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Vitamin D supplementation and severity of atopic dermatitis: pre-post assessment

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KEYWORDS
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Abstract
Background/objectives: There is evidence that vitamin D (VD) supplementation may help in the management of atopic dermatitis (AD). The aim of this study was to assess the influence of VD supplementation on the severity of AD.
Methods: Pre-post interventional study with prospective data collection in patients younger than 14 years. The severity of AD was determined through SCORAD (SCORing Atopic Dermatitis) and classified as mild (SCORAD<25), moderate (≥25 and <50), and severe (≥50). Skin prick test was performed in all patients. Serum VD levels were classified as sufficient (≥30 ng/mL), insufficient (29 to 21 ng/mL), and deficient (≤20 ng/mL); and those with inadequate levels received oral supplementation of VD for 3 months, and were reassessed after treatment.
Results: A total of 152 patients were included. Patients with sufficient vitamin levels had lower SCORAD values ($p=0.04$). Further, 116 patients (76.3%) received VD supplementation and after 3 months, VD levels were significantly higher (35.9 ng/mL) compared to baseline levels (23.7 ng/mL, $p<0.001$). At the same time, a reduction in the SCORAD index was observed (19.4 before vs 12.3 after supplementation, $p<0.001$). Considering other factors that could influence the decrease in AD severity after VD supplementation, female gender was associated with a worse treatment response ($p=0.02$).
Conclusion: Vitamin D supplementation could be an adjuvant in reducing the severity of atopic dermatitis.

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Introduction

The effects of vitamin D (VD) on immunomodulation and calcium homeostasis have been known for years.[1] The physiological role that VD plays in the skin is well known: regulating chemokine production, counteracting autoimmune inflammation, and inducing differentiation of immune cells in a way that promotes self-tolerance.[2] Moreover, it seems that VD has also an influence in the clinical course of some immunologic-based diseases, such as asthma, allergic rhinitis, and atopic dermatitis (AD).[3]

AD is a common inflammatory skin disorder characterized by recurrent eczematous lesions and intense itch. The pathophysiology is complex and involves a strong genetic predisposition, epidermal dysfunction, and T-cell driven inflammation. Although type-2 mechanisms are dominant, there is an increasing evidence that the disorder involves multiple immune pathways.[4] And the current view about the pathogenesis of AD stems from the integration of different hypotheses: the influence of microbiota, food allergy, and the role of VD.[5]

Recent articles controversially suggest a possible influence of VD in the development of AD[6,7] since both positive[8] and negative results have been found.[9] Some studies assume that VD serum levels have no significant association with the severity of AD[10,11] while others suggest otherwise.[12,13] Vitamin D supplementation may also have effects on immunological aspects and integrity of the epidermal barrier,[14] leading to clinical improvement of AD.[15,16]

Available data on vitamin D and AD are conflicting; most of the articles have non-prospective designs or include small sample sizes.[17,18] In addition, several variables could influence data analysis, but they are rarely assessed: such as the geographical location of the study, seasonality, diet, severity of AD, sun exposure, and current/previous treatments.

The present study aims to determine whether vitamin D supplementation can decrease the severity of AD in patients with inadequate levels.

Methods

Study design and subjects

Prospective interventional pre-post study in a tertiary Hospital in Curitiba (Paraná, Brazil – latitude 25° 250 40 "S). The patients were evaluated between January 2014 and January 2016, and were categorized according to the seasons of the year: spring (from September 22 to December 20), summer (December 21 to March 19), fall (March 20 to June 06), and winter (June 21 to September 21). It included children up to 14 years of age, who met the criteria of Hanifin and Rajka[19] for AD diagnosis and who underwent VD serum measurement and the skin prick test. The Ethics Committee of the Institution approved the study.

Patients who are receiving vitamin D supplementation 6 months prior to the consultation and/or those with the following conditions were excluded: hyperimmunoglobulin E syndrome; chronic systemic diseases, except asthma or allergic rhinitis; previous systemic therapy or phototherapy for treatment of AD; previously diagnosed VD deficiency; and chronic systemic corticosteroid therapy.

Written informed consent was obtained from all parents and verbal consent was obtained from all children. The study was approved by the Ethics Committee of Hospital de Clínicas, Universidade Federal do Paraná.

The assessment of the severity of AD

The severity of AD was evaluated by the SCORAD (Scoring Atopic Dermatitis),[20] applied by the same physician. The disease was classified as mild (score <25), moderate (≥25 to <50), or severe (≥50).

Skin prick test

The skin prick test was performed on the volar face of the forearm for the common standard allergens (*Dermatophagoides pteronyssinus*, Blomia, dog and cat epithelium, cockroaches, fungus, and grass pollen). Glycerin 50% was used as negative control and histamine (10 mg/mL) as positive control. The reaction was evaluated after 20 min and the test was considered positive when the wheal was 3 mm bigger than the negative control or more.

Laboratory assessment – serum levels of VD

Blood samples from all patients were obtained on the day of the first evaluation. Serum VD levels were measured as (25 [OH] D), by the Chemiluminescence Microparticle Immunoassay (CMIA), and classified as sufficient (≥30 ng/mL), insufficient (29 to 21 ng/mL), and deficient (≤20 ng/ml) in a descriptive analysis.[21]

Vitamin D supplementation and patients' reassessment

Patients with inadequate vitamin concentrations were treated with VD oral supplementation. The group with deficiency levels received 50,000 IU of VD, per week, for 4 weeks. In the cases of insufficiency, 15,000 IU per week was prescribed, also for 4 weeks. A maintenance of single dosage of 15,000 IU per week was used for all individuals with inadequate levels, for 2 months after the first 4 weeks of treatment, totaling a 3-month period of oral supplementation.

These patients were then re-evaluated after 3 months with complete dermatological examination, including the SCORAD, and VD serum levels. All participants were instructed to normally maintain the use of moisturizers and topical treatments, such as topical corticosteroids or topical calcineurin inhibitors during the study period.

The clinical and laboratory evaluations of patients during the study are summarized in the flow chart shown in Figure 1.

Statistical analysis

Data were analyzed in the Statistica 10.0® program (Statsoft Tulsa, OK), using Pearson's chi-square and Kruskal–Wallis (ANOVA) tests. The univariate logistic regression model and Pearson's correlation were used to examine the relationship between serum VD and SCORAD values. Multivariate

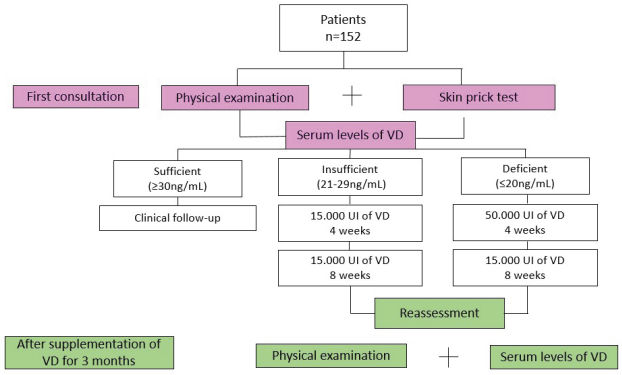


Figure 1 Flowchart of clinical and complementary assessments of patients during the research.
Note: The pictures selected in pink indicate the procedures performed at the first consultation; the green pictures indicate the procedures after 3 months of vitamin D supplementation; VD=vitamin D; UI=international units.

logistic regression was applied to evaluate the association between the other variables and AD. For all tests, a significance level of 5% was considered. The sample was estimated in order to obtain at least 90% statistical power.

Results

The study included 152 patients: 89 girls (58.5%), whose clinical and sociodemographic profiles are shown in Table 1; 94 patients (61.8%) reported daily solar exposure considered adequate for VD synthesis (6 to 8 min daily, three times a week, arms and legs exposed, without sunscreen). Patients with sufficient VD levels had lower SCORAD values (p=0.4) and 32.9% patients were found with deficient VD levels (Table 1).

Further, 116 patients (76.3%) had insufficient or deficient serum levels of VD. The presence of allergic sensitization was not related to the severity of AD (median SCORAD of 23.9 in the participants with positive skin prick test vs 19.6 in the negative group, p=0.56).

After 3 months of oral VD, the vitamin levels were found to be significantly higher (35.9 ng/mL) compared to baseline (23.7 ng/mL; p<0.001) and there was a reduction

Table 1 Clinical and sociodemographic profile of the 152 patients.

Characteristics	n (%)
Gender (F/M)	89 (58.5)/63 (41.5)
Age at first evaluation (median, range)	6.6 years (2-14.0 years)
Presence of bacterial infection	26 (17.1)
Age group	
Infant/toddler	23 (15.1)
Pre-school	69 (45.4)
School-aged	34 (22.4)
Adolescent	26 (17.1)
Fitzpatrick skin phototype	
1	3 (2.0)
2	28 (18.4)
3	59 (38.9)
4	39 (25.6)
5	20 (13.1)
6	3 (2.0)
Season on first assessment	
Winter	58 (38.2)
Spring	36 (23.7)
Summer	32 (21.0)
Autumn	26 (17.1)
1-14 min	
15-60 min	
61-120 min	
121-480 min	
More than 480 min	
Yes	
No	
Positive	
Negative	
SCORAD (median, range)	
Mild (SCORAD <25)	
Moderate (≥25 to <50)	
Severe (≥50)	
[25 (OH) D] (median, range)	
Sufficient (≥30)	
Insufficient (21-29)	
Deficient (≤20)	
Mild AD	
Moderate AD	
Severe AD	

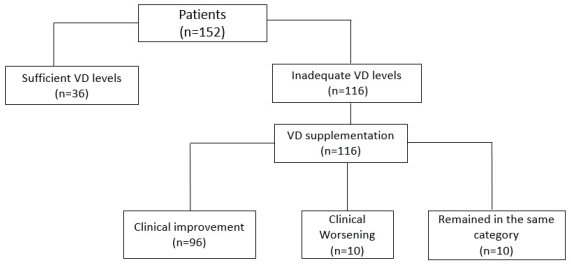
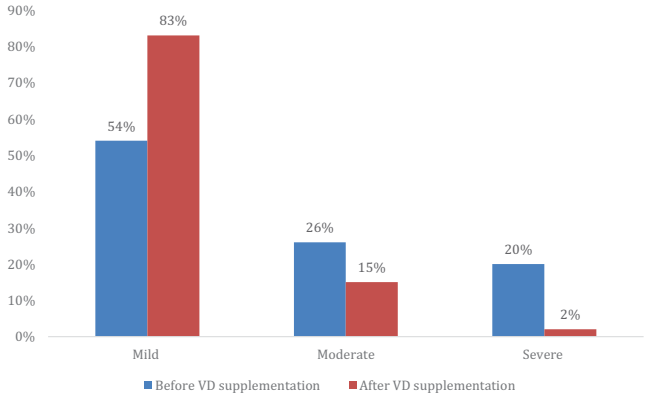


Figure 2 Flowchart of patients according to serum vitamin D levels and clinical response after vitamin supplementation.
Note: VD=vitamin D; Inadequate VD levels=insufficient and deficient serum levels of vitamin D.

in SCORAD index (19.4 before vs 12.3 after supplementation, p<0.001). After VD supplementation, DA was reclassified by SCORAD. There was a change in severity category with improvement of AD in 96 patients (82.7%). Graph 1 shows the severity of AD by SCORAD before and after VD supplementation (p=0.03).

Even after supplementation, 20 children did not improve: 10 patients had worsened disease severity and 10 remained in the same category (Table 2).

Analyzing the group who had improvement of AD severity after oral VD with the group that had no improvement at all, it was found that pre-school age (29.1% and 40.0%, respectively, p=0.04) and winter (15.6% and 60%, respectively, p=0.01) showed worse response to treatment.



Graph 1 Comparison percentual of patients classified by SCORAD before and after vitamin D supplementation.

Table 2 Evaluation of clinical response of patients after vitamin D supplementation.

	DA severity	
	With clinical improvement *(n=96) N (%)	Without clinical improvement** (n=20) N (%)
Variables	n (%)	n (%)
Gender (F/M)	51 (53.1)/45 (46.9)	16 (80.0)/4 (20.0)
Age at first evaluation (median, range in years)	6.2 years (0.2-13.6)	7.0 years (1.6-14.0)
Presence of bacterial infection	18 (18.7)	8 (40.0)
Season on first assessment		
Winter	42 (43.7)	9 (45.0)
Spring	21 (21.8)	7 (35.0)
Summer	16 (16.7)	0 (0)
Autumn	17 (17.8)	4 (20.0)
Atopic dermatitis severity index		
SCORAD (median, range)	13.9 (0.0-40.0)	37.0 (25.4-63.0)
AD severity category		
Mild (<25)	95 (98.9)	0 (0)
Moderate (≥25 to <50)	1 (1.1)	17 (85.0)
Severe (≥50)	0 (0)	3 (15.0)
Serum levels of vitamin D (ng/mL)		
(25 [OH] D) (median, min-max)	41.7 (7.8-99.1)	22.7 (7.7-40.5)
VD level category (ng/mL)		
Sufficient (≥30)	77 (80.2)	5 (25.0)
Insufficient (21-29)	13 (13.6)	10 (50.0)
Deficient (≤20)	6 (6.2)	5 (25.0)

AD=atopic dermatitis; SCORAD=SCORing Atopic Dermatitis. *change in AD severity category; ** same severity category or worsened disease severity.

Table 3 Multivariate logistic regression including factors that could influence clinical improvement after vitamin D supplementation.

Variable	OR	CI	p
Gender	4.09	1.22-13.72	0.02
Age	1.29	0.76-2.19	0.33
Season	1.11	0.72-1.69	0.62
Phototype	0.80	0.47-1.36	0.42
Familiar income	0.93	0.51-1.69	0.82
Sunscreen use	0.49	0.14-1.68	0.26
Adequate solar exposure	2.34	0.76-7.17	0.13
Secondary bacterial infection	1.86	0.54-6.44	0.32
Skin prick test	1.32	0.45-3.82	0.60
Treatments in use	2.23	0.65-7.61	0.19

OR=Odds ratio; CI=Confidence interval.

Bacterial infection was less common in the group that showed improvement of AD after oral VD (15.6% vs 70.0% in the group that remained in the same severity category, p=0.01).

According to the multivariate logistic regression model regarding the several factors that could influence VD supplementation in the reduction of the AD severity, female sex showed significant lower response to treatment (p=0.02) (Table 3).

The patients have reported no side effects of oral VD during the treatment period.

Discussion

In the present study, VD supplementation reduced the severity of AD in children with inadequate vitamin levels. Inadequate VD levels were found in 76.3% of patients and 32% had VD deficiency. Peroni et al. evaluated 37 children with AD and found deficient VD levels in 21%.[12] Chiu et al., in a cohort study of 94 children with AD, showed that 39% had VD deficiency. A previous study of 105 children with AD from our pediatric dermatology outpatient clinic demonstrated that 42.9% had deficient levels of VD.[10] Therefore, the percentage of AD patients with deficient levels of VD varies from 20% to 43%, and this can be due to the different levels of VD considered as deficient and insufficient levels among the authors.

Despite the differences in the classification of VD levels, participants of the present study were classified according to the criteria of the Endocrine Society Clinical Practice Guideline of 2011.[11] Currently, new studies and other values are being considered for VD level assessment.[23]

In our study, patients with sufficient vitamin levels had lower SCORAD values, in agreement with other authors, who related VD deficiency with greater severity of AD.[3] A study of 498 Chinese children with AD and 328 non-allergic controls concluded that serum levels of VD were inversely proportional to the severity of AD (p<0.001).[23] Akan et al. evaluated 73 children and concluded that the VD levels of

participants with moderate and severe AD were significantly lower than those with mild disease ($p=0.01$).[24]

In contrast to these findings, Chiu et al. evaluated VD levels in 94 children with AD and found no significant association with the severity of the disease ($p=0.99$).[10] In our previous study, no difference was found between VD levels and SCORAD.[11] We believe that this can be explained by the fact that AD is a multifactorial disease and involves environmental, genetic, pharmacological, and psychosomatic mechanisms. In addition, the chronic nature of AD can hinder the detection of this data by cross-sectional studies.

If patients with low VD levels had a more severe clinical picture, would vitamin replacement help in the control of the dermatosis? In the present study, after 3 months of oral VD supplementation, it was found that serum vitamin D levels were significantly higher compared to baseline levels. Concomitantly, a reduction in the SCORAD index was observed. Therefore, VD supplementation was an effective adjuvant treatment in reducing the severity of AD.

Sidbury et al. reported effects of oral supplementation with VD in children with AD in winter. The patients were evaluated by means of a scoring system called Eczema Area and Severity Index (EASI) – one group was subjected to daily supplementation with 1000 IU of VD ($n=5$) and the other group used placebo ($n=6$), for 1 month. There was improvement in the EASI score in the group that used VD ($p=0.04$).[17]

Camargo et al. conducted a double-blind study of 107 children with AD aged 2 years to 17 years in Mongolia, during winter. Oral cholecalciferol (1000 IU/day) versus placebo was randomized for 1 month. VD supplementation improved DA severity in this population, in which geographic location determines less sun exposure.[16]

VD supplementation was an effective treatment in reducing the severity of AD in 39 Italian children. After 3 months of daily supplementation of 1000 IU/day, there was an increase in serum levels of VD (22.9 ± 8.0 vs 29.4 ± 10.7 ng/ml, $p=0.01$) and SCORAD reduction (46.1 ± 15.6 vs 22.5 ± 15.2, $p<0.001$).[15]

In the present study, after VD supplementation, the severity of the disease was re-assessed. In the group of patients who showed clinical improvement after the intervention, girls had worse response to treatment. Female gender has already been associated with lower levels of VD,[25,26] but the reason is not elucidated.

There is consolidated scientific evidence that differences in allergic responses of female and male patients may be affected by both gender and sex. In addition, men and women not only present different clinical and symptomatic manifestations for the same pathology but also develop substantially different therapeutic responses.[27,28] A Korean survey of 2.748 adolescents aged 12 years to 18 years found that low levels of serum VD were not associated with high AD severity in male adolescents but were significantly related to more severe AD in the female group ($p=0.02$).[29]

Among the patients supplemented with VD in the present study, 10 of them presented clinical worsening: all of them were school-aged and their evaluation took place in winter. It is known that AD presents periods of remission and relapse, so the clinical worsening can be explained by the expected course of this dermatosis.

After VD supplementation, another 10 patients remained in the same severity category and this was influenced by secondary bacterial infection in this group. Bacterial infection is a common complication of AD, and is frequently responsible for exacerbation or maintenance of skin lesions.[30]

It is known that the current guidelines recommended for the treatment of AD is the use of modalities including emollients/moisturizers, topical corticosteroids, topical calcineurin inhibitors, and even systemic immunosuppressants. Further, the emerging therapeutics for AD focuses on intervening in the inflammatory pathway by using several biologics and small molecules targeting various AD-related pathways (omalizumab, lebrikizumab, tralokinumab, nemolizumab, dupilumab, baricitinib, abrocitinib, upadacitinib, and tradipitant).[31,32] However, the potential role of VD in suppressing inflammatory responses indicate that the supplementation has a possible therapeutic role for many skin diseases such as AD.[5,15,17]

The limitations of this study were the lack of follow-up of patients with sufficient VD levels in the first evaluation and the lack of evaluation of patients' nutritional status and diet, which may also influence serum VD levels.

The design of this study was different from others recently published[8,15] because VD serum levels were obtained before vitamin supplementation. It is highly recommended to access the necessity for supplementation of vitamin D as well as to prescribe adequate doses of VD, according to the serum levels obtained.

Future studies may elucidate the questions raised herein and help in understanding the factors that influence the difficulty of individual clinical response of patients with AD.

Conclusion

Patients with AD, especially those with moderate to severe disease, showed inadequate VD serum levels. After vitamin D oral supplementation, there was an improvement in VD serum levels and a decrease in AD severity, showing that this vitamin may have some role in skin inflammation of AD.

VD effects are not yet totally understood and longitudinal studies assessing long-term effects of VD supplementation on patients with AD are necessary. The high percentage of individuals with AD and deficient levels of VD indicate the necessity of assessing this vitamin's serum levels in patients with AD.

Declarations of interest

The Authors declare that there is no conflict of interest.

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References

1. Alves M, Bastos M, Leitão F, Marques G, Ribeiro G, Carrilho F. Vitamina D-importância da avaliação laboratorial. Rev Portug Endocrinol Diab Metab. 2013;8(1):32-9. https://doi.org/10.1016/j.rpedm.2012.12.001
2. Sirufo MM, et al. Osteoporose em Doenças da Pele. Int J Mol Sci. 2020;21(13):4749. https://doi.org/10.3390/ijms21134749
3. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. Eur Respir J. 2010;35(6):1228-34. https://doi.org/10.1183/09031936.00100609
4. Langan SM, et al. Dermatite atópica. Lancet. 2020;396(10247):345-60. https://doi.org/10.1016/S0140-6736(20)31286-1
5. De Martinis M, et al. Food allergy insights: a changing landscape. Arch Immunol Ther Exp (Warsz). 2020;68(2):8. https://doi.org/10.1007/s00005-020-00574-6
6. Sharma S, Kaur T, Malhotra SK, et al. Correlation of vitamin D3 levels and SCORAD index in atopic dermatits: a case control study. J Clin Diagn Res. 2017;11(7):1-3. https://doi.org/10.7860/JCDR/2017/27188.10223
7. Robl R, Carvalho VO, Uber M, Abagge KT, Pereira RM. Vitamina D e dermatite atópica: o que há de novo? Braz J Allergy Immunol. 2013;1(5):261-6. https://doi.org/10.5935/2318-5015.20130036
8. Samochocki Z, Bogaczewicz J, Jeziorkowska R, et al. Vitamin D effects in atopic dermatitis. J Am Acad Dermatol. 2013;69(2):238-44. https://doi.org/10.1016/j.jaad.2013.03.014
9. Thuesen B, Heede N, Tang L, et al. No association between vitamin D and atopy, asthma, lung function or atopic dermatitis: a prospective study in adults. Allergy. 2015;70(11):1501-4. https://doi.org/10.1111/all.12704
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(1):40-6. https://doi.org/10.1016/j.jaad.2013.01.010
11. Robl R, Uber M, Abagge KT, Lima MN, Carvalho VO. Serum vitamin D levels not associated with atopic dermatitis severity. Pediatr Dermatol. 2016;33(3):283-8. https://doi.org/10.1111/pde.12795
12. Peroni D, Piacentini G, Cametti E, Chinellato I, Boner A. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol. 2011;164(5):1078-82. https://doi.org/10.1111/j.1365-2133.2010.10147.x
13. Su O, Bahalı AG, Demir AD, et al. The relationship between severity of disease and vitamin D levels in children with atopic dermatitis. Postepy Dermatol Alergol. 2017;34(3):224. https://doi.org/10.5114/pdia.2017.66054
14. Hata TR, Kotol P, Jackson M, et al. Administration of oral vitamin D induces cathelicidin production in atopic individuals. J Allergy Clin Immunol. 2008;122(4):829. https://doi.org/10.1016/j.jaci.2008.08.020
15. Di Filippo P, Scaparrotta A, Rapino D, et al. Vitamin d supplementation modulates the immune system and improves atopic dermatitis in children. Int Arch Allergy Immunol. 2015;166(2):91-6. https://doi.org/10.1159/000371350
16. Camargo CA, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy Clin Immunol. 2014;134(4):831-5.e1. https://doi.org/10.1016/j.jaci.2014.08.002
17. Sidbury R, Sullivan A, Thadhani R, Camargo C. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. Br J Dermatol. 2008;159(1):245-7. https://doi.org/10.1111/j.1365-2133.2008.08601.x
18. Javanbakht MH, Keshavarz SA, Djalali M, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. J Dermatol Treat. 2011;22(3):144-50. https://doi.org/10.3109/09546630903578566
19. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;92:44-7.
20. Oranje A, Glazenburg E, Wolkerstorfer A, Waard-van der Spek D. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol. 2007;157(4):645-8. https://doi.org/10.1111/j.1365-2133.2007.08112.x
21. Holick MF, Brinkley NC, Biscchoff-Ferrari HA, et al. Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:1911-30. https://doi.org/10.1210/jc.2011-0385
22. Wang SS, Hon KL, Kong APs, Pong HNh, Wong GWk, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. Pediatr Allergy Immunol. 2014;25(1):30-5. https://doi.org/10.1111/pai.12167
23. 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(3):359-63. https://doi.org/10.1111/pde.12058
24. Andıran N, Çelik N, Akça H, Doğan G. Vitamin D deficiency in children and adolescents. J Clin Res Pediatr Endocrinol. 2012;4(1):25-9. https://doi.org/10.4274/jcrpe.574
25. Tolppanen A-M, Fraser A, Fraser WD, Lawlor DA. Risk factors for variation in 25-hydroxyvitamin D3 and D2 concentrations and vitamin D deficiency in children. J Clin Endocrinol Metab. 2012;97(4):1202-10. https://doi.org/10.1210/jc.2011-2516
26. National Institutes of Health. Consideration of sex as a biological variable in NIH-funded research. Notice Number: NOT-OD-15-102. Bethesda, MD: NIH Research Office on Women's Health; 2016.
27. De Martinis M, Sirufo MM, Suppa M, Di Silvestre D, Ginaldi L. Sex and gender aspects for patient stratification in allergy prevention and treatment. Int J Mol Sci. 2020;21(4):15355. https://doi.org/10.3390/ijms21041535
28. Lee KS, Song J-H, Rha Y-H, Choi S-H. Vitamin D deficiency as a risk factor of a topic dermatitis in Korean female adolescents. J Allergy Clin Immunol. 2015;135(2):AB262. https://doi.org/10.1016/j.jaci.2014.12.1798
29. Balma-Mena A, Lara-Corrales I, Zeller J, et al. Colonization with community-acquired methicillin-resistant Staphylococcus aureus in children with atopic dermatitis: a cross-sectional study. Int J Dermatol. 2011;50(6):682-8. https://doi.org/10.1111/j.1365-4632.2010.04751.x
30. Chu CY. Treatments for childhood atopic dermatitis: an update on emerging therapies. Clin Rev Allergy Immunol. 2020;1-14. https://doi.org/10.1007/s12016-020-08799-1
31. Sirufo MM, De Martinis M, Ginaldi L. Omalizumab an effective and safe alternative therapy in severe refractory atopic dermatitis: a case report. Medicine. 2018;97(24). https://doi.org/10.1097/MD.0000000000010897