

Serum Vitamin D Levels Not Associated with Atopic Dermatitis Severity

Renata Robl, M.D., Marjorie Uber, M.D., Kerstin Taniguchi Abagge, M.D.,
Monica Nunes Lima, M.D., and Vânia Oliveira Carvalho, M.D.

Division of Pediatric Dermatology, Department of Pediatrics, Federal University of Paraná, Hospital de Clínicas da UFPR, Curitiba, Parana, Brazil

Abstract

Background/objectives: The objective of the current study was to determine the relationship between serum vitamin D levels and the severity of atopic dermatitis (AD) in a Brazilian population.

Methods: This was a cross-sectional study of patients younger than 14 years of age seen from April to November 2013. All patients fulfilled the Hanifin and Rajka Diagnostic Criteria for AD diagnosis. Disease severity was determined using the SCORing Atopic Dermatitis index and classified as mild (<25), moderate (25–50), or severe (>50). Serum vitamin D levels were classified as sufficient (≥ 30 ng/mL), insufficient (29–21 ng/mL), or deficient (≤ 20 ng/mL).

Results: A total of 105 patients met the inclusion criteria. Mild AD was diagnosed in 58 (55.2%) children, moderate in 24 (22.8%), and severe in 23 (21.9%). Vitamin D deficiency was observed in 45 individuals (42.9%). Of these, 24 (53.3%) had mild AD, 13 (28.9%) moderate, and 8 (17.7%) severe. Insufficient vitamin D levels were found in 45 (42.9%) individuals; 24 (53.3%) had mild AD, 9 (20.0%) moderate, and 12 (26.7%) severe. Of the 15 individuals (14.2%) with sufficient vitamin D levels, 10 (60.7%) had mild AD, 2 (13.3%) moderate, and 3 (20.0%) severe. The mean vitamin D level was 22.1 ± 7.3 ng/mL in individuals with mild AD, 20.8 ± 6.5 ng/mL in those with moderate AD, and 21.9 ± 9.3 ng/mL in those with severe AD. Variables such as sex, age, skin phototype, season of the year, and bacterial infection were not significantly associated with vitamin D levels.

Conclusion: Levels of 25-hydroxyvitamin D were deficient or insufficient in 85% of the children, but serum vitamin D concentrations were not significantly related to AD severity.

INTRODUCTION

Clinical and epidemiologic studies have suggested that vitamin D deficiency may be associated with severity of atopic dermatitis (AD) (1–5).

In an evaluation of serum vitamin D levels in individuals with AD, Peroni et al (6) reported that vitamin D deficiency may be related to the severity of AD, and in a study of 73 children, vitamin D

Address correspondence to Renata Robl, M.D., Rua Cruz e Souza 68–Guabirota, Curitiba, Paraná, CEP 81510160, Brazil, or e-mail: natarobl@hotmail.com.

levels were significantly lower in participants with moderate to severe AD than in those with mild AD (1).

Some studies have suggested that vitamin D supplementation promotes alterations in immunity and epidermal barrier integrity, potentially leading to clinical improvements in AD, and is useful as an adjuvant treatment (5,7,8). In a double-blind clinical study, Amestejani et al (9) randomly selected 30 adults to receive 1,600 UI/day of vitamin D supplementation for 60 days and 30 to receive placebo. SCORing Atopic Dermatitis (SCORAD) scores significantly improved independent of initial disease severity in treated patients (9).

Although studies have investigated the effect of vitamin D on AD severity, the results are controversial. In a cross-sectional study of 94 patients ages 1 to 18 years, Chiu et al (10) used the SCORAD and serum vitamin D measurements to demonstrate that serum vitamin D levels did not significantly correlate with disease severity.

Considering these conflicting results, the objective of this study was to determine whether there is a relationship between AD severity and serum vitamin D levels in children.

METHODS

This was a cross-sectional study of children with AD seen in a Brazilian tertiary hospital in Curitiba, Paraná, in the southern part of the country (latitude 25° 25' 40" S). Patients were evaluated between April 1 and November 30, 2013, and categorized according to the season of the year in which the evaluation was performed: winter (June 21–September 21), spring (September 22–December 20), and autumn (March 20–June 20).

Children up to 14 years old who met the Hanifin and Rajka criteria (11) for AD with serum vitamin D level measurements were included. Our institution's Human Research Ethics Committee approved the study.

Use of vitamin D supplements within the past 6 months, hyperimmunoglobulin E syndrome, chronic systemic disease except asthma or allergic rhinitis, previous systemic therapy or phototherapy for AD, previous diagnosis of vitamin D deficiency, and long-term systemic corticosteroid therapy were exclusion criteria.

All patients underwent a dermatologic examination, including examination of the skin and mucosa. A pediatric dermatologist evaluated disease severity using the SCORAD index (12) and AD was classified

as mild (SCORAD score <25), moderate (25–50), or severe (>50).

All patients provided a single blood sample on the first day of the evaluation, and serum vitamin D levels were measured as 25-hydroxyvitamin D (25(OH)D) using a chemiluminescence microparticle immunoassay.

Vitamin D levels were classified for a descriptive analysis according to American Endocrine Society criteria as sufficient (≥ 30 ng/mL), insufficient (21–29 ng/mL), or deficient (≤ 20 ng/mL). Patients with inadequate vitamin D levels (deficient or insufficient) were subsequently given a vitamin D supplement (13).

Sex, age, skin phototype according to the Fitzpatrick classification (14), previous treatments, and the presence of cutaneous infections during the study period were analyzed.

The data were analyzed using Statistica 10.0 software (Statsoft, Tulsa, OK). Chi-square, Pearson, and Kruskal–Wallis analysis of variance tests were used. Univariate logistic regression was used to determine the relationship between serum vitamin D levels and SCORAD scores, and multivariate logistic regression was used to evaluate the association between the other variables and AD. The level of statistical significance for all tests was $p < 0.05$. The sample size was estimated to obtain a minimum test power of 90%.

RESULTS

A total of 105 patients with AD (median age 6.3 years, range 3 months to 14 years; 59 [56.2%] female) were evaluated during the study period. Evaluations were performed in the winter for 74 (70.4%) patients and in the autumn for 28 (26.8%).

The most common skin phototypes were Fitzpatrick type III ($n = 48$ [45.7%]) and IV ($n = 26$ [24.7%]). Sixteen patients (15.2%) had signs of a secondary bacterial infection at the time of evaluation. The group characteristics are described in Table 1.

The median SCORAD score was 27.9, and mild AD was diagnosed in 58 (55.2%) children, moderate in 24 (22.8%), and severe in 23 (21.9%).

Vitamin D deficiency was observed in 45 patients (42.9%), insufficient vitamin D levels in 45 (42.9%), and sufficient in 15 (14.2%). Figure 1 shows the distribution of patients in each AD severity category according to their vitamin D levels.

The median serum vitamin D concentration (25(OH)D) was 21.7 ng/mL in the study sample. Mean vitamin D levels were 22.1 ± 7.3 ng/mL in partici-

TABLE 1. *Clinical and Demographic Characteristics of the Sample*

Characteristic	Value
Season, <i>n</i> (%)	
Winter	74 (70.4)
Autumn	28 (26.8)
Spring	3 (2.8)
Sex, <i>n</i> (%)	
Male	46 (43.8)
Female	59 (56.2)
Skin phototype, <i>n</i> (%)	
I	2 (1.9)
II	24 (22.9)
III	48 (45.7)
IV	26 (24.8)
V	4 (3.8)
VI	1 (0.9)
Bacterial infection, <i>n</i> (%)	
Yes	16 (15.2)
No	89 (84.8)
AD severity (SCORing Atopic Dermatitis score), <i>n</i> (%)	
Mild (≤ 25)	58 (55.2)
Moderate (25–50)	24 (22.8)
Severe (> 50)	23 (22.0)
Vitamin D level (ng/mL), <i>n</i> (%)	
Sufficient (≥ 30)	15 (14.2)
Insufficient (21–29)	45 (42.9)
Deficient (≤ 20)	45 (42.9)
Vitamin D level (ng/mL), mean $\pm$ standard deviation	
Mild AD	22.1 $\pm$ 7.3
Moderate AD	20.8 $\pm$ 6.5
Severe AD	21.8 $\pm$ 9.3

AD, atopic dermatitis.

pants with mild AD, 20.8 ± 6.5 ng/mL in those with moderate AD, and 21.9 ± 9.3 ng/mL in those with severe AD.

Serum vitamin D levels in relation to the different eczema severity values for each patient are shown in Fig. 2. No association was observed between vitamin D concentration and SCORAD score ($p = 0.60$).

Figure 3 shows serum vitamin D levels according to the SCORAD severity classification; there was no significant difference between the groups. No significant association was observed between AD and the other variables, including sex, age, skin phototype, season of the year, secondary bacterial infection, and antibiotic or corticosteroid use (Table 2).

DISCUSSION

Vitamin D has been recognized for its effects on immunomodulation and calcium homeostasis (3,15,16). Studies have shown an inverse correlation between AD and serum vitamin D levels (1–9,17). The data in the literature are controversial in regard to the relationship between vitamin D levels and disease severity (10).

Peroni et al (6) evaluated 37 children with AD and found deficient vitamin D levels in 21%. Chiu et al (10) showed that 39% of a cohort of 94 children with AD who were evaluated had vitamin D deficiency. A Korean study found that lower serum vitamin D levels were not associated with AD in male adolescents but were significantly related to AD in female adolescents (18). In our sample, 42.9% of the children had vitamin D deficiency. Thus the percentage of individuals with AD with vitamin D deficiency varies from 20% to 42% between studies, demonstrating the importance of evaluating serum levels of this vitamin in patients with AD.

Different factors can influence serum vitamin D levels, and few have been evaluated or analyzed in scientific studies. For example, the geographic location of the study, diet, seasonality, AD severity, and treatments used can all affect serum vitamin D levels. One of the best-known factors is sun exposure. Curitiba has the fewest sunny days of any Brazilian state capital. In 2013, there were 116 sunny days in Curitiba (32% of the years), compared with 184 in New York, 142 in London, 143 in Prague, and 134 in Berlin (19). Therefore, sun exposure is an important fact to be considered, and it was not measured in the study. Slight changes in sun exposure could have significantly influenced the number of patients with insufficient or deficient vitamin D levels.

There is no consensus in the literature on the ideal serum vitamin D concentration for normal patients, but serum levels above or below the accepted normal range seem to have clinical consequences and influence the physiopathology of allergic diseases (6). There is also controversy regarding the recommended replacement dosage for this vitamin, especially in children with AD.

Several authors have found a significant association between inadequate vitamin D levels and AD severity, but these studies evaluated a small number of patients (1–5,20). Similar to the current study, Chiu et al (10) evaluated serum vitamin D levels in 94 children with AD and found no significant association with disease severity ($p = 0.99$).

In contrast to these findings, the multivariate regression model used in our sample indicated no association between inadequate vitamin D levels and variables such as sex, age, skin phototype, previous treatments, and cutaneous infection. Chiu et al (10) reported that lower serum vitamin D concentrations (25(OH)D) were associated with being 3 years of age or older ($p < 0.001$), female sex ($p < 0.001$), phototype VI ($p = 0.04$), and being evaluated in winter ($p = 0.04$).

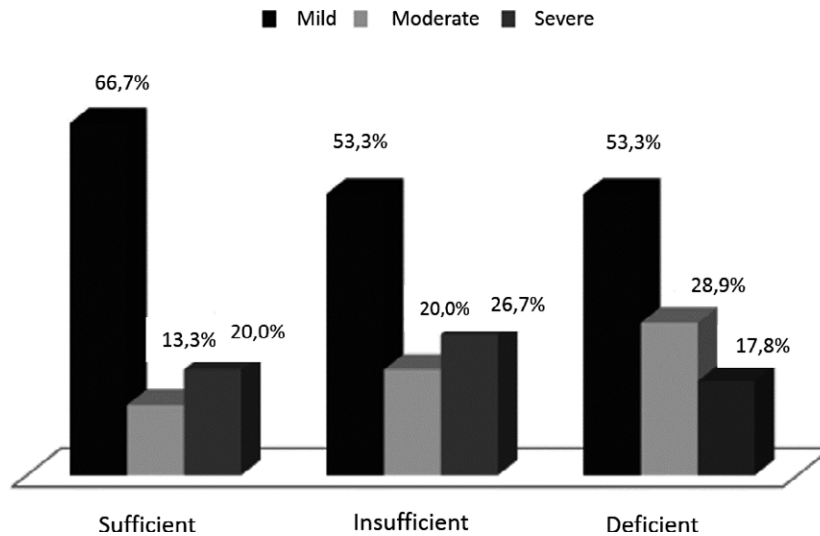


Figure 1. Distribution of atopic dermatitis severity (SCORing Atopic Dermatitis) according to serum vitamin D levels.

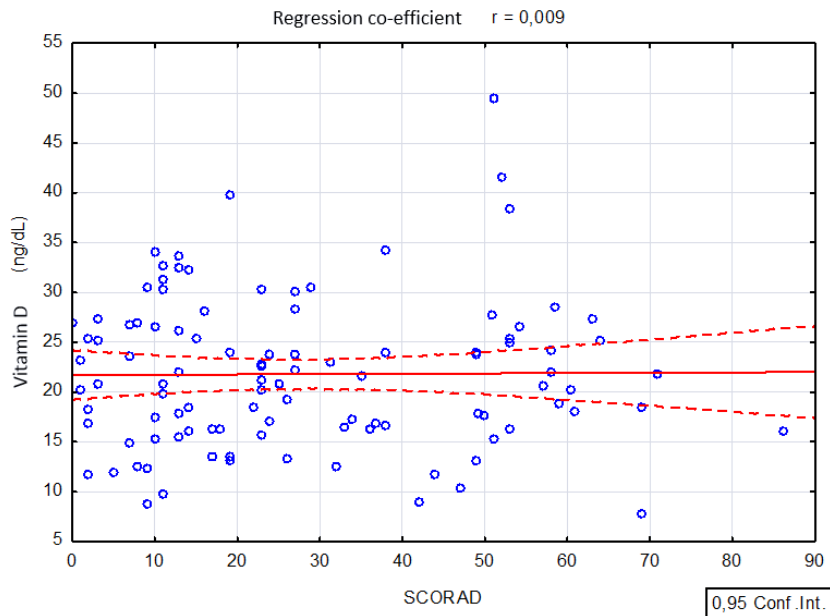


Figure 2. Correlation between serum vitamin D levels and individual SCORing Atopic Dermatitis values.

The skin of patients with AD is more susceptible to cutaneous bacterial infections and there is an association between bacteria proliferation and disease severity (19). A deficit in cathelicidin, an antimicrobial peptide, may be responsible for the increases in these infections. Recent studies have shown that vitamin D supplementation induces cathelicidin expression and reduces cutaneous antigens (8,21). In our study, we did not find an association between serum vitamin D levels and clinically detectable infection.

The capacity of vitamin D synthesis depends on factors such as the quantity of sun exposure, the time of year (less production in winter),

geographic latitude, hour of day, body covering, melanin content, and sunscreen use (13). Some authors have shown that correlations between inadequate serum vitamin D levels and AD severity are also related to atopic sensitization. Patients with and without sensitization can have different pathophysiological mechanisms and clinical presentations.

In a study by Akan et al (1), 45.2% of children demonstrated allergic sensitization (determined by an immediate hypersensitivity skin test), and there was a negative correlation between SCORAD score and insufficient serum vitamin D levels in the sensitization

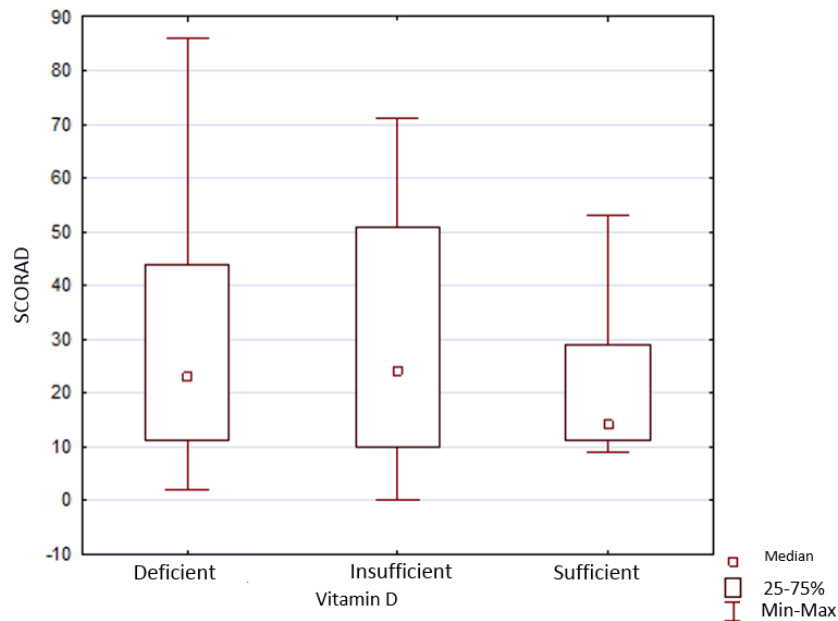


Figure 3. Serum vitamin D levels in relation to atopic dermatitis severity, as evaluated by SCORing Atopic Dermatitis values.

TABLE 2. Risk Factors Associated with Deficient Vitamin D Levels: Multivariate Logistic Regression

Variable	Odds ratio (95% confidence interval)
Female	0.59 (0.15, 2.25)
Age	0.54 (0.13, 2.39)
Skin phototype III	1.26 (0.46, 3.42)
Winter	0.20 (0.02, 1.73)
Presence of bacterial infection	0.73 (0.13, 4.09)
Antibiotic treatment	0.89 (0.23, 3.38)
Corticoid use	0.53 (0.12, 2.32)

group. No correlation was observed in the nonsensitization group.

Although it is important to recognize and consider these influential factors and variables, the heterogeneity of the studied groups can create a challenge when designing clinical studies and can result in multiple confounding variables in statistical analyses.

This study demonstrated that children with AD had lower-than-normal vitamin D levels without a relationship with disease severity. Nevertheless, the role of vitamin D in AD must be clarified, especially if there is a relationship with atopic sensitization and if vitamin D replacement can reduce clinical severity.

CONCLUSION

Serum vitamin D concentrations were deficient or insufficient in most patients in the studied sample but

were not significantly related to AD severity. Further studies are needed to determine whether vitamin D deficiency is more prevalent in children with AD or whether other factors such as race or geographic location contribute to the high incidence of inadequate vitamin D levels observed in the present study. It is also important to evaluate whether vitamin supplementation has an influence on treatment response, because this could support the role of vitamin D as an important adjuvant therapy in AD treatment.

REFERENCES

1. Akan A, Azkur D, Ginis T et al. Vitamin D level in children is correlated with severity of atopic dermatitis but only in patients with allergic sensitizations. *Pediatr Dermatol* 2013;30:359–363.
2. Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. *Curr Opin Allergy Clin Immunol* 2012;12:179.
3. Mutgi K, Koo J. Update on the role of systemic vitamin D in atopic dermatitis. *Pediatr Dermatol* 2013;30:303–307.
4. Reinholz M, Ruzicka T, Schaubert J. Vitamin D and its role in allergic disease. *Clin Exp Allergy* 2012;42:817–826.
5. Sidbury R, Sullivan A, Thadhani R et al. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol* 2008;159:245–247.
6. Peroni D, Piacentini G, Cametti E et al. Correlation between serum 25-hydroxyvitamin D levels and severity

- of atopic dermatitis in children. *Br J Dermatol* 2011;164:1078–1082.
7. Javanbakht MH, Keshavarz SA, Djalali M et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatolog Treat* 2011;22:144–150.
8. Hata TR, Kotel P, Jackson M et al. Administration of oral vitamin D induces cathelicidin production in atopic individuals. *J Allergy Clin Immunol* 2008;122:829.
9. Amestajani M, Salehi BS, Vasigh M et al. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. *J Drugs Dermatol* 2012;11:327–330.
10. Chiu YE, Havens PL, Siegel DH et al. Serum 25-hydroxyvitamin D concentration does not correlate with atopic dermatitis severity. *J Am Acad Dermatol* 2013;69:40–46.
11. Hanifin JMRG. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92:44–47.
12. Oranje A, Glazenburg E, Wolkerstorfer A et al. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol* 2007;157:645–648.
13. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
14. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988;124:869–871.
15. Castro APM, Solé D, Rosário Filho N et al. Guia prático para o manejo da dermatite atópica-opinião conjunta de especialistas em alergologia da Associação Brasileira de Alergia e Imunopatologia e da Sociedade Brasileira de Pediatria. *Rev Bras Alerg Imunopatol* 2006;29:268–282.
16. Heine G, Anton K, Henz BM et al. 1α , 25-dihydroxy-vitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. *Eur J Immunol* 2002;32:3395–3404.
17. Santos HL, Filho NAR. Relação entre vitamina D e doenças alérgicas. *Rev Bras Alerg Imunopatol* 2012;35:15–24.
18. Lee KS, Song J-H, Rha Y-H et al. Vitamin D deficiency as a risk factor of atopic dermatitis in Korean female adolescents. *J Allergy Clin Immunol* 2015;135:262.
19. Secondary. [online]. Available at <http://www.embratur.gov.br> (accessed on November 21, 2014).
20. Cheng HM, Kim S, Park G-H et al. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. *J Allergy Clin Immunol* 2014;133:1048–1055.
21. Benson A, Toh J, Vernon N et al. The role of vitamin D in the immunopathogenesis of allergic skin diseases. *Allergy* 2012;67:296–301.