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Original Research Paper

Pediatrics

THE BURDEN OF CHILDHOOD ASTHMA: IS VITAMIN D DEFICIENCY BLAMED?

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ABSTRACT

Objective: The aim of this study was to investigate the role of vitamin D in childhood asthma by measuring serum vitamin D levels in both asthmatic and healthy non-asthmatic children.

Study design: Asthmatic children (n= 150) and healthy controls (n=150) were recruited from Makassed General Hospital from October 2014 to May 2016. Interviews with parents of all the children were based on a questionnaire that included variables such as demographic information, assessment of non-dietary covariates, vitamin D intake, type of feeding, and serum 25-hydroxyvitamin D assays were performed. The diagnosis of asthma and its severity was assessed according to Global Initiative for Asthma guidelines.

Results: The prevalence of vitamin D deficiency was significantly higher (96%) in asthmatic children compared to (56%) healthy controls (P <0.0001). Moderate and severe degrees of vitamin D deficiency (46.6% and 29.1% respectively) were significantly higher in asthmatic children compared to these in healthy controls (24.2% and 0% respectively) (P < 0.0001). Positive family history of asthma (76%, P < 0.0001), less physical activity (51%, P <0.0001) and sun light exposure (51.4%, P = 0.001) were significantly higher in asthmatic group. It was also shown that the degree of vitamin D deficiency is significantly correlated to asthma severity (P < 0.001).Vitamin D deficiency was a significant correlate for asthma (OR: 23.18, 95% CI: 7.81 - 68.83, P < 0.0001).

Conclusion: The study findings revealed a high prevalence of Vitamin D deficiency in asthmatic children, which was found as a strong risk factor for childhood asthma among Lebanese children.

KEYWORDS : Vitamin D level; Asthmatic children; healthy non-asthmatic children; asthma

Introduction:

Childhood asthma is one of the most common chronic diseases in children and is one of the leading causes of morbidity (1). Currently, the burden of asthma in both the developed and the developing world is significant and increasing rapidly with more than 300 million people affected worldwide (2). The prevalence of asthma and allergies in some Western countries has reached alarming proportions, affecting more than one third of children from the general population (1–3).

Although it is known that positive atopic status, exposure and sensitization to environmental allergens, and/or familial history of allergic disease are significant risks factors associated with the development of asthma, recent evidence suggests that vitamin D deficiency may also predispose to childhood asthma (4).

Vitamin D has received tremendous amount of attention recently due to the ever-increasing reports of association between vitamin D deficiency and a wide range of conditions, from cancer to fertility to longevity (5).

Vitamin D is a potent modulator of the immune system and is involved in regulating cell proliferation and differentiation (6).

The fascination of disease association with vitamin D deficiency comes from the relatively easy solution to overcome such a risk factor, that is, either by increase in sun exposure and/or diet supplementation.

Epidemiological evidence suggests that there is a worldwide epidemic of vitamin D deficiency, and lack of vitamin D has been linked to increased incidence of asthma, and increased severity of asthma in children (7).

Considering the high prevalence of vitamin D insufficiency and allergic diseases in the Lebanese population, a cross-sectional study was conducted to better understand the significance of vitamin D deficiency and investigate its impact on asthma and its severity in children. Furthermore, the study assessed the non-dietary covariates and feeding practices in the study sample in order to determine the major contributing factors of vitamin D deficiency in young Lebanese with asthma.

Materials and Methods

After obtaining the approval of the Research and Ethics Committee at Makassed General Hospital and written informed consent from patient s` families, a total of 300 patients were recruited from Makassed General Hospital (tertiary referral center) from October 2014 to May 2016.

Study Subjects

The study included asthmatic (n= 150) and healthy (n=150) children who were recruited from Pediatric floor, Pediatric intensive care unit, Pediatric emergency department, and outpatient clinic. The study subjects included both asthmatic children (asthmatics group), as those diagnosed by GINA criteria (2), and healthy non-asthmatic children (non-asthmatics group), aged between 2 and 14 years old, chosen from similar environmental backgrounds with similar epidemiologic characteristics. Excluded from the study were children receiving vitamin D therapy subsequent to any disease (e.g. Rickets), anti-epileptic therapy or long term steroid treatment besides asthma were excluded from the study, and those with chronic diseases other than asthma, such as lung disease, renal disease, liver disease and endocrine diseases.

Study Design

The study used a cross-sectional design to examine whether there were differences in serum vitamin D levels between asthmatic and non-asthmatic healthy children and to test for any associations between vitamin D deficiency and development of asthma in children.

Sampling Technique

The study included two groups:

Non-asthmatics group who were selected randomly from healthy children who visited our health care center for management of acute illnesses other than asthma. They were healthy, non-asthmatics and were taking no medication at the time of study.

Asthmatics group included asthmatic children who visited our hospital at the same period of the study and were diagnosed to have asthma according to the Global Initiative for Asthma (GINA) criteria (2), which include:

1) A physician`s diagnosis of asthma
2) Symptoms of recurrent (i.e. more than two) episodes of wheezing, cough, shortness of breath, or combination of these
3) Documented reversibility with bronchodilators
4) Symptoms of and/ or use of medication for asthma in previous six months

The asthmatics group was further divided into 4 subgroups according to the classification of asthma severity (2) in the recruited patients as follows:
- Intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

Data Collection Methods, Instruments used, Measurements
1) Informed consent was obtained from all parents or guardians.
2) Questionnaires

Questionnaires involved collection of data on subjects' dietary intake (particularly vitamin D), demographics (age, gender, place of residence) as well as morphometric measures (height and weight). Body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. BMI < 85th percentile was considered normal weight, 85–95th percentile as overweight and > 95th percentile as obese. Other variables like physical activity and sun exposure were collected from the study participants at the time of interview. Regarding diet, we collected information on dietary intake, vitamin D intake and type of feeding. One section of the questionnaire was 'assessment of dietary and vitamin D intake'. There were questions on food consumption like fortified food, sea food, fatty/oily fish, eggs, cod liver oil, milk fortified with vitamin D, and supplement consumption like multivitamin and vitamin D supplement. The children who were taking this food daily were considered as taking 'vitamin D supplement'. Finally there was a part for asthma classification according to the severity.

3) A trained phlebotomist collected venous blood sample to determine serum 25 hydroxyvitamin D (25(OH) D) levels. Subjects were classified into four categories according to serum 25 (OH) D level into:

(1) Severe vitamin D deficiency, 25(OH) D < 10 ng/ml;
(2) Moderate deficiency, 25(OH) D: 10–19 ng/ml;
(3) Mild deficiency, 25(OH) D: 20–29 ng/ml;
(4) Normal/optimal level is between 30–80 ng/ml.

According to the recommendations of other studies, we categorized vitamin D levels as deficient if 25(OH) D was < 20 ng/ml, insufficient if it was 20–29 ng/ml and sufficient if it was > 30 ng/ml (8, 9).

Data Management and Analysis Plan

Descriptive statistics was carried out for categorical variables by number and percent and for continuous variables by mean and standard deviation. Groups were compared by using the chi square test for categorical variables or the Student's t-test for continuous ones. Predictors of the outcome were identified by using the multivariate logistic regression for categorical variables. Results were presented as odds ratio (OR) and 95% confidence interval (95% CI) for logistic regression analyses. The Statistical Package for Social Sciences (SPSS, version 21) program was used for data entry, management, and analyses. A p-value of <0.05 was used to indicate statistical significance.

Results

Table 1 shows the demographic characteristics of the study population.

The mean age was almost similar between the two study groups. Almost half (56.8%) the asthmatic children and the non-asthmatic (56.9%) were younger than 5 years of age.

The male sex was dominant in both groups but it was highly significant in the asthmatic group (P < 0.001).

The place of living was divided into Beirut, North, South and Mount Lebanon. The majority of our patients were living in Beirut in both groups. However, there was no difference in place of living between the two groups (P = 0.43).

The prevalence of vitamin D deficiency in asthmatic and non-asthmatic children was shown in table 2.

Moderate vitamin D deficiency was found in 46.6% of asthmatics and 24.2% of non-asthmatics, while 29.1% of asthmatics had severe deficiency compared to 0% of non-asthmatics. Moderate and severe degree of vitamin D deficiency was significantly higher in asthmatic children compared to non-asthmatics (P < 0.0001).

Dietary practices and vitamin D supplementation with breast milk in the asthmatics and non-asthmatics groups are also described in table 2.

Of healthy non-asthmatic children, 56.9% were breast-fed for longer than 6 months compared to 45.9% of asthmatics but it was not statistically significant (P = 0.06). There was no difference in the formula feeding practice or duration of vitamin D supplementation during breastfeeding between the two groups (P = 0.24 and 0.55 respectively).

Regarding the non-dietary covariates, asthmatics were more likely to have a wheatish skin complexion (62.5%) compared to controls (48%) (P = 0.001), they participated in less physical activity (P < 0.001), had lower exposure to sunlight (P = 0.001) and were more likely to be overweight or obese than their age-matched non-asthmatic counterparts (P = 0.01) (table 2).

In asthmatics, there was a strong familial risk of asthma (P < 0.0001) and familial history of vitamin D deficiency was more prevalent in asthmatic children (14.9%) compared to non-asthmatics (5.2%) (P = 0.005)

Figure-1 reveals the distribution of serum vitamin D level in asthmatic and control children in our study population. Sufficient vitamin D levels of ≥ 30 ng/ml were found in 43.8% of non-asthmatic healthy children, compared with only 3.4% of asthmatic children. Mild vitamin D deficiency was found in 32% of non-asthmatics group, compared with 20.9% of the asthmatic group. Moderate vitamin D deficiency was found in 46.6% of asthmatic children and in 24.2% of the non-asthmatics group. Severe vitamin D deficiency was found in 29.1% of asthmatic children and was 0% in the healthy non-asthmatics group. There was a significant difference in the degree of vitamin D deficiency between the two groups (P < 0.0001).

Table 3 shows the association between vitamin D deficiency and the degree of severity of asthma. The majority of asthmatic patients with intermittent asthma had mild deficiency of vitamin D (76.2%) while (69.4%) of mild persistent group had moderate deficiency of vitamin D (P < 0.0001). On the other hand, more than half the patients (59%) of the patients with moderate and all patients (100%) with severe persistent asthma had severe vitamin D deficiency (P < 0.0001).

Table 4 shows predictors for development of asthma in children using multivariate logistic regression analysis. Deficiency in vitamin D level (OR: 23.18, 95% CI: 7.81 - 68.83, P < 0.0001), less physical activity (OR: 2.70, 95% CI: 1.16 - 6.29; P < 0.0001) and family history of

asthma (OR: 6.96, 95% CI: 3.56 - 13.61; P <0.0001) were the major predictors of asthma in this group of Lebanese children. Familial history of vitamin D deficiency was a significant contributing risk factor amongst asthmatic children (P = 0.005). Reduced sunlight exposure (P = 0.001), elevated child's BMI (P = 0.01) were also considered as other contributing risk factors.

Discussion

The present cross-sectional study provides an epidemiological support for the association between vitamin D deficiency and asthma, as most children with asthma were either vitamin D insufficient or deficient. The prevalence of vitamin D deficiency was significantly higher (96%) in asthmatic children compared to controls (56%) (P < 0.0001), with the majority of severe vitamin D deficiency (29.1%) belonged to the asthmatic group (P < 0.0001). A few epidemiological studies have reported a similar finding that Vitamin D deficiency is associated with an increased incidence of asthma and allergy symptoms (8). Ginde et al. have presented evidence to show that low vitamin D levels are associated with higher frequency of respiratory tract infections in asthmatic patients and with increased asthma severity (10). However, some studies failed to confirm these results. An Australian multicenter Study reported that there was no association between any of the Vitamin D related measures and childhood asthma and allergic disorders (11).

Interestingly; our study population showed that the male sex is significantly higher in the asthmatic group (P < 0.0001), which supports studies on gender differences in childhood asthma, where boys are consistently reported to have more prevalent wheeze and asthma than girls (12).

In the study population, more than half the healthy children (56%) were vitamin D deficient revealing the high prevalence of vitamin D deficiency in Lebanon. The reasons for widespread vitamin D deficiencies in various populations are not completely understood. However, it is suggested that increased prosperity and adoption of a Western lifestyle (increased time spent indoors resulting in less exposure to sunshine) may be contributing to our vitamin D deficiency, resulting in a predisposition to the development of allergic diseases including asthma (13). Our results have shown that asthmatic children have significantly reduced exposure to sunlight (P = 0.001) and are less physically active (P < 0.0001). It is known that cutaneous synthesis of vitamin D is dramatically decreased in individuals who spend time in doors and those who use protective clothing and sunscreen against ultraviolet radiation (sunlight). For this reason, vitamin D deficiency has been documented in many populations around the world regardless of the degree of sun exposure and is more common among the non-White population (14, 15). In our study, 62.5% of asthmatic children had a wheatish skin color and 17.1% had darker skin (P = 0.001). Dark skin is known to reduce the penetration of sunlight. A study done by Gordon et.al in infants and toddlers from an urban population, in which the majority had darker skin pigmentation, found that 40% of these children were vitamin D insufficient (<30 ng/ml) (16). Similarly, 42% of healthy urban adolescents with darker skin pigmentation had vitamin D levels less than 20 ng/ ml (17). Inadequate sun exposure and skin pigmentation might be the reasons for the low level of vitamin D in asthmatic children. The same concept of reduced sunlight penetration of skin was suggested in obese people (15).Our study showed that 23% of asthmatic patients were more overweight compared to 12.4% of control (P = 0.01).

Epidemiologic data suggest a possible association between maternal intake of vitamin D during pregnancy and risk of childhood wheezing/asthma in offspring as presented by Devereux et al. (18). In this study, we have shown that familial history of vitamin D deficiency was significantly higher in parents of asthmatic children and was a significant risk factor in the development of the disease (P = 0.005). Nonetheless, the genetic factor plays a major role, where our study showed that family history of asthma was highly significant also in asthmatic patients (P < 0.0001) making it a major predictor for asthma.

In our study population, we studied the association of low vitamin D level with the severity of asthma. When analyzing the association between vitamin D level and severity of asthma in asthmatic children, a negative correlation was found between serum vitamin D and asthma severity, which increased significantly as serum vitamin D decreased. Recent studies, done in Italy and Costa Rica, showed that vitamin D deficiency led to increase in the risk of asthma attacks (8, 19), while others showed no relationship (20, 21).

Even though, the definitive role for vitamin D in the pathogenesis of asthma has not been identified, but it is suggested that its deficiency related to asthma severity in multiple ways. First, by its effect on the immune system (helper T cell type 1, helper T cell type 2, and regulatory T cells (22). Xystrakis and his colleagues have shown that vitamin D restores the capability of regulatory T cells from steroid-resistant patients with asthma to secrete IL-10 (a potent anti-inflammatory cytokine) in response to steroids (23).

Second, by its effect on lung function which is explained by the fact Vitamin D inhibits the formation of matrix metalloproteinase as well as fibroblast proliferation and influences collagen synthesis; these actions mean that 1, 25-dihydroxy vitamin D may influence tissue remodeling and probably lung function (24).Third, Vitamin D stimulation has been shown to influence microarray gene expression in bronchial smooth muscle cells, and may suggest a role for vitamin D in airway remodeling (25).

The results, in our study, revealed that the majority (76.2%) of asthmatic patients with intermittent asthma had mild vitamin D deficiency, and 69% of asthmatic patients with mild persistent asthma had moderate vitamin D deficiency, whereas, more than half of patients with moderate persistent asthma (59%) and most of the patients with severe persistent asthma had severe vitamin D deficiency (P < 0.0001).These results revealed that serum vitamin D level is a marker for asthma severity in childhood.

The current study identified vitamin D deficiency as a strong predictor for childhood asthma (OR: 23.18, 95% CI: 7.81 - 68.83, P < 0.0001), giving the answer of our study question. Improving vitamin D status is promising in the primary prevention of asthma and in decreasing exacerbations of the disease. Given the emerging association between low vitamin D levels and asthma, strong consideration should be given to routine vitamin D testing in children, particularly those with asthma, and supplementation should be provided accordingly. More studies should be done to evaluate the patients of asthma after being supplied by vitamin D and repleting its store to detect any improvement in the asthma attacks. Our study had some limitations, as the small sample size (n=300) and being held in single referral center. Our study design also was cross-sectional limiting the ability to establish a causal link between vitamin D deficiency and asthma morbidity.

But, to our knowledge, our study is by far the only study done to test for association between vitamin D level and asthma severity in Lebanon.

Conclusion

The present study investigated the role of Vitamin D in childhood asthma. The data showed lower serum vitamin D levels in children with asthma than healthy children.

Vitamin D insufficiency was common in the study sample whereas severe Vitamin D deficiency was significantly higher in children with asthma than in healthy children. Vitamin D deficiency and less physical activity were major contributors to asthma, along with important role to sun exposure and familial history of asthma and vitamin D deficiency. Moreover; severity of asthma was found to be correlated with decrease vitamin D level.

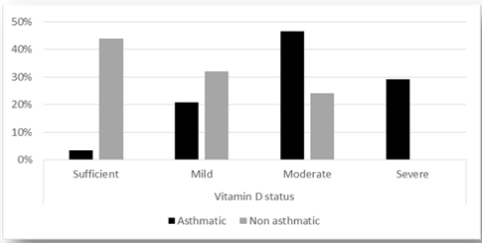

Figure 1: The distribution of serum vitamin D level in asthmatic and control children in our study population

Table 1: Demographic characteristics of the studied asthmatic and non-asthmatic children

Demographic characteristics		Asthmatics N (%)	Non-asthmatics N (%)	P-value
Age Group	< 5 years	84 (56.8%)	87 (56.9%)	0.99
	5-10 years	52 (35.1%)	53 (34.6%)	
	11-14 years	12 (8.1%)	13 (8.5%)	
Age, mean (±SD)		5.09 (±2.97)	4.91 (±2.93)	0.58
Sex	Male	98 (66.2%)	72 (47.1%)	0.001
	Female	52 (33.8%)	78 (52.9%)	
Place of Living	Beirut	105 (70.9%)	95 (62.1%)	0.43
	South	3 (2%)	5 (3.3%)	
	North	11 (7.4%)	14 (9.2%)	
	Mount Lebanon	29 (19.6%)	39 (25.5%)	

Table 2: Assessment of dietary and non-dietary covariates in studied asthmatic and control children

Covariates		Asthmatic N (%)	Non-asthmatic N (%)	P- value
Vitamin D Deficiency		143 (96.6%)	86 (56.2%)	<0.0001
Vitamin D status	Sufficient	5 (3.4%)	67 (43.8%)	<0.0001
	Mild	31 (20.9%)	49 (32%)	
	Moderate	69 (46.6%)	37 (24.2%)	
	Severe	43 (29.1%)	0 (0.0%)	
Type of feeding	Breastfeeding			
	≤6 months	80 (54.1%)	66 (43.1%)	0.06
	>6 months	68 (45.9%)	87 (56.9%)	
	Formula feeding			
	Never	14 (9.5%)	16 (10.5%)	0.24
	≤6 months	8 (5.4%)	16 (10.5%)	
	>6 months	126 (85.1%)	121(79.1%)	
Vitamin D supplements during breastfeeding		99 (66.9%)	110 (71.9%)	0.35
Current vitamin D supplements		14 (9.5%)	22 (14.4%)	0.19
Duration of vitamin D supplements in months, mean (±SD)		6.26 (±4.42)	5.92 (±3.80)	0.55
Familial history of Asthma		113 (76.4%)	37 (24.2%)	<0.0001
Familial history of vitamin D deficiency		22 (14.9%)	8 (5.2%)	0.005
Color of skin	White	31 (20.4%)	60 (40.5%)	0.001
	Wheatish	95 (62.5%)	71 (48.0%)	
	Brown or black	26 (17.1%)	17 (11.5%)	
Physical activity	Vigorous physical activity	72 (48.6%)	119 (78.3%)	<0.0001
	Less physical activity	76 (51.4%)	33 (21.7%)	
Less exposure to sunlight		76 (51.4%)	106 (69.3%)	0.001
BMI	Normal (<85th percentile)	109 (73.6%)	133 (86.9%)	0.01
	Overweight (85–95th percentile)	34 (23.0%)	19 (12.4%)	
	Obese (>95th percentile)	5 (3.4%)	1 (0.7%)	

Table 3: The association between vitamin D deficiency and the degree of severity of asthma

		Asthma Intermittent	Asthma Mild Persistent	Asthma Moderate Persistent	Asthma Severe persistent	P-value
Vitamin D Status	Sufficient	3 (14.3%)	2 (3.2%)	0 (0.0%)	0 (0.0%)	<0.0001
	Mild	16 (76.2%)	14 (22.6%)	1 (1.6%)	0 (0.0%)	
	Moderate	2 (9.5%)	43 (69.4%)	24 (39.3%)	0 (0.0%)	
	Severe	0 (0.0%)	3 (4.8%)	36 (59.0%)	4 (100.0%)	

Table 4: Predictors for development of Asthma in Children

Independent variables	Odds Ratio (OR)	95% CI	P-value
Vitamin D deficiency			
Mild	9.09	3.02-27.33	
Moderate	23.18	7.81-68.83	<0.0001
Exposure to sunlight	1.74	0.77-3.95	0.001
Family history of asthma	6.96	3.56-13.61	<0.0001
Less physical activity	2.70	1.16-6.29	<0.0001
Family history of vitamin D deficiency	0.70	0.21-2.31	0.005
Child BMI			
Overweight	0.70	0.30 - 1.61	0.01

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