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Association of Vitamin D Status with Pulmonary Function in Adult Asthmatics: A Case Control Study

Abilash M*, Reeta R and Pajanivel R

Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, Pondy-cuddalore ECR Road, Pillayarkuppam, Puducherry, India

Abstract

Calcitriol is the active form of Vitamin D. 7-Dehydrocholesterol in our skin gets converted to cholecalciferol when it is exposed to sunlight which gets hydroxylated in liver and kidney to finally form 1,25-DihydroxyCholecalciferol (Calcitriol) which is the active form of Vitamin D. The role of calcitriol in physiological and pathophysiological processes has been recognized only in the last couple of years. Research shows that calcitriol plays a role in several diseases involving the respiratory system. It plays an important role in immune regulation through interactions with vitamin D receptors (VDRs) expressed on airway immune cells. Higher calcitriol concentrations have been associated with better pulmonary function as measured by forced expiratory volume in 1 s (FEV_1) in a large cross-sectional study of the U.S. population in the National Health and Nutrition Examination Survey (NHANES) III.

Aim: The aim of the study was to assess and correlate serum vitamin D status with severity and degree of control of asthma.

Methods: Case control study was conducted in south Indian population with uncontrolled asthma/acute exacerbation of asthma. Serum 25 (OH) Vitamin D was estimated using an immunoassay method which was based on established spectrophotometric & automated procedures, approved by International Federation for Clinical Chemistry (IFCC) and pulmonary function test using a portable MIR winspiro spirobank II spirometer. Data were compared by using student 't' test. Pearson's correlation was done to see the association among vitamin D and pulmonary function test.

Results: Serum vitamin D levels were significantly lower in uncontrolled asthma/acute exacerbation of asthma. ($p<0.05$) Positive correlation of vitamin D with FEV_1 and FEV_1/FVC ratio is seen. (P value <0.05, r value 0.643 and p value <0.05, r value 0.714 respectively).

Conclusion: Vitamin D levels are significantly low in uncontrolled asthma. Asthmatics with a higher level of vitamin D have better pulmonary function and thereby a better quality of life.

Keywords: Vitamin D; Pulmonary function test; Adult asthmatics

Introduction

Vitamin D

Calcitriol (1,25-DihydroxyCholecalciferol or Vitamin D3) is the active form of Vitamin D. Vitamin D synthesis begins when 7-Dehydrocholesterol in our skin is exposed to sunlight which leads to the formation of Cholecalciferol. The Cholecalciferol undergoes hydroxylation by 25-hydroxylase in the liver to form 25-Hydroxy Cholecalciferol. 25-HydroxyCholealciferol gets hydroxylated in the kidney once again by 1-alpha-hydroxylase to form 1, 25-Dihydroxycholecalciferol (Calcitriol) which is the active form of Vitamin D. The importance of calcitriol in calcium balance and bone stability has been well known. Its activities on various pathological processes have been identified only in recent years [1]. Research shows that calcitriol has a part in diseases like cancer, infectious disorders, heart disorders and also many pulmonary disorders [2,3]. Increased levels of calcitriol has been associated with better lung function, measured by forced expiratory volume in 1 second (FEV_1) as reported in a cross-sectional study of the U.S. population in the National Health and Nutrition Examination Survey (NHANES) III [4].

The prevalence of Vitamin D deficiency has increased in the people during recent years. The majority of circulating 25-hydroxycholecalciferol, the immediate precursor of calcitriol is derived from sun exposure, with a limited dietary contribution. The highly prevalent Calcitriol deficiency in the population is mainly due to being indoor most of the time, sunscreen usage and low consumption of calcitriol-containing foods [1]. Calcitriol is hidden away in the fatty tissue, thus obesity being highly prevalent these days also adds to the highly prevalent vitamin D deficiency problem.

Asthma

Asthma is a highly prevalent disease affecting a huge population worldwide. It is a lung disease due to specific triggers leading to chronic inflammatory process of the lower respiratory tract, hyper-responsiveness of the airway and obstruction of the lower respiratory tract. The Clinical features are wheeze, cough, dyspnea and tightness of the chest. It is frequently treated with two types of medicines viz., Daily controlled inhaled corticosteroids and a bronchodilator which are actually β-adrenergic agonists [5]. The cytokines released by the T-helper cell type-2 (T_H2) like interleukin (IL)-4, IL-5, and IL-13, causes an increased response in the asthmatic airway leading to eosinophilia, mast cell degranulation and increased levels of immunoglobulin E (IgE) [6-8]. Impairment of tolerance to immunity and interactions between cells and mediators of inflammation usually leads to airway injury which is commonly

***Corresponding author:** Dr. Abilash.M, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, Pondy-cuddalore ECR Road, Pillayarkuppam, Puducherry, 607402 India; E-mail: abilash_murali94@hotmail.com

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called as airway "remodeling" [9]. Airway remodeling ultimately leads to hypertrophy of the smooth muscle, hyperplasia of the epithelial goblet-cell and pulmonary extracellular matrix proteins which are permanent causing an increase obstruction to airflow and the various clinical features of the disorder [10].

Asthma and calcitriol

There are many literatures stating there is a relationship between 25-OH Cholecalciferol levels and respiratory symptoms due to asthma, which may be due to modulatory effects on the immune system by vitamin D [11,12]. The change to urban lifestyles has led to asthma being highly prevalent. Various dietary hypotheses for prevention of asthma were proposed based on observational studies [13]. In these studies, various antioxidants like Vitamin D were hypothesized to help in decreasing the severity of asthma. Although, various foods are fortified with vitamin D, many adults have deficiency of Vitamin D, which may be due to decreased exposure to sun, Obesity and decreased calcium in diet which causes a decrease in bioavailability of vitamin D [14]. Also, in people with asthma, decreased 25(OH) Cholecalciferol levels were associated with high odds of exacerbations of their asthma leading to increased utilization of healthcare in the preceding year [15]. Many studies have noted associations between a decrease in serum 25(OH) D concentrations and a decrease in lung function, increase in airway hyper responsiveness to methacholine challenge test, and a blunted response to glucocorticoid. In a case-control study of obese subjects who were divided into groups with and without asthma, there was no association between 25-OH Cholecalciferol and prevalence of asthma [16-18]. A clinical trial which focused on the role of vitamin D in diseases due to allergy was done by Rappaport et al. They found that Vitamin D supplementation caused a significant relief in symptoms due to asthma and hay fever in >96% of patients who were suffering from asthma and allergies which were seasonal. Thus the therapeutic effectiveness of Vitamin D in asthma patients was hypothesized [19]. Few studies focused on a genetic association between vitamin D and asthma in a large group of population. Some studies explored the relationship between polymorphisms in Vitamin D Receptor and asthma. They found an association between various polymorphisms in Vitamin D Receptor and asthma. Some studies found that there was no such association [20].

Aims and Objectives

Aim

The goal of this study was to measure and correspond serum vitamin D status with severity and degree of control of asthma.

Objectives

To assess the vitamin D status in asthma patients wherein measuring 25 hydroxy cholecalciferol was used as the marker of the patients' vitamin D status. To estimate the serum calcium and phosphate levels in asthmatics. To correspond and correlate the 25-OH Cholecalciferol status with severity of asthma and degree of control. Association, if any present, between 25-OH Cholecalciferol concentration and Lung functions which was measured as forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), and FEV_1/FVC ratio.

Hypothesis

We hypothesized Severity of asthma correlates with 25-OH Cholecalciferol levels along with 25-OH Cholecalciferol levels affects the pulmonary function in asthma patients.

Methodology

Cases

[n=60]: This was a Retrospective case control study undertaken in adults with asthma attending the outpatient department of pulmonary medicine in a tertiary level hospital in Puducherry a state in southern part of India The study was done during May and June 2013. The Institute Human Ethical Committee reviewed the protocol of the study and approved it. All the participants were informed about the study and a written consent was obtained from all of them. The subjects were diagnosed according to GINA guidelines and grouped into two groups (Based on the clinical features i.e. number of exacerbation the patient had in a week and Pulmonary Function tests). They are divided into two groups. **Group 1**: Subjects with asthma that was well controlled – (Symptomatic less than or equal to 2 days per week, FEV_1>80% of predicted and a Normal FEV_1/FVC ratio). **Group 2**: Subjects with asthma that was uncontrolled /had frequent acute exacerbations (Symptomatic almost daily and all throughout the day often 7 days a week, FEV_1<60% of predicted and a decreased FEV_1/FVC ratio). Exclusion criteria: patients with other chronic clinical conditions, metabolic, hepatic and renal disorders and other pulmonary diseases were excluded from the study, since all the above mentioned conditions may alter the vitamin D status.

Study parameters

Outcome measures monitored were the following: The subjects were informed about the procedure. After obtaining a written consent, five milliliters (ml) of venous blood was obtained from the subjects. The below mentioned parameters were determined from all the venous samples obtained. The parameters were estimated using established spectrophotometric & automated procedures, approved by the International Federation of Clinical Chemistry and Laboratory medicine (IFCC)). Vitamin D Status serum 25(OH) Cholecalciferol were assayed in all subjects using Immunoassay method using kits manufactured by BioMerieux India Ltd. Deficiency of Vitamin D was defined as serum 25(OH) vitamin D<20 ng/ml. Insufficient levels of 25-OH Vitamin D was defined as serum levels between 20-30 ng/ml. Desirable or Sufficient levels of 25-OH Vitamin D was defined as serum levels >40 ng/ml. Serum calcium ortho-cresol phthalein complexone (OCPC) method in an automated analyzer. Serum phosphate by the method of fiske and subbarow in an automated analyzer. Pulmonary function test a portable MIR winspiro spirobank II spirometer was used by a pulmonologist to perform PFTs in all the participants according to European respiratory society guidelines. The following parameters were documented: FEV_1, FVC and a ratio between FEV_1 and FVC.

Statistical analysis

The data was expressed as mean+/- SD. Analysis of the data was done using unpaired student 't' test. Correlation analysis was done using Pearson's Correlation. The statistical tests were considered statistically significant when the p value was <0.05. The Statistical analysis was done using SPSS version 17 software.

Observation and Results

All physiological and biochemical parameters were expressed as mean ± SD; results were compared by using an unpaired Student't' test (Table 1). In our study the serum Vitamin D levels were significantly high in well controlled/stable asthma patients compared to uncontrolled/exacerbated asthma (p<0.05). We did not observe any statistically significant differences for the other parameters.

Parameters	Well controlled asthma n=30		Uncontrolled asthma n=30		'p' value
	Mean	± SD	Mean	± SD	
Calcium (mg/dl)	9.2	± 0.5	9.3	± 0.3	>0.05
Phosphorous(mg/dl)	3	± 0.3	3.1	± 0.5	>0.05
Vitamin D (ng/ml)	26.9	± 2.9	19.6	± 1.9	<0.05*
FVC % predicted	90.9	± 15.8	93.2	± 16	>0.05
FEV1 % predicted	85.4	± 16	53.2	± 15.6	<0.05*
FEV1/FVC ratio	92	± 7	65.9	± 7.4	<0.05*

Table 1: Comparison of parameters between well controlled and uncontrolled asthma patients (students t test).

Variables (n=60)	FEV1 %	FEV1/FVC RATIO
Serum Vitamin D (ng/ml)	p<0.01* r= 0.643	P<0.01* r=0.714

Table 2: Association of serum Vitamin D values with FEV1 and FEV1/FVC ratio.

*indicates p value <0.05 which is considered statistically significant FVC: Forced Vital Capacity FEV1: Forced Expiratory Volume in 1 Second.

*indicates p value <0.01 which was considered statistically significant Association was evaluated by Pearson's correlation method.

Table 2 shows the association of the serum 25-OH Cholecalciferol levels with FEV1 and FEV1/FVC ratio. The Correlation was significantly positive between Vitamin D and FEV1 and Vitamin D and FEV1/FVC ratio with a p value of <0.01 and r value of 0.643 and p value of <0.01 and r value of 0.714 which indicates that there is a positive correlation between increased Vitamin D levels and a good pulmonary function.

The importance of Calcitriol on various pathological processes have been Identified only in recent years. Calcitriol also has a role in many pulmonary disorders as well. It helps in regulations of the immunity by interacting with vitamin D receptors (VDRs), expressed on immune cells in the Respiratory tract. They act as nuclear steroid hormone receptors and helps in regulation of gene transcription associated with inflammation and immunomodulation [4]. Higher levels of Calcitriol has been associated with better lung function which is measured by forced expiratory volume in 1 s (FEV_1) in a cross-sectional study of a large U.S. population in the NHANES III [4]. There are very few studies in south Indian population comparing pulmonary function with vitamin D status in asthmatic patients. This study was planned to find if an association is present between lung function and serum levels of Vitamin D.

In this study sixty adults who had asthma attending the outpatient department of pulmonary medicine were included. The subjects were diagnosed according to GINA guidelines and grouped into two groups namely group 1 and 2 which included subjects with well controlled asthma and subjects with uncontrolled asthma/acute exacerbation of asthma. (a)– serum 25(OH) Cholecalciferol levels (b) Serum calcium, (c) Serum phosphate and (d) Lung function test were assessed and compared between the two groups. A correlation analysis was done to see if there was an association between pulmonary function and vitamin D.

This study documents that high levels of vitamin D was seen in asthma patients who had well controlled asthma as compared to uncontrolled group ($p<0.05$). There was a significant positive correlation observed between vitamin D and FEV1 and a ratio between FEV1 and FVC (p value<0.05, r value 0.643 and p value<0.05, and r value 0.714 respectively).

This study indicates that significantly high levels of Vitamin D are seen in well controlled asthma patients as compared to the uncontrolled group. A significant positive correlation was seen between the levels of vitamin D and pulmonary function test. This indicates that increased levels of vitamin D are associated with a better pulmonary function.

Discussion

It is believed that due to abundant sunshine in India, Vitamin D deficiency is uncommon, which is not true these days [21]. Vitamin D deficiency which was a hidden problem for many years has now become a new emerging global threat, reaching epidemic proportions in both the developing and developed world alike. In our study, adults with poorly controlled asthma had vitamin D deficiency. There was a significant association between low serum vitamin D levels and airway obstruction, which was evaluated by FEV1 and ratio between FEV1 and FVC. Hence we can assume that Vitamin D has a major role to play in airway remodeling, hence the deficiency of Vitamin D leads to frequent exacerbations of the obstructive symptoms of asthma. The association between 25-OH Cholecalciferol levels and pulmonary function in asthma patients was observed to be positive. This observation was similar to a study done by Scragg et al. and Li et al. [16,17]. Higher levels of vitamin D was seen in asthma patients who had well controlled asthma compared to asthma patients who had poorly controlled asthma in our study. This is similar to studies by Richards, et al. who demonstrated that Poor Pulmonary function and asthma control was associated with low serum Vitamin D levels [22]. This is assumed to have occurred based on the fact that vitamin D, by its ligand influences the down regulation of the glucocorticoid receptor thereby inhibiting the proliferation of smooth muscle [20-23]. A Study by Boswell et al. showed that there was an association between low levels of vitamin D status and asthma patients who had poor clinical response to glucocorticoids [24]. These studies show the therapeutic potential of Vitamin D in asthma patients who had severe asthma by enhancing the response to steroids. Hence we can say that Vitamin D by its influence on controlling the Smooth muscle proliferation and its effect on Glucocorticoid receptor plays a very important role in controlling the frequent exacerbations of the obstructive symptoms of asthma, Hence we need to supplement Vitamin D to patients having poorly controlled asthma in order to reduce frequent exacerbations thereby improving their quality of life [25-27].

Limitations, Implications and Conclusion

Limitations

The size of the sample was low. 1, 25 dihydroxy cholecalciferol could have been estimated along with 25-hydroxycholecalciferol.

Other immunological parameters like IgE, Eosinophil could also have been included.

Implications

There is association between Deficiency in vitamin D levels and severity of asthma and also decreased lung function. This study suggests that a decrease in the severity of asthma, exacerbations and an improvement in pulmonary function can be achieved by in taking adequate levels of vitamin D.

Conclusion

In conclusion to our study we have important information about the levels of vitamin D in adult asthmatics in Puducherry population. We were able to prove that deficiency of Vitamin D in patients with asthma is common and more so in patients with asthma that was uncontrolled and also had frequent episodes of acute exacerbations. We also found significant correlation between serum levels of vitamin D and lung function test.

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