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Is high prevalence of vitamin D deficiency evidence for asthma and allergy risks?

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Summary

Background: *Studies suggest a link between vitamin D deficiency and development of asthma and allergic diseases.* ***Aim:*** *To determine a) the association between vitamin D and asthma among children , b) difference in level of vitamin D in asthmatic children and control, and c) effect of vitamin D on atopy markers.* ***Setting:*** *Case-control study done, between October 2009 to July 2010, on asthmatics and controls (<15 years) at Pediatric Allergy–Immunology Clinics and Primary Health care Clinics (PHC), Qatar.* ***Methods & subjects:*** *A total of 483 cases and 483 controls matched by age, gender and ethnicity. Socio-demographic & clinical data was collected through physician diagnosis and questionnaire. Their health status was assessed by past or present clinical manifestations, family history, physical examination, BMI, and serum 25(OH) vitamin D, calcium, and phosphorus.* ***Results:*** *44.8% of asthmatic and 50.0% of controls were males, and 55.2% of asthmatic and 50% of controls were females. The mean age (± SD, in years) for asthmatic versus controls was 7.0±3.8 vs. 8.4±3.6. Vitamin D deficiency was more prevalent in asthmatics than controls. The mean value of Vitamin D in asthmatics was much lower than the normal value, and there was a significant difference found in the mean values of vitamin D between asthmatics (17.5±11.0) and the controls (20.8±10.0). Furthermore, there were statistically significant differences between asthmatic subjects and controls with respect to serum level of vitamin D (p<0.001). Lower Vitamin D levels were associated with more allergic disease and elevated serum IgE.* ***Conclusion:*** *Serum vitamin D levels were lower in asthmatic than control. Vitamin D deficiency was higher among children with asthma, allergic rhinitis, atopic dermatitis, acute urticaria, and food allergy. In addition, vitamin D deficiency was associated with IgE atopy markers in asthmatic children more than controls.*

Introduction

Asthma affects nearly 300 million people worldwide (1). It is the most common chronic disease among children where almost 90% of children are diagnosed by age of 6. It has tremendous negative impact through increased asthma exacerbations, hospital admissions, absence from school, and high health care costs (2, 3). Asthma prevalence has been increasing in both developed as well as developing countries (3). The exact causes of such a rise are poorly understood. However viral infection with "asthmogenic" viruses in early childhood (4), environmental pollution (5), changes in life style and evolving dietary habits have been suspected in genetically susceptible/high risk patient population (6, 7). In some emerging societies of the Middle East such as those in Qatar, UAE and Oman, the prevalence of asthma is quite

elevated reaching 19.8%, 13.6% and 20.7% (8-12), respectively. These rates are comparable to those in some of the industrialized or westernized countries (1).

Vitamin D deficiency is a major health problem noticed in many parts of the world (13). It is not restricted to sunshine-limited regions of the globe. It is still commonly seen in sunshine-abundant areas such as Asia-Pacific (14), Indian subcontinent (15), Africa and Middle East regions (16). There are several studies indicating that in the Gulf region, vitamin D deficiency is quite common among people especially in Qatar (17-19), Kuwait (20), UAE (21), and Saudi Arabia (22). The exact causes of such a high rates are not known. However, it is speculated that maternal deficiency during pregnancy (23), poor oral supplementation of vitamin D during childhood, and restricted exposure to sunshine might be risk factors for Vitamin D deficiency in children in this region (9, 17, 19). The aim of this study was a) to use a case-control design to find the association between vitamin D and asthma and allergic diseases, b) to study the difference in level of vitamin D in asthmatic & allergic children and control subjects, and c) to determine whether vitamin D level correlates with markers of atopy.

Subjects and methods

This is a case-control study which was designed to determine the relationship between vitamin D and asthmatic in young Qatari population below 15 years of age. The survey was conducted over a period from October 2009 to July 2010. This current study based on the 483 asthmatic cases and matched with age, gender and ethnicity of 483 control subjects.

The study was approved by the Hamad General Hospital, Hamad Medical Corporation. All human studies have been approved by the Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the persons who agreed to participate in this study gave their informed consent prior to their inclusion in the study.

Data collection

Selection of asthmatic subjects

The diagnosis of asthma and other allergic diseases such as allergic rhinitis, atopic dermatitis, urticaria and food allergy was based on physician-diagnosis. Asthmatic subjects aged below 15 years were identified from Pediatric Allergy-Immunology. Clinics as a part of cohort study a random sample of 671 asthmatic children approached and 483 gave consent and participated in study with a response rate (72%).

Selection of controls

Control subjects aged below 15 years were identified from community as a healthy and if not ever been diagnosed as asthmatic or if they never used any inhaler or asthmatic medication. This group involved a random sample of 603 healthy subjects who visited the PHC for any reason other than acute or chronic disease, and only 483 subjects included due to the either refusal of the mother or difficulty in drawing blood from very uncooperative subjects; with a response rate (80.1%). The healthy subjects were selected in a way matching to the age, gender and ethnicity of cases to give a good representative sample of the studied population.

Laboratory investigation

For biochemical assessment of vitamin D, the immunochemical method was used for analysis. Subjects were classified into two categories: Vitamin D deficiency which is defined as serum 25-hydroxy vitamin D (25(OH) D is lower than 30 ng/ml and optimum levels are between 30 – 80 ng/ml (15). Venous blood samples were collected into plain tubes, and serum was separated and stored at -70°C until analysis. 25-OHD was estimated using a kit DiaSorin/the Diagnostic Specialist (DiaSorin Corporate Headquarter, Saluggia (Vercelli), Italy). The treated samples were then assayed using a competitive binding radioimmunoassay (RIA) technique. Vitamin D levels were transformed to a log10 scale for data analysis. In descriptive analyses, we also categorized vitamin D levels as deficient (<20 ng/ml), insufficient (20-30 ng/ml), and sufficient (>30 ng/ml) on the basis of previous recommendations (19-21, 28, 33). Serum levels of these biochemical parameters were determined according to standard laboratory procedures. Furthermore, during the screening period, each patient provided a complete history and a comprehensive examination was performed. Blood was collected for eosinophil count, total serum IgE, and specific IgE levels for a panel of common allergens.

The questionnaire was designed to meet the objective of this study. The survey was conducted by physicians and based on standardized interviews performed by trained health professionals and nurses. The participants were interviewed

by health professionals and nurses concerning their socio-demographic information such as age, gender, place of residence (urban and semi-urban), type of house, monthly income, and consanguinity. Height and weight were measured using standardized methods and all the participants wore light clothes and no shoes for this part of the examination. The BMI was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. Furthermore, information on type of allergic diseases was collected. The survey instrument was then tested on 20 randomly selected on children visiting Ped. Allergy-Immunology Clinics of the Hamad General Hospital (cases) and 20 randomly selected healthy subjects from the children visiting PHC.

Data are expressed as median, geometric mean, arithmetic mean and standard deviation (SD) unless otherwise stated. Student-t test was used to ascertain the significance of differences between mean values of two continuous variables and nonparametric Mann-Whitney test was used. The Fisher's exact test (two-tailed) and Chi-square tests were performed to test for differences in proportions of categorical variables between two or more groups. Pearson's correlation coefficient was used to evaluate the strength of association between variables. The level $p<0.05$ was considered as the cut-off value for significance.

Results

Of the total number of children surveyed, 44.8% of asthmatic and 50.0% of healthy children were males and 55.2% of asthmatic and 50% of healthy children were females. The mean age (± SD, in years) for asthmatic versus control children was 7.0±3.8 vs. 8.4±3.6. There were stati-

Table 1 – Socio-demographic characteristics of the studied asthmatic and control subjects

Variables*	Asthmatic children n=483 (%)	Control children n=483 (%)	p-value
Age group (years)			
<5	204 (42.2)	183 (37.9)	
5-10	125 (25.9)	118 (24.4)	0.159
11-16	154 (31.9)	182 (37.7)	
Sex			
Male	247 (51.1)	266 (55)	0.245
Female	236 (48.9)	198 (45)	
Body Mass Index(BMI)			
Normal (<85th percentile)	335 (69.3)	376 (77.8)	0.008
Overweight (85-95th percentile)	121 (25.1)	92 (19)	
Obesity (>95th percentile)	27 (5.6)	15 (3.1)	
Place of living			
Urban	439 (90.9)	448 (92.8)	
Semi-urban	44 (9.1)	35 (7.2)	0.348
Household Income (QR) *			
5000-9999	131 (27.1)	91 (18.9)	
10000-14999	153 (31.7)	187 (38.7	0.005
>15,000	199 (41.2)	205 (42.4)	
No. of people living at home			
2-5	118 (24.4)	135 (28.0)	
6-10	270 (59.9)	284 (58.8)	.023
>10	95 (19.7)	64 (13.3)	
No. of bedrooms **	5.7±1.7	5.1±1.8	0.048

**1$ =3.65 QRs; ** Results are expressed as mean (±SD) for continuous variables and numbers of subjects (percentage of group) for categorical variables.*

stically significant differences between asthmatic and control subjects with respect to BMI (p<0.001).

Table 1 shows socio-demographic characteristics of the studied children according to asthmatic and control subjects.

Table 2 presents allergic diseases in asthmatic and control children studied.

Table 3 shows allergy biomarker values among asthmatic and control children. The study revealed that vitamin D deficiency was considerably higher in asthmatic children compared to healthy children. The mean value of vitamin D in asthmatic children was much lower than the normal value and there was a significant difference found in the mean values of vitamin D between asthmatic (17.5±11.0 with median 16) and control children (26.8±9.9, p<0.0001; and with median 25, p = 0.006). Besides mean IgE was statistically significant higher in asthmatic compared to control children (p<0.001).

There was significant correlation between vitamin D deficiency and total IgE in asthmatic compared to controls (r=0.232 vs. 0.188, p=0.001).

Table 4 reveals vitamin D level in asthmatic and allergic children compared to control children. Asthma and allergic diseases tended to be higher with lower Vitamin D levels.

Table 2 - Allergic diseases in asthmatic and control children.

Variables*	Asthmatic children n=483 (%)	Control children n=483 (%)	p-value
Allergic rhinitis			
Yes	177 (36.6)	95 (19.7)	0.0001
No	306 (63.4)	388 (80.3)	
Recurrent wheezing			
Yes	46 (9.5)	7 (1.4)	0.0001
No	437 (90.5)	476 (98.6)	
Urticaria			
Yes	52 (10.8)	10 (2.1)	0.0001
No	431 (89.2)	473 (97.9)	
Food allergy			
Yes	40 (8.3)	62 (12.8)	0.0279
No	443 (91.7)	466 (87.2)	
Other allergic diseases			
Yes	183 (37.9)	39 (8.1)	0.0001
No	300 (62.1)	444 (91.9)	

Table 3 - Allergy Biomarkers in asthmatic and control children.

Biochemistry parameters	Asthmatic children n=483	Control children n=483	t test value	p-value
Age* (years)	7.7±3.1	7.9±3.6	1.082	0.146
Serum Vitamin D (ng/ml) *	17.2±11.0	26.8±9.9	-8.719	<0.001
Median of Vitamin D(ng/ml)	16.0	25		0.006
Absolute eosinophil count ($X10^3$/ul)*	512.3±37.8	481.9±28.2	0.878	0.383
Log_{10} IgE*	2.0±0.7	1.7±0.6	5.369	<0.001
Median of IgE (kIU/L)	174.5	70		<0.001
Geometric mean of IgE (kIU/L)	120.1	58.7		<0.001
White blood cells ($X10^3$/ul)*	9.71±3.3	10.82±3.6	-4.886	<0.0001

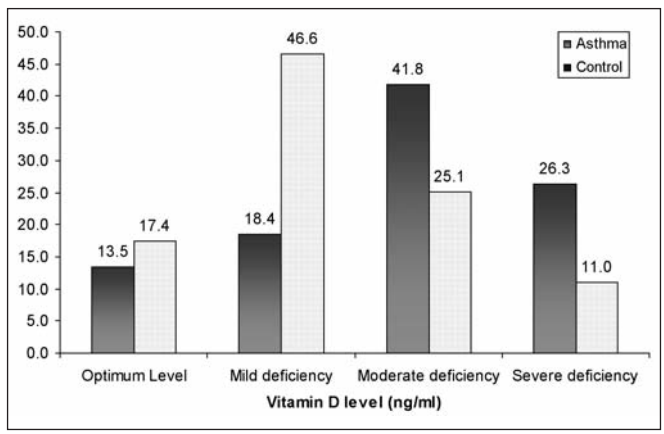
** Results are expressed as mean ± SD*

Table 4 - Serum vitamin D level in asthmatic and allergic diseases and control children studied.

		Vitamin D deficiency			
Variables	Sufficient vitamin D level (30-80) n = 149(%)	Mild (20-30) n = 314 (%)	Moderate (10-20) n = 323 (%)	Severe (<10) n = 180 (%)	p-value
Asthma					
Yes	33 (22.1)	49 (15.6)	83 (25.7)	38 (21.1)	0.019
No	116 (77.9)	265 (84.4)	240 (74.3)	142 (78.9)	
Allergic rhinitis					
Yes	48 (32.2)	77 (24.5)	96 (29.7)	51 (28.3)	0.301
No	101 (67.8)	237 (75.5)	227 (70.3)	129 (71.7)	
Recurrent wheezing					
Yes	10 (6.7)	15 (4.8)	20 (6.2)	8 (4.4)	0.700
No	139 (93.3)	229 (95.2)	303 (93.8)	172 (95.6)	
Acute urticaria					
Yes	8 (5.4)	15 (4.8)	22 (6.8)	17 (9.4)	0.212
No	141 (94.6)	299 (95.2)	301 (93.2)	163 (90.6)	
Food allergy					
Yes	14	18	21	9	0.0279
No	135	296	302	171	
Other allergic diseases					
Yes	19 (12.8)	54 (17.2)	79 (24.5)	70 (38.9)	0.0001
No	130 (87.2)	260 (82.8)	244 (75.5)	110 (61.1)	

Figure 1 gives serum level of vitamin D among asthmatic and control children. There were statistically significant differences between asthmatic and control subjects with respect to serum level of vitamin D ($p<0.001$).
Logistic regression was performed and found that obesity and BMI were confounding factors of vitamin D insufficiency in children ($p<0.001$).

Figure 1 - Serum level of vitamin D among asthmatic and control children



Discussion

To the best of our knowledge, there are no population-based studies that have examined the association between Vitamin D and asthma and allergic diseases in young children. This study demonstrates an association between circulating levels of vitamin D and asthma and allergic diseases such as allergic rhinitis, acute urticaria, atopic dermatitis and food allergy. Besides, it showed that there is a correlation between vitamin D deficiency and IgE, one of the markers of atopic sensitization. Over the last several years, there has been emerging evidence about the possible association of vitamin D deficiency and childhood asthma. Devereux et al showed that decreased maternal intake of vitamin D during pregnancy increases the risk of developing asthma later on during childhood (23). Hol-

quin study on 36 asthmatic, age 11-54 year old, revealed lower vitamin D levels in asthmatics compared to controls (p=0.03) (24). Pascual et al (25) revealed that serum vitamin D levels correlated with lung functions tests, namely FEV1 and FVC, in asthmatics. Brehm et al study on serum vitamin D levels form 1024 children with mild-to-moderate asthma showed that vitamin D insufficiency is associated with higher risk of severe asthma exacerbations over a 4-year period (26). Furthermore, it has been reported that vitamin D deficiency in childhood asthma are associated with increased inhaled and oral steroid use (27).

As far as the association of vitamin D levels with other allergic diseases, data from USA and Australia indicates a possible role for vitamin D in the pathogenesis of anaphylaxis, as noticed by the geographic variations in epinephrine prescriptions (28, 29). The analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) on 18,228 adults identified a higher prevalence of allergic rhinitis with vitamin D serum levels (30). There are no studies on vitamin D levels with acute urticaria in children. However, Thorp study on 50 adults with chronic urticaria showed that vitamin levels were significantly lower in subjects with chronic urticaria compared with controls (p=0.16) (31). In atopic dermatitis subjects, vitamin D supplementation induced local cathelicidin production, thus reducing defects in the innate immune system that might be responsible for increase in cutaneous infections (32). Record review of 1002 young children presenting to the emergency departments with food allergy reactions showed seasonal variation food allergy of with season of birth of the child, possibly indicating an involvement of vitamin D in the pathogenesis of food allergy (33).

In our study, of the markers of atopy, only serum IgE levels revealed a significant inverse correlation with vitamin D levels in asthmatic children compared with controls (p=0.001). Devereux recently showed that serum vitamin D levels were found to be inversely associated with markers of asthma severity in asthmatic children (23). Effects of vitamin D on the immune system has been reviewed elsewhere (34, 35). It has important immunomodulatory properties and it enhances innate immunity by inducing the expression of antimicrobial substances, cathelicidins (32), and also increasing regulatory T cells (Tregs) (36), the cells that cells play a important role in controlling allergic diseases such as asthma (37).

Vitamin D supplementation potentially has a paradoxical effect on development of later allergy (38), and it has been revealed that 25(OH)D levels are associated with elevated IgE concentrations (39). In our sample, this is vitamin D supplementation is unlikely to have contributed in development of allergy since routine vitamin D supplementation has just been introduced very recently. Hughes et al (40), have demonstrated the possible role of geographic factors such as latitude and exposure to ultraviolet radiation and vitamin D on development of asthma and hay fever among Australian children. In our study, latitude and exposure to ultraviolet radiation exposure could be confounding factors. However, we think they had limited if any effect for the following reasons: the first, unlike Australia, Qatar is a geographically limited area; second, the population we studied is limited to the capital, Doha; third and the exposure to ultraviolet radiation in our sample is expected to be same in the study and control groups.

In addition, obesity and BMI were confounding factors of vitamin D insufficiency in children. These two factors have been shown to be associated with vitamin D insufficiency in children as well as adults (38-39).

Strengths of our study include large sample size, case-control designed, age, gender and ethnicity-matched, and physician-diagnosed asthma and allergic diseases. There are few limitations in our study including lack of data oral intake of vitamin D and sun exposure, and the number of different types of allergic diseases was relatively small.

Conclusion

The present study revealed that vitamin D deficiency was higher in asthmatic children compared to healthy children. Vitamin D deficiency was associated allergic rhinitis, acute urticaria, atopic dermatitis and food allergy, some markers of atopy thus increasing risk of asthma and allergic diseases. Supplementing infants with vitamin D might be a safe and effective strategy for reducing the risk of asthma and allergic diseases, but further studies need to be done.

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