British Journal of Medicine & Medical Research
10(6): 1-10, 2015, Article no.BJMMR.19890
ISSN: 2231-0614

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Serum Vitamin D Concentration in Asthmatic Children and Its Association with Recovery Time from an Asthma Exacerbation

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AJ and KH designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author SZA managed the literature searches, analyses of the study, performed the spectroscopy analysis and author AC helped in sample collection, author SM managed the experimental process. Authors FA and HD helped in statistical analysis. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/19890
Editor(s):
(1) E. Umit Bagriacik, Department of Immunology, Gazi University, Turkey.
Reviewers:
(1) Anonymous, Istanbul University, Turkey.
(2) Gauri Mankekar, ENT, PD Hinduja Hospital, Mumbai, India.
(3) Maged Refaat, Immunology, Ain Shams University, Egypt.
Complete Peer review History: http://sciencedomain.org/review-history/10659

Original Research Article

Received 2nd July 2015
Accepted 25th July 2015
Published 23rd August 2015

ABSTRACT

Introduction: The relationship of vitamin D and asthma is known but the association between vitamin D and time required to recover from acute asthma exacerbation has not been studied.
Aims: To find an association between serum vitamin D levels and time required to recover from an asthma exacerbation (recovery days) in asthmatic children from age 5 to 15 years. And to find

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association of other risk factors of asthma on recovery days.
Study Design: It was a cross sectional study.
Place and Duration of Study: Department of Paediatrics, Qatar Hospital Orangi Town and Abbassi Shaheed Hospital, Karachi, between February 2012 to June 2014.
Methodology: We included 99 asthmatic children (60 male and 39 females; age range 5 to 15 years) at the time of an acute asthma exacerbation. Spirometry was done using Vitalograph (alpha) (UK). FEV1/FEVC ratio <80% was used to confirm acute asthma exacerbation. Serum vitamin D levels were measured by chemiluminescence method using Abbott's ARCHITECT clinical chemistry analyzer. Children were followed up for confirming recovery by spirometry. FEV1, FVC and FEV1/FVC ratio within the reference ranges (The Thoracic Society of Australia and New Zealand and Polgar) were taken as normal.
Results: Applying Poisson regression model it was found out that that there was no association between vitamin D levels and time to recover from asthma (*P* =.398). 28.6% (n=2) children showed early recovery when recovery days were associated with exposure to home environment (*P* =0.000).
Conclusions: Despite the fact that 95% of the subjects with asthma had either vitamin D deficiency or insufficiency but there was no significant association between vitamin D levels and the time required to recover from an asthma exacerbation. Further studies are needed to establish the role of vitamin D in asthma.

Keywords: Asthma; exacerbation; vitamin D; Children; FEV1; FVC; FEV1/FVC.

1. INTRODUCTION

Asthma is a disease that affects any age group [1]. According to Global Initiative for Asthma (GINA), asthma is defined as "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation." [2]. It is the most common chronic disease among the children [3]. The prevalence of asthma has been on the rise since 1960 and it is considered as an epidemic [4]. In 2004 Masoli et al. in collaboration with GINA made a report that tried to ascertain the global prevalence for asthma. According to that report 300 million people worldwide had asthma and it was expected to gain another 100 million people by the year 2025 [5]. It has a negative impact on the behavior and psychological development of the child [6]. It puts a great burden not only on the individual in the form of poor quality of life and use of financial resources but as well as society in the form of utilization of health services. It is estimated that about one fourth of the population develops asthma by the age of 40 years [3]. Lara et al., 2011 reported that In USA people with asthma missed 10.5 million days of school and 14.2 million days of work. Similarly there were 1.75 million hospital visits related to asthma and 456,000 hospitalizations due to asthma. In Pakistan the data on the prevalence of asthma is limited. Adeel et al., 2014 estimated the prevalence of asthma to be 10.2% in children from 3 to 13 years of age in a study done in Karachi, Pakistan [7]. Over the last few decades the deficiency and insufficiency of vitamin D has been recognized increasingly across the globe in general population. A number of diseases have been associated with lower vitamin D levels including allergic diseases like asthma and COPD [8]. Like asthma, deficiency of vitamin D is considered as an epidemic affecting about over a billion of world's population [9]. The level of vitamin D between 20–29 ng/mL is labeled as vitamin D insufficiency. Whereas, vitamin D levels ≤20 ng/mL is labeled as vitamin D deficiency. Several studies have reported that in USA and Europe more than 40% of the adult population of age more than 50 years is deficient in vitamin D. Whereas, in pre teen white girls it is about 48% [10]. The prevalence of vitamin D deficiency varies among the different countries of Europe, Asia and Middle East [11]. In Pakistan, the prevalence for vitamin D deficiency was 40% in children at national level [12]. An association between asthma and low vitamin D levels was put forward to explain the observation that both were common during winter and in areas where climate was temperate [13,14]. According to vitamin D hypothesis there is an inverse relationship between vitamin D levels and asthma risk and asthma severity. Several epidemiological studies have shown that severity of asthma, asthma control and lung functions are associated with decreased levels of vitamin D.

This however did not hold good in a recently published Vitamin D and asthma (VIDA) study where supplementation with vitamin D failed to show betterment in the control of asthma in adults [14]. So, despite these studies, the role of low levels of vitamin D in asthma, asthma morbidity and asthma control is unclear [15]. There are studies that correlate asthma severity, asthma frequency, asthma exacerbations, FEV1 and FEV1/FVC ratio to low vitamin D levels in children [16,17]. However, there are no studies so far that correlate vitamin D levels with time to recover from an acute asthma exacerbation in children.

2. OBJECTIVES

1. To assess the effect of Vitamin D levels on recovery days in asthma patients.
2. To find association of other risk factors of asthma on recovery days.
3. To find an association between type of asthma and recovery days.

3. METHODOLOGY

Asthmatic children (99), aged 5 to 15 years, diagnosed by a pediatrician on the basis of GINA guidelines who have had two or more asthma exacerbations (attacks) were included at the time of an acute exacerbation. Children who had any cardiovascular, renal or hepatic disease were excluded from the study. Also, those children who could not perform spirometry were excluded from the study. Detailed history was recorded and performa was filled after obtaining informed consent. Anthropometric measurements were taken. Complete physical examination was performed. Spirometry was done using Vitalograph (alpha) (UK) to establish an acute attack according to American Thoracic Society (ATS) guidelines year 2007. Each subject was informed about the procedure, instrument, its role and purpose of the study.

Researcher recorded all the spirometric readings and guided the subjects enthusiastically. The subject was asked to perform the test before actual recording. Once satisfied that subject was performing the test satisfactorily, readings were recorded. FEV1/FEVC ratio <8% was used to confirm acute asthma exacerbation.10ml of blood was collected in a gel tube. It was centrifuged and serum was separated. 1ml of this serum was sent for estimation of vitamin D levels to Ziauddin Laboratory. Remaining was stored at -80^{0}C for use if the sample was needed for repeating the test. Serum vitamin D levels were measured by chemiluminescence method using Abbott's ARCHITECT clinical chemistry analyzer. Children were followed up to confirm recovery by spirometry. When the values for their FEV1 and FEV1/FVC ratio fell within the normal reference ranges for age, height and gender (The Thoracic Society of Australia and New Zealand for age ≥8 years and height ≤125 cm and Polgar for age ≤8 years and height 125 cm) they were said to have recovered. Time from the day of first spirometry (done during an acute exacerbation) to the time when the spirometry confirmed recovery, was recorded in days. This was the time required to recover from an acute asthma exacerbation and was labeled as recovery time. We divided recovery groups into three categories, on the basis of mean and standard deviation (7 day + 3days) of the recovery days, as (i) early recovery <7 days (ii) normal recovery 7 to 10 days and (iii) late recovery >10 days. This study was approved by the ethical committee of the Ziauddin University. Funds for the research were provided by Ziauddin University.

4. RESULTS

Since the outcome variable- recovery in days was a discrete variable, count data (Poisson regression analysis model) was applied to see the effect of Vitamin D levels on recovery days.

In this Poisson regression model the predicted scores are in the form of logarithm of counts, rather than actual counts. In this form the unstandardized coefficient b_o=2.008 is the predicted logarithms of the count when Vitamin D levels are zero and b_1 is the predicted change in the logarithm of the counts corresponding to a 1 unit change in vitamin D levels.

The exponentiation of the intercept$e2.008 = 7.44$, is the predicted number of recovery days for a person who has zero vitamin D levels.

The exponentiation of the regression coefficient for Vitamin D,$e - .002 = 0.998$, is the predictive multiplicative effect of a 1 unit change in Vitamin D on number of recovery days. A person with a vitamin D level of 17 is expected to recover 1 (.998) day earlier than a person with a vitamin D level of 16.

Assumptions for application of Poisson regression model were fulfilled. Descriptive analysis of recovery days showed variance smaller than the mean. Ratio of deviance to the degrees of freedom is close to 1 (1.18) (Table 1 and Fig. 1).

Majority of the asthmatics who had either intermittent or mild persistent asthma recovered within the normal recovery time (Fig. 2). Table 2 shows association of various risk factors for asthma with time to recover from asthma in days. The children were divided in three groups, early, normal and late recovery depending on the time to recover from asthma attacks in days. It was seen that majority of the children 90.10% (n= 51) had normal recovery, whereas, 8.90% (n= 5) belonged to the late recovery group who performed exercise.

Table 1. Poisson regression Model

	Poisson regression
Intercept	2.008
Standard error	.0557
P value	0.000
Vitamin D	-.002
Standard error	.0026
P value	0.398

$$\log(\lambda_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik}$$

Model: log (recovery in days) = 2.008 – 0.002 (vitamin D)

However the association was not significant. Associating home environment with recovery groups it was noted that 28.60% (n=2) children had early recovery (*P* =0.000). Similarly, finding the associations between allergy to pollens, changes in weather, allergy to dust and viral infections of respiratory tract to the recovery days from asthma exacerbation it was seen that majority of the children recovered within the normal recovery time period without significant association.

5. DISCUSSION

We conducted the study in 99 children with age group 5 to 15 years who had asthma. There are studies which show that reduced vitamin D levels are associated with asthma in children [18]. Other studies also demonstrate that low levels of vitamin D in mothers during pregnancy are associated with increased risk of asthma in children at 6 and 14 years of age [19]. Our search for data on recovery time from asthma in children did not yield results for past 5 years so we searched Pubmed and Google Scholar for any year.

Table 2. Association of risk factors for asthma on recovery time

Variable		Recovery groups						*P* value
		Early recovery		Normal recovery		Late recovery		
		N	%	n	%	n	%	
Exercise	Yes	0	0	51	91.10	5	8.90	0.102
	No	3	7	38	88.40	2	4.60	
Exposure to insects	Yes	0	0	2	100	0	0	0.892
	No	3	3.10	87	89.70	7	7.20	
Home environment	Yes	2	28.60	5	71.40	0	0	0.000
	No	1	1.10	84	91.30	7	7.60	
Allergy to pollens	Yes	0	0	42	89.40	5	10.60	0.115
	No	3	5.80	47	90.40	2	3.80	
Weather	Yes	2	2.30	77	89.60	7	8.10	0.343
	No	1	7.70	12	92.30	0	0	
Smoke	Yes	2	3.60	51	91.10	3	5.30	0.712
	No	1	2.30	38	88.40	4	9.30	
Allergy to dust	Yes	2	2.30	79	89.70	7	8	0.305
	No	1	9.10	10	90.90	0	0	
Allergy to animals	Yes	1	5.90	16	94.10	0	0	0.360
	No	2	2.40	73	89	7	8.60	
Allergy to smell	Yes	0	0	33	97.10	1	2.90	0.211
	No	3	4.60	56	86.20	6	9.20	
Viral infections	Yes	1	2	45	88.20	5	9.80	0.463
	No	2	4.20	44	91.60	2	4.20	
Allergy to foods	Yes	1	3.60	25	89.30	2	7.10	0.980
	No	2	2.90	64	90.10	5	7	
Emotional response	Yes	0	0	8	88.90	1	11.10	0.767
	No	3	3.30	81	90	6	6.70	

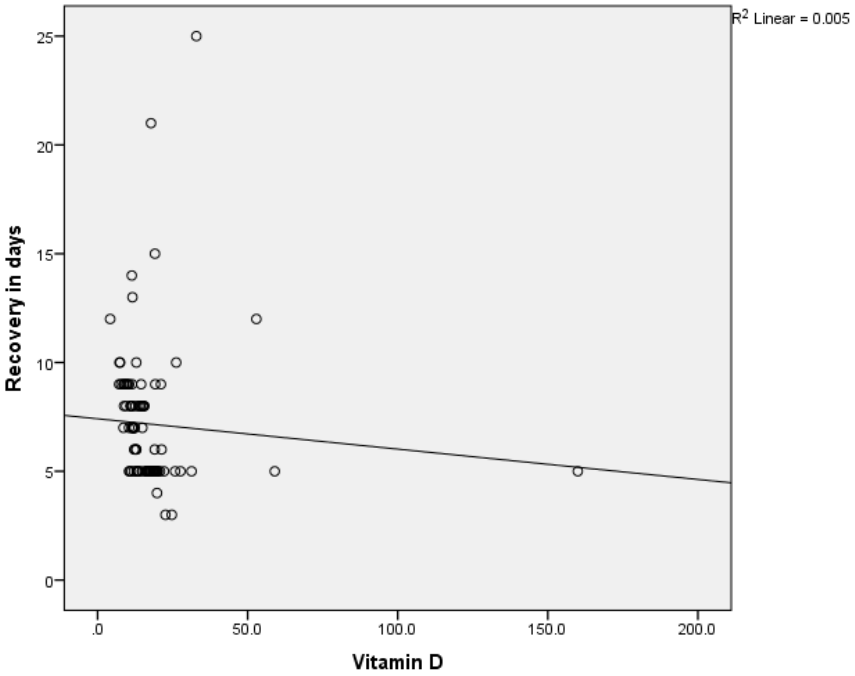

Fig. 1. Scatter plot of outcome versus Vitamin D levels

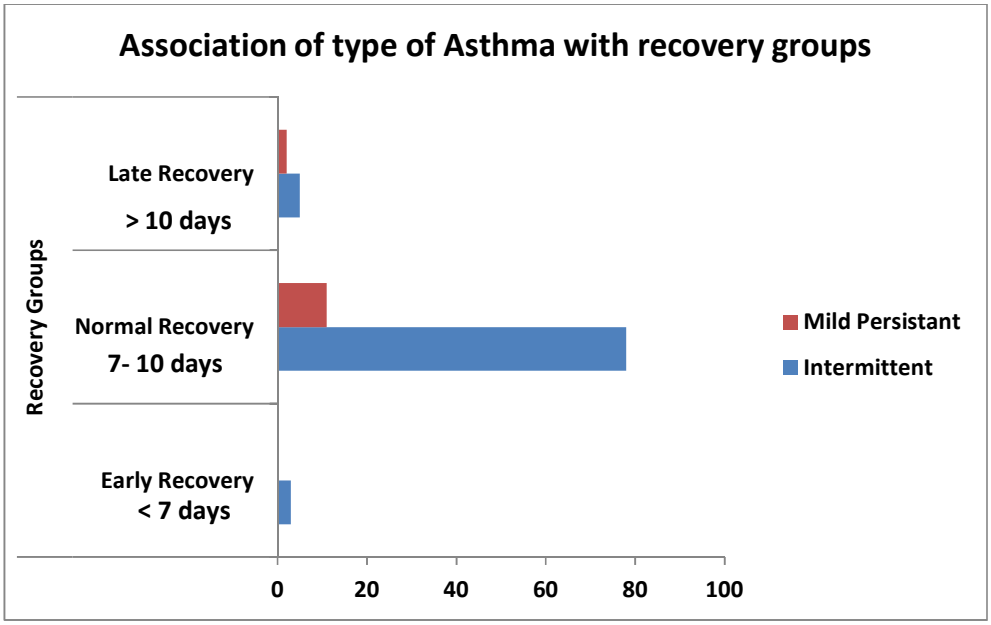

Fig. 2. Association of types of asthma with recovery groups

The studies on recovery time were few and far between and even those were for adults. Those studies usually did not single out asthma. Instead they considered asthma in chronic obstructive pulmonary disease (COPD) and/or related it with other allergic diseases. To the best of our knowledge, this is the first study that correlates vitamin D levels with time to recover from asthma exacerbation in children. We did not find any significant association between vitamin D levels and days to recover from an acute asthma* exacerbation (recovery days). This is the first finding. Further research in various ethnic variants may provide important information.

Vitamin D is not present in foods that we eat usually. The cutaneous synthesis of vitamin D is considered to be the primary and the major source of vitamin D available to the humans [20]. Secondary source includes either foods fortified with vitamin D or its supplements [21]. Contrary to the belief, vitamin D deficiency has been documented in people living in areas of abundant sunshine [22]. Role of vitamin D in bone metabolism is well understood. However, research showed that there was more to vitamin D than just bone metabolism. It implicated the role of vitamin D in diseases other than bone, like cancers (prostate, breast and colon), Systemic Lupus Erythematosus, Cystic fibrosis, Coronary heart disease and different pulmonary diseases like respiratory infections (Pneumonia and Tuberculosis), Chronic Obstructive Pulmonary Disease (COPD) and asthma. The involvement was attributed to the presence of vitamin D receptors in cells which play an important role in immune modulation for example, macrophages, monocytes B and T lymphocytes. It was postulated that vitamin D can decrease inflammatory response generated by macrophages/monocytes without their ability to kill the invading pathogens in the respiratory infections. These respiratory infections act as triggers to cause an acute exacerbation of allergic disease like asthma. Also, vitamin D can dampens the effect of immune response favoring more T helper 2 cells by increasing T regulatory cells and inhibiting T helper 1 cells. This shift reduces the allergic response generated by T helper 1 cells thus reducing asthma and its exacerbation [23-24].

Our study found no significant association between exercise and recovery time (P= 0.102). Similar findings were reported by Greening et al., 2014 in their study on patients who suffered from chronic obstructive lung disease and asthma to find that early rehabilitation intervention can improve recovery in patients admitted in hospital with acute exacerbations well as decrease the number of hospital admissions due to exacerbations. This rehabilitation included exercise like aerobics and resistance training. This study included 389 patients admitted with an acute exacerbation. They were divided into two groups randomly. Group one was of people who were given rehabilitation intervention (n=196). Group two was the control group belonging to people who had usual care (n= 193). 233 patients had to be readmitted once per year showing no significant difference between the two groups (hazard ratio 1.1, 95% confidence interval 0.86 to 1.43, *P* =0.4) [25]. It was thought that exercising help to stretch lungs and bronchial tree which may lead to decrease resistance to airflow [26]. Our findings could be due to the fact that majority of the children in our study did not have enough time to spend in sports. They were limited to home because the parents are afraid to send their children outside to play and also because the amount of homework and additional teaching hours in the form of tuitions and religious education like recitation of Holy Quran, required children to spend more time indoors. This is also aggravated by the fact that whatever time children have, they spend it indoors watching TV, surfing internet or playing games on computers.

In our study it was seen that the people who had risk factors at home that increased asthma symptoms, recovered earlier (*P* =0.000). This is in contrast to findings in a study by Kearney et al. [27]. They correlated indoor housing conditions including exposure to cockroaches with respiratory symptoms like wheeze, chest tightness and coughing of phlegm in farmworker occupants (n=352). They did not find any significant association of cockroaches to the respiratory symptoms. They also found that home environmental conditions including air conditioners and pest infestations like dust mites were not related to asthma [27]. These house mites usually infest carpets, furniture, mattresses and pillow linings in the home [28]. In our study the association was seen only in two children. It requires further studies with a bigger sample size to understand the association.

In our study we did not find any effect of smoke on recovery time from asthma (*P*= 0.712). In study by Norbäck et al. [29] association between asthma, allergy and eczema to building characteristics, home environment and energy use for heating was sought in Stockholm. They used stratified random sampling. 7554 buildings with multifamily participated. The buildings that had more than 30 dwellings (flats), 30 dwellings were randomly selected. In buildings with 30 dwellings all were included. In each building one person more than 18 years of age was selected randomly. All the subjects were sent a consent form and a questionnaire. They found no association between environmental tobacco smoke and asthma [29]. However they did not measure nor reported its effect on recovery time.

In our study there was no significant association between pollens (from different plants) to the

recovery time from asthma. In another study it was reported that exposure to grass pollens between age 4 and 6 months increased asthma at 7 years of age. But again neither they nor any other disease that we searched yielded any association between recovery time from asthma and pollens, to the best of our knowledge [30]. It could be due to the fact that there are very few grounds and even among those grounds very few have proper plantation. Also majority of the people do not keep plants in their homes. So the exposure to the pollens was minimal.

In our study we did not find any association between food and recovery time from asthma (P= 0.980). Different studies and reviews identified a relationship between food allergy and asthma. One such study was by Liu et al. [31]. They found that food allergy to peanut, milk, egg and shrimp was associated with asthma. The study included 8203 participants whose serum IgE against specific foods (peanuts, cow milk, egg white and shrimps) was measured. They used age- based criteria and food-specific IgE were used to define likely Food Allergy (LFA), possible FA and unlikely FA to establish estimates of clinical FA. Demographic risk factors and associations with asthma and other similar conditions were based on self-reported data. Increased risk of all measures of food sensitization was seen in participants with doctor diagnosed asthma compared to no asthma. Also it was seen that adjusted odds ratio for emergency visit for asthma in the past year (6.9; 2.4-19.7) and for current asthma (3.8;1.5- 10.7) were both noticeably increased. Children also had increased risk for food allergies [31]. Similar findings were reported in a systematic review conducted by Lee et al., 2013. It was observed that even in young and infant Koreans the allergies to plant like (such as soy, peanut, walnut and other tree nuts, wheat flour, buckwheat flour and other cereals, kiwi fruit and other fruits) are not rare [32]. Other studies also correlate rice allergies with worsening of asthma [33]. However, again none of them correlate them with recovery time from asthma. Our findings could be attributed to the fact that the awareness of any relationship between asthma and food allergies is scarce in our society leading to recall bias.

Our study did not show any significant association between asthma recovery groups (early. normal and late recovery) and allergy to animal dander (cats, dogs and birds like pigeons, parrots etc.) (P= 0.360). There were studies that measured the effect of exposure to pets and asthma but none of them measured any association with recovery time. Also the evidence is contradictory. In a systematic review it was observed that exposure to smoke, mould, pets and many dietary factors were important in the development of asthma in 9 years old children [34]. Similarly, in a case control study children who had severe asthma showed elevated levels of serum IgE levels against furry animals (cat, dog or horse) in children age 13 years as compared to controls of age 14 years [35]. However, a research was conducted in China to assess the effect of pet ownership and air pollution on the respiratory health of the children yield contradicting results. It included 30,149 children in the age group 2-12 years of age. These belonged to 25 cities of 7 districts of northeast China. This study showed that there were decreased effects of air pollution on asthma and respiratory symptoms in the children who had pets [36]. These findings can be due to the reason that majority of the children had no pets in their homes. Also religious obligations in majority peoples' view do not allow birds like pigeons and dogs to be kept as a pet.

Again we did not find any study that showed any relationship of recovery time with smell or fragrances. Our study found no significant association of smell (including but not limited to fragrances from different sources like perfumes, joss sticks and air fresheners) with recovery from an acute asthma attack (*P*= 0.211). One reason could be the fact that majority of the children belonged to low socioeconomic class where perfumes and air fresheners are not used regularly. Further, the use of perfumes by the children is very uncommon.

In our study, comparing types of asthma with recovery groups we found that children who had mild persistent asthma did not recover early. They either fell into normal or late recovery groups. However, children with intermittent asthma showed early recovery as well. This is similar to another study done in Turkey where they found that moderate and severe persistent asthma required more time to recover [37]. Our study demonstrated that there was no significant association between vitamin D levels and time to recover from asthma in children.

6. CONCLUSIONS

Despite the fact that majority of the asthmatic children had either vitamin D deficiency or

insufficiency but there was no significant association between vitamin D levels and the time required to recover from asthma. However asthma is not totally free of low vitamin D levels in the form of either insufficiency or deficiency. Further there is a need for educating parents regarding asthma and it risk factors so that they may be able to understand the disease better. This will help them in improving the quality of life of their children who have asthma by avoiding the risk factors and preventing asthma exacerbations thereby reducing morbidity in the population and reducing the burden of expenditure on both parents and society in the form of reduced visits to hospitals. However, there is a need for further large interventional studies to establish the role of vitamin D in asthma.

ACKNOWLEDGMENTS

We owe thanks to Ziauddin University for financial assistance.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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