D, whereas another group of 30 patients was given a placebo. After 60 days, a significant improvement, assessed by SCORAD and Three Item Severity score, in patients with mild, moderate, and severe AD ($P < 0.05$), was observed.²⁹ Samochocki et al²² measured vitamin D levels in patients with AD and assessed the influence of 2000 IU daily vitamin D supplementation on the clinical manifestation of the disease after 3 months. This cross-sectional study was performed with 95 patients with AD, and the control group consisted of 58 healthy subjects. Only 20 individuals with the lowest (4–15 ng/mL) vitamin D concentration were selected for an oral supplementation of vitamin D. The vitamin D level was measured before and after the supplementation. Three months' supplementation nearly doubled, statistically significantly, the patients' serum vitamin D levels. These changes were associated with a lower mean objective SCORAD and SCORAD index ($P < 0.001$) and decrease in the severity of skin lesions (reported subjectively by patients). However, 10% of the patients declared no improvement, but objective SCORAD and SCORAD indices decreased. The authors also identified a group of patients with AD prone to bacterial skin infections and winter exacerbations of AD, who had vitamin D levels of less than 30 ng/mL. It was found that vitamin D deficiency may probably be responsible for the most intensive skin lesions localized on body regions not exposed to sun.²² Not all interventional studies proved the clinical effect of vitamin D supplementation on AD. In Hata and colleagues²³ study, mentioned previously, the vitamin D levels were measured before and after the 21-day follow-up supplementation of 4000 IU vitamin D. The results showed no change in the mean EASI score following supplementation.²³

VITAMIN D EXPOSURE IN UTERO AND THE PREVALENCE OF ATOPIC DERMATITIS

Atopic dermatitis, 1 of the most common skin disorders seen in infants and children, usually has its onset during the first 6 months of life, which implicate early environmental exposure in pregnancy as a relevant risk factor.⁵ Among the various factors responsible for early programming in utero, vitamin D has been highlighted.³⁰ During pregnancy, the fetus is exposed to vitamin D through cord blood supply and the ability of 25-hydroxyvitamin [25(OH)]

vitamin D to cross the placenta.³¹ Experimental studies have found a high correlation between the vitamin D levels of pregnant mothers and their newborns.^{32–34} There has been growing evidence from animal and in vitro models that the active metabolite of vitamin D may play an important role in fetal lung development and early programming of fetal immune response.^{35–37} Thus, it has been speculated that maternal vitamin D status in pregnancy may influence the risk of asthma and atopy in the offspring. The epidemiological studies have demonstrated an association between maternal vitamin D intake during pregnancy and early childhood wheeze, asthma, allergic rhinitis, and food allergy. However, these findings remain inconsistent.^{34,38–44} Likewise, there are conflicting data surrounding the effect of vitamin D exposure in utero on the development of allergic skin disorders, especially AD. Some studies have shown that higher maternal vitamin D levels increase the risk of atopic eczema,^{15,42} whereas others demonstrated a protective effect⁴⁵ or found no association.⁴⁶ However, it is worth mentioning that these studies were based on questionnaire-derived data about the maternal dietary intake of vitamin D rather than objective measures and may therefore reflect “chance” findings.

Over the past 3 years, there have been at least 6 studies that investigated the associations between vitamin D exposure in utero and atopic eczema in the offspring.^{33,34,47–51} Four studies evaluated cord blood,^{33,34,47,50} and 2 studies evaluated maternal vitamin D levels,^{33,49} whereas 1 study evaluated only the effect of maternal vitamin D intake during pregnancy.⁴⁸

In 2012, Jones et al³⁴ published the first study to examine cord blood vitamin D levels as an indicator of vitamin D status in utero in relation to infant eczema outcomes. Lower cord blood vitamin D concentrations were observed in infants who had developed eczema by 12 months of age, and eczema was almost 3 times more likely in those with concentrations of less than 50 nmol/L in comparison with those with concentrations of 75 nmol/L or greater. Interestingly, the risk of eczema declined significantly as cord blood 25(OH)D increased.³⁴ Confirming these findings, a more recent prospective birth cohort study of French mother-and-child pairs reported an inverse association between cord serum vitamin D levels and the risk of early- and late-onset AD, as well as AD by the age of 1, 2, 3 and 5 years.⁴⁷

Contrary to the aforementioned studies, Miyake et al⁴⁸ found that a higher maternal intake of vitamin D during pregnancy significantly increased the risk of infantile eczema (odds ratio, 1.63; 95% confidence interval, 1.07–2.51). Although the main strength of this study is the relatively large sample size, a major limitation is that the authors did not use objective measures of maternal vitamin D status. This study examined the maternal dietary intake of vitamin D during pregnancy, which has been questioned as a means of effectively establishing the total vitamin D status in utero and may lead to considerable misclassification of total exposure.⁴⁸

However, there have been some recent studies suggesting that vitamin D exposure in utero does not contribute to the development of AD. The largest prospective study to date showed that maternal vitamin D concentration in pregnancy was not associated

with eczema and other atopic outcome in the offspring. In addition, there was no suggestion that either deficient or high concentrations of maternal vitamin D was associated with an increased risk of these outcomes.⁴⁹ Along these lines, Weisse et al,³³ in a LINA (Lifestyle and environmental factors and their Influence on Newborns Allergy risk) cohort study, did not find an association of maternal and cord blood vitamin D levels with atopic eczema, either symptomatic or physician diagnosed. These findings are supported by another birth cohort study that evaluated the association between cord blood vitamin D level and asthma and allergy-related conditions during preschool age in 257 children from COPSAC₂₀₀₀ (Copenhagen Prospective Studies on Asthma in Childhood). Eczema was diagnosed in 42% of the study group. There was no statistically significant correlation between fetal vitamin exposure and the development of eczema during preschool age.⁵⁰

Because of the conflicting findings from observational studies using maternal and cord 25(OH) vitamin D levels, Goldring et al⁵¹ performed an interventional study and assessed children whose mothers had taken part in a randomized controlled trial of prenatal vitamin D supplementation, to determine the effect of prenatal vitamin D supplementation on the risk of allergic diseases in offspring. In this study, pregnant women were randomized at 27 weeks' gestation to no treatment, 800 IU ergocalciferol daily until delivery, or a single oral dose of 200,000 IU cholecalciferol. Neither daily nor single oral bolus vitamin D supplementation in late pregnancy prevented atopic eczema or other allergic diseases or allergic inflammation.⁵¹

THE PLAUSIBLE ROLE OF VITAMIN D IN THE IMMUNOPATHOGENESIS OF ATOPIC DERMATITIS

Vitamin D₃ intake is the combination of dietary consumption and UV exposure. 7-Dehydrocholesterol present in the epidermal cells, thanks to solar radiation, is converted to previtamin D₃, which is released into the blood. Exposure to UVB radiation plays an important role in the production of vitamin D and in 90% protects the body's supplies. The remaining 10% is supplied with diet.⁵² Several studies have reported an inverse association of sunlight exposure and AD severity and the fact of the disease worsening during winter.¹⁸ In countries of high latitude with less sun exposure, AD is also more prevalent, which can prove the role of vitamin D in the course of AD.⁵³ In addition, UVB phototherapy is a well-known and widely accepted treatment method for AD.⁵⁴ Recent experimental studies have proposed UVB-induced vitamin D as a mediator responsible for the epidermal barrier recovery and subsequent decrease in severity of AD symptoms.^{18,55} There is well-documented evidence that vitamin D modulates epidermal keratinocyte proliferation and differentiation.^{56,57} Furthermore, experimental data have suggested that vitamin D plays an important role in the maintenance of the epidermal barrier by synthesis of skin protein such as filaggrin, involucrin, and loricrin, essential to proper skin barrier structure.^{55,58,59}

In addition to its effects on the skin barrier function, vitamin D plays a key role in mediating the normal function of the innate and adaptive immune responses.^{9–11} It has been demonstrated that vitamin D has potent immunomodulatory properties, leading to a shift from proinflammatory to a more tolerogenic immune status and inducing antimicrobial peptide synthesis.⁶⁰ Liu et al^{10,61} demonstrated the connection between the vitamin D-mediated activation of Toll-like receptors, the production of cathelicidin, and the diminished sensitivity to bacterial infection.^{10,61} It was also found that in patients with AD, vitamin D levels are positively correlated with serum cathelicidin and its production in both keratinocytes and neutrophils.⁶² In addition, Hata et al⁵⁹ checked that after oral supplementation of vitamin D in AD-diagnosed patients cathelicidin levels in skin lesions increased significantly. Vitamin D also has impact on the innate immune system by enhancing chemotaxis and the phagocytic capabilities of macrophages and by increasing the nitric oxide production.^{10,11} Furthermore, functional analyses have shown that vitamin D suppresses dendritic cell maturation and thereby attenuates antigen presentation accompanied by lower interleukin 12 (IL-12) and IL-23 cytokine secretion but an increased production of a tolerogenic IL-10.^{9,60,63} In addition, vitamin D modulates the adaptive immune system via direct effects on T-cell proliferation and activation.^{9–11,63,64} In principle, the treatment of T cells with vitamin D inhibits the secretion of proinflammatory T_H1 (IL-2, interferon γ , tumor necrosis factor α) cytokines but increases the proliferation of allergy-associated T_H2 cells and promotes the production of more anti-inflammatory T_H2 (IL-3, IL-4, IL-5, IL-10) cytokines.^{64–66} Recently, calcitriol was also found to directly suppress IL-17 production on a transcriptional level, but the precise role of vitamin D as a regulator of T_H17 cells has yet to be fully elucidated.^{10,11,67} On the other hand, studies conducted in vitro and in vivo have demonstrated that vitamin D treatment increased the number of regulatory T cells, which have been shown to play an important role in the prevention of AD development by the suppression of proallergic mechanisms.^{68–70} In B cells, initial studies have indicated that vitamin D could directly regulate B-cell proliferation and decrease immunoglobulin production.^{63,71} Subsequent reports have confirmed that calcitriol and vitamin D receptor agonists suppressed IgE production either by cultured human B cells or in an allergy mouse model.^{71–73}

In summary, it has been established that vitamin D is a modulator of the innate and adaptive immune function and has a key role in T_H1-T_H2 balance. However, whereas in vitro vitamin D appears to support a shift from T_H1 to T_H2 cells, it seems likely that in vivo its effects on T cells are more complex.¹⁰

CONCLUSIONS

We have reviewed the literature from the past 3 years assessing the role of vitamin D in AD development and severity. The studies presented above differ in both the methodology and outcomes and provide conflicting results. Some studies have evaluated the

prevalence of AD in vitamin D–deficient individuals. A lower serum vitamin D level was associated with AD prevalence in a few reports. It is worth mentioning that low serum levels of vitamin D are observed both in AD and non-AD patients. It is not possible to determine clearly whether the deficiency increases the risk of AD.

Most of the reports measuring the correlation between serum concentration of vitamin D and AD severity demonstrated the relevant association between low serum vitamin D levels and the increased symptoms of the disease. However, there are studies that found no significant role of vitamin D concentration in AD severity.

In recent years, numerous interventional studies have been published on the supplementation of vitamin D, which seems to have a significant, therapeutic role on AD. Some of them revealed a positive association between vitamin D supplementation and AD prevalence and severity, whereas the others revealed no significant improvement. It is worth mentioning that the limitation of these studies results from using different doses of vitamin D (1000–4000 IU) without specifying adequate serum levels and also from the fact that the overall time of intervention varied between presented studies and was, in most cases, too short. In addition, in 1 of the studies, the initial vitamin D serum was not measured at all. However, it cannot be discounted that vitamin D supplementation at a higher dose might protect against AD, which is why the safety and efficacy of higher dose supplementation need to be explored.

The link between vitamin D exposure in utero and AD in offspring has also received considerable attention in literature. Although recent studies have gone beyond estimating maternal vitamin D dietary intake to directly measure maternal or cord blood vitamin D levels as an indicator of vitamin D status in utero, the results are still contradictory. However, some studies are limited by the high-risk nature of the population, which may not be representative of other populations of pregnant women. Another limitation of these reports is the reliance on a single vitamin D measurement as well at various time points in different studies. Therefore, it is not possible to determine whether a lack of vitamin D may differentially influence AD risk in certain stages of embryofetal development. In addition, not all studies adjusted the analyses for various potential confounders such as the season of birth, maternal age at delivery, passive smoking, or older siblings.

Taken together, it is not possible to unambiguously determine the role of vitamin D in the prevalence, severity, and course of AD. Some confounding and unidentified variables mentioned in existing studies appear to lead to inconclusive or inconsistent results.

Presented studies are limited by their mostly case-control or cross-sectional design involving data collected at 1 point in time, whereas in prospective trials the assessment of the cause-effect relationship is much better. Another limitation is the small numbers of participants enrolled in the previously mentioned studies, which may result in a rather low statistical power and lead to false-negative results. The conflicting results can be also attributed to the differences in ethnicity and sex. Moreover, some studies examined children, whereas some studies examined adults, and in others, reports on both these age groups were included, which may also affect the results.

The inconsistent findings may also be a result of the different ways utilized to determine the presence and severity of AD ranging from self-administered questionnaire-based diagnosis and parental report of a physician diagnosis or of AD symptoms to physician diagnosis. This can lead to selection and recall bias, as well as misclassification, as AD displays potential problems with interobserver variation. Similarly, the severity of AD was assessed by the same or by several different physicians and also various measurement scales, such as SCORAD, EASI, Three Item Severity, Nottingham Eczema Severity Score, or the Rajka and Langeland scoring system, which were used to evaluate the severity of symptoms. Even if the rates were similar, meaningful comparison of the results may be difficult to perform.

The observed contradictions between studies may result from the lack of standardization for the vitamin D serum level's measurement and no universal cutoff value of vitamin D deficiency and insufficiency. In literature, target levels of vitamin D are determined mainly regarding its role in bone metabolism and not in atopic diseases. It is worth remembering that the serum level of vitamin D is not a simple biological marker as many factors affect vitamin D status. This is not only dietary vitamin D intake or supplemented dose, but also other dietary factors that regulate its homeostasis and multiple nondietary confounders such as age, genetic determinants, the subject's physical activity, passive smoking, adiposity, sleep time, and sunlight exposure. These potential confounders affecting the endogenous vitamin D production have not been controlled in some presented studies.

As the vitamin D level strongly depends on variation in sun exposure, it is difficult to determine the influence of carrying out research at a particular time of the year. Furthermore, if UVB phototherapy is a successfully used treatment method in AD, variation in sun exposure due to latitude, season of blood sampling, time of day, atmospheric components, clothing, use of sunscreen, and skin pigmentation and inaccurate control of these confounders may explain the conflicting results between presented studies. In addition, it should be emphasized that UVB-induced vitamin D has been suggested as a mediator of improvement in the symptoms and severity of AD, but it seems to be possible that only a part of the benefit of UV light exposure is due to improved vitamin D status, which may also contribute to observed contradictions. It is also possible that damage to the skin caused by AD led to low vitamin D absorption from the sun, or maybe these 2 mentioned factors are unrelated and also did not change the outcomes significantly. Moreover, further studies are required to determine the potential impact of any medical cointerventions such as topical corticosteroids or emollients on vitamin D deficiency and currently obtained results.

Finally, the studies mentioned in this article did not assess vitamin D receptor gene polymorphisms or other potentially important genetic variations, which may result in altered responsiveness to vitamin D. Multiple gene-gene and gene-environment interactions are also likely to contribute to the observed discrepancies.

Because of the existence of a relationship between serum vitamin D level and AD development, nowadays, it is obvious that more studies, especially prospective randomized ones, should be provided to prove if the supplementation of vitamin D affects AD prevalence and severity. Also the mechanism of the action by which vitamin D produces its effect in AD should be clarified. It would be also important to determine the optimal level of vitamin D that decreases both the risk of the development and severity of AD, as studies' results, determining if vitamin D levels are correlated with AD prevalence and severity, are contradictory.

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