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The role of vitamin D deficiency in environmental health and childhood asthma

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ABSTRACT

Asthma is the most common chronic childhood disease, and many of its risk factors have been identified. Although various studies on the link between vitamin D and asthma have been conducted, the role of vitamin D in the onset of asthma as an environmental health problem has not been well identified. This study aims to investigate the link between serum vitamin D level and asthma in children in Kashan, Iran. This case-control study was conducted on the asthmatic (n=99) and non-asthmatic (n=99) children. Asthma was monitored and examined using spirometry and by an allergy and asthma specialist. The patients were divided into three groups (mild, moderate, or severe) in terms of asthma severity. The age-matched children in the control group were selected from among non-asthmatic children. Serum vitamin D level was measured using radioimmunoassay (RIA) technique. **Results:** The mean serum vitamin D level of asthmatic children and the children in the control group was 14.76±14.19 ng/ml and 30.47±9.7 ng/ml, respectively ($p < 0.001$). The mean serum vitamin D level of the children with mild, moderate, and severe asthma was 17.6±14.2 ng/ml, 14.6±6.99 ng/ml, and 11.9±4.6 ng/ml, respectively, which was significantly less than the control group ($p < 0.001$). Serum vitamin D levels were not significantly different in terms of asthma severity. **Conclusion:** The results of this study showed that serum vitamin D level in asthmatic children is significantly less than in non-asthmatic children.

Keywords: vitamin D, Asthma, environmental health

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INTRODUCTION

Asthma is a complex inflammatory disease which results from the interaction of multiple genetic and environmental factors [1]. It is the most common childhood disease, affecting an estimated 300 million children worldwide. In the United States, more than 8 million children suffer from this disease [2]. The prevalence of asthma is different in various countries, and it increases as distance from the equator increases. In the studied populations, the prevalence of asthma has been reported to be 0.7 to 18.4% [3]. Despite many efforts to prevent asthma, the prevalence of this disease is increasing to the extent that in the United States, it has increased from 8.7% in 2001 to 9.6% in 2009 [4]. Previous studies have shown that genetic predisposition, allergen exposure and sensitivity, lifestyle, and exposure to environmental pollutants are among the risk factors for asthma [5-8]. It seems that other factors such as vitamin status can play a role in making children susceptible to asthma.

Vitamin D has been shown to have an immunomodulatory effect, playing a role in in regulating cell proliferation and differentiation [9-11]. Epidemiological studies are indicative of the epidemic of vitamin D deficiency worldwide [10, 11]. Some studies have shown that vitamin D deficiency is associated with the increased prevalence of asthma [12, 13]. Studies have also found that vitamin D deficiency increases asthma severity in children [14]. The proposed mechanisms for the link between vitamin D level and the risk of asthma are divided into prenatal (in the womb) and postnatal periods. It seems that vitamin D plays a role in developing the lungs during the embryonic period. A study on an animal model showed that vitamin D deficiency in pregnant mice decreases lung volumes, compared to the group with sufficient amount of vitamin D [15]. In postnatal period, vitamin D deficiency, which is caused by impaired lung development and increased susceptibility to respiratory infections, increases the risk of developing asthma [16-18].

Studies on the link between serum vitamin D level and childhood asthma have reported different and sometimes contradictory results [19, 20]. The difference in the results of the present study might be due to climatic and racial differences among patients. Since the results of studies are inconsistent and no studies on the link between serum vitamin D level and childhood asthma have been conducted in Kashan, Iran, this study aims to investigate the link between serum vitamin D level and asthma as an environmental health problem in children in Kashan.

MATERIALS AND METHODS

This case-control study was conducted on 198 children aged 5-15 living in Kashan, Iran. The study was conducted from March 2015 to May 2015. The samples of the case group were selected from among the children referring to the allergy and asthma clinic of Shahid Beheshti Hospital in Kashan, Iran to continue their treatment. Asthma diagnosis was confirmed using spirometry and by a pediatric allergy and asthma specialist, and at least 6 months had passed since the diagnosis. According to the results of Forced Expiratory Volume (FEV1), these children were divided into three groups in terms of asthma severity, namely mild (FEV1>80%), moderate (FEV1<80%), and severe (FEV1<60%). A total number of 33 children were selected

from each group using convenience sampling. To this end, all eligible children were included in the study until the required sample size for each group was achieved. The patients were excluded from the study if they suffered from metabolic bone disease, congenital disorders affecting vitamin D absorption, kidney failure, congenital gastrointestinal anatomical abnormalities, exocrine pancreatic insufficiency (EPI), and chronic liver disease.

The samples of the control group were selected from among the children referring to the health care centers of Kashan to receive routine health care. The samples were matched to the case group on age and sex. All the children of the control group were examined by a pediatric allergy and asthma specialist for asthma diagnosis, and then a peak flow meter was used to manage asthma. The children who were diagnosed with asthma based on the results of their physical examination or the readings on the peak flow meter were excluded from the study. The same exclusion criteria that were used for the case group were also applied to the children of the control group. Any children who did not meet any of the exclusion criteria was excluded from the study.

After children's parents were provided with the explanations about the objectives and how to carry out the study, their written consents were obtained. Then the checklist including demographic information (age, sex, and place of residence), economic status (median household income), parental education, duration of asthma, history of allergic diseases, height, weight, and body mass index (BMI) was filled out. To measure serum vitamin D level, 5 cc of venous blood was drawn from the cubital vein of all participants. All blood samples were centrifuged immediately after drawing the blood and inserting identification numbers. After separation, the serum was frozen at -20°C. After sampling was completed and the required sample size was obtained, the prepared serums were thawed and serum vitamin D level was measured using radioimmunoassay (RIA) technique and a commercial ELISA kit (DRG Instruments, Marburg, Germany). Serum levels less than 20 ng/mL, equal to 20-30 ng/mL, and greater than 30 ng/mL were considered vitamin D deficiency, insufficient vitamin D reserves, and normal, respectively.

The data of this study were analyzed using SPSS 18. Quantitative and qualitative results were reported as mean ± standard deviation (SD) and absolute and relative frequency, respectively. Data distribution was analyzed using the Kolmogorov-Smirnov test. The independent t-test, the Mann-Whitney U test, Pearson's chi-squared test, and Fisher's Least Significant Difference (LSD) post-hoc test were also used for data analysis. $P < 0.05$ was considered significant.

RESULTS

In this study, 198 children with the average age of 9.5±3.21 were investigated in two groups, namely case and control. The average age of the children in the case and control groups was 10.12±3.06 and 9.32±3.41, respectively. The mean duration of asthma for the children in the case group was 2.8±1.46 years. Demographic and clinical features of these children are shown in table 1.

The mean serum vitamin D level in asthmatic children and the children in the control group was 14.76±14.19 ng/mL and 30.47±9.7 ng/mL, respectively ($P < 0.001$). The frequency of vitamin D deficiency and insufficiency in the asthmatic children was 11.1% and 84.8%, respectively. The frequency of vitamin D deficiency and insufficiency in the children in the control group was 23.2% and 35.4%, respectively. Moreover, 4% of the asthmatic children and 41.4% of the children in the control group had a sufficient serum vitamin D level ($P < 0.001$).

Serum vitamin D concentration in the children with mild, moderate, and severe asthma was 17.66±14.2 ng/mL, 14.64±6.99 ng/mL, and 11.98±4.65 ng/mL, respectively. The comparison of the mean serum vitamin D level at various asthma severities using Fisher's Least Significant Difference (LSD) post-hoc test showed that although serum vitamin D level decreases as asthma severity increases, the difference between the two groups is not statistically significant.

DISCUSSION

This study was designed and carried out to investigate the link between serum vitamin D level and asthma in children. In this study, 198 children were divided into four groups (non-asthmatic, mild asthma, moderate asthma, and severe asthma) and investigated in

Table 1. Demographic and clinical characteristics

Characteristics	Group		P value
	Case, (n=99)	Control, (n=99)	
Gender [a]			0.46
Male	60 (60.6)	65 (65.7)	
Female	39 (39.4)	34 (34.3)	
Place [a]			0.45
City	84 (84.4)	80 (80.8)	
Village	15 (15.2)	19 (19.2)	
Economic Status [a]			0.01
High	54 (54.5)	72 (72.7)	
Middle	36 (36.4)	17 (17.2)	
Poor	9 (9.1)	10 (10.1)	
Maternal education [a]			0.47
Illiterate	23 (23.2)	20 (20.2)	
Primary School	24 (24.2)	15 (15.2)	
Secondary School	20 (20.2)	25 (25.3)	
High School	16 (16.2)	20 (20.2)	
University	16 (16.2)	19 (19.2)	
Allergy History [a]			0.12
No	47 (47.5)	58 (58.6)	
Yes	52 (52.5)	41 (41.4)	
Body Mass Index [b]	19.43±4.9	17.97±3.51	0.06

[a] Values presented as No (%)

[b] Value presented as mean±Standard Deviation

terms of serum vitamin D level. The results showed that serum vitamin D level in asthmatic children is significantly less than in non-asthmatic children.

Various studies in this regard have been conducted in different parts of the world. A study by Brehm et al. on 616 children in Costa Rica showed that about 28% of asthmatic children suffer from decreased levels of vitamin D, and serum vitamin D level in these children is inversely related to asthma severity, serum IgE level, and number of eosinophils [11]. In a study by Al-Yasin et al. (2011) in Shiraz, 50 asthmatic and 50 non-asthmatic children were investigated in terms of serum vitamin D level. The results of their study showed that serum vitamin D level in asthmatic children was considerably less than in the children in the control group. The prevalence of vitamin D deficiency (serum levels less than 30 ng/mL) in asthmatic and non-asthmatic children was 16% and 4%, respectively [21]. Gupta et al. conducted a study on 86 British children and found that vitamin D level in normal (non-asthmatic) children was significantly greater than in asthmatic children. They also found that serum vitamin D level in children significantly decreases as asthma severity increases [22]. The results of several other separate studies have also been similar to those of the present study and aforementioned studies [16, 19, 23].

Several clinical trials have investigated the effect of administrating different doses of vitamin D on the function of respiratory tract and level of asthma control in children. Arshi et al. conducted a study on 130 asthmatic children in Tehran for 24 weeks. They investigated the effect of administrating an initial dose of 100.000 IU of vitamin D and a weekly dose of 50.000 IU of vitamin D. They found that the FEV1 in the children receiving vitamin D was significantly better than in the children in control group during the last week of the study [25]. In another clinical trial, Baris et al. investigated 50 asthmatic children. In their study, in addition to immunotherapy, all the children of one group were administered 650 IU of oral vitamin D daily. The children were examined 6 and 12 months after treatment. The results of their study showed that asthma symptoms in the group receiving vitamin D were significantly less severe than in other groups [26]. The same results were also observed in a study by Lewis et al. [27].

The link between Asthma and vitamin D can be studied from different perspectives. The effect of vitamin D on the growth and development of the respiratory system during the embryonic period is worth being studied. Various studies have shown that administration of vitamin D supplements during pregnancy can improve lung function and decrease the prevalence of asthma in children [28-30]. Although the effect of vitamin D on improving lung function has been recognized, how vitamin D is involved in the maturation of the respiratory system during the embryonic period is not well recognized. It has been observed that vitamin D stimulates DNA synthesis in alveolar type-II cells and enhances lung maturation [31]. However, another study has shown that vitamin D is not well coordinated with surfactant protein gene expression in alveolar type-II cells [32].

Respiratory tract infections are one of the leading causes of asthma exacerbation in children and adults. Moreover, these infections are believed to be the cause of asthma [33, 34]. Studies have shown that vitamin D deficiency is associated with increased risk of respiratory tract infections. For example, after modifying seasonal and demographic factors, Monlezun et al. found that vitamin D deficiency is associated with a 58% greater risk of developing respiratory tract infections [35]. Lower respiratory tract infection (LRTI) was also more common among infants with vitamin D deficiency [36, 37].

The protective role of vitamin D against damage caused by lipopolysaccharides (endotoxins) is another possible mechanism for the anti-asthma effect of vitamin D. Exposure to endotoxins is one of the risk factors for asthma. Although studies have shown that vitamin D can reduce the damage caused by endotoxin injection in birds [38]. However, it is not clear how vitamin D exerts its functions against inhaled endotoxins.

Increased levels of inflammatory cytokines such as interleukin-17 (IL-17), interleukin-23 (IL-23), and interleukin-10 (IL-10) as well as T helper 17 (Th17) cells have been observed in most allergic diseases such as asthma and atopic eczema [39]. Th17 often exerts its functions through IL-17; and this interleukin induces the expression of pro-inflammatory cytokines and chemokines and causes infiltration and tissue damage. IL-23 induces the production of IL-17, exerting its role in the inflammation [40, 41]. It has been observed that serum IL-17 level is associated with asthma severity, and asthma control reduces as IL-17 increases [42, 43]. In animal models, administration of vitamin D has significantly decreased the production of IL-17 [44]. Moreover, this treatment severely inhibits the production of IL-23. As the production of these two interleukins is inhibited, the active inflammation subsides [45], which can finally reduce asthma severity or prevent asthma.

CONCLUSION

The results of this study showed that serum vitamin D level in asthmatic children is significantly less than in non-asthmatic children.

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Conflict of Interest
The authors have no conflict of interest to disclose.

Authors' Contribution
Marzieh Heidarzadeh developed the study concept and design and the acquisition of data, interpretations of data, and drafting of the manuscript. Davood Ramezani nezhad, Amir Hossein Movahedian and Mansour Sayyah developed the protocol, analysis of data and drafting of the manuscript.

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