

Vitamin D Status in Egyptian Children With Allergic Rhinitis

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Abstract

Objective: This study aimed to assess the serum levels of vitamin D in an Egyptian cohort of children with allergic rhinitis (AR) and to evaluate any correlation of vitamin D status with the disease severity. **Patient and methods:** One hundred twenty children with AR and 100 healthy children were included in our study. We studied the serum levels of vitamin D 25(OH)D and 1,25(OH)2D in all participants. The associations between vitamin D levels and clinical characteristics of AR were examined. **Results:** In AR group, the serum levels of calcium, (25(OH)D and 1,25(OH)2D levels were significantly lower ($p < .0001$, $p < .001$, and $p < .0001$, respectively) in AR children than in controls. Furthermore, the mean 25-OHD3 levels in patients with moderate/severe AR were significantly lower than those with mild AR ($p < .001$). We found significant negative correlations between mean 25(OH)D levels and total nasal symptom score ($r = -.62$, $p = .002$) and total immunoglobulin E levels ($r = -.27$, $p = .013$) in AR group. **Conclusions:** Vitamin D deficiency is a frequent finding among Egyptian children with AR when compared to the healthy group. A significant inverse association was observed between vitamin D levels and AR disease severity.

Keywords

allergic rhinitis, vitamin D, children

Introduction

Allergic rhinitis (AR) is one of the most important allergic airway diseases in children. It is an allergic disorder of the mucous membranes of the nasal passages. Allergic rhinitis is caused by an immune-mediated inflammatory reaction characterized by raised serum immunoglobulin E (IgE), mucus hypersecretion, and eosinophilic cell infiltration.^{1,2} Patients usually presented with paroxysmal sneezing, watery rhinorrhea, and nasal blockage.³ At present, AR is considered a major health problem affecting up to 40% of children worldwide, which may interfere with sleep and quality of life in AR children and impose a considerable burden on public health in economic terms.^{1,3} The exact etiology of AR remains poorly understood, and it is an active area of research.² Vitamin D deficiency is progressively documented as a possible etiologic or disease-modifying factor in many allergic disorders, including asthma,⁴ eczema,⁵ and food allergy.⁶ However, a few pieces of research have studied the relationship between vitamin D status and AR in children, especially in the Middle East. The epidemiologic pattern for the deficiency of vitamin D is coupled with the rising epidemic of atopic and allergic diseases in the developed countries so raises the likelihood of an association between the 2 variables.² This study aimed to assess the serum levels of vitamin D in a large Egyptian cohort of children with AR and to evaluate any correlation of vitamin D status with the disease severity.

Materials and Methods

Compliance With Ethical Standards

The procedures of our study were following the regulations of the relevant clinical research Ethics Committee and with those of the code of ethics of the world medical association Declaration of Helsinki). Written informed consents of parents of all children were taken after explanation of the study

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objectives and its benefits for their children. Faculty of Medicine, Assiut University Ethical Committee approved the study protocol.

Study Design

This was a case-controlled study undertaken in Assiut and Al-Azhar University Hospitals, Assiut city, Egypt.

Patients

This study included 120 patients aged 7 to 13 years with AR who were recruited to the study from 2 outpatient clinics in Al-Azhar and Assiut University Hospitals, Assiut, Egypt during winter 2016 (from September to December to avoid the seasonal variation in vitamin D levels.). The diagnosis of AR was performed according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and supported by a skin prick test.⁷ Skin prick tests were performed using the same antigens for all patients with a wide panel of most widespread aero-allergens in our locality, which included house dust, hay dust, mixed mites, mixed molds, mixed pollens, and cat epithelium. In addition to the allergens tested, there were positive and negative controls. The positive control, was a histamine solution, should become itchy within a few minutes, then red, and swollen with a wheal in the center. The negative control was a saline solution and should show no reaction. A senior otorhinolaryngologist evaluated all patients and controls before the children were recruited into the study. The severity grading and classification of all children with AR were performed based upon ARIA criteria into mild or moderate-severe rhinitis⁷ and total nasal symptom score (TNSS, nasal congestion, runny nose, itchy nose, and sneezing). Total nasal symptom score was assessed in all patients depending on the severity of AR manifestations. For every symptom TNSS has the following scores: 0 = no symptom; 1 = mild, unremarkable symptoms; 2 = moderate, disturbing but tolerable; and 3 = severe, disturbing, interfere with routine activities and/ or sleep.⁸ One hundred age- and sex-matched nonatopic, healthy children were recruited as normal control group. Any treatment with systemic corticosteroids and antihistamines were stopped 2 weeks before the study. The exclusion criteria were: (1) any accompanying disease that could affect vitamin D status, for example, rheumatologic diseases, chronic gastrointestinal and renal diseases, and endocrine disorders; (2) children who had received some drugs, for example, vitamin D, calcium-containing drugs, and immunotherapy; (3) patients with other types of rhinitis, for example, infectious, drug-induced, hormonal, or another non-AR.

Laboratory Investigations

Venous blood samples were collected from all patients and controls after 12-hour fasting between 8:00 and 10:00 AM. Serum samples were separated after centrifugation for 10 minutes and kept in -80°C until the day of analysis. All patients

Table 1. Demographic and Laboratory Characteristics of Study Patients.^a

Variable	Children With Allergic Rhinitis (n = 120)	Healthy Controls (n = 100)	P Value
• Age	6.29 $\pm$ 4.03	7.08 $\pm$ 2.91	NS
• Gender	54 males, 66 females	43 males, 57 females	NS
• Weight	29.5 $\pm$ 14.6	30.1 $\pm$ 13.9	NS
• Height	118.0 $\pm$ 24.6	115.0 $\pm$ 31.8	NS
• BMI	18.1 $\pm$ 6.2	19.2 $\pm$ 8.3	NS
• Total IgE, IU/mL	306.2 $\pm$ 57.9	52.8 $\pm$ 17.8	<.0001 ^b
• Calcium, mg/dL	8.9 $\pm$ 3.01	10.3 $\pm$ 2.91	<.0001 ^b
• 25(OH)D, ng/mL	27.5 $\pm$ 14.3	36.2 $\pm$ 19.8	<.001 ^b
• 1, 25(OH)2D, ng/mL	19.9 $\pm$ 16.4	29.5 $\pm$ 12.7	<.0001 ^b
• Vitamin D status, n (%)			
Normal (>30 ng/mL)	28 (23.3%)	52 (52%)	.002 ^b
Deficiency (<20 ng/mL)	37 (30.8%)	8 (8%)	<.0001 ^b
Insufficiency (20-30 ng/mL)	55 (45.9%)	40 (40%)	NS

Abbreviations: BMI, body mass index; IgE, immunoglobulin E; NS, non-significant.

^aData expressed as mean (standard deviation).

^bSignificant.

and controls underwent laboratory tests which included total IgE levels were measured by enzyme-linked immunosorbent assay. Serum calcium was measured using the automated standard laboratory method. All samples were assessed in duplicates. Serum 25(OH)D and 1,25(OH)2D were quantified by radioimmunoassay using Immuno-Diagnostic systems-kits (Immunodiagnostic System Ltd, Boldon Business Park, Boldon, Tyne and Wear, United Kingdom). Serum 25OHD3 levels <20 ng/mL were considered as vitamin D deficiency, levels between 20 and 30 ng/mL as vitamin D insufficiency, while levels from 30 and 80 ng/mL were considered as normal.⁹

Statistical Analysis

We analyzed our data by the Statistical Package for Social Sciences version 22 (SPSS Inc, Chicago, Illinois, USA). Data were expressed as the mean (standard deviation [SD]). The mean values in AR and healthy groups were compared by the unpaired Student *t* test and Mann-Whitney *U* test. The correlation coefficient *r* was generated by Spearman rank correlation. Statistical significance was defined as *p* < .05.

Results

Table 1 shows demographic and laboratory criteria of all study participants. Table 2 shows the classification and nasal manifestations of all patients. Our study was conducted on 220 children. There were 120 children in the AR group (mean age 6.29 [4.03] years; 54 [45%] males) and 100 children in control group (mean age: 7.08 [2.91] years; 43 [43%] males). There was no statistical difference between both groups in age,

Table 2. Classification, Nasal Signs, and Symptoms of Patients With Allergic Rhinitis.

ARIA Classification	Number (%)
• Mild AR	62 (51.6%)
• Moderate/severe AR	58 (48.4%)
Clinical manifestations	Number (%)
• Rhinorrhea	115 (95.8%)
• Sneezing	116 (96.6%)
• Nasal obstruction	108 (90%)
• Nasal itching	98 (81.6%)

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma.

Table 3. Relationship Between Total Nasal Symptom Score and Vitamin D Levels.

Score	Number of Patients	25(OH)D Levels (Mean [SD])	<i>r</i>	<i>P</i>
4-6	62	29.2 (14.7)	-.62	.002
7-9	28	21.6 (11.8)		
10-12	30	19.4 (12.5)		

Abbreviation: SD, standard deviation.

gender, socioeconomic status, and anthropometric data. No significant differences were found on comparison of birth month and season of birth between children with AR and healthy controls.

Children with AR had significantly higher total serum IgE and calcium levels than those of the healthy control group ($p < .0001$ for each). The mean serum levels 25(OH)D and 1,25(OH)2D of were significantly lower in AR group than in healthy children ($p < .001$ and $p < .0001$ respectively, Table 1).

In the present study, only 23.3% of AR children had normal serum 25-OHD concentration (>30 ng/mL) versus 52% of controls ($p = .002$), 45.9% of the patient group had vitamin D insufficiency (20-30 ng/mL) versus 40% in healthy controls ($p = .4$). Vitamin D deficiency (<20 ng/mL) was found in 30.8% of AR group versus 8% of healthy children ($p < .0001$, Table 1).

According to AR severity between both groups, we found the mean 25-OHD3 levels in patients with moderate/severe AR were significantly lower than those with mild AR ($p < .001$). Correlation analyses between vitamin D levels and various parameters were done in our study. We found a significant positive correlation between 25(OH)D and calcium (calcium levels ($r = .29$, $p = .023$). Besides, we found significant negative correlations between mean 25(OH)D levels and TNSS ($r = -0.62$, $p = .002$, Table 3) and total IgE levels ($r = -0.27$, $p = .013$) in AR group. No significant difference was found in comparison of birth month and season of birth between children with AR and healthy controls.

Discussion

Our study identified essential results in the growing area of vitamin D levels and allergic children. This study investigated vitamin D status in a large cohort of children with AR. We observed that vitamin D deficiency is a frequent finding among children with AR when compared to healthy controls. In line with our report, Dogru and Suleyman¹⁰ studied 76 children with AR and 65 healthy patients. They evaluated 25(OH)D3 levels in both groups, and the mean serum 25(OH)D3 levels of AR children were significantly lower than healthy group (18.07 ± 6.1 ng/mL vs 24.03 ± 9.43 ng/mL; $p = .001$). However, contrary to our finding, they failed to find any significant relationship between vitamin D deficiency and the severity of AR. Another study (11) compared the levels of 1,25(OH)2D3 in 30 children with AR having recurrent tonsillitis and 30 controls. The median levels of 1,25(OH)2D3 were significantly lower in AR group when compared to healthy children (34.65 pg/mL vs 52.86 pg/mL; $p = .001$). In the same report,¹¹ the researchers found significantly lower 1,25(OH)2D3 values ($p < .05$) in children with severe nasal symptoms. Yenigun et al¹² and Goksugur et al¹³ investigated 2 small groups of children with allergic rhinoconjunctivitis; they found significantly lower vitamin D levels in patients with allergic rhino-conjunctivitis when compared to controls. In recent years, the importance of vitamin D in the immune system and allergic diseases has received much interest in research. There is a general agreement that the shift from a Th1 to Th2 phenotype in CD4⁺ T cells is the primary pathogenesis of AR, but the precise mechanism of AR is still not clear. Current researches showed that Th17 and T-regulatory cells are essential in the pathogenesis of AR.^{12,14} Vitamin D inhibits the proliferation of T-lymphocytes and increases Th1 to Th2 switch by stimulation of the development of Th2 cells. In addition, it enables the induction of T-regulatory cells and suppresses the development, transcription, and bioactivity of Th17 cells.^{12,14} These data indicate that there is a relationship between vitamin D and AR morbidity.¹⁵ Deficiency of vitamin D leads to contraction of the smooth muscles and disturbance of prostaglandin regulation with impairment of Th1–Th2 balance which increases airway inflammation.¹⁶

Some clinical and epidemiological studies have reported significant associations between vitamin D intake during pregnancy and its serum level with the incidence of AR in different ethnic groups. Two studies^{17,18} reported a positive relationship between maternal vitamin D intake and AR. Erkkola et al¹⁷ reported an inverse relationship between maternal intake of vitamin D during late pregnancy and the risk of asthma (confidence interval [CI]: 0.64-0.99) and AR (CI: 0.75-0.97) in 5-year-old children. Bunyavanich et al¹⁸ studied a cohort of 1248 mother–child pairs, and they found that the intake of each 100 IU of vitamin D/d during the first and second trimesters was associated with 21% (odd ratio[OR]: 0.79 [95% CI: 0.67-0.92] and 20% (OR: 0.80 [95% CI: 0.68-0.93] reduced odds of ever AR at school age. Bener et al¹⁹ reported that vitamin D deficiency was significantly associated with AR children. Another report by Jung et al²⁰ used the data from the annual

Korean National Health and Nutrition Examination 2009 Survey. They reported lower mean vitamin D levels in patients with AR when compared to the healthy adult group, after adjusting demographic data, body mass index, sun exposure, socioeconomic status, exercise, and body fat percentage. Arshi et al¹⁶ measured vitamin D levels in adult patients with AR and compared their data to the general population (no control group). The prevalence of severe 25(OH)D deficiency was significantly higher in patients with AR than the normal population, (30% vs 5.1% respectively; $p = .03$). Inconsistent with our results and the previous studies, there were few studies that reported no association between AR and vitamin D levels or positive association with the use of vitamin D.²¹⁻²³ Hyppönen et al²¹ found that regular use of vitamin D supplementation was associated with an increased risk of atopy and AR. Other studies^{22,23} observed no significant association between serum vitamin D levels and AR. Our data were not consistent with the previous findings; this may be due to differences in study designs, the age of the patients selected, different methods of clinical assessment of AR, and laboratory investigations of vitamin D levels.

Recently, Aryan et al² performed a systematic review and meta-analysis about vitamin D status and AR. They found that the association of vitamin D status with AR was age- and sex specific. Children with serum 25(OH)D more than 30 ng/mL had lower odds for having AR. However, this was not significant (OR: 0.91, 95% CI: 0.81-1.01), while this figure was significant in adults (OR: 0.64; 95% CI: 0.51-0.81).

Conclusions and Recommendations

Vitamin D deficiency is a frequent finding among Egyptian children with AR when compared to the healthy group. A significant inverse association was observed between vitamin D levels and AR disease severity, therefore determining vitamin D levels should be considered in the assessment of children with AR. Additional studies are required to determine the effects, dose, and duration of vitamin D therapy for the management of AR. Moreover, more studies are essential to fully elucidate the actual mechanism of action of vitamin D in AR.

Authors' Note

All authors have read and agreed with the content of this study and no portion of this work has been published previously or is under consideration for publication elsewhere and is an original article. Khaled Saad, Abobakr Abdelmoghny, Mohamed Diab Aboul-Khair, Yasser Farouk Abdel-Raheem, Bahaa Hawary conceptualized the study design, writing of the paper, collection of sample and interpretation of data. Asmaa M. Zahran and Mohamd A. Alblihed did all the laboratory tests for our studied children. Amira Elhoufey and Ahmed El-Sayed Hammour did the statistical analysis of data. The protocol of this study was in accordance with the regulations of the relevant clinical research Ethics Committee and with those of the code of ethics of the world medical association Declaration of Helsinki. Written informed consents of caregivers of all children were taken according to the Ethical Committee of Faculty of Medicine, Assiut University, Egypt, the date of approval January 2, 2015 (number 126-1-2015).

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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