Prevalence of vitamin D deficiency and insufficiency among adult asthmatic patients in Karachi

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Abstract: Vitamin D deficiency has assumed pandemic proportions all over the world. It has been documented as a frequent problem in studies of young adults, elderly person and children in other countries, but there is no reliable data on vitamin D status of adult asthmatic patients in Pakistan. To determine the prevalence of vitamin D deficiency and insufficiency in adult asthmatic patients with moderate to severe asthma using a cross-sectional study design in Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi.311 adult asthmatic patients with moderate to severe asthma were recruited from JPMC, tertiary care hospital in Karachi. Questionnaires were administered together demographics, height, weight, nutritional and physical activity assessment. Blood samples for vitamin D measurement were also taken. Results show high prevalence of vitamin D deficiency and insufficiency (88.10%) in adult patients with moderate to severe persistent asthma. Vitamin D deficiency and insufficiency was more frequently observed in female than in male patients.67.66% of the female patients had serum vitamin D level less than 20 ng/ml as compare to 56.1% of the male patients (p=0.01).

Keywords: Vitamin D deficiency, asthma, 25-Hydroxy Vitamin D**.**

INTRODUCTION

Asthma is a common chronic lung disease that involves inflammation of the pulmonary airways and bronchial hyper-responsiveness, which manifests as lower airway obstruction in response to specific triggers (Expert Panel Report 3, 2007). Asthma affects 22 million people in the USA and 300 million people worldwide (Erkkola *et al.*, 2009) and this fig projected to rise by 50% every decade (Braman, 2006). According to GINA report prevalence of asthma is 4.3% in Pakistani population (GINA report, 2012). This necessitates continuing efforts to review current knowledge and to research for new insight into the pathogenesis and treatment of this complex disorder. Recently, newer physiological functions for vitamin D have been identified which suggest that vitamin D deficiency (VDD) could be related to onset of asthma (Camargo *et al.,* 2007; Devereux *et al.,* 2007). In fact, increased prenatal vitamin D intake may reduce childhood asthma risk by as much as 40% (Litonjua, 2009). In addition to this low levels of vitamin D have been linked to increased asthma severity in older children (Ginda *et al.,* 2009).

Epidemiologic and genetic studies as well as research using animal models suggest vitamin D plays a vital and complex role in immune system function and regulation (Ginda *et al.,* 2009; Liu *et al.,* 2007). Vitamin D modulates a variety of processes and regulatory systems including host defense, inflammation, immunity, and repair (Herr*et al.,* 2011). Furthermore, a significant relationship between higher percent-predicted forced expiratory volume in 1 second (FEV_1), force vital capacity (FVC) values and the increased circulating concentrations of 25-hydroxyvitamin D [25(OH)D] has been demonstrated in a large study of approximately 14000 subjects in the United States (Black and Scragg, 2005). In children, low vitamin D levels have been found to be associated with increased frequency of asthma exacerbations (Brehm *et al.,* 2010), increased markers of allergy and asthma severity (Devereux *et al.,* 2007; Brehm *et al.,* 2009). All these findings suggest a possible role of vitamin D in respiratory health outcomes.

Despite the significant role of sunlight in vitamin D synthesis, the studies carried out in the last two decades have shown a high prevalence of VDD in tropical countries, such as China, Turkey, India, Iran and Saudi Arabia. The prevalence of VDD reported varies between 30% and 93% in different studies (Mansoor *et al.,* 2010; Masud, 2007; Malabana *et al.,* 1998). Prevalence of 92% of VDD has been identified in healthy asymptomatic volunteers in a study from Agha Khan University hospital (Zuberi *et al.,* 2008). Prevalence of VDD of 92% and 81% in ambulatory patients has been reported from centers in Karachi and Lahore recently (Masud, 2007; Baig *et al.,* 2007). Similarly, studies had done in India report the prevalence of low levels of vitamin D to be ranging between 80-85% in-group of postmenopausal women and local hospital staff (Harinarayan, 2005; Arya, 2007). Prevalence of vitamin D deficiency and insufficiency was found out to be 80% in healthy adults living in urban Tehran, Iran (Hashempour *et al.,* 2006). Pakistan is one of the sun-drenched countries of the world, but VDD is also frequent among Pakistanis, which was first noted in the Pakistani immigrants in UK in early 1970s. Evidence

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supports the strong association between vitamin D status and risk of chronic disease (Mansoor *et al.*, 2010).

Though VDD has assumed pandemic proportions all over the world, there are no reliable data on vitamin D status of adult asthmatic patients in Pakistan. Therefore, this study was carried out to determine the prevalence of VDD in adult asthmatic patients in Karachi, Pakistan.

MATERIAL AND METHODS

This study was conducted during the period of August 2012 to October 2012, at department of Pharmacology and therapeutics, Basic Medical Sciences Institute, Karachi. Patients were enrolled according to the criteria defined by National Clinical guidelines for management of asthma from Jinnah Postgraduate Medical Centre, one of the major tertiary care hospitals in Karachi. The study protocol was reviewed and approved by research ethics committee of the Jinnah Postgraduate Medical Centre and University of Karachi. Written informed consent was taken from all the study participants, according to the declaration of Helsinki (WMA revises the Declaration of Helsinki. 2013). We included 311 unrelated adult asthmatic patients with moderate to severe asthma (FEV_1 percent predicted value between 50 to 80 %) of either sex, aged between 18 to 60 yrs. We excluded the patients on vitamin D therapy or drugs that modulate serum vitamin D levels, such as systemic glucocorticosteroids and anticonvulsant, patients with chronic liver or kidney disease, inherited bone diseases, hypo or hyperparathyroidism, home bounded patients and smokers.

Diagnosis of asthma

Asthma diagnosis was made based on the patients' symptoms plus objective evidence from lung function tests according to the criteria defined by the American Thoracic Society (1995).

Sample size

Keeping in the view the aim of our study, prevalence of vitamin D deficiency in adult asthmatic patients, the sample size was calculated using the sample size determination in health studies software provided by the world health organization. The reported collective prevalence of vitamin D insufficiency and deficiency in our region is between 85-98%. The sample size calculated was 272 however we work on 311 patients.

Data collection

Information on age, sex, smoking status, asthma duration, co-morbidity status (such as diabetes mellitus, hypertension and ischemic heart disease), sun exposure (approximate number of minutes per day spent in sunlight) and medication use were collected via a questionnaire. The physical assessment performed to measure blood pressure, weight and height.

Assessment of Serum 25OHD Concentrations

Serum level of 25(OH)D is thought to be the best circulating biomarker of vitamin D metabolic status reflect contribution from all sources of vitamin D, including diet and sun exposure (Holicks, 2007). Measurement of serum vitamin D was done by well-known labs. We categorized vitamin D levels into deficient (<20ng/ml), insufficient (20-30ng/ml) and sufficient (>30ng/ml) based on previous recommendations.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences, SPSS 16.0 was used for data analysis. Analysis was done between the three groups of serum 25(OH) D, based on the above cut-offs, with respect to their demographics and clinical characteristics. Descriptive analysis was done for demographic and laboratory tests and proportions were determined. One-Way ANOVA test was conducted among the three groups. P-value of < 0.05 was considered statistically significant. All values are given as mean $\pm$standard deviation.

RESULTS

The mean age of the sample was 45.14$\pm$8.87 years. The mean level of serum 25(OH) D was 18.71$\pm$12.3ng/ml, with sample vitamin D levels ranging from 5 to 76ng/ml. There were statistically non-significant differences in relation to the age between the three groups (p=0.447). When we compare body mass index (BMI) vitamin D deficient patients having higher BMI as compare to vitamin D insufficient and sufficient patients (p<0.0001).

Prevalence of vitamin D deficiency and insufficiency in adult asthmatic patients

These results show high prevalence of vitamin D deficiency and insufficiency in our sample patients. Out of 311 patients 88.10% patients had low serum vitamin D level, <30ng/ml. Out of these patients 61.09% patients were vitamin D deficient having serum vitamin D level <20ng/ml, while 27.02% patients had insufficient serum vitamin D level (20 to 30ng/ml). Only 11.89% of the patients had were vitamin D sufficient (<30ng/ml) (shown in table 1). The prevalence of vitamin D deficiency has been shown in fig. 1.

Correlation between gender and serum vitamin D level

Vitamin D deficiency was more frequently observed in female than in male patients, 67.66% of the female patients had serum vitamin D <20ng/ml as compare to 56.1% of the male patients (p<0.001). In addition to this mean serum vitamin D level in female patients was significantly low as compare to male patients (p<0.001). Mean serum vitamin D level in female patients was 16.66$\pm$11.9ng/ml while of males was 20.25$\pm$12.4ng/ml (shown in fig. 2).

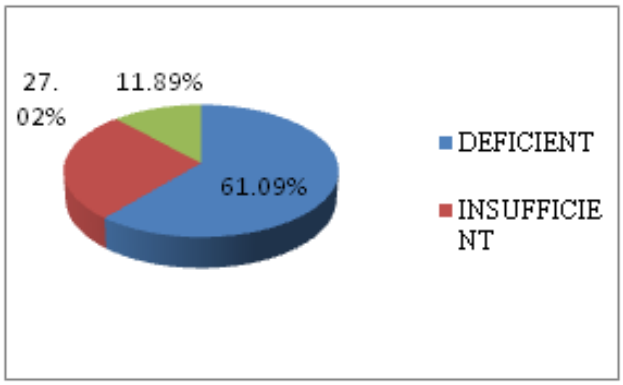

Fig. 1: Pie chart shows the prevalence of vitamin D deficiency and insufficiency in adult asthmatic patients.

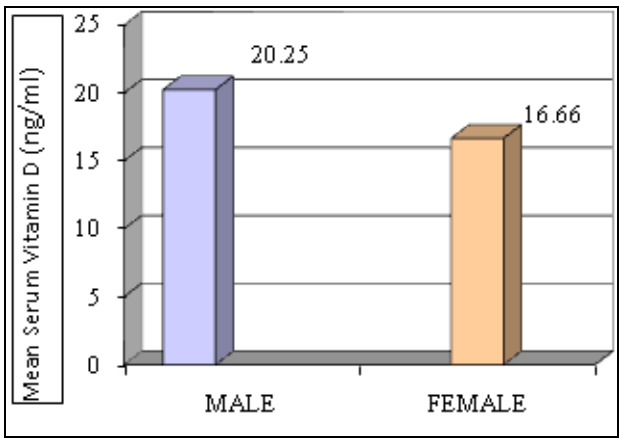

Fig. 2: Mean serum vitamin D level in male and female asthmatic patients.

DISCUSSION

In this study of Pakistani adult asthmatic patients, vitamin D deficiency (VDD) and insufficiency was highly prevalent (88.1%) and was significantly associated with gender, body mass index and airway obstruction, as evaluated by FEV_1 (data not given). As all participants are Pakistanis living in Karachi, this homogeneous population has relatively fewer unmeasured orr uncontrolled confounding factors by ethnicity (i.e. skin color) and other variables, such as sun exposure level.

Previous studies have consistently shown that VDD is prevalent in general South Asian populations (Mansoor *et al.*, 2010; Masud, 2007; Hashempour *et al.*, 2006; Harinarayan, 2005; Arya *et al.*, 2007). There are multiple factors which contribute to low serum vitamin D level including low vitamin D intake, dark skin, urban environment (Lee *et al.*,2007), high rates of poverty (Saintonage *et al.*,2009) and obesity (Gordon *et al.*,2004).

Vitamin D could be involved in asthma pathogenesis through several mechanisms. Vitamin D is involved in the regulation of innate as well as adoptive immune functions, including the response to respiratory infection (Dimeloe *et al.*, 2010). Vitamin D receptor (VDR) and metabolic enzymes have been found in many cells including immune cell type (Litonjua, 2009). VDR gene polymorphisms have been shown to be associated with asthma risk in both Caucasians and Chinese (Raby *et al.*, 2004; Sadi *et al.*, 2009). In addition to affecting immune cells, vitamin D also affects airway smooth muscle function and proliferation, which has a direct relevance for lung function in asthma and in airway remodeling (Damera *et al.*, 2009). Evidence suggests that vitamin D deficiency is associated with increased airway hype rresponsiveness, lower pulmonary functions, worse asthma control, and possibly steroid resistance. Lung epithelial cells express high baseline levels of 1alpha-hydroxylase, which allows the conversion of inactive calcidiol to active calcitriol locally within the lung. Calcitriol has been shown to inhibit the synthesis and release of certain cytokinesfrom airway smooth muscle cells, such as platelet-derived growth factor, and matrix metalloproteinases, thereby leading to decreased lung inflammation and smooth muscle cell proliferation. Vitamin D also increases synthesis of interleukin 10 by $CD4^+$, $CD25^+$, $Foxp3^{\pm}$T-regulatory cells and dendritic cells, while concurrently inhibiting dendritic cell activation by down regulating expression of co-stimulatory molecules CD40 and CD80/86. In experimental models of allergic airway disease, IL-10 shows anti-inflammatory properties and decreased airway hyper-responsiveness (Sandhu, 2010). More recently, vitamin D has been reported to inhibit IL-17 production, an inflammatory cytokine involved in allergic diseases, including asthma (Tang, 2009; Louten, 2009).

Our results that found BMI and female sexare associated with lower vitamin D level were also reported in previous studies (Holick, 2007, Kumar *et al.*, 2009). Of particular relevance is the observed inverse relationship between BMI and vitamin D levels ($r= -0.385$; $p<0.0001$) a finding previously reported in adults without asthma (Parikh *et al.*, 2004).

Our results were well in line with a Chinese study by Li Fei *et al.*, (2011). According to them VDD was highly prevalent in Chinese adults asthmatic patients, with 88.9% of the subjects having 25(OH) D less than 50 nmole/l. Another study by Chinellato *et al.*, (2011) showed only 9.4% of Italian asthmatic children had a significant serum 25(OH) D level. A study by Freishtat *et al.*, (2010) showed high prevalence of VDD among African-American youth with asthma in Washington, DC. In our sample of adult asthmatic patients overall distribution of vitamin D levels was considerably lower than of a previously reported Costa Racia cohort of children with asthma in which only 28% of levels were <30ng/ml (Brehm *et al.*, 2009).

Table 1: Demographic characteristics of the patients (n=311) with respect to serum vitamin D level.

	Deficiency Group	Insufficiency Group	Sufficiency Group	P-value
No of patients	190 (61.09%)	84 (27.02%)	37 (11.89%)	-
Serum Vitamin D (ng/ml)	10.80±3.85	25.29±2.49	42.32±10.3	0.0001
Age (years)	45.34±8.70	45.46±9.48	43.41±8.34	0.447
Gender				
Male	100 (56.1%)	54 (30.33%)	24 (13.48%)	-
Female	90 (67.66%)	30 (22.55%)	13 (9.77%)	-
BMI (Kg/m^2)	24.59±3.42	22.83±2.54	20.78±2.25	0.0001

Notes: Data is expressed as mean ± standard deviation. Probability determined using One-way ANOVA Test. Statistical values <0.05 is considered significant.

Our findings were also consistent with the findings from a study by Sutherland *et al.,* (2010) of 54 US adult asthmatics, who found a significant inverse association between BMI and serum vitamin D. We also observed that obese participants tended to have lower vitamin D concentrations. Obesity has been demonstrated to increase asthma risk, and associated with an impaired response to glucocorticosteroids (Sutherland *et al.,* 2009; Halder *et al.,* 2008).

A study by Bener *et al.,* (2012) conducted in Qatar also showed high prevalence of VDD in children with asthma than controls. Overall 68.1% of children with asthma and 36.1% of the control children were vitamin D deficient. A study by Gordon *et al.* (2004) found a high prevalence of VDD in healthy adolescents presenting for primary care in hospital located in Boston. According to them 66.1% of the patients was vitamin D deficient or insufficient. According to them BMI is significantly associated with 25(OH) D levels.

A study by Wu *et al.,* (2012) who measured 25(OH) D levels in the serum of children with persistent asthma at the time of enrollment in the Childhood Asthma Management Program shows contradictory results. Of the 1,024 subjects, 663 (65%) were vitamin D sufficient, 260 (25%) were insufficient, and 101 (10%) were deficient. This may be due to their food fortification policies. This study also shows inverse relation between vitamin D level and BMI. Vitamin D deficient asthmatic children were more likely to be older, and have higher BMI compared to vitamin D sufficient and insufficient subjects.

Finally, a study with bronchial biopsies by Gupta *et al.* (2011) conducted in London, demonstrated an inverse association of vitamin D levels and airway smooth muscle mass. According to them the prevalence VDD was 94, 54 and 33 % in severe therapy resistance asthma, moderate asthma and controls. In vitro vitamin D influenced airway smooth muscle remodeling by exerting an inhibitory effect on passively sensitized airway smooth muscle growth and contractility (Damera *et al.,* 2009). Airway remodeling is an important feature of asthma and is correlated with airflow limitation (Fish and Peters, 1999).

The present study has certain limitations. The patients included in this study are typical for a large tertiary care hospital and may not be representative of the overall population of patients with asthma. However, given the large overall study population it is unlikely that the results change if more patients with milder disease were included. It is possible that patients with asthma symptoms reduced their outdoor activities, which thus led to a reduced exposure to sunlight. However, given that we exclude all home bounded people, it is likely to have a negligible effect on our results.

CONCLUSION

This study suggests high prevalence of vitamin D deficiency and insufficiency state in a group of adult asthmatic patients living in Karachi. We recommend that similar type of study should be conducted on large scale, over a period of longer duration. There is a need to study the determinants for a high degree of VDD in our population, in a situation of ample sunlight. There is an urgent need for public education about the role of vitamin D in health, to avoid the complications of VDD. Optimum sunlight exposure lifestyle modifications and vitamin D supplementation can help to prevent the serum 25(OH)D deficiency state.

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