Int.J.Curr.Microbiol.App.Sci (2016) *5*(12): 544-550

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 5 Number 12 (2016) pp. 544-550**
Journal homepage: http://www.ijcmas.com

Original Research Article http://dx.doi.org/10.20546/ijcmas.2016.512.060

Vitamin D Intervention in Children with Allergic rhinitis: A Pilot Randomized Controlled Trial

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Keywords

Vitamin D, Allergic rhinitis, calcium and phosphorous homeostasis IgE.

Article Info

Accepted:
18 November 2016
Available Online:
10 December 2016

A B S T R A C T

Vitamin D plays a well-known important role in calcium and phosphorous homeostasis, and bone metabolism. The immune-modulator effects of vitamin D are widely investigated, and documented. Recently, there has been global interest in the association between vitamin D and allergic diseases in adults, however, pediatric studies remains not conclusive. The aim of this study was to evaluate the levels of vitamin D as well as the effect of vitamin D supplementation in children with allergic rhinitis. This study included 100 children with allergic rhinitis, aged 6-12 years, after initial assessment and comparison to control group, they were divided into 2 groups, 50 patients of them received oral vitamin D3 (cholecalciferol) 1000 IU/day supplementation for 6 months, other 50 patients received placebo for same period. Control group were composed of 50 subjects (matched age, 25 boys and 25 girls). Serum levels of vitamin D, IgE, skin prick test, beside clinical and patient reported reflective total nasal symptom score, were evaluated. Serum 25-hydroxyvitamin D levels were significantly lower (18.4± 6.1 ng/mL) in children with allergic rhinitis when compared to control group (27.58± 9.4 ng/mL), and vitamin D levels were inversely correlated with immunoglobulin-E levels(r=-0.317, P<0.001)**.** After 6 months supplementation of oral vitamin D ,serum levels of vitamin D were significantly improved, clinical and patient reported reflective total nasal symptom score, were significantly improved compared to patients with allergic rhinitis not received vitamin D supplementation. This study demonstrates the possible relationship between vitamin D levels and allergic rhinitis in children, and its ability to improve both clinical and laboratory impairment in such patients.

Introduction

The prevalence of allergic diseases has continued to rise in recent years, in children as in adults. Allergic rhinitis (AR) is one of the most common allergic conditions (Meltzer, 1997). Mortality is not associated with AR, but significant morbidity occurs, in USA, annually an estimated 824,000 school days are missed, and an estimated 4,230.000 days of reduced quality –of- life functions are reported (Christakos *et al*., 2013).

The role of vitamin D in calcium homeostasis and bone mineralization is well

established, but the role of vitamin D as an immune modulator just recently evaluated. The role of vitamin D in allergic diseases as asthma, widely investigated, but results are not conclusive (Christakos *et al*., 2003).

The aim of this study was to evaluate the levels of vitamin D as well as the effect of vitamin D supplementation in children with allergic rhinitis.

Subjects and Methods

Trial design and participants

We conducted a 6-month randomized, parallel-group, double–blind, placebo-controlled pilot trial included100 children(50 boys and 50 girls) aged 6-12 years with allergic rhinitis who were visiting the outpatient department of pediatrics in Tanta University Hospital, Egypt, from March to September 2016.After initial assessment and investigations, this group was divided into two groups, each one 50 children, Group I received oral vitamin D3 (cholecalciferol) 1000 IU/day supplementation, and Group II received placebo. Control group were composed of 50 subjects (matched age, 25 boys and 25 girls) with no history or symptoms of allergic diseases, did blood tests including serum 25-hydroxyvitamin D level in outpatient department.

Diagnosis of AR was made according to the Allergic Rhinitis and its Impact on Asthma 2008 criteria (3). AR patients reported one or more typical symptoms of chronic rhinitis (rhinorrhea, nasal obstruction, sneezing, and nasal itching).At enrollment, patients were required to have a positive skin prick test for at least one known allergen and high IgE level .Each patient also had to achieve a minimum patient reported reflective total nasal symptom score (rTNSS; evaluation of symptom severity during the preceding 12 hours) of at least 6 of 12 on the day of the initial screening visit. Loratidine was the only rescue medication permitted for use on an as –needed basis .The maximum dosage allowed was 5mg/day.

Exclusion criteria included: other chronic respiratory diseases (e.g. asthma), recent nasal biopsy; nasal trauma or surgery within 2 months, disordered calcium or vitamin D metabolism, oral medications interfering with vitamin D metabolism; or vitamin D supplementation greater than 400 IU/day in the past 3 months.

Written consent had been taken from all patients car-givers and underwent ethical committee

Laboratory tests and allergy skin tests

The best estimates of vitamin D status are provided by measuring serum 25-hydroxyvitamin D(25(OH)D).Blood samples were collected at baseline and stored at -70 C until serum 25 (OH)D levels were measured. In our measurements, the intra assay coefficient of variation was 4%, and the inter assay coefficient of variation was 8%.We categorized low serum 25(OH)D as less than 25 ng/mL, and high serum 25(OH)D as above 50 ng/mL. It is measured at the beginning of the study, after 3 and 6 months.

Immunoglobulin E (CAP system, Pharmacia-Upjohn, Uppsala, Sweden) was measured in accordance with the manufacturer's instructions.

Allergy skin test for 17 common allergens (*Der f*, *Der p*, Acarussiro, *Tyrophagus putrescentiae*, cat epithelia, dog epithelia, *Alternaria*, *Aspergillus*, birch, alder, hazel, pine, bermuda, timothy, orchard, ragweed,

and mugwort) was performed . Saline and 0.5% histamine HCl were used as a negative and positive control, respectively. After 15 minutes, a positive test results defined as a wheal diameter at least 3 mm larger than the control wheal.

Statistical analysis

Analysis of variance was used for comparing the AR and control groups. Pearson correlation test was used for assessing the relationship between variables. A *P* value <0.05 was considered statistically significant. All data were analyzed with PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA)

Results and Discussion

Of the 100 patients, 50(50%) were males and 50 (50%) were females. The age of subjects ranged from 6-12 years (mean age, 8.6± 3.4 years). Before vitamin D supplementation, mean serum 25-hydroxyvitamin D level was significantly lower (18.4± 6.1 ng/mL) in the AR group than control group (27.58± 9.4 ng/mL), and immunoglobulin E level was significantly higher (462.7 ± 500.9 IU/mL) in the AR group when compared to control group (155.3±90.4 IU/mL).There was no difference between both groups regarding body mass index, age and sex (Table 1)**.** Vitamin D level was negatively correlated with IgE levels in AR patients (Figure 1)

After vitamin D supplementation, mean serum 25-hydroxyvitamin D level was significantly higher(38± 5.1 ng/mL) in the AR group who received vitamin D than AR patients who did not receive vitamin D (19.2± 5.4 ng/mL)with *P* value<0.001, and immunoglobulin E level was significantly lower (288± 172.9 IU/mL) in AR group who received vitamin D than AR patients who did not receive vitamin D (433.2±87.4IU/mL)with *P* value<0.001, There was no difference between both groups regarding atopy, age and sex (Table 2).

Improvement in the average morning and evening rTNSS were significantly greater in AR group received vitamin D compared to AR group not received vitamin D (table 3).

The improvement in the average patient-reported individual symptoms during the 6 months of treatment was significantly greater for rhinorrhea, nasal congestion, and sneezing in the in AR group received vitamin D compared to AR group not received vitamin D (data not shown).

No patients in AR group who received vitamin D supplementation had elevated total 25 OHD above 50 ng/ml at 3 and 6 months samples, urinary Ca: Cr was normal for all subjects. There were several minor fluctuations in serum calcium, phosphorus and ALP in AR groups over 6 months (measured monthly); none were of clinical significance. No serious clinical or laboratory adverse health events occurred

Vitamin D modulates innate immunity and adaptive immunity. Most of the cells belonging to the innate immune system, such as macrophages and dendritic cells (DCs), have receptors for vitamin D. In macrophages and DCs of the innate immune system, 25-hydroxyvitamin D undergoes hydroxylation by CYP27B1. The active form of vitamin D, 1, 25-hydroxyvitamin D, induces inhibition of DC maturation and suppression of antigen presentation. Also, activated vitamin D modulates helper T-cell action (Vlaykov *et al*., 2013).

Vitamin D interferes with T-cell proliferation by suppressing Th1 cytokine secretion. The effect of vitamin D on Th2 cells is still under debate. However, there is

one study which demonstrates that vitamin D leads to an increase in interleukin (IL)-10 expression and a decrease in IL-2 expression followed by hypoergia in regulatory T cells, which is associated with a harmful immune response (Searing *et al*., 2010; Gorman *et al*., 2007). Also, vitamin D decreases IL-12 production; thus it can reduce the differentiation of Th1 cells and increase the differentiation Th2 cells, which are responsible for allergic reactions. Vitamin D also modulates the secretion of IgE by interrupting the proliferation of B-lymphocyte (Mahon *et al*., 2003; Reinholz *et al*., 2012; Cheng *et al*., 2014).

In our study, AR patients showed lower serum vitamin D levels than controls. Jung *et al.*, (2013) reported that there was potential relation between vitamin D deficiency and AR prevalence in Korean adults. A study performed in 2012 reported that vitamin D deficiency occurs more often in AR patients than in the normal population. A cohort study reported by Mai *et al.*, (2014) in Norwegian adults showed that lower vitamin D levels were related to increased prevalence of AR among men.

Our study showed a significant negative correlation between Immunoglobulin E and serum vitamin D levels in AR patients. A study on asthma demonstrated that the serum IgE level and the serum 25-hydroxyvitamin D level are negatively correlated in children, but not in adults (Goleva *et al*., 2012). Hartmann *et al.*, (2011) indicated that targeting the vitamin D receptor (VDR) hinders the B cell-dependent allergic immune reaction. In VDR knockout mice, the serum IgE levels are elevated. *In vitro*, 1, 25-dihydroxyvitamin D, as a natural VDR agonist, directly interferes with the IgE production of educated B-lymphocytes.

Table.1 Demographics, Vitamin D, IgE compared between allergic rhinitis and control subjects

Variable	**AR (n=100)**	**Control(n=50)**	***P* value**
Sex(M:F)	(50:50)	(25:25)	NS
Age(yr)	8.6± 3.4	8.1 ±4.2	NS
Atopyn(%)	100(100)	5(10)	<0.001
Serum 25(OH)D (ng/mL)	18.4± 6.1	27.58± 9.4	<0.003
IgE(IU/mL)	462.7 ± 500.9	155.3±90.4	<0.001
Body mass index(kg/m^2)	27,9 ±4.9	25.8 ± 6.1	NS

Table.2 Demographics, Vitamin D, IgE compared between allergic rhinitis groups at the end of the study.

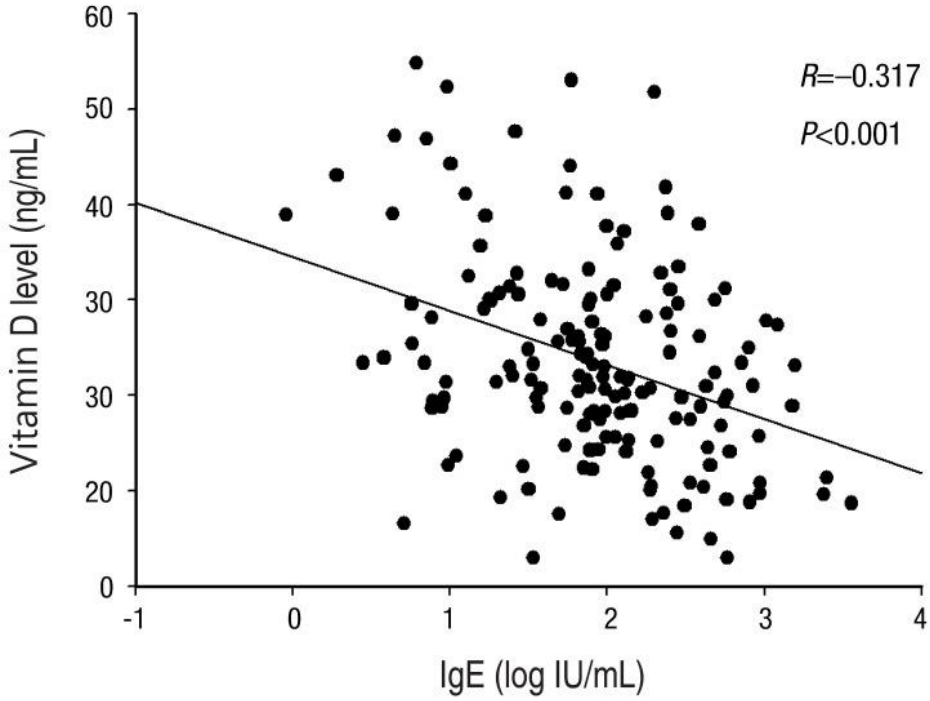
Variable	**Group I(n=50)**	**Group II(n=50)**	***P* value**
Sex(M:F)	(27:23)	(23:27)	NS
Age(yr)	8.2± 3.4	8.9±4.2	NS
Atopyn(%)	50(100)	50(100)	NS
Serum 25(OH)D (ng/mL)	38± 5.1	19.2± 5.4	<0.001
IgE(IU/mL)	288± 172.9	433.2±87.4	<0.001

Table.3 Changes from baseline in monthly average morning and evening patient-reported rTNSS over the 6 months of treatment

Group IGroup II			
Baseline, mean (SD) 8.3(1.4)	8.7(1.6)		
Overall LS changes from baseline, mean	- 2.72		- 2.11
95 % CI		- 1.0 5 to - .18	
P value		0.004	

CI, confidence interval; LS, least squares; rTNSS, reflective total nasal symptoms score

Fig.1 Correlation between serum IgE and vitamin D levels before vitamin D supplementation. Vitamin D level was negatively correlated with IgE levels (r=-0.317, P<0.001)



After 6 months of vitamin D supplementation, AR patients who received it showed a significant improvement in vitamin D levels compared to AR group not received it. This improvement was associated with significant improvement in the clinical (rTNSS) signs of AR, as well as significant decrease in serum IgE in AR patients who received vitamin D compared to AR group not received it. This improvement may be explained by the role of vitamin D in improving resistance to viral infection (a main trigger for rhinitis exacerbations), modulating the inflammatory response (Di Rosa *et al*., 2011), either directly or indirectly by improving response to antihistamines (Wang *et al*., 2004).

Similar effects were recorded in children with asthma who received vitamin D supplementation. Many researches (Searing *et al*., 2010; Reinholz *et al*., 2012) documented the beneficial role of vitamin D in adults with atopic diseases, in parallel with our results in children.

In controversy to our results, Cheng *et al*., (2014) found a Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, this can be explained by the fact that such study conducted on adult patients, of specific ethnic group (only Korean. Even in Korean patients, other studies find low levels of vitamin D in adults with AR.

In conclusion, the effect of vitamin D on allergic diseases remains inconclusive despite performing many systematic studies. The present study suggests a possible correlation between vitamin D deficiency and AR in children, and supplementation of vitamin D (1000 IU/Day) associated with clinical and laboratory improvement. Further studies are required to confirm the relationship between AR and vitamin D level, and to explore the underlying mechanisms.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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How to cite this article:

Samir Maher Hassan, Mohamed M. Abd Elmageed and Mohamed Galal El Senosy. 2016. Vitamin D Intervention in Children with Allergic rhinitis: A Pilot Randomized Controlled Trial. *Int.J.Curr.Microbiol.App.Sci.* 5(12): 544-550.
doi: http://dx.doi.org/10.20546/ijcmas.2016.512.060