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Ultraviolet index: a light in atopic dermatitis and vitamin D research?*

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Abstract: Background: The role played by vitamin D in atopic dermatitis is controversial and has been the focus of many studies. The ultraviolet index has not been considered in this type of research.
Objectives: The objectives of the study were to assess 25-hydroxy vitamin D [25(OH)D] serum level in atopic dermatitis patients and control group, to investigate the association between atopic dermatitis clinical severity (using the SCORing Atopic Dermatitis index - SCORAD) and 25(OH)D serum levels, and to evaluate the independent predictors, including Ultraviolet index, SCORAD and 25(OH)D.
Methods: We conducted a cross-sectional study of 106 atopic dermatitis patients. A control group was matched with a subsample of 54 participants with atopic dermatitis. SCORAD index, laboratory tests, and local Ultraviolet index were assessed.
Results: The atopic dermatitis patients had serum 25(OH)D levels and mean UVI significantly higher than the control group. Immunoglobulin E and Ultraviolet index were associated with the SCORAD index. Skin type, age and Ultraviolet index were independent predictors of 25(OH)D.
Conclusions: Although statistically significant, the different levels of 25(OH)D between the paired groups may be attributed to the higher mean Ultraviolet index in atopic dermatitis patients. Since Ultraviolet index is an independent predictor of SCORAD index and of 25(OH)D level, it may work as a confounding factor in studies involving atopic dermatitis and 25(OH)D and must be considered in this kind of research.
Keywords: Dermatitis, atopic; Ultraviolet rays; Vitamin D

INTRODUCTION

Atopic dermatitis (AD) is a prevalent disease in childhood. Its etiopathogenesis is complex and is not completely understood.[1] Two major characteristics of AD are skin barrier dysfunction and immune dysregulation.[2]

Vitamin D is a fat-soluble vitamin synthesized mainly in the skin when exposed to ultraviolet B (UVB).[3] The biological actions of vitamin D have been widely studied in recent decades. Its extraskeletal actions are now better understood, and vitamin D has been linked to a broad range of autoimmune, neoplastic, inflammatory, degenerative, metabolic and allergic diseases.[4] In this context, clinical trials have failed to demonstrate a causal relationship.

Given the immunomodulatory role of vitamin D combined with its action in skin barrier formation and recovery, reducing transepidermal water loss and stimulating the production of antimicrobial peptides (AMP) by keratinocytes, macrophages, and neutrophils, it is reasonable to suppose that there is a link between the actions of vitamin D and the etiopathogenesis of AD.[3,5-9] However, findings related to the association between vitamin D and atopic diseases are scarce and conflicting. Some researchers have demonstrated the association between AD and hypovitaminosis D or low vitamin D intake, whereas other studies have shown higher chance of AD with high vitamin D intake.[10-14] A negative association between vitamin D and AD clinical severity has been reported but not confirmed in other studies.[15-17] Recently, clinical improvement of the disease after vitamin D supplementation has been demonstrated.[16,18,19]

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There is no consensus regarding optimal serum levels of 25-hydroxy vitamin D [25(OH)D], the metabolite used to determine the overall status of vitamin D, or the time of its storage after the 25-hydroxylation of vitamin D in the liver. The Endocrine Society established that the adequate level of vitamin D is between 30 and 100 ng/ml, the insufficient level is between 20 and 29.9 ng/ml, and deficient level is < 20 ng/ml.[20]

Ultraviolet (UV) radiation exerts immunosuppressive effects in AD patients and has been used successfully in the treatment of AD, in methods like phototherapy or heliotherapy.[21] However, overexposure to UV radiation from the sun and artificial UV radiation sources is a public health concern. UV radiation predisposes to skin cancer development and eye damage. In 1995, in order to raise public awareness about the excessive exposure to UV and the need to adopt protective measures, the World Health Organization (WHO), together with several partner organizations, developed the Global Solar Ultraviolet Index (UVI). The UVI is a measurement of UV radiation levels reaching the Earth's surface. The WHO defines five UVI exposure categories: low, moderate, high, very high, and extreme.[22,23] UVI is easily obtained from meteorological centers. Nevertheless, it has not been considered in research involving the association between AD and 25(OH)D and its influence is unknown, as seen in the published results.

The main objectives of the present study were to investigate the prevalence of hypovitaminosis D in patients with AD and a matched control group, the association of AD clinical severity with 25(OH)D levels, and to analyze the independent predictors of 25(OH)D and AD clinical severity, including UVI among the tested variables.

METHODS

This cross-sectional study used a convenience sample of the pediatric dermatology outpatient clinic of the Hospital Universitário de Brasilia, located in Brasilia, Brazil (latitude 15º46' S, longitude 47º55' W). Data were collected by a single interviewer. The study was approved by the Research Ethics Committee at the School of Medicine of the University of Brasilia.

Inclusion criteria for the AD group were: age between 0 and 18 years old and diagnosis of AD according to Hanifin & Rajka criteria.[24] The use of emollients, topical corticosteroids and oral antihistamines was allowed. Exclusion criteria were: systemic diseases; vitamin supplementation in the last 6 months; use of topical calcineurin inhibitors or oral corticosteroids in the past 4 weeks; phototherapy; use of anticonvulsants, anticoagulants or antifungal drugs; and dermatoses or therapies that lead to reduced or increased sun exposure.

Inclusion criteria for the control group were age between 0 and 18 years old and adequate characteristics for the matching criteria. The control group patients were matched (1:1) with a subsample of 54 AD patients, selected according to the chronological order in which these patients entered the study. The control case was matched to an index case according to gender (same gender); age (same age ± 2 years); body mass index, BMI (same BMI ± 2 kg/m^2); and Fitzpatrick skin type scale (same skin type ± 1). The controls who met the same exclusion criteria as the cases and the individuals with any kind of atopy, psoriasis, and rosacea were excluded. The patients of the AD and control groups were selected from the same pediatric dermatology outpatient clinic.

The present study was conducted from November 2012 to October 2013. AD severity was assessed using the total SCORing Atopic Dermatitis (SCORAD) index.[25] The following data were collected from AD patients: age, gender, skin type, BMI, other personal atopy [asthma or allergic rhinitis (AR)], familial atopy, age of onset of AD symptoms, SCORAD index, 25(OH)D, immunoglobulin E (IgE), complete blood count, and stool test. The data needed for matching and 25(OH)D were collected from the control group. We calculated the mean of local maximum UVI in the 30 days prior to clinical evaluation individually in AD and control patients (Figure 1).

All cases and controls had their serum 25(OH) D levels measured using the immuno-chemiluminescence method - LIAISON XL platform (Diasorin, Sallugia, Italy). The 25(OH)D status was determined according to the reference values adopted by The

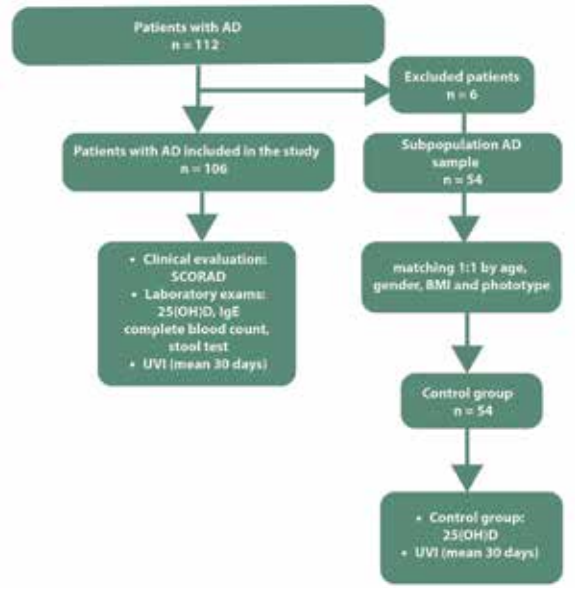

Figure 1: Inclusion flowchart (patients with AD and controls)

Endocrine Society.[20] Total serum IgE was measured by immunonephelometry using the BN II and BN ProSpec systems (Siemens, Marburg, Germany). Complete blood counts were performed using Cell-Dyn Ruby Abbott (Abbott Laboratories, Abbott Park, Illinois USA), and the stool tests were conducted using the spontaneous sedimentation method. Local UVI was obtained daily via the Brazilian Center for Weather Forecasting and Climate Studies site (available at http://satelite.cptec.inpe.br/uv/). The UVI was estimated using a mathematical-physical model, which describes transfer of UV radiation emitted by the sun in the Earth's atmosphere.

Data were statistically analyzed using SAS 9.3 (SAS Institute, Cary, NC, USA). The associations included quantitative and qualitative variables. Associations were considered to be statistically significant when the p-value was < 0.05. Unless otherwise specified, we used the Pearson linear correlation coefficient to analyze two quantitative variables and the Kruskall-Wallis test for qualitative variables. Paired Student's t test was used to compare 25(OH)D and UVI between the pairs of the matched groups. Multivariate analysis was performed using multiple linear regression.

RESULTS

Our sample consisted of 106 AD patients and 54 control group patients (Table 1). The prevalence of 25(OH)D insufficiency was 41.51% and of deficiency 16.04%, resulting in a 57.55% prevalence of hypovitaminosis D in the AD group. The local UVI in the period of completion of the study ranged from high to extreme levels (Figure 2). The stool tests did not detect presence of helminths.

Hypovitaminosis D was present in 77.78% of the control group (Table 2). The 54 AD patients had mean 25(OH)D significantly higher than those in the control group (mean difference 3.4 ng/ml, t = 2.45, p = 0.018). The marginal homogeneity test was performed to compare the 25(OH)D status between the groups. The hypothesis of marginal equality could not be rejected (p = 0.089); therefore, the proportion of patients with deficient, insufficient and adequate 25(OH)D levels did not differ between the groups. Index patients had mean UVI significantly higher than the control group (mean difference 2.54 index points, t = 6.10, p < 0.001).

The quantitative analysis of variables using the SCORAD index and 25(OH)D level was not statistically significant (n = 106, r = 0.342, p = 0.727) (Figure 3). Multiple linear regression analysis (r^2 = 0.230) showed that IgE and UVI were predictors significantly associated with SCORAD (β = 0.002, 95% CI [0.001, 0.004], p < 0.001 and β = -1.35, 95% CI [-2.357, -0.352], p = 0.009, respectively). The associations between SCORAD and the other variables [age, gender, Fitzpatrick skin type,

Table 1: Clinical, epidemiological, and laboratory characteristics of the AD group

	Subjects with AD (n = 106)
Age (years)	8.2 ± 4.0
Gender	
Male	38 (35.85%)
Female	68 (64.15%)
Fitzpatrick skin type	
II	7 (6.60%)
III	30 (28.30%)
IV	65 (61.32%)
V	4 (37.78%)
BMI (kg/m2)	17.8 ± 3.7
Asthma or AR	
Yes	60 (56.60%)
No	46 (43.40%)
Familial history of atopy	
Yes	72 (67.92%)
No	34 (32.08%)
Age of onset (years)	2.1 ± 2.8
SCORAD index	28.3 ± 15.3
Mild AD	49 (46.23%)
Moderate AD	48 (45.28%)
Severe AD	9 (8.49%)
25(OH)D (ng/ml)	29.0 ± 9.7
Sufficiency	45 (42.45%)
Insufficiency	44 (41.51%)
Deficiency	17 (16.04%)
Total IgE (IU/ml)	1242.8 ± 2297.7
Eosinophils (%)	7.7% ± 5.0
UVI (mean of 30 days)	11.65 ± 2.81

Values expressed as mean ± standard deviation or n (%)

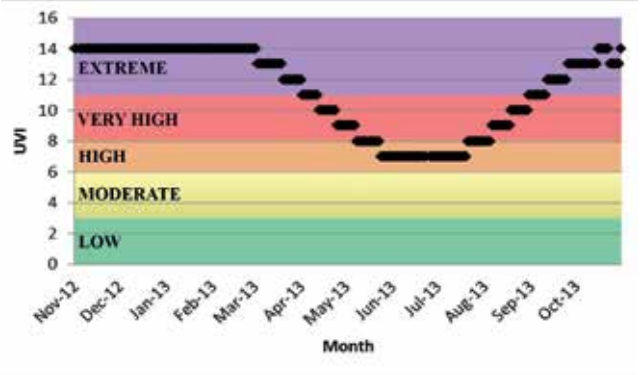

Figure 2: Maximum daily UVI in the city of Brasilia during the study

Table 2: Epidemiological and laboratory characteristics of AD subgroup and control group

	AD subgroup (n = 54)	Control group (n = 54)
Age (years)	9.1 ± 4.1	9.0 ± 4.3
Gender		
Male	22 (40.74%)	22 (40.74%)
Female	32 (59.26%)	32 (59.26%)
Fitzpatrick skin type		
II	1 (1.85%)	5 (9.26%)
III	17 (31.48%)	9 (16.67%)
IV	35 (64.82%)	39 (72.22%)
V	1 (1.85%)	1 (1.85%)
BMI (kg/m2)	17.7 ± 2.6	17.8 ± 2.5
25(OH)D (ng/ml)	29.0 ± 8.8	25.6 ± 7
Sufficiency	23 (42.59%)	12 (22.22%)
Insufficiency	21 (38.89%)	33 (61.11%)
Deficiency	10 (18.52%)	9 (16.67%)
UVI (mean of 30 days)	12.85 ± 2.09	10.31 ± 2.54

Values expressed as mean ± standard deviation or n (%)

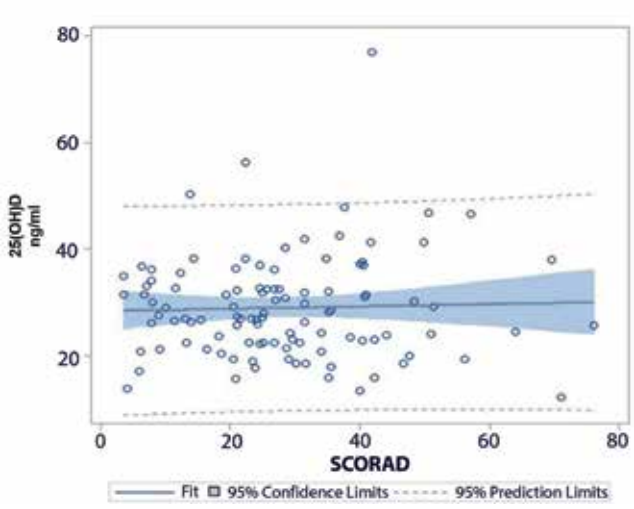

Figure 3: Correlation between 25(OH)D and SCORAD

BMI, asthma or AR (yes or no), familial history of atopy (yes or no), age of onset of AD and eosinophils] were not statistically significant ($p > 0.05$).

Multiple linear regression analysis ($r^2 = 0.188$) showed that the variables skin type, age and UVI were predictors significantly associated with 25(OH)D. Patients with skin type II and III showed mean 25(OH)D level of 5.4 ng/ml higher than patients with skin type IV and V (β = 6.102, 95% CI [2.116, 10.088], p = 0.003). Older patients were associated with lower 25(OH)D levels than younger patients (β = -0.570, 95% CI [-1.044, -0.096], p = 0.019). Furthermore, the higher the UVI, the greater the levels of 25(OH)D (β = 0.739, 95% CI [0.086, 1.391], p = 0.027). The associations between 25(OH)D levels and the other variables [gender, BMI, asthma or AR (yes or no), familial history of atopy (yes or no), total IgE and eosinophils] were not statistically significant ($p > 0.05$). There was no significant seasonal effect on either SCORAD or 25(OH)D level.

DISCUSSION

The prevalence of hypovitaminosis D was 57.55% in the AD group. This prevalence rate is similar to that reported by Weng *et al.*[26] (55%) and Peters *et al.*[27] (60%) in adolescents. This prevalence was higher in the control group, affecting 77.78% of these patients. Such high prevalence rates are a reason for concern, since maximizing the peak of bone mass during adolescence and early adulthood is considered to be the best protection against age-related bone loss and late risk of osteoporosis.[28] Although this study was conducted in a city with high UVI, ranging from high to extreme, this was not enough to prevent the high prevalence of 25(OH)D insufficiency. Other authors have also found low levels of 25(OH)D in healthy individuals living in sunny regions.[29]

We demonstrated that AD subgroup patients had 25(OH)D levels higher than matched controls. However, 25(OH)D status was not statistically different between the groups. Because small variations in the serum 25(OH)D level may not be clinically significant, the association between categorical variables seems to be more appropriate. Although some studies suggest a positive association between atopy and vitamin D, we believe that the higher level of 25(OH)D in AD patients is linked to the higher UVI in this group, as demonstrated by the paired analysis in our sample.[14,30,31] We found no statistically significant association between 25(OH)D levels and AD clinical severity, which is in agreement with recent publications.[16,17,32]

In terms of independent variables associated with AD severity, the association with IgE is well known and has been reported by several other studies.[33] Despite its inclusion among the diagnostic criteria of AD, it has not been established whether IgE sensitization is useful to the management and research of AD.

Age, skin type and UVI were significantly associated with serum 25(OH)D levels, according to the multivariate analysis. The older the patient, the lower the serum 25(OH)D level. The reason for this association in a young population is not clear, although it has been previously reported.[26] We agree with the authors who suggest that older children and adolescents may spend less time playing outdoors or may have a reduced oral supplementation of vitamin D.[17,26] The reduction in the 25(OH)D levels in higher skin types is expected because melanin competes for UVB photons. Considering the

physiology of vitamin D, the positive association between UVI and 25(OH)D is expected, since UVB radiation promotes the photolysis of 7-dehydrocholesterol and initiates the synthesis of vitamin D.[34]

The association between UVI and SCORAD was expected, even though UVI has been poorly considered in AD researches. Once the UVB radiation is needed for the physiological synthesis of vitamin D and UV radiation simultaneously exerts immunosuppressive effects in AD patients and reduces the clinical severity of AD, including UVI as an independent variable is of the utmost importance in the context of AD and 25(OH)D.[35-37]

We found no influence of the season on AD severity and 25(OH)D levels, maybe because the study was conducted in a very sunny city throughout the year, with low variation of its maximum UVI level. Most studies associate seasons to atopic diseases without considering the UVI. However, we consider that environmental influence on AD and 25(OH) D may be best measured with the UVI, at least in areas with poorly defined seasons. The association between UVI and AD is a recent theme and there are few published studies. Silverberg *et al.* demonstrated lower prevalence of AD in U.S. states with the highest UVI.[38] The same way, studies associate UVI to other diseases (e.g., hay fever and prostate cancer) in a populational basis.[39,40] We could not find studies that assessed UVI individually.

Although created in order to raise awareness of the need for sun protection, we consider that the importance of UVI is beyond the scope of its creation and we advocate its use in research involving diseases that may be influenced by UV radiation, such as AD and psoriasis. UVI represents an important confounding factor and may distort results, especially in places with large variation of this index. In this context, considering UVI is highly important when subjects are compared.

It must be emphasized that the maximum daily UVI score does not represent the actual daily sun exposure of the participants. We did not measure time and duration of UV exposure in volunteers. Therefore, the variable UVI cannot be considered the only predictor of UV exposure. The ideal method for accurate and reliable measure of individual UV exposure would be personal UV dosimeters. Personal UV dosimeters are able to provide a dynamic and objective measurement of cumulative UV exposure, since its result is determined by the daily variations of UV exposure and by environmental conditions. The most widely used chemical dosimeters are polysulfone or polyphenylene oxide. Nowadays electronic devices are also available.

We considered a period of 30 days prior to clinical evaluation to calculate mean UVI individually. However, there is no consensus about the amount of UV exposure needed to maintain vitamin D levels. We established this period considering the half-life of 25(OH)D (about two to three weeks), the related improvement of AD severity after 4 weeks of climatotherapy, and variation of individual habits of sun exposure, trying to reach intentional and non-intentional sun exposure periods.[34,41] The production and degradation of 25(OH)D is a continuous process. Establishing the ideal period to measure UV effects both in 25(OH)D production and immunosuppression on an individual basis is a hard task in clinical research and needs to be better evaluated in prospective studies. To the best of our knowledge, this is the first study to consider UVI in research associating 25(OH)D and AD. Once mean UVI is significantly associated with 25(OH)D and SCORAD, the 30 days period may be a starting point to evaluate this issue.

This study was strictly controlled by the researchers, thus minimizing measurement biases. All tests were performed at the same laboratories, therefore ensuring technical uniformity. This strategy is of paramount importance for the measurement of 25(OH)D levels because of the well-known inter assay variation.[34] Our study limitations include the lack of evaluation of the following variables: sun exposure, dietary vitamin D intake, clothing, sunscreen use, albumin, serum calcium levels, magnesium and phosphorus, BMD, markers of bone turnover, and renal function. Furthermore, although largely used, the chemiluminescence method used to measure 25(OH)D is not the most accurate and has wide variability.[34,42] Since this was a cross-sectional study, only a single point in time was evaluated. The level of 25(OH)D may vary greatly over short time intervals, depending on vitamin D intake and sun exposure.[43]

CONCLUSION

In conclusion, we found higher levels of 25(OH)D in AD patients than in paired controls, probably because of the higher mean UVI of those patients. There was no association between SCORAD and 25(OH)D. The role of vitamin D in atopic diseases is controversial and continues to be investigated worldwide. The extent of its impact on the immune system and specifically on allergic diseases has yet to be elucidated. We demonstrated the relevance of UVI as a predictor of 25(OH)D and of SCORAD, even though we had not considered solar exposure of participants. UVI can be easily obtained and should be included in studies involving 25(OH)D and diseases influenced by UV because it may represent a confounding factor and distort results. The use of UVI individually in clinical research may shed some light and eliminate any shadow of doubt in AD and vitamin D research.❑

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