Clinical characteristics of asthmatic children with Vitamin D deficiency at Jordan University Hospital: A retrospective study

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Abstract

Objective: Bronchial asthma is the most common chronic condition in the pediatric population around the world. Increasing evidence suggests an association between Vitamin D deficiency and asthma. This study aims to evaluate the prevalence of vitamin D deficiency in children with bronchial asthma in Jordan University Hospital, investigate the clinical characteristics of the study population, and examine the correlation between vitamin D levels and asthma severity and control. **Methodology:** A retrospective chart review was conducted on 201 asthmatic children, aged 1 to 18 years, who received medical care at Jordan University Hospital from 2015 to 2018. Vitamin D levels were recorded for all study populations. Patient demographic and clinical characteristics such as body mass index, feeding status, pulmonary function test, and pediatric intensive care admissions were collected. Demographic and clinical characteristics were compared among three categories of vitamin D levels, and a correlation between asthma severity and vitamin D level was assessed. **Results:** Out of 201 participants included in the study, 51.7% were vitamin D deficient, 26.6% were vitamin D insufficient, and 21.6% were vitamin D sufficient. The following variables had significant correlations with vitamin D levels; frequency of inhaled Salbutamol usage (p=.028), PICU admissions (p=.011), feeding status at six months (p=.039), and the number of admissions per year (p=.028).**Conclusion**: Vitamin D deficiency is prevalent in asthmatic children and correlates with the severity and control of asthma in our target population. Health care providers of asthmatic children are encouraged by our results to assess vitamin D levels in these patients.

Keywords: Asthma, Children, Jordan, Pediatrics, Vitamin D.

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1. Introduction

Asthma is one of the most common chronic diseases of childhood affecting approximately 6.3 million children and remains a significant cause of disability and death (1). The inflammatory process results from an interplay between environmental and genetic factors and is classically characterized by reversible airway obstruction. However, frequent attacks may result in airway remodeling, a persistent structural change (2). In 2016, asthma ranked the 27th leading cause of disease burden in low-and middle-income countries (3). Despite the scarcity of epidemiological data in Jordan, it is reported that asthma has a 6.2% prevalence rate in children aged 13-14 years, demonstrating a bias towards females (4).

Moreover, the disease prevalence rate has undergone a two-fold increase over the last ten years (5). Many prenatal, postnatal, and environmental risk factors have been identified for asthma (6). Notably, vitamin D deficiency is increasingly receiving attention due to its integral function within the complex inflammatory pathways of asthma (7).

The Prevalence of vitamin D deficiency is increasing worldwide and depends on skin pigmentation, sun exposure, breastfeeding, and supplementation. In addition to the proven complications of vitamin D deficiency, various studies investigated its relation to the incidence and severity of multiple conditions such as asthma (8). Vitamin D plays an integral role in immune system regulation, which aids in supporting the pro-inflammatory response of the respiratory epithelium in asthma (9). However, evidence from clinical trials was inconclusive as they failed to establish a true benefit of vitamin D supplementation in the treatment of asthma (7,10).

In Jordan, vitamin D deficiency was substantial among the pediatric population, including newborns during the summer and spring seasons (11). Studies addressing prevalence rates of vitamin D deficiency in asthma and its impact on asthma severity and control within the Jordanian pediatric population are scarce. This study aims to evaluate the clinical profiles of asthmatic children with vitamin D deficiency at Jordan University Hospital. Moreover, it investigates the most significant risk factors associated with the development of asthma in the study population. It demonstrates whether low vitamin D levels could predict more severe and persistent asthma in later life stages.

2.0 Methodology

2.1. *Population*

This retrospective cohort study was conducted on all physician-diagnosed asthmatic patients with vitamin D deficiency visiting Jordan University Hospital's (JUH) respiratory clinics from 2015 until 2018. Exclusion criteria included the following: patients older than 18 years and younger than 12 months, patients with incomplete records, patients with chronic diseases other than asthma, and patients who were lost to follow-up. The study's final sample size was 201 patients composed of asthmatic children between 1 and 18.

2.2. *Data Collection*

An extensive chart review was conducted to extract the study variables, including demographic information such as age and sex, morphometric measures such as height, weight, and body mass index(BMI), medication history, laboratory results, presence of other atopic conditions, previous vitamin D supplementation, the severity of asthma within the last four months, the treatment regimen used for asthma for the past one year among other clinical variables. Data collection was

performed from July to December 2019.

2.3. *Asthma Severity*

The severity of asthma was estimated through the following variables: the number of hospital admissions in the preceding year due to asthma, frequency of night awakening and sleep disturbances due to asthma, frequency of inhaled Salbutamol usage per week, and effect of asthma on daily activity. These variables are complemented by pulmonary function tests (PFTs) when available. Severity was categorized as intermittent, mild persistent, moderate persistent, and serious persistent based on the guidelines provided by the Global Initiative for Asthma (GINA) criteria (12).

2.4. *Laboratory Results*

Extracted laboratory variables include white blood cell (WBC) count, eosinophil count [count over 400 is considered abnormal], IgE count [count over 180 IU/ml were considered elevated] and vitamin D levels [X < 20 ng/ml is considered deficient, 20 > X >30 ng/ml is insufficient and X > 30 ng/m; is sufficient]. Vitamin D levels were categorized in accordance with recommendations from published studies (13).

2.4. *Pediatric Risk Factors*

The chart review assessed the records for several pediatric-oriented variables such as feeding status during the first six months of age, pediatric ICU (PICU) admissions, birth weight, and term status at birth.

2.5. *Statistical Analysis*

All collected data were organized, coded, and imported to the Statistical Package for Social Sciences (SPSS) version 23. All results are presented in the form of descriptive statistics such as means, ranges, and standard deviations. Data are presented as mean and SD for continuous variables and frequencies and percentages for categorical variables. Chi-square was utilized to investigate the association between any two sets of categorical variables. Moreover, the study will use the ANOVA test to evaluate the impact of changing vitamin D levels on the status of numerical variables. Logistic regression was utilized to assess the predictors of vitamin D levels. A P-Value of less than 0.05 is considered statistically significant.

2.6. *Ethical Considerations*

The study's protocol and proposal were reviewed and accepted by the Jordan University Hospital's Institutional Review Board (IRB) and the University of Jordan's research ethics committee. The processes within the study's protocol conform to the guidelines of the Declaration of Helsinki.

3.0 Results

3.1 Study population demographic data:

A total of 201 pediatric patients between 1 and 18 years were included in this study, with a mean age of 7.3 years (± 3.8). Our data showed male dominance, with a male to female ratio of 2.8:1. The mean body mass index (BMI) was 18.58 (± 5.89).

Approximately 81.1% of the studied participants resided in urban locations compared to 18.4% in rural areas. The parents' education level showed that 30.4% had school degrees, while 69.6% had received higher education. Participants' demographic data are demonstrated in table 1.

3.2 Study population clinical and laboratory Data :

The mean age of diagnosis of asthma and asthma-related conditions was 3.6 years (3.0). Asthma was the most common preliminary diagnosis (49.3%), followed by reactive airway disease RAD (48.3%), while allergic bronchitis, bronchiolitis, and seasonal atopy were less common (0.5%). The average of admissions in the last calendar year was 1.8

admissions/year (±2.7). The average of admission was 2.9 days (±3.7). About 91.0% of the patients received oral or intravenous steroids. The results showed that 38.8% of the patients had a history of other atopic diseases, including but not limited to: allergic rhinitis, eczema, and food allergy. Participants' mean birth weight is 2.93 kg (± 0.71).Additionally, 52.7% had a first-degree relative with a history of asthma. The mean FEV1 measurement was 1.70 L (± 0.68). Clinical characteristics and laboratory measurements are shown in table 2.

3.2.A. Vitamin D levels :

Figure 1 demonstrates that out of our studied sample, 51.8% were vitamin D deficient, 26.6% were vitamin D insufficient, and 21.6% were vitamin D sufficient.Participants' mean serum vitamin D level was 22.8 ng/ml(± 15.90). Regarding the correlation between vitamin D level and different demographic data of the study population, feeding status during the first six months significantly correlated with categories of vitamin D levels (p=.039). No significant correlations were found with other demographic variables like gender, birth weight, residence location, and education level. A significant difference was found between the frequency of reported upper respiratory tract infection (URTI) symptoms and serum vitamin D categories (p = .019). Using Binary Logistic Regression to identify possible predictors of categories vitamin D level, formula feeding during the first six months of feeding is a significant predictor of higher vitamin D levels (table 4) (ß=1.113 p=.003).

3.2.Bد Severity of Asthma and Vitamin D levels :

Concerning the severity of the presenting symptoms, our results show that 63.7% of patients experienced night waking due to their symptoms, while 36.3% found their symptoms affected daily activities. Of these patients, 71.6% claimed to improve after taking Salbutamol, 14.9% experienced no improvement, and 13.4% became worse. In addition to that, 24% of participants used inhaled Salbutamol more than three times per week (Table 3). Forty-eight children (23.9%) of the study population were admitted to PICU with acute asthma exacerbations. PICU admission was found to have a significant correlation with lower vitamin D levels (p=.011). Additionally, A significant difference was found between the frequency of Salbutamol usage and different vitamin D categories (p = .028). Another variable that we extrapolated was the number of admissions per year and the duration of hospital admissions; however, the average admission period demonstrated statistically insignificant differences (p=0.331).

Compared with the different categories of vitamin D levels, the number of admissions showed a significant difference (p=0.028) between the three categories of vitamin D serum levels. When examining the relationship between FEV1 measurements (pre-bronchodilator use) and different vitamin D categories, there was no statistical difference between the groups (p=0.535). However, post-hoc analysis demonstrates that participants with sufficient vitamin D levels exhibit higher FEV1 values. No significant association between different vitamin D levels and other severity prediction variables such as night waking due to symptoms, the effect on daily activity, and clinical improvement after Salbutamol use

4. Discussion

The Prevalence of asthma and vitamin D deficiency has been on the rise worldwide (14). The body of literature demonstrates

that vitamin D engages in developing diseases associated with immune system dysfunction and/ or inflammatory dysregulation (15,16). The role of vitamin D in these complex etiologies lies in its ability to regulate gene transcription entangled in the inflammatory process of the respiratory epithelium and the presence of its receptors on immune cells (9). Since asthma is a chronic respiratory disease characterized by eosinophilic airway inflammation and enhanced activity of immune cells, it is proposed that vitamin D plays a role in the development and prognosis of asthma. Thus, it influences its clinical picture and impacts its treatment outcomes. Our study investigated the clinical characteristics of asthmatic patients and whether different vitamin D categories impacted these characteristics.

The study's results demonstrate that asthmatic children's mean serum vitamin D level is 22.8 ng/ml. This indicates a general trend of vitamin D insufficiency across the entire sample. However, this level of vitamin D is higher than what was reported by previous studies in Jordan, as they have reported a 7.8 ng/ml age-adjusted mean vitamin D level among asthmatic children in Northern Jordan (17). Such a dramatic difference could be attributed to the moderate rates of vitamin D supplementation (67.2%) reported by our sample or the changes in JUH's management guidelines characterized by an increase of vitamin D prescriptions. Nonetheless, our results are higher than that of the comparative literature in the region (10,14,18,19).

Among asthmatic children, 51.8% were vitamin D deficient, 26.6% were vitamin D insufficient, and 21.6% were vitamin D sufficient. The high prevalence of vitamin D deficiency in asthmatic children can be attributed to the changing lifestyles as more children spend more time indoors, which impacts their share of sunlight exposure (20). Moreover, this reasoning is backed by the fact that 81.1% of the study's population reside in urban and industrialized sites, where reported high asthma prevalence rates (21). Reports show that outdoor exposure affects vitamin D levels and that asthmatic children tend to be less physically active and more prone to staying indoors to avoid asthma-related environmental triggers (22).

Our analysis demonstrates a significant association between feeding status at sixth month and the different categories of vitamin D ($p = 0.039$). Logistic regression shows that formula feeding during the initial six months of feeding is a positive predictor of vitamin D levels ($ß=1.113$, $p=.003$). This can be classified as a side effect of exclusive breastfeeding since there are modest vitamin D levels in breast milk, which calls for interventions in the form of parent awareness campaigns and vitamin D supplementation for such populace if identified early (23).

Our findings illustrate that PICU admissions and Salbutamol usage frequency were significantly associated with the varying categories of vitamin D ($p = 0.011$, $p = 0.028$), respectively. The fact that vitamin D deficient asthmatics are more likely to have a history of PICU admissions and increased frequency of Salbutamol usage later in life indicates that vitamin D deficiency influences the initial presentation and prognosis of asthma very early stage. Furthermore, statistical analysis found a meaningful difference in the number of hospital admissions among different asthmatics with varying vitamin D levels ($p=.028$). The association between lower serum vitamin D levels and more severe asthma exacerbations has been confirmed in previous reports. 25-OH vitamin D deficiency was reported to be

associated with a higher rate of severe exacerbations in children with asthma in a Childhood Asthma Management Program (CAMP) (24). This relationship was supported by several other reports (25, 26). Several mechanisms have been postulated in the literature to explain the association between vitamin D deficiency with severe asthma exacerbations; first, vitamin D has an essential role as an immune-system modulator and is believed to correlate with pediatric asthma (27). Second, vitamin D deficiency may impede patients' response with asthma to steroid therapy, and a synergistic effect of vitamin D and corticosteroids in asthma outcomes was reported (28). A final and equally important mechanism we explored is the association between vitamin D deficiency and upper respiratory tract infections, a leading trigger for asthma exacerbations (29,30).In our study, the presence of URTI at presentation correlated with lower vitamin D levels. This finding relates to a previous report that suggests that vitamin D has a protective effect against viral infections and asthma exacerbations in children (31). However, the literature is already in conflict regarding such issues. Some studies report a relationship between vitamin D levels with the number of asthma attacks and usage of health services. In contrast, others fail to replicate similar results (32,33). The lack of association could be due to the disease's heterogenicity and the different mechanisms involved in the development of pediatric asthma other than atopy or vitamin D deficiency.

Despite the mixed reports for the association between vitamin D with epidemiology and prognosis of asthma, multiple studies demonstrate the benefits of vitamin D supplementation. Such effects include better asthma control, reduced admissions, improved lung function, reduced rate of treatment failure, and decreased asthma exacerbations rates (34–37). Since additive vitamin D to food failed to eliminate vitamin D deficiency, more efforts need to be done to alter the guidelines in terms of vitamin D doses, recommended sunlight exposure, and duration of exposure (32,37)

Our study has several limitations. The first is the relatively small sample size, which hindered our ability to detect high statistical power associations. The study was conducted in a single center, which might have resulted in a sample not representative of Jordanian Asthmatic children. Furthermore, the study could not evaluate factors associated with vitamin D levels aside from crude supplementation (diet, sun exposure, and clothing). Finally, no control subjects were included to confirm the increase in the Prevalence of vitamin D deficiency in asthmatic children compared to non-asthmatics.

5. Conclusion

Our study showed that vitamin D deficiency was highly prevalent in asthmatic patients as more than half of the patients had deficient vitamin D levels. Vitamin D deficiency correlated with the severity of asthma in children reflected by more PICU admissions and more frequent hospital admissions. Future prospective studies in Jordan are encouraged to investigate the correlation between vitamin D level and the development of bronchial asthma and its severity and study the effect of vitamin D supplementation in asthma control and its progression into later childhood and adulthood. Given these ramifications, asthma management guidelines need to be altered to address low vitamin D levels as early as possible.

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Tables

Table 1: Demographic profile of participants

Item		Mean (SD)	N (%)	P-Value
Age		7.3 ± 3.8		**<0.001**
Weight (kgs)		27.8 ± 14.8		—
Height (cm)		120.4 ± 26.2		—
Gender	Male		148 (73.6)	0.295
	Female		53 (26.4)	
Residence	Urban		163 (81.5)	0.077
	Rural		37 (18.5)	
Parents' education	High school Degree		59 (30.4)	0.711
	University Degree		135 (69.6)	

Table 2: Correlation between clinical and laboratory characteristics of participants with vitamin D level *

Item		N (%)	mean ± SD	P-Value
Age at diagnosis (in years)			3.6 ± 3.0	0.235
Admissions in the last calendar year			1.8 ± 2.7	**0.028**
Average duration admission (in days)			2.9 ± 3.7	0.331
Birth weight (in Kgs)			2.9 ± .7	0.528
Preliminary Diagnoses	Allergic Bronchitis	1 (.5)		—
	Allergic Rhinitis	2 (1)		—
	Asthma	99 (49.3)		—
	Bronchiolitis	1 (.5)		—
	Reactive Airway Disease	97 (48.3)		—
	Seasonal Atopy	1 (.5)		—

Item		N (%)	mean ± SD	P-Value
Family history of asthma		106 (52.7)		0.838
Personal history of atopic condition		78 (38.8)		0.740
Use of steroids		183 (91)		0.763
PICU admission		48 (23.9)		**0.011**
Feeding status during the first 6 months	Breastfeeding	103 (51.2)		**0.039**
	Formula	37 (18.4)		
	Mixed	61 (30.3)		
Symptoms at presentation	Cough	153 (76.1)		0.136
	Wheeze	96 (47.8)		0.791
	Shortness of Breath	47 (23.4)		0.953
	Fever	18 (9.0)		0.755
	Upper Respiratory Tract Infections	17 (8.5)		**0.019**
	Headache	1 (.5)		0.626
Laboratory work up	WBC (103/µL)		9.3 ± 3.1	**0.024**
	Vitamin D (ng/ml)		22.8 ± 16.0	—
	FEV 1 (pre-bronchodilator use) (L)		1.7 ± .7	0.535

*Correlation was performed by Chi-square test . P-Value < 0.05 was considered statistically significant.

Table 3: Correlation between Severity variables responses and vitamin D level*:

Item.		No.	%	P-Value
Night waking due to symptoms	Yes	73	36.3	0.931
	No	128	63.7	
	Total	**201**	**100**	
Effect on daily activities	Yes	128	63.7	0.931
	No	73	36.3	
	Total	**201**	**100**	
Clinical improvement	Improved	30	14.9	0.476
	Remained the same	144	71.6	
	Worsened	27	13.4	
	Total	**201**	**100**	
Salbutamol usage frequency	<1/week	72	35.8	**0.028**
	>3/week	48	23.9	

Item.		No.	%	P-Value
	0/week	32	15.9	
	1/week	34	16.9	
	2/week	15	7.5	
	Total	**201**	**100**	

***Correlation was performed by Chi-square test . P-Value < 0.05 was considered statistically significant.**

Table 4: Predictors of low vitamin D levels by Binary Logistic Regression :

Independent Variable		Beta Coefficient	P-value	Odds Ratio	95% Confidence Interval	
					Lower	Upper
Gender		.124	.740	1.131	.545	2.348
Urban Residence		-.668	0.129	.513	.217	1.213
BMI		.006	.839	1.006	.951	1.064
Birth Weight		.015	.954	1.015	.604	1.706
Use of Steroids		.211	.735	1.234	.545	2.348
Vitamin D Supplementation		.303	.391	1.354	.678	2.704
History of Atopic Diseases		.094	.789	1.098	.554	2.704
Family History of Atopic Diseases		-.148	.658	.863	.544	1.658
Feeding status for the first 6 months	**Mixed**	.556	.225	1.761	.706	4.396
	Formula	1.113	**.003**	3.042	1.444	6.410
PICU Admission		-.523	.253	.593	.242	1.452
Admissions in the Last Calendar Year		0.072	.313	1.075	.217	1.213
Duration of Admissions		-.012	.819	.988	.894	1.093
Age at Diagnosis		-.047	.420	.954	.852	1.069

Figures

Figure 1:

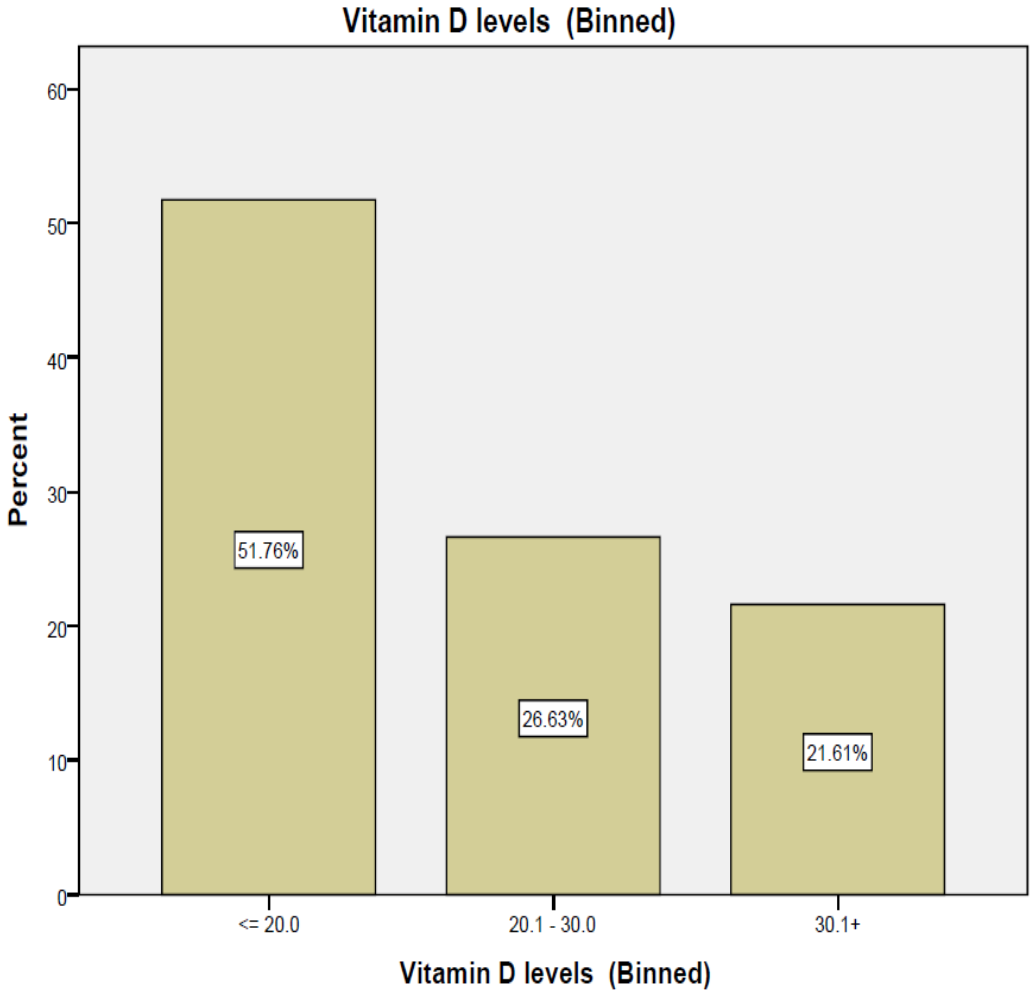

Figure 1. Distribution of children with asthma (n=201) categorized according to serum 25-OH vitamin D levels. Deficiency, <20 ng/ml; insufficiency,20–29 ng/ml; sufficiency, >30 ng/ml.

الخصائص السريرية للأطفال المصابين بالربو ونقص فيتامين (د) في مستشفى الجامعة الأردنية: (دراسة مرجعية)

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الملخص

الخلفية والأهداف: الربو القصبي هو أكثر الحالات المزمنة شيوعًا بين الأطفال حول العالم، وتشير الأدلة المتزايدة إلى وجود ارتباط بين نقص فيتامين (د) والربو، وتهدف هذه الدراسة إلى تقييم مدى انتشار نقص فيتامين (د) لدى الأطفال المصابين بالربو القصبي في مستشفى الجامعة الأردنية والى فحص الخصائص السريرية لمرضى الربو المدخلين بالدراسة وفحص الارتباط بين مستويات فيتامين (د) وشدة الربو والتحكم فيه.
المنهجية: أجريت هذه الدراسة الرجعية على 201 طفل مصاب بالربو تتراوح أعمارهم بين 1 و18 سنة، والذين تلقوا رعاية طبية في مستشفى الجامعة الأردنية من 2015 إلى 2018. وتم تسجيل مستويات فيتامين (د) لجميع الأطفال المشمولين بالدراسة. وتم جمع الخصائص الديموغرافية والسريرية للمرضى مثل مؤشر كتلة الجسم، وحالة التغذية، واختبار وظائف الرئة والدخول إلى العناية المركزة للأطفال، وتمت مقارنة الخصائص الديموغرافية والسريرية بين ثلاث فئات من مستويات فيتامين (د) وتم تقييم الارتباط بين شدة الربو ومستوى فيتامين (د). **النتائج:** من بين 201 مشاركًا شملتهم الدراسة، كان 51.7٪ يعانون من نقص حاد في فيتامين (د)، و26.6٪ لديهم مستوى غير كافٍ، و 21.6٪ لديهم مستوى كافٍ (طبيعي) من فيتامين (د). وكان للمتغيرات التالية ارتباطات كبيرة مع مستويات فيتامين (د): التكرار لاستخدام السالبوتامول المستنشق (p= .028)، والدخول إلى وحدة العناية المركزة للأطفال (p= .011) وحالة التغذية في الست شهور الأولى من العمر (p= .039) . **الاستنتاج:** نقص فيتامين (د) منتشر في الأطفال المصابين بالربو ويرتبط بشدة الربو والسيطرة عليه في اللأطفال المصابين بالربو المشمولين بالدراسة، وتشجيع مقدمي الرعاية الصحية للأطفال المصابين بالربو من خلال نتائجنا إلى أن يعملوا على تقييم مستويات فيتامين (د) عند هؤلاء المرضى.

الكلمات الدالة: الربو، الأطفال، الأردن، طب الأطفال، فيتامين د.