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ORIGINAL ARTICLE

Relationship between Severity of Asthma Attacks and Vitamin D Levels in Children

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Background: Asthma is the most common chronic disease in childhood. The increased prevalence of asthma has led to extensive research on its mechanism. Vitamin D is one of the factors believed to be effective in asthma. The present study was conducted to investigate the relationship between the frequency and severity of asthma attacks and Vitamin D levels in children. **Materials and Methods:** The study population consisted of children with asthma aged 5–12 years. Three-milliliter blood samples were taken from the patients and their serum Vitamin D levels were measured using electrochemiluminescence. Data were analyzed using descriptive statistics, including frequency distribution tables and mean and standard deviation. **Results:** Thirty children were enrolled in the study. None of the children had any history of Vitamin D supplementation. There were no differences between the children with mild and moderate asthma in terms of the demographic variables. There were no significant relationships between the severity of asthma and blood and biochemistry factors. Serum Vitamin D levels were 59.8 ng/ml in the patients with mild asthma and 42.8 ng/ml in those with moderate asthma ($P < 0.05$). Vitamin D levels had a negative correlation with the severity of asthma. **Conclusion:** The findings showed that lower levels of Vitamin D increase the severity of asthma. Vitamin D levels should, therefore, be consistently monitored in patients with asthma.

Key words: Children, Vitamin D, asthma

INTRODUCTION

Asthma is one of the common respiratory diseases of childhood.[1] Asthma is a form of severe allergic reaction caused by specific immunological reactions to allergens.[2] This disease is caused by the temporary obstruction of air flow due to chronic inflammation of the airways.[3] According to studies, the incidence of allergic diseases has been increasing worldwide, especially in industrialized countries due to the changes in lifestyle from rural to urban.[4-6] From the 1970s, this increase has become quite evident in developed countries, with the annual prevalence of asthma being 5%–7%. In Iran, the prevalence of asthma is 5%–15%. In other words, about six million people in Iran are asthmatic.[7] Asthma is one of the most common atopic diseases in childhood[8] and the main reason for children's referral to the emergency department and hospitalization.[9] The prevalence of asthma is twice higher in children than adults.[8] The incidence of childhood asthma is currently growing and was about 8% in 2001, and the percentage of people with asthma reached 9.6% in 2009, and the same trend continues. The Centers for Diseases Control and Prevention predicts that there will be more than 400 million people with asthma worldwide by the year 2025.[10]

The immune pathogenesis of asthma is the production of high levels of immunoglobulin (Ig) E via B lymphocytes. This antibody is inserted into mast cells and basophils by binding to specific Fcε receptors. After encounter with allergens, these cells become activated and cause the release of inflammatory mediators.[11]

Some studies have shown a relationship between Vitamin D and asthma and low Vitamin D levels have been linked to

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the impairment of immunity.[12] Vitamin D is supplied from two sources: sunlight and food. The ultraviolet component of sunlight causes the formation of Vitamin D precursors in the skin, and this process is completed in the liver (where it results in the production of 25-hydroxy Vitamin D) and the precursors are then converted to the active form (1,25 dihydroxyvitamin D) in the kidney.[13] Vitamin D, in its active form, plays a role in the regulation of inherent and acquired immune responses by contributing to the inhibition of the T-cell proliferation and the reduction of TH1 cytokines such as interleukin (IL)-2 and interferon γ.[14] The effects of Vitamin D on TH2 responses is controversial, as some studies have shown its role in IL-4 inhibition, while others have reported IL regulation by Vitamin D.[15] This vitamin also leads to the inhibition of TH17 by the induction of IL-17. The effect of Vitamin D on the regulatory T-cells and IL-10, which suppresses TH2 responses, can explain the beneficial effects of Vitamin D on asthma.[16] There is little information about the Vitamin D levels of asthmatic patients and also the risk factors of Vitamin D deficiency in Asia, especially in children.[17] The present study was therefore conducted to investigate the relationship between Vitamin D levels and asthma control in Iranian children.

MATERIALS AND METHODS

The present comparative observational study was approved by the Ethics Committee of Najafabad University of Medical Sciences. Approval number: 15010101892004 & Approval Date:08/09/2011. The study population consisted of children with asthma aged 5–12 years. Informed written consent was obtained from the participants. The children were included in the study after the confirmation of their disease by an allergy specialist or pediatric pulmonologist. A total of 33 children with asthma aged 5–12 years were selected as the study participants. Three milliliters of venous blood was taken from each patient and their serum Vitamin D level was tested in a medical laboratory using Electrochemiluminescence (ECLIA). According to the ECLIA protocol, a Vitamin D concentration <10 ng/ml indicates a severe deficiency, 10–30 ng/ml indicates deficiency, 30–100 ng/ml normal levels, and higher than 100 ng/ml indicates toxic levels. A two-part questionnaire was also administered in the patients. The first part evaluated factors such as habitat, exposure to sunlight, diet, and the amount of Vitamin D supplementation. The second part was based on a standard questionnaire examining the severity of asthma, the frequency of attacks, and the dose and route of medication administration. Table 1 presents the definitions of asthma severity. In this stage, three of the participants were excluded from the study due to their failure to complete the entire questionnaire and the sample size was reduced to 30 children.

Table 1: Asthma exacerbation severity

	Mild	Moderate
Dyspnea	Walking	Talking
Talks in	Sentences	Phrases
Alertness	May be agitated	Usually agitated
Respiratory rate	Increased	Increased
Accessory muscle	Usually not	Usually
Wheezing	Moderate	Loud
Pulse rate	<100	100-120
Paradoxical pulse (mmHg)	Absent	10-20
PEFR (%)	≥70	40-69
PaO_2 (mmHg)	Normal	≥60
Pco_2 (mmHg)	<42	<42
02sat	>95%	90%-95%

PEFR=Peak expiratory flow rate

Statistical analysis

SPSS software (version 22; SPSS Inc., Chicago, Ill., USA) was used for the analysis of the data. According to the results of the Kolmogorov–Smirnov test, which indicates the abnormality of the data distribution, Mann–Whitney's test was used to compare the mean of continuous data between the two groups (severity of asthma), and the Chi-square test and Fisher's exact test were used to compare the frequency distribution of qualitative data among the two groups (severity of asthma), and Spearman's correlation coefficient was used to evaluate the relationship between the variables. In all the analyses, the significance level was considered <0.05.

RESULTS

Of the 30 children with respiratory allergic diseases and asthma, 15 (30%) were boys and 15 (30%) were girls, and their mean age was 7.05 ± 3.11 years.

The distribution of the number of days in the week during which the children were exposed to sunlight was as follows:

Two patients (6.7%) had the lowest possible exposure, two (6.7%) were exposed to sunlight 3 days a week, two (6.7%) were exposed 5 days a week, ten (33.3%) were exposed 6 days a week, and 14 (46.7%) were exposed to sunlight every day. The maximum number of exposure days in a week was seven and the average was 5.8. In terms of the frequency distribution of the total hours of exposure per week, two patients had the lowest possible exposure to sunlight, 11 had one to 3 h of exposure per week, ten patients had four to 6 h, five had 7–9 h, and two were exposed to sunlight more than 10 h per week. The average duration of exposure to sunlight was 4.8 ± 2.9 h/week.

As for the frequency distribution of the consumption of oral corticosteroids, ten patients (33.3%) had consumed these

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drugs for 1–10 days, two patients (6.7%) for 11–20 days, and one patient (3.3%) for more than 20 days; 17 patients (56.7%) did not report a history of corticosteroid use. As for the route of corticosteroid administration, 21 patients (70%) had not received it through injections, while 8 (26.7%) and 1 (3.3%) patients had a received corticosteroid injection 1 day/year and 2 days/year, respectively. As for corticosteroid sprays, 12 of the 30 patients (40%) had used corticosteroid sprays 1 to 20 days/year, four (13.3%) had used sprays for 21–50 days/year, and six (20%) had used sprays more than 50 days/year. Eight patients (26.7%) had not used corticosteroid sprays. The distribution of the number of days of oral corticosteroid use over the past year based on the severity of asthma showed that the differences were not statistically significant between the patients ($P = 0.578$); therefore, the number of days of oral corticosteroid use per year did not have any effects on the severity of asthma [Table 2].

Moreover, the frequency distribution of the number of injectable corticosteroids during the past year based on the severity of asthma was statistically significant ($P = 0.040$), indicating that the number of injectable corticosteroids per day negatively affects the severity of asthma. The frequency distribution of the number of days of spray corticosteroid use over the past year was also statistically significant ($P = 0.026$), indicating that the dose of corticosteroid spray per day negatively affects the severity of asthma [Table 2].

Table 2: Baseline characteristics based on the severity of asthma

Variable	Mild (*n*=17) (%)	Moderate (*n*=13) (%)	*P*
Gender			
Male	9 (52.9)	5 (38.5)	0.462
Female	8 (47.1)	8 (61.5)	
Age (year)			
5-8	13 (76.5)	11 (84.6)	0.672
>8	4 (23.5)	2 (15.4)	
Oral corticosteroid intake (days)			
0	11 (64.7)	6 (46.2)	0.578
1-10	5 (29.4)	5 (38.4)	
11-20	1 (5.9)	1 (7.7)	
>20	0 (0)	1 (7.7)	
Corticosteroid injection (days)			
0	15 (88.2)	6 (46.2)	0.040
1	2 (11.8)	6 (46.2)	
2	0 (0)	1 (7.6)	
Corticosteroid spray (days)			
0	6 (35.2)	2 (15.4)	0.026
1-20	8 (47.1)	4 (30.8)	
21-50	2 (11.8)	2 (15.4)	
>50	1 (5.9)	5 (38.4)	

As for the history of Vitamin D intake, none of the children used Vitamin D supplements.

As for respiratory disorders, 14 of the 30 patients (46.7%) had a history of hospitalization and 16 (53.3%) had no such history. Nine (30%) of patients had never had respiratory attacks, 14 (46.7%) had had less than five attacks, and seven (23.3%) had had five or more attacks.

In terms of the distribution of asthma severity in the study population, 17 patients (56.7%) had mild and 13 (43.3%) had moderate asthma.

Regarding the relationship between Vitamin D levels and asthma severity, the mean Vitamin D level was 59.8 ± 18 ng/ml in those with mild asthma and 42.8 ± 18.5 ng/ml in those with moderate asthma, suggesting a statistically significant difference ($P = 0.02$) and indicated that Vitamin D levels are higher in children with mild asthma.

As for the relationship between gender and the severity of asthma in the patients, the present findings showed that nine (52.9%) of the patients with mild asthma were male and eight (47.1%) were female. In those with moderate asthma, five (38.5%) were male and eight (61.5%) were female, which indicates that gender has no effects on the severity of asthma ($P = 0.462$).

As for the relationship between age and the severity of asthma, 13 patients with mild asthma were in the age group of 5–8 years with a frequency of 76.5% and four patients with mild asthma (23.5%) were in the age group of 8–12 years old. As for moderate asthma, 11 patients (84.6%) were in the age group of 5–8 years and two (15.4%) in the age group of 8–12 years ($P = 0.672$).

As for the relationship between exposure to sunlight over 1 week and the severity of asthma, the present findings showed that children with mild asthma had 5.5 ± 2.4 days of exposure on average, while the children with moderate asthma had an average of 6.3 ± 0.8 days, which do not suggest a statistically significant difference ($P = 0.24$) and suggests that the number of days of exposure to sunlight has no effects on the severity of asthma.

As for the relationship between the duration of exposure to sunlight over 1 week and the severity of asthma, the patients with mild asthma had an average exposure duration of 4.1 ± 3.1 h/week and those with moderate asthma had an average of 5.2 ± 2.5 h/week. This difference was not statistically significant ($P = 0.35$), which indicates that the number of hours of exposure to sunlight does not affect the severity of asthma.

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Regarding the relationship between the number of respiratory attacks leading inactivity in the mild asthma group, seven patients (41.2%) had had no respiratory attacks, nine (52.9%) had had less than five attacks, and one (5.9%) had had five or more attacks. In the moderate asthma group, five patients (38.4%) had experienced less than five respiratory attacks and eight (61.6%) had experienced five or more attacks. This difference was statistically significant ($P = 0.001$), which shows that the number of respiratory attacks is correlated with the severity of asthma. Table 3 presents the respiratory drugs used by the patients. As for the relationship between hemoglobin (Hb) levels and the severity of asthma, the present findings have shown a mean Hb of 13.7 ± 1.2 g/L in the mild asthmatic group and 13.2 ± 1.2 g/L in the moderate asthmatic group. This difference was not statistically significant ($P = 0.19$).

The mean white blood cell (WBC) count was 8900/mL in the mild asthmatic group and 9400/mL in the moderate asthmatic group. The difference was not statistically significant ($P = 0.6$).

As for the relationship between polymorphonuclear cells (PMNs) and the severity of asthma, the results showed a mean PMN ratio of 49.3% ± 12.9% in the mild asthmatic group and 54.8% ± 17.6% in the moderate asthmatic group. The difference was not statistically significant ($P = 0.4$).

The results showed a mean platelet (Plt) count of 269,200/mL in the mild asthmatic group and 260,700/mL in the moderate asthmatic group ($P = 0.7$).

As for the relationship between serum calcium (Ca) and phosphorus (Ph) and the severity of asthma, the present findings showed mean Ca and Ph levels of 9.1 and 4.5 in the mild asthmatic group and Ca and Ph levels of 9.1 and 4.6 in the moderate asthmatic group. The difference was not statistically significant ($P = 0.96$ and $P = 0.7$ for Ca and Ph, respectively).

The median of alkaline phosphatase (ALP) level was 562.3 ± 236 in the mild asthmatic group and the mean Alk level was 701.2 ± 286 in the moderate asthmatic group ($P = 0.2$).

As for the relationship between serum zinc level and the severity of asthma, the present findings showed a mean zinc level of 99.4 ± 30.4 in the mild asthmatic group and 93.9 ± 16.1 in the moderate asthmatic group. The difference was not statistically significant ($P = 0.22$), indicating that the severity of asthma does not affect serum zinc level in asthma patients.

Regarding the correlation between Vitamin D levels in asthma patients and gender, the male patients had a mean level of 55.3 ± 21.5 ng/ml and the females a mean of 49.7 ± 17.2 ng/ml, which do not make for a statistically significant difference ($P = 0.22$) and shows that the gender of the patients did not affect their Vitamin D levels. In addition, Vitamin D was not significantly correlated with other factors such as age, gender, corticosteroid, Hb, WBC, PMN, Plt, Ca, Ph, Alk, and zinc [Table 4].

DISCUSSION

Asthma is a common problem that afflicts more than a million people in the world. Chronic asthma is a chronic respiratory tract disease causing increased wheezing, shortness of breath, heavy chest sensation, and coughing, especially at night or early in the morning.[18] Vitamin D deficiency was first reported around 300 years ago in people who had migrated to industrial centers and were deprived of the sun; in developing

Table 3: The distribution of the respiratory drugs used by the patients

Respiratory drug	Frequency (%)
None	5 (16.8)
Salbutamol spray	6 (20)
Oral salbutamol	1 (3.3)
Theophylline G + salbutamol spray	1 (3.3)
Salbutamol spray + oral salbutamol	1 (3.3)
Salbutamol spray + other drugs	12 (40)
Theophylline G + salbutamol spray + oral salbutamol	1 (3.3)
Theophylline G + salbutamol spray + other drugs	2 (6.7)
Theophylline G + salbutamol spray + oral salbutamol + other drugs	1 (3.3)

Table 4: The correlation coefficient between Vitamin D levels and the other variables

Variable	Correlation coefficient	P
Age	0.001	0.99
Days of exposure to sunlight	−0.15	0.43
Hours of exposure to sunlight	0.002	0.99
Oral corticosteroid intake (days)	−0.07	0.72
Corticosteroid injection (days)	−0.08	0.68
Corticosteroid spray (days)	−0.22	0.24
Number of respiratory attacks	−0.24	0.19
Hb	0.22	0.23
WBC	−0.11	0.54
PMN	0.14	0.5
Plt	−0.33	0.07
Ca	0.18	0.32
Ph	−0.06	0.76
ALP	−0.32	0.1
Zinc	−0.04	0.82

HB=Hemoglobin; WBC=White blood cell; PMN=Polymorphonuclear cells; Ca=calcium; Ph=phosphorus; Plt=platelet; ALP=Alkaline phosphatase

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countries, many instances of it were reported from the early 20th century.[19] In recent years, Vitamin D deficiency is believed to have been controlled, but recent studies suggest that new epidemics of Vitamin D deficiency have emerged worldwide.[20] About 1 billion people in the world are estimated to have Vitamin D deficiency.[19] Vitamin D deficiency is reported as an epidemic problem in most countries, even in areas with strong sunlight.[21]

Vitamin D regulates WBC proliferation and the expression of inflammatory cytokines through lymphocyte and macrophage receptors.[22] The Vitamin D receptor stimulates the expression of antimicrobial peptides in neutrophil epithelial cells and macrophages.[14] Vitamin D can, therefore, help reduce the risk of asthma by strengthening and modifying the immune system. In the present study, the mean concentration of Vitamin D was 59.8 ng/ml in mild asthma and 42.8 ng/ml in moderate asthma, which suggest a statistically significant difference ($P = 0.02$).

In a similar study, Gupta *et al*. examined the relationship between Vitamin D levels and the severity of airway disease in children with asthma and found that Vitamin D levels were linked to asthma severity and pulmonary function, and the use of Vitamin D supplements was proven effective in the management of treatment-resistant asthma.[23] The results reported by Hollams were similar to the present findings.[24] Vitamin D deficiency has been shown to be associated with more severe diseases in children with asthma and could apparently lead to severe asthma; however, if the deficiency is corrected, Vitamin D will play a protective role against the progression of asthma, and Vitamin D supplementation can, therefore, be the most effective treatment for severe asthma. In a study by Brehm *et al*., Vitamin D was found to have a low serum concentration in most severe asthmatic patients, which means that Vitamin D levels have been associated with the severity of asthma. One of the reasons that may have led to this conclusion is that children with severe asthma have less physical activity and exposure to sunlight, which can lead to a Vitamin D deficiency.[25]

A link has recently been identified between Vitamin D and allergic diseases such as asthma. Since Vitamin D is known to be a major moderator of immune system responses, one of its most important effects may be on atopic allergic responses by inducing regulatory T-cells and producing IL10. Vitamin D deficiency is also a risk factor for increases in the frequency and severity of allergic diseases. Some studies have investigated the relationship between Vitamin D and IgE levels. Brehm *et al*. demonstrated a relationship between IgE levels and Vitamin D and showed that there is an inverse relationship between Vitamin D levels and IgE production.[26]

In another study, Hyponnen showed a nonlinear relationship between serum Vitamin D levels and IgE. At concentrations of 30–120 nmol/L, Vitamin D produces little change in IgE levels, while at concentrations below 25 nmol/L and above 135 nmol/L, it causes a significant increase in IgE levels. These results suggest that both very low amounts and high amounts of Vitamin D can contribute to the intensification of allergic responses.[27]

The present study further showed that the use of corticosteroids have similar effects for the treatment of asthma in injectable and spray forms, but the oral use of corticosteroids is less effective. In addition, the injectable and spray forms are easier to use and more user-friendly. I, therefore, seems that oral corticosteroid therapy can be replaced with corticosteroid sprays and injections.[28]

Furthermore, Vitamin D deficiency leads to disorders in the metabolism of Ca and Ph. In cases of Vitamin D deficiency, the intestinal absorption of Ca is reduced and hypocalcemia is induced, which can increase the parathyroid hormone. In these conditions, called secondary hyperparathyroidism, Ca is removed from the bones in order to maintain normal serum Ca, which can lead to osteomalacia and exacerbated osteoporosis in adults.[29] In this study, Ca and Ph levels were also found to be low in asthma, with averages of 1.9 and 5.4, respectively. In patients with moderate asthma, the mean levels of Ca and Ph were estimated as 1.9 and 6.4, respectively. The present findings showed no correlation between Ca absorption and Ph and asthma intensity, which is similar to the results reported by Derakhshani and Hosseini.[30]

Regarding the level of Vitamin D based on gender, some studies have shown that Vitamin D levels are related to gender and the rate is lower in women;[17] however, some studies have not reported such findings. In a study by Hall and Agrawal Vitamin D deficiency potentially affected the inflammatory response in the airways in bronchial asthma.[31] In another study in 2016, the authors concluded that Vitamin D insufficiency was more frequent in asthmatic children compared to the controls and associated it with poor asthma control, as similar to the present findings.[32] More studies are required to define the optimal level of Vitamin D and its dosage and duration of supplementation.[33]

CONCLUSION

In the present study, the patients with mild asthma had higher Vitamin D levels compared to those with moderate asthma, and this difference was statistically significant. These findings suggest that Vitamin D deficiency may affect the inflammatory responses in the airways in asthmatic children. To conclude, a low Vitamin D level is associated with the severity of asthma.

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Conflicts of interest

There are no conflicts of interest.

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