SUNTEXT REVIEWS

SunText Review of Pediatric Care
ISSN: 2766-5216

Open Access
Research Article
Volume 3:1

Relationship between Vitamin D Blood Levels and the Incidence of Allergic Manifestations in Infants

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Received date: 04 January 2022; **Accepted date:** 12 January 2022; **Published date:** 17 January 2022

Citation: Drali O, Arab M, Lamdjadani N, Delacourt C, Hadchouel A (2022). Relationship between Vitamin D Blood Levels and the Incidence of Allergic Manifestations in Infants. SunText Rev Pediatr Care 3(1): 127.

DOI: https://doi.org/10.51737/2766-5216.2022.027

Abstract

Introduction: Known since antiquity for its antirachitic action, vitamin D has benefited a considerable revival of interest over the past twenty years in research topics. It is considered to be a physiological regulator of the proliferation and differentiation of many cell types and as a modulator of the body's immune defenses. Vitamin D seems to play a role in intrauterine and postnatal lung development, and several studies suggest its involvement in the development of asthma and allergies. The objective of this study was to find out any association between the incidence of wheezy symptoms and atopic manifestations, and insufficient vitamin D status in a population of young Algerian children. It was a retrospective study by phone questionnaire. As part of a first work, the objective of which was to make an inventory of vitamin D status in young Algerian children, a measurement of total 25 OHD (D2 + D3) was carried out in 397 children aged 9 to 24 months living in an urban environment (Algiers) between 2014 and 2016. For the present project, all the parents of these children were contacted by phone to answer a questionnaire. A statistical analysis was applied to assess the relationship between the vitamin D status of the child aged from 9 to 24 months and the incidence of the various pathological manifestations 2 years later.

Results: A 397 children from the initial study were eligible for our study, 348 children collected. 29.9% of children had a vitamin D deficiency (25 OHD≤20 ng / ml) and 15.5% had a vitamin D severe deficiency (25 OHD≤10 ng / ml). The optimal vitamin D level (25 OHD≥ 30 ng / ml) was only reached in 28.7% of children. The incidence of asthma was significantly higher in children with vitamin D deficiency compared to those without vitamin D deficiency (p = 0.001). The mean vitamin D concentration was significantly lower in children with asthma than in children without asthma (p = 0.0001). Vitamin D levels were also associated to other atopic manifestations (rhinitis, food allergy and atopic dermatitis).

Conclusion: Confirmation of an impact of vitamin D deficiency in the first 2 years of life on the appearance of atopic manifestations in young children would be of major interest for the update of the Algerian national recommendations concerning supplementation in vitamin D.

Keywords: Vitamin D; Atopic manifestations; Children; Algeria

Introduction

Allergic (atopic) diseases result from an interaction between individual genetic susceptibility and exposure to environmental factors. The prenatal and early postnatal periods of life have been identified as "windows of opportunity" during which immune responses can be permanently programmed. Besides a clear genetic basis in allergic diseases, environmental factors, including

vitamin D status, can exert an important influence on the development of allergies and therefore represent an opportunity to prevent or delay the onset of these pathologies.

Known since antiquity, for its antirachitic action, vitamin D has benefited from a considerable revival of interest over the past twenty years in research topics and the scientific literature is enriched every day with new data concerning this topic. Studies on its structure and that of its receptor, its metabolism, its mechanisms and its ubiquitous field of action have gradually shifted this compound from the status of vitamin to that of hormone. It is also considered to be a physiological regulator of the proliferation and differentiation of many cell types and as a modulator of the body's immune defenses. Vitamin D appears to play a role in intrauterine and postnatal lung development, and several studies suggest its involvement in the development of asthma and allergies [1,2].

Aims

Find out any association between the incidence of atopic manifestations and vitamin D deficient status in a population of young Algerian children.

Material and Methods

This is a retrospective study undertaken by phone questionnaire. An inventory of vitamin D status in young Algerian children by measuring total 25 OHD (D2 + D3) was carried out in 397 children from nine (9) to 24 months old living in an urban environment (Algiers) between 2014 and 2016. PTH, calcemia, phosphoremia, albuminemia and creatinemia were also measured. For this study, part of this population was included. The sample was taken according to a random survey by simple lot drawing by numbering (statistical method validated by the WHO). All regulatory approvals were obtained (Ministry of Health, Ministry of Higher Education and Scientific Research and the National Statistics Office).

Inclusion Criteria

We have included children:

- Aged from 9 months to 5 years old.
- Residing in the commune of Hussein Dey.
- Having received vitamin D at 1 and 6 months according to the national scheme (after verification of the health record).
- Free from any chronic or acute pathology, which may interfere with the metabolism of vitamin D (skin, digestive, hepatic, parathyroid and renal pathologies).
- Not receiving any vitamin D or calcium treatment in the 3 months preceding inclusion.
- Not receiving any treatment, which could interfere with the metabolism of vitamin D or the phosphocalcic metabolism: anticonvulsants, steroids, and rifampicin.
- Having a vitamin D dosage available due to their participation in the princeps study.

Exclusion criteria

The following cases were excluded from the study:

- Children born or consulting at the above-mentioned structures but not from the commune of Hussein Dey.
- Children with an incomplete national prevention scheme (a single intake of vitamin D).

Preparation of the phone questionnaire (validated by the Ministry of Health, the Ministry of Higher Education and Scientific Research and the National Statistics Office). A phone questionnaire was established to respond to the objective of the study.

This questionnaire was divided into several parts:

General data

Date of birth, sex, previous vitamin D supplementation.

Collection of clinical manifestations

Explanations to the objectives and the modalities of the survey were provided to parents by phone. After obtaining the parents 'informed consent, a schedule for answering the questionnaire was set so as not to disrupt the parents' daily activity. During the study, the total 25-OHD was assayed on serum after centrifugation by the VIDAS BioMérieux analyzer, which allows the immuno-enzymatic determination of 25OHD by the ELFA technique (Enzyme Linked Fluorecent Assay) by combining an immunoenzymatic phase by competition to a final fluorescence detection. This technique measures the two forms 25 OH D3 and 25OH D2 expressed in ng/ml in accordance with international recommendations. The vitamin D standards used for the evaluation of our results are those accepted by the majority of authors: Vitamin D deficiency (25 OHD≤20 ng / ml), vitamin D severe deficiency (25 OHD≤10 ng / ml). The optimal vitamin D level (25 OHD≥ 30 ng / ml).

Statistical analyses

Quantitative variables were expressed as means with their standard deviation. The comparison of the quantitative variables between the different groups was carried out by the Student's t-test; the homogeneity of the variances was verified through the Levene test. Qualitative variables were expressed in terms of frequency and percentage. The comparison of the distributions of the qualitative variables between the different groups was achieved by the Chi-square test. Fisher's exact test was used when

the Chi-square test was not feasible (theoretical or calculated numbers < 5).The results were considered significant at the 5% level. The analyses were carried out with SPSS 22 software.

Results

Description of the population

A 397 children from the initial study were eligible for our study, 348 children collected. 8.8% were lost to follow-up. We recruited the children during the 4 seasons in order to appreciate the seasonal variation of the vitamin D concentration. The distribution of the sample was homogeneous between the four seasons (p = 0.08).The average age of the children in our series was 5 years ± 0.74 with a sex ratio of 1.01 (175 boys / 173 girls). Calcemia, phosphoremia, albuminemia and the assessment of kidney function showed no abnormalities. The average serum total vitamin D concentration in our series was 23.3 ± 12.1 ng / ml, significantly lower than the current recommendations for benefiting from the extra skeletal effects of vitamin D (25 OHD> 30 ng / ml) with a mean PTH level at 30.3 ± 13.2 pg / ml(normal). Results of serum levels of total 25 OHD are shown in (Table 1).

Table 1: *Blood vitamin D level according to the season.*

Season	**Spring**	**Summer**	**Autumn**	**Winter**	**P**
Mean ± SD (ng/ml)	24,3 ± 11,5	30,3 ± 11,6	20,6 ± 11,3	15,9 ± 8,7	0.0001

Table 2: *Prevalence of vitamin D status according to the various thresholds.*

Vitamin D level	**N**	**Frequency (%)**
Severe deficit	54	15,5
Deficit	104	29,9
Insufficiency	90	25,9
Optimal	100	28,7

Table 3: *Correlation between the vitamin D levels and the incidence of the allergic rhinitis.*

	Allergic rhinitis		**Total**	**P**
	NO	**YES**		
Number Prevalence of vitamin D deficiency	338	10	348	
	46,4%	100%		0,001
Vitamin D concentration(ng/ml)	23,6 ± 12	10,02 ± 2,8		0,001

Table 4: *Correlation between of vitamin D level and the incidence of the atopic dermatitis.*

Atopic dermatitis			**Total**	**P**
NO		**YES**		
Number	341	7	348	
Prevalence of vitamin D deficiency	46,9%	100%		0,005
Vitamin D concentration(ng/ml)	23,5 ± 12	21,01 ± 2,7		0,003

Table 5: *Correlation between vitamin D plasma levels and the incidence of the food allergy.*

Food allergy			Total	P
	NO	YES		
Number Prevalence of vitamin D deficiency	343	5	348	
	47,2%	100%		0,02
Vitamin D concentration(ng/ml)	23,4 ± 12,1	13,4 ± 4,1		0,05

Table 6: *Correlation between the vitamin D level and the occurrence of asthma.*

	Asthma		Total	P
	NO	YES		
Number Prevalence of vitamin D deficiency	312	36	348	
	43,3%	88,9%		0,001
Vitamin D concentration(ng/ml)	24,3 ± 12	14,4 ± 7		0,0001

The highest vitamin D concentrations were found in summer with an average concentration of 30.3 ± 11.6 ng / ml compared to winter when the average concentration was 15.9 ± 8.7 ng / ml, this difference was highly significant (p = 0.0001). 29.9% of children had a vitamin D deficiency (25 OHD≤20 ng / ml) and 15.5% had a vitamin D severe deficiency (25 OHD≤10 ng / ml). The optimal vitamin D level (25 OHD≥ 30 ng / ml) was only reached in 28.7% of children 17% of children had atopic manifestations. Ten children had allergic rhinitis. Seven children suffered from atopic dermatitis. Food allergies were reported in 5 children, allergy to cow's milk protein in 4 children, 1 child had an allergy to strawberries. The diagnosis of asthma was reported in 36 children (Table 2).

Relationship between vitamin D concentrations in young children and the incidence of atopic manifestations

All patients with allergic rhinitis were deficient in vitamin D. The mean vitamin D concentration was lower in children with allergic rhinitis compared to children who did not have allergic rhinitis (p = 0.001) (Table 3). Patients with atopic dermatitis were deficient in vitamin D. The mean vitamin D concentration was lower in children with atopic dermatitis compared to children who did not have atopic dermatitis (p = 0.003) (Table 4). Patients with a food allergy were deficient in vitamin D. The concentration of vitamin D was lower in children with a food allergy compared to children who did not have food allergy allergic rhinitis insignificantly (p = 0, 05) (Table 5). The incidence of asthma was significantly higher in children with vitamin D deficiency compared to those without vitamin D deficiency (p = 0.001). The mean vitamin D concentration was significantly lower in children with asthma than in children without asthma (p = 0.0001) (Table 6).

Discussion

The incidence of atopic manifestations varies significantly depending on the vitamin D status in our population of younger Algerian children. Average vitamin D concentrations were lower in children who developed these disorders. As a result, vitamin D deficiency would expose to the risk of the occurrence of allergic manifestations in our population confirming the results of the majority of studies published on this topic. Our comments will cover several aspects. We will first make a critical analysis of the approach adopted and the problems encountered during the investigation. We will compare our results with the data in the literature in second step by discussing them. Our study presents some positive points. The sample size is quite large and both sexes were well represented. Vitamin D plasma concentrations were assessed during the 4 seasons demonstrating the effect of seasonality on the variation in the level of 25 OHD. The 25 OHD assay technique has been validated by several expert reports and allows the determination of the two forms of vitamin D used for all patients. The study suffer some weaknesses and limitations. This survey made by a questionnaire suffers from its declarative and therefore subjective character. Thus, the low incidence of food allergies in our study could be explained by this declarative nature and questioning only the parents. The study is limited to the commune of Hussein Dey alone. There is no standard definition of vitamin D status. Currently, many experts support a 25 OHD threshold greater than 30 ng / ml to consider a normal level [3]. This threshold is justified by the wish to allow the subjects to benefit from the effect of vitamin D on the bone but also on other pathologies while others fix the threshold of 20 ng / ml as minimum threshold in order to optimize calcium absorption [4]. Several pediatric consensus define in children the deficit at

the threshold of 20 ng / ml and the vitamin D deficiency at the threshold of 10 ng / ml [5]. The diversity of the populations studied, in particular in terms of latitude, geographic origin or age, the variability of the assay techniques and the lack of real consensus on the reference thresholds for defining the deficit makes international comparisons difficult. However, there is an increase in the vitamin D deficit in all latitudes and all continents [6,7]. Several studies dedicated to the relationship between vitamin D, asthma and allergies have increased significantly. Experimental evidence in rats shows that fetal type II alveolar epithelial cells express vitamin D receptor (VDR), suggesting that lung maturation is sensitive to exposure to vitamin D [8,9]. In humans, Kho et al. examined gene expression profiles during human fetal lung development and identified a number of genes associated with the vitamin D signaling pathway whose expression was developmentally regulated [10]. Although the exact role of these vitamin D-linked genes in fetal lung development remains to be fully explored, several genes (LAMP3 PIP5K1B, SCRAB2 and TXNIP) have also been found to be significantly overexpressed in cells derived from asthmatic children, suggesting thus a link between the vitamin D pathway genes, fetal development and asthma, [11]. Zosky studied the effects of vitamin D deficiency in a mouse model. The offspring of vitamin D deficient mice had reduced lung volume compared to that of mice with optimal vitamin D status. Vitamin D also appears to affect the development of the immune system in utero. Chi et al [12] using data from the Urban Environment and Childhood Asthma study, showed that vitamin D concentrations in cord blood were inversely associated with the proportion of CD25 +, CD25 Bright and CD25 + FoxP3 regulatory T cells. After birth, vitamin D has immunomodulatory effects on the allergen-induced inflammatory pathways by acting on the VDR expressed on various immune cells, including B cells, T cells, dendritic cells and macrophages [13,14]. Many of these cells, such as activated macrophages and dendritic cells, are able to synthesize biologically active vitamin D from circulating 25 OHD [15,16]. This mechanism allows immune cells to rapidly increase local levels of vitamin D, which are potentially needed to shape adaptive immune responses [17,18]. Low levels of vitamin D seem to be inversely correlated with the severity of atopic dermatitis. Sharief et al have shown that higher levels of IgE are associated with vitamin D deficiency in children and adolescents [19]. Similarly, in another publication, mean serum 25 (OH) D levels were lower in children with moderate to severe atopic dermatitis [20]. Which is consistent with our results. A small trial aimed to explore the impact of vitamin D supplementation in the pediatric population on allergic diseases. A study as part of a larger pilot study of vitamin D supplementation investigated the effect of this supplementation on atopic dermatitis in 11 children [21]. The children were randomized to 1000 IU per day of ergocalciferol or placebo for 1 month. There was a tendency to improve scores for atopic dermatitis, but due to the small number and short duration of the trial, the results were not statistically significant. Few studies have investigated vitamin D status in allergic rhinitis and food allergy in children [22]. May et al. [23] studied the relationship between the serum 25OHD level and the incidence of allergic rhinitis. The study included a random sample of the population (N = 1351), serum 25OHD levels <20 ng / ml were associated with an increased risk of allergic rhinitis (OR adjusted to 2.55, p = 0.001), these results are similar to ours. It has been suggested that a vitamin D deficiency could alter the integrity of the epithelial barrier, which would lead to increased and inappropriate exposure of the mucosa to food antigens as well as an immune imbalance favoring sensitization, which would compromise immunological tolerance. Therefore, early correction of vitamin D deficiency could enhance mucosal defense, maintain healthy microbial ecology and tolerance to allergens, and reduce the risk of food allergies in children. Mullins et al [24] and Vassallo et al [25] reported significantly higher food allergy rates in children born in autumn / winter, suggesting a relationship between food allergy rates and monthly exposure to Sun. Two studies used data from the National Health and Nutrition Survey (NHANES) conducted in the United States [26,27]. In an analysis of 3136 children and adolescents, allergic sensitization to 11 allergens was more frequent in those with a vitamin D deficiency (<15 ng / ml) after a multivariate adjustment. Awareness included food allergens (peanuts and shrimp), indoor allergens (dog, cockroach, Alternaria sp) and pollen (oak, birch). The prevalence of vitamin D deficiency in asthmatic and non-asthmatic children was determined in several case-control studies, it varied considerably between the different studies ranging from 3% to 77%, and moreover children without asthma had more vitamin D levels sufficient compared to asthmatic children consistent with the results of our study. Several studies have been carried out on African-American, [28] Qataris, [29] Iranian children, [30] and all show that the prevalence of vitamin D deficiency is higher in asthmatic children than in controls. Bener et al [31] had carried out in 2012 a case-control study including 966 healthy children and in asthmatics of equal age [32]. The authors found that vitamin D deficiency was associated with an increased risk of asthma (adjusted OR: 4.82 CI: 2.4-8.6). Another analysis of 6,857 participants 6 years aged and older showed that vitamin D levels were inversely associated with asthma [33]. Several studies have studied the association between 25OHD and asthma exacerbations measured in terms of hospitalizations and treatment with oral corticosteroids. Except the study of Gergen, all studies have shown that a low serum vitamin D concentration is associated with an increased risk of exacerbation of asthma (RR = 0.64 CI: 0.5-0.8). Asthma control studies. Have evaluated control and exacerbations based on the frequency of dosing and dosage of

treatments, or the number of emergencies. Brehm et al [34] correlated their data with vitamin D concentrations. Gergen and Van Oeffelen found that a high serum 25OHD concentration was associated with a reduction in the severity of asthma whereas Chinellato and Gupta did not found any association. In the PIAMA birth cohort of more than 300 children, serum vitamin D concentrations were inversely associated with the prevalence of asthma in children from four to 8 years old [35]. Hollams et al [36], in a cohort of more than 600 Australian children, have shown that higher levels of vitamin D at 6 years protect against the development of asthma, rhino-conjunctivitis and allergy. Several studies have examined the relationship between vitamin D deficiency and exacerbations of asthma [37]. Brehm et al were the first to show that vitamin D deficiency (<30 ng / ml) was associated with an increased risk of severe asthma exacerbations leading to emergency visits or hospitalizations after an analysis of data collected from 1024 participants of the childhood asthma management program (CAMP) [38]. Searing et al, in a cross-sectional study involving 100 asthmatic children, demonstrated inverse associations between vitamin D and serum IgE levels, [39] the number of positive skin tests for pneumallergens, lung function and use of corticosteroids by inhalation or orally. Other studies have also shown that lower levels of vitamin D are associated with poorer lung function and the presence of exercise-induced bronchoconstriction [40] in children with asthma [41]. Bump et al [42] have shown in vitro that vitamin D increases the bioavailability of glucocorticoids in bronchial smooth muscle cells, suggesting an additional beneficial role of this vitamin in the prevention and treatment of asthma. The role of vitamin D in preventing asthma and allergies in children remains controversial. Although most of the published data report a protective effect of higher vitamin D levels or vitamin D consumption, some studies do not find this link. Thus, five prospective studies on large cohorts evaluated the relationship between 25OHD levels and asthma, and found no association. Other clinical trials would be useful to resolve these inconsistencies [43].

Conclusion

The incidence of atopic manifestations varies significantly depending on vitamin D status in a population of young Algerian children. Vitamin D levels were lower in children who developed these conditions. Therefore, vitamin D deficiency would expose to the risk of the appearance of atopic manifestations. However, there is still much controversy about the role of vitamin D in allergic conditions. Large-scale randomized controlled trials are needed to better understand the effectiveness of vitamin D in children with atopic conditions. Future longitudinal and interventional cohort studies are needed to determine whether vitamin D supplementation could be used as a low-cost public health measure to reduce the incidence of asthma and atopy in children.

Declaration of Interest

No conflict of interest.

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