TITLE PAGE

Vitamin D deficiency in Jordanian children with bronchial asthma : a cross sectional study

Type of manuscript : Original article

Running Head: Pediatrics Asthma and Vitamin D Deficiency

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Number of pages: : 21

Number of figures: 4

Number of tables : 3

Abstract word count: 250 words

Main text word count: 4,620 words (including tables, figures ,references and declarations)

Vitamin D deficiency in Jordanian children with bronchial asthma: a cross sectional study

Abstract:

Background: Asthma is the most common chronic diseases that affect children and its prevalence is increasing worldwide posing a great burden on healthcare systems.

A growing body of evidence suggests an association between vitamin D deficiency and asthma. The current study aimed to assess serum vitamin D level in Jordanian children with bronchial asthma and to examine the correlation between vitamin D levels and asthma severity and control. **Methods:** A cross sectional study was conducted in the Pediatric Chest Clinic at AlKarak Governmental Hospital South of Jordan from May 2015 to February 2016. Serum level of 25-hydroxyvitamin-D was determined for 98 Children aged 1 to 14 years and diagnosed with bronchial asthma (6-14years) or recurrent wheezing episodes(<6 years). The severity of asthma was determined based on the Global Initiative for Asthma (GINA) assessment, the Asthma Control test (ACT) and the Childhood Asthma Control Test (C-ACT). The results were considered significant if $P \leq .05$. Statistical analysis was performed using SPSS 21 (IBM, Armonk, NY, United States of America, 2012).

Results: Vitamin D levels were deficient and insufficient in 41(41.8%) and 34(34.7%) of asthmatic children, respectively. Only 23(23.5%) had sufficient vitamin D levels. A significant correlation was found between the severity of asthma symptoms and vitamin D deficiency (Pearson Chi-squared=.028). **Conclusion**: Vitamin D deficiency is highly prevalent in children with bronchial asthma in Jordanian population and correlates significantly with asthma severity. Assessment of vitamin D levels in children with bronchial asthma is required in a larger scale studies in Jordan.

Keywords: Asthma, Deficiency, Pediatrics, Jordan, Vitamin D

Introduction:

Asthma is one of the most common chronic diseases worldwide and has increased in prevalence over the last few decades. [1] In Jordan, bronchial asthma constitutes a great burden, as it affects approximately 10% of the population, according to official reports from the Ministry of Health. The etiology of asthma is complex and likely caused by multiple interactions between genetic and environmental factors. Environmental factors such as atmospheric pollution, dietary changes, allergen-sensitization, and modifications in lifestyle may be responsible for the increasing prevalence of asthma.[2] Additionally, impaired immunogenic tolerance and interplay between cells and inflammatory mediators may further promote airway obstruction.

Recently, the effects of vitamin D as a hormone have gained increasing attention. Besides its numerous classical functions (calcium absorption, bone mineralization, and neuromuscular function regulation), vitamin D is also believed to be a potent immune system regulator, having a potential role in various allergic diseases. Vitamin D seems to have regulatory effects on every part of the immune system, whereas vitamin D deficiency has been linked to an array of immunologically based diseases, such as asthma.[3] Unfortunately, despite adequate exposure to sunlight and satisfactory diet, vitamin D deficiency is still widespread in many countries such as Jordan.[4]The global increase in asthma and allergic diseases may be linked to lower serum vitamin D levels. Several studies indicated an association between vitamin D deficiency and increased incidence and severity of childhood asthma.[5,6] However conflicting results were also reported demonstrating either no effects or adverse effects for vitamin D on asthma incidence or severity which made the association between vitamin D and asthma unclear.[7]

The epidemic increase in asthma and related allergic disease is a major public health problem worldwide.[1] Thus, identification of new risk factors for developing asthma such as vitamin D deficiency is important to improve control of asthma, to reduce morbidity of asthma and more importantly to help prevention of the disease in early life. Therefore, we conducted a cross sectional study to assess the level of serum vitamin D in children with bronchial asthma in Alkarak city of Jordan. Additionally, we compared severity and control of asthma between different levels of vitamin D in the subjects of the study.

Patients and Methods:

Study design and setting

A total of 98 asthmatic and wheezing children aged 1 to 14 years were included in the study who were referred to the Pediatric Chest Clinic at Alkarak Governmental Hospital South of Jordan from May 2015 to February 2016. All families were consented. The study was approved by the Ethics Committee of Mut'ah University, research project number of 20153 .Procedures were followed in accordance with the Helsinki Declaration of 1975.

All study subjects were diagnosed with asthma and recurrent wheezing episodes (early asthma), according to the Global Initiative for Asthma (GINA) criteria: 1) a physician's diagnosis of asthma, 2) symptoms of recurrent (i.e., more than two) episodes of wheezing, cough, shortness of breath, or a combination of these, 3) documented reversibility with bronchodilators, and/or 4) use of medication for asthma in the previous 6 months.[8]

Asthma severity and control of symptoms in study population were determined by the following: Global Initiative for Asthma (GINA) classification, ACT or C-ACT score, use of systemic steroids, and admission to hospital due to asthma within the last 12 months. Patients were categorized into either intermittent, mild persistent, moderate persistent, or severe persistent asthma according to GINA classification.[8]Additionally,a validated questionnaire, the Asthma Control Test (ACT) questionnaire, was used for children 12 years and older. The Childhood ACT (C-ACT) was used for children between 4 and 11 years of age. An ACT ≤19 and C-ACT >19 were considered poor and good control, respectively. [9]

Patients who were taking vitamin D supplements were excluded from the study. Patients' detailed personal medical histories were recorded, and a thorough physical examination was performed for each patient. Children included were screened for the presence of allergic conditions other than asthma, including allergic rhinitis, atopic dermatitis/eczema, allergic conjunctivitis, and food allergies. History of breastfeeding during the first six months of life was also screened.

Vitamin D measurement:

The vitamin D level was assessed by measuring plasma 25-hydroxyvitamin-D3, a vitamin D metabolite that is considered a reliable measure of the plasma vitamin D level. A venous blood sample was obtained; serum was separated and stored at −70 °C until analysis.

Serum 25(OH)D was measured using a commercially available kit (DiaSorin Liaison Total rapid automated assay (DiaSorin, Stillwater, MN))based on the recommendations of previous studies.[4,10] We categorized vitamin D levels as deficient, insufficient, and sufficient if the 25(OH)D level was <20 ng/ml, 20-29 ng/ml, and >29 ng/ml, respectively.[4]

Skin prick testing:

To assess the association between atopy and vitamin D deficiency in asthmatic children included in the study, skin prick testing for common inhaled allergens was performed on study children. The test was performed with 11 standardized allergen extracts from a commercial test kit (Stallergenes Greer, London, UK) in accordance with published guidelines. [11]

The 11 tested inhaled allergens were cat pelt, Salsola kali, two strains of house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farina), cereal mix, olive pollen, grass mix, mould (Alternaria), dog fur, compositae, and wall-pellitory. The test was reported to be positive if the prick site swelled to form a wheal with a diameter greater than 4 mm. A positive control (histamine) and a negative control (normal saline) were used to avoid false-positive (dermatographism) or false-negative results. Parents and caregivers of the tested children were requested to stop systemic antihistamines or leukotriene modifiers 4 to 5 days prior to testing**.**

Statistical analysis:

Data are described using means and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. The frequency of vitamin D deficiency in children with bronchial asthma is presented as frequency distributions. The relevant demographic and clinical characteristics of Vitamin D deficient patients were compared with those with normal vitamin D levels using the chi-square test. Multiple logistic regression was used to investigate the possible predictors of low vitamin D levels in the study population. The correlation between vitamin +D levels and the severity of asthma was performed using

the Pearson Chi-square test. The results were considered significant if $P \leq .05$. Statistical analysis was performed using SPSS 21 (IBM, Armonk, NY, United States of America, 2012).

Results:

Between May 2015 and February 2016, a total of 98 patients who were referred to Alkarak chest clinic and diagnosed with wheezing (≤5years) or asthma (6-14) were included in the study.

Table 1 shows the demographics and clinical characteristics of patients in term of associated allergic conditions, use of inhaled and/or systemic steroids, exclusive breast feeding during first 6 months and classification of asthma according to GINA. Patients were categorized into either intermittent, mild persistent, moderate persistent, or severe persistent asthma according to GINA criteria (Table 1).

Table 1: Demographics and clinical characteristics among study patients

Age, years (Mean± SD)	7.67±3.83
Sex, n (%) Male Female	 65 (66.3%) 33 (33.7%)
Associated allergic conditions:	
Allergic rhinitis	71 (76.3%)
Conjunctivitis	24 (26.4%)
Food allergy	2 (2.2%)
Eczema/atopic dermatitis	23 (25%)
Use of inhaled corticosteroids	67 (72%)
Exclusive breast feeding during first 6 months	17 (17.3%)
GINA Classification :	
Intermittent	38 (41.3%)
Mild persistent	23 (25%)
Moderate persistent	23 (25%)
Severe persistent	8 (8.7%)

Figure 1 shows vitamin D levels in patients of the study. Vitamin D was deficient in 41 children (41.8%), insufficient in 34 (34.7%), and sufficient in only 23 (23.5%). Age distribution among three categories of vitamin D level is demonstrated in table 2.

Table 2: Serum vitamin D levels and age distribution in study population

	Deficiency (<20 ng/ml)	Insufficiency (20-30 ng/ml)	Sufficient (>30 ng/ml)
Frequency n(%)	41 (41.8%)	34 (34.7%)	23 (23.5%)
Age (years) (mean, SD)	8.85±3.48	6.97±6.50	5.00±3.89

We examined the correlations between the patients' serum vitamin D levels and some demographic and health characteristics. Demographic variables, such as age, sex, family history of asthma, and the presence of other allergic conditions were evaluated (Table 3). Age showed a significant correlation with vitamin D levels. Vitamin D was inversely proportional with age (P<.05, R^2=0.105) (Figure 2). Younger children tended to have more sufficiency in their serum vitamin D levels than older children (Table 2). Among associated allergic conditions other than asthma (allergic rhinitis, allergic conjunctivitis, food allergy, and eczema), allergic rhinitis was the only condition with a significant correlation with vitamin D levels (P=.036) (table3).

Table 3: Multiple logistic regression analysis for the clinical demographics of the study population:

Clinical variables	p-value	AOR0	95.0% CI for AOR	
			Lower	Upper
Age	0.021	0.866	0.767	0.979
Sex	0.957	1.094	0.041	29.086
Associated allergic diseases:				
Allergic rhinitis	0.036	3.170	1.077	9.325
Allergic conjunctivitis	0.614	1.869	0.165	21.191
Eczema	0.900	0.852	0.070	10.372

With regard to the correlation between vitamin D level and severity of asthma, we compared children within the three groups of vitamin D levels: deficiency, insufficiency, and sufficiency, in terms of severity of their asthma condition.

A significant correlation was found between asthma severity according to the GINA classification and vitamin D levels (Figure 3) (*P*= 0.028). 14.3% of children with insufficient vitamin D levels and 6.7% of children with deficient levels had severe persistent asthma, whereas none of the children with sufficient levels were reported to have such asthma severity .

Moreover, the number of patients with vitamin D deficiency or insufficiency who used systemic corticosteroids to treat asthma exacerbation within the last year (48.8% and 52.9%, respectively) was significantly higher than those who had sufficient vitamin D levels, 21.7% (Pearson Chi-squared=0.047) (Table 4).

Table 4. Association between vitamin D level and different asthma assessment measures:

Vitamin D level		Deficiency n=41	Insufficiency n=34	Sufficient n =23	*p*-value
Use of Systemic steroids within last 12 months		20 (48.8%)	18 (52.9%)	5 (21.7%)	0.047
Admission to hospitals within last 12 months		29 (70.7%)	24 (70.6%)	13 (56.5 %)	0.449
Skin prick testing (n=76)	- ve	10 (27.0%)	7 (30.4%)	3 (18.8%)	0.711
	+ve	27 (73.0%)	16 (69.6%)	13 (81.2%)	

P value, *P*earson Chi-squared; *p* value ≤0.05 was considered to indicate statistical significance; -ve, negative response, +ve, positive response

Utilizing ACT and C-ACT questionnaires as measures of asthma control, there was a significant difference among the three groups of vitamin D levels as children with lower vitamin D levels had a lower ACT score (*P*=0.05) (Figure 4).

Sixty-seven children in the study group were tested for atopy using skin prick testing for 11 common inhaled allergens. No significant differences were found among the three vitamin D groups with regards to skin prick testing (*p*=0.711) (Table 4).

Discussion:

The current cross-sectional study assessed levels of serum vitamin D in children with bronchial asthma or wheezing episodes in Alkarak city of south Jordan. We observed high prevalence of vitamin D deficiency (<20 ng/ml) and insufficiency (20 and 29 ng/ml) in children with asthma or recurrent wheezing (40.1%, 34.7%). Accordingly, sufficient vitamin D levels (vitamin D levels ≥30 ng/ml) only represented 23.5% of the asthmatic patients. This finding is consistent with previous studies that showed that vitamin D deficiency is prevalent in asthmatic children in many regions of the world and particularly in the Middle East.[5]In a study conducted in Qatar, 52.9% of children with bronchial asthma had insufficient vitamin D levels.[12]In a similar study in Turkey, 67% of asthmatic children had deficient vitamin D levels, whereas 20% were vitamin D insufficient.[13] Several other reports published globally have also confirmed the high prevalence of vitamin D deficiency in children with asthma.[14,15] Reverse causality may account partly for the fact that children with bronchial asthma tend to avoid outdoor activities and thus have less sun exposure than those without bronchial asthma and subsequently have lower vitamin D levels. However, studies previously have shown that even high levels of sunlight exposure do not ensure adequate vitamin D levels.[16]

We aimed to determine whether we could establish a correlation between vitamin D levels and different demographic and clinical characteristics in our study population, only age showed a significant correlation with vitamin D levels. Younger children had higher serum vitamin D levels. This is consistent with findings in other countries, such as the US, UK, and New Zealand, where prevalence of low vitamin D status increase with age, with adolescents being the most affected age group.[17] Among the co-existing allergic conditions, only allergic

rhinitis showed a significant correlation with vitamin D levels similar to a previous study conducted in the south of Jordan.[18]This further supports the important role of vitamin D in modulating the immunological response in different respiratory or allergy-related conditions.

In terms of the correlation between vitamin D deficiency and the severity of asthma , our study shows a significant association between the severity of asthma determined by the GINA classification and status of vitamin D deficiency. Asthmatic children with vitamin D deficiency were more likely to have severe and moderate persistent asthma compared with those with sufficient levels of vitamin D who had intermittent or mild asthma. This association was also significant in other measures of the severity of asthma; children with lower vitamin D levels used systemic steroids to treat asthma exacerbations more frequently and had lower clinical severity scores of ACT and C-ACT .There was also a clear trend that did not reach significance that asthmatic patients with low vitamin D levels had hi\her rate of hospital admissions and use of systemic corticosteroids, indicating more frequent exacerbation of asthma episodes. The relationship between serum vitamin D levels and subsequent severe asthma exacerbations or hospitalization was investigated by previous studies, and vitamin D deficiency was shown to be associated with higher rate of severe exacerbations in asthmatic children in a large CAMP (Childhood Asthma Management Program) study.[19] This was supported by several other reports as well.[20,21]

This association can be explained in several aspects. Vitamin D has an important role as a modulator in the immune system.[3,22] It is also believed to correlate with inflammatory indicators of pediatric asthma; a significant inverse correlation between serum levels of 25-

OH vitamin D-3 and IgE in pediatric patients with asthma was found.[23]In addition, a strong association between vitamin D deficiency and respiratory tract infections, a leading trigger for asthma exacerbations, was reported.[24] On the other hand, several clinical and epidemiological studies have suggested that there may be a synergistic effect of vitamin D and corticosteroids in asthma outcomes.[25] This can suggest that vitamin D deficiency may impedes response of asthmatic patients to steroid therapy .

In contrary to our findings some studies reported inverse associations or no associations between asthma or recurrent wheezing and vitamin D which may reflect heterogeneity of asthma, differences between populations and research methodologies or diagnostic tools. Previous clinical trials of vitamin D supplementation revealed mixed outcomes. In some studies, prenatal vitamin D supplementation or during infancy resulted in better lung function and asthma control in childhood.[26]In contrast, other studies showed increase in prevalence of asthma, allergic rhinitis and atopy. Vitamin D supplementation might be beneficial for certain groups of asthmatic children and at certain age and dose. This may necessitate conducting randomized clinical trials on the benefits of vitamin D on a large scale.

Our results signify the importance of studying vitamin D levels in children with bronchial asthma in south Jordan. However, a high prevalence of vitamin D deficiency in the study population could also be a reflection of the fact that vitamin D deficiency is prevalent in the Jordanian population. A study of vitamin D levels in newborn infants in Jordan showed extremely high rates of vitamin D deficiency at approximately 94%.[27]A national study of 1077 Jordanian children of preschool age (12–59 months) showed 19.8% deficiency (<12 ng/ml) and 56.5% insufficiency (<20 ng/ml).[28] In addition, Vitamin D supplementation

combined to other asthma medications has been shown to improve the inflammatory response of children with asthma. [29] However, to our knowledge, this has not been assessed in Jordan.

It is worth mentioning that we did not have a control group in this study to assess vitamin D levels in children without bronchial asthma.

Our results did not show a strong association between atopy (positive skin prick test to inhaled allergens) and vitamin D deficiency. However, previous studies have shown that low vitamin D levels were associated with an increased risk of atopy and asthma.[30]The lack of association could be due to multiple mechanisms by which vitamin D can affect asthma other than atopy.

Conclusion:

Our results showed that vitamin D deficiency was highly prevalent in asthmatic patients because almost half of the tested patients had low vitamin D levels. Vitamin D deficiency correlated with the severity of asthma in children and this is reflected by higher GINA scores, more frequent hospital admissions, and more frequent use of systemic steroids to treat exacerbations compared with asthmatic children with normal vitamin D levels. This shows the important role vitamin D plays in the pathogenesis and severity of asthma and possibly other allergic conditions.

Therefore, assessment of serum vitamin D levels in patients with bronchial asthma is important and can be beneficial for assessment, follow-up, and treatment. We recommend that all children diagnosed with bronchial asthma have their serum blood tested for vitamin D levels. The current study is an observational study; hence further research is needed to

help with understanding the role of low vitamin D in asthma and the Jordanian population. Future research should be performed on to assess the effects of vitamin D supplementation on asthma severity and control of symptoms.

Abbreviations: (GINA) Global Initiative for Asthma assessment, (ACT) The Asthma Control test, and (C-ACT) the Childhood Asthma Control Test.

Declarations:

1- **Ethics approval and consent to participate:**

This study was approved by the Mu'tah Faculty of Medicine Ethics committee .All children's parents had given consent to participate . All children's parents or care givers had given consent to utilize collected data.

2-**Consent for publication:**

Consent for publication was obtained from all children parents and care givers .

3- **Data Availability :**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

4- **Competing interests:**

The authors declare that they have no competing interests.

5-F**unding:**

This work was funded by the Deanship Of Scientific Research at the University of Mu'tah. Research project number :20153 (reference number ;University of M'utah) .The fund body contributed in data collection .

2-**Author's contributions:**

1-**EZ :** contributed in conception of work ,interpretation of data ,drafting the manuscript .Approved the submitted version .

2-**NN** : contributed in analysis and interpretation of data and approved the submitted version.

3-**SA**: contributed in design of the work, the acquisition of data and approved the submitted version.

4-**AT**:contributed in acquisition and interpretation of data and approved the submitted version .

5-**EB**: contributed in design of the work, acquisition of data and approved the submitted version .

6-**EA:** contributed in acquisition of data ,drafting the manuscript and approved the submitted version.

7-**AS**: contributed in interpretation of data ,drafting the work and approved the submitted version.

8-**EM:** : contributed in interpretation and analysis of data, drafting the work and approved the submitted version.

- All authors are personally accountable for the author's own contributions and are accountable that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acknowledgements :

The authors would like to acknowledge Ibrahim Aldmour and Futoun Alrawashdeh for their assistance in data collection.

Figure titles :

Figure 1: Distribution of serum vitamin D levels among asthmatic children

Figure 2 :Correction between vitamin D plasma levels and age (p-value = 0.002)

Figure 3: The Box Plot of serum vitamin D levels by severity. (P= 0.028)

Figure 4: The Box Plot of serum vitamin D level by ACT and C-ACT score

Figure legends :

Figure 1: Distribution of serum vitamin D levels among asthmatic children. Vitamin D was deficient in 41.8% , insufficient in 34.7%, and sufficient in 23.5% .

Figure 2 : Correction between vitamin D plasma levels and age , Vitamin D was inversely proportional with age with younger children having more sufficient serum vitamin D levels than older children (p-value = 0.002) .

Figure 3: The Box Plot of serum vitamin D levels by severity. A significant correlation observed between asthma severity by GINA classification and vitamin D levels (P= 0.028). GINA: Global Initiative for Asthma Assessment.

Figure 4: The Box Plot of serum vitamin D level by ACT and C-ACT score. Children

with lower vitamin D levels had a significantly lower ACT score .(P=0.05). ACT: Asthma

Control test .C-ACT ;Childhood Asthma Control Test .

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