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ORIGINAL RESEARCH

A study on association of serum vitamin d levels in patients with bronchial asthma

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ABSTRACT

Background: Bronchial asthma represents one of the common chronic diseases worldwide. The adaptive and innate immune systems play important role in pathogenesis of asthma. Vitamin D has several effects on adaptive & innate immune systems that might be relevant in the protection against or reduction of asthma morbidity, in primary prevention of asthma & in modulation of severity of asthma exacerbations. Several studies suggest there is probable relation between asthma-related symptoms and vitamin D status via the immune modulatory effects of vitamin D.**Methodology:**A cross-sectional descriptive study was conducted over a period of one and half year duration among 100 cases of bronchial asthma including admitted patients and those attending OPD aged more than or equal to 18 years visiting Bapuji Hospital and OPD, Davangere.**Results:**This study shows serum vitamin D levels were decreased in asthmatic patients. In case of severe asthmatic patients, serum vitamin D levels were significantly reduced. Asthmatics with vitamin D deficiency showed peripheral blood eosinophilia (674.96±261.1).**Conclusion:**There is important association between serum vitamin D (both deficiency or insufficiency) and adult bronchial asthma. A strong correlation is also seen between the serum vitamin D level, asthma severity and absolute eosinophil count.

Key words: Bronchial asthma, Vitamin D

INTRODUCTION

Bronchial asthma is one of the most common chronic diseases & prevalence has increased worldwide in the last few decades affecting approximately 300 million people. This poses an immense burden on healthcare resources[1].Asthma is a prolonged inflammatory disorder which is related with hyper responsiveness of the airways and leads to symptoms such as dyspnoea, chest tightness, wheezing and cough mainly at night or early in the morning[2].

The pathogenesis of asthma is very complex and is not fully elucidated yet. A variety of cells and inflammatory mediators play a critical role in initiating, perpetuating and coordinating the repeated cycles of inflammation.

The complex interaction between inflammatory mediators & cells and impairment of immunogenic tolerance promotes airway injury. This is known as airway "remodeling"[3].This remodeling involves hypertrophy of smooth muscle, deposition of airway extracellular matrix proteins and hyperplasia of epithelial goblet cell, which may lead to increase airflow obstruction and finally causing the respiratory symptoms[4].

Several dietary hypotheses have been proposed in context with asthma[5-6] and among them vitamin D status is of particular interest. Cholecalciferol or vitamin D, a fat-soluble vitamin is a prohormone with several active metabolites that act as hormones[12]. Studies suggest that there is probable relation between asthma-related symptoms and vitamin D status via the immune modulatory effects of vitamin D[3, 6].

Vitamin D also play a role in the pathogenesis of asthma[7].Asthmatic patients with low vitamin D levels have more severe symptoms and poor asthma control[8].The severity of vitamin D deficiency correlates with the number of medications being used to control asthma, suggesting a possible link with treatment resistance[9].Vitamin D by inhibiting the repeated cycles of chronic inflammation reduces airway remodelling which is the major pathologic change seen in the lungs of asthmatic patients[13].

Vitamin D reduces inflammation by decreasing the levels of proinflammatory cytokines and increasing the levels of anti-inflammatory cytokines like interleukin 10[14]. Vitamin D also reduces bronchial smooth muscle cell hypertrophy and hyperplasia[15].

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Vitamin D through its action on VDR influence the immunological cascade by suppressing response of T2 high lymphocytes, reducing production of IL5 and decreasing eosinophil counts. In vitamin deficiency or insufficiency raised peripheral blood eosinophils is seen[16, 17].

Studies *in vivo* and *in vitro* have demonstrated that treatment with vitamin D may reduce inflammatory signaling in many cell types which are involved in the pathogenesis of asthma; inhibiting differentiation, maturation, and cytokine release from mast cells, neutrophils and eosinophils and effectively reducing airway hyper-responsiveness, inflammation, and remodeling[10, 11].Of the various new therapies Vitamin D has been found to have a role in the treatment of bronchial asthma[12].

Therefore the aim of this study is to study about association of serum vitamin D levels in patients with bronchial asthma.

OBJECTIVES OF STUDY

1. To study the effect of serum vitamin 'D' levels in patients with bronchial asthma.
2. To assess severity of asthma in patients with vitamin D deficiency.
3. To assess how serum vitamin D levels influence peripheral blood eosinophil counts in patients with bronchial asthma.

METHODOLOGY

SOURCE OF DATA

This is a cross sectional, descriptive study conducted among Bronchial Asthma patients aged more than or equal to 18 years visiting Bapuji Hospital and OPD, Davangere. The study will be conducted over a period of one and half year duration.

METHOD OF COLLECTION OF DATA

STUDY DESIGN: Cross sectional descriptive study.

STUDY PERIOD: August 2022 to February 2024.

PLACE OF STUDY: Department of Respiratory Medicine, J.J.M.M.C., Davangere.

SAMPLE SIZE:100 cases of bronchial asthma including in-patients and OPD patients.

SAMPLING METHOD

1) Consecutive patients will be selected.

The data for this study will be collected from subjects fulfilling inclusion and exclusion criteria and will be included in study after taking informed and written consent.

INCLUSION CRITERIA

1. Patients who are willing to participate in the study.
2. Patients diagnosed with Bronchial Asthma based on spirometry-Post bronchodilator increase in FEV1 ≥ 12% and ≥ 200ml.

EXCLUSION CRITERIA

1. Patients who do not give consent for the study
2. Patient who are already on nutritional support for VITAMIN D deficiency
3. Patient aged more than 80 years, patients with COPD, ILD, concomitant lung cancer, present or past history of TB, decompensated cardiac disease were excluded from the study.

METHOD

Subjects are selected according to inclusion and exclusion criteria after written informed consent.Detailed history will be elicited from subjects to rule out those coming in exclusion criteria.

STATISTICAL ANALYSIS

- The data collected was entered into excel sheet and was analysed using SPSS version 25.0. Qualitative variables were expressed as frequencies(percentages) and quantitative variables as mean±SD and as median. Student's 't' test was applied to check if there was significant difference between the two means. P-value<0.05 was considered to be statistically significant and p-value<0.01 was considered as highly statistically significant.

RESULTS

In this study of 100 individuals, the mean age of the sample was 39.9 years, with a notable standard deviation of ±12.75 years, indicating a diverse age distribution. Examining age groups, the data reveals 6 individuals aged ≤20 years, 23 each in the 21-30 years and 31-40 years age, 25 individuals aged 41-50 years, 18 in the 51-60 years range, and 5 individuals over 60 years old.

Table 1: Distribution of study subjects as per Age

Age (in years)	DM(n=100)
Mean age	**39.9±12.75**
≤20	6
21-30	23
31-40	23
41-50	25
51-60	18
>60	5

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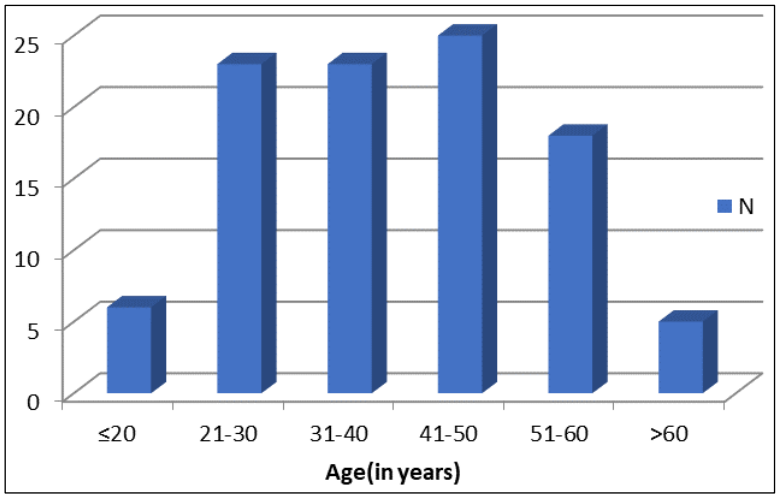
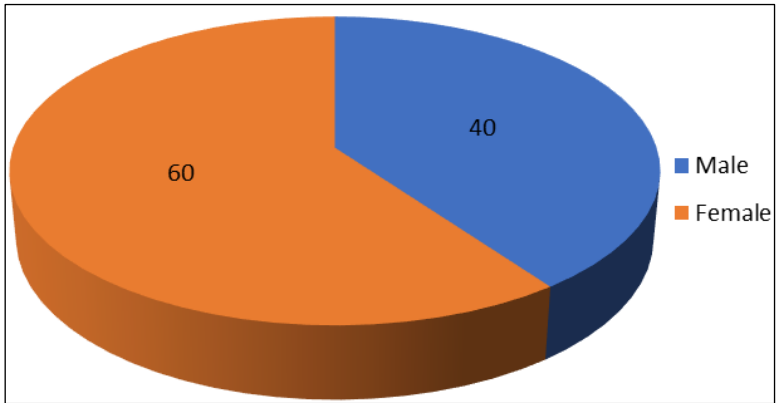


Graph 1: Bar graph of age distribution in years

The distribution of sex among the 100 individuals is as follows: 40 individuals identified as male, constituting 40% of the sample, while 60 individuals identified as female, making up the remaining 60%.

Table 2: Distribution of study subjects as per gender

Sex	
• Male	40(40)
• Female	60(60)



Graph 2:Pie chart of distribution of study subjects as per gender

Among 40 male and 60 female bronchial asthma patients 17 males and 37 females showed vitamin d deficiency with no significant statistical difference found among the two groups i.e.<0.059.

Table 3: Comparison of serum vitamin D levels among gender of study subjects.

Variable	**Vitamin D**		**p-value**
	<20 ng/mL	**≥20 ng/mL**	
Sex			
• Male	17	23	0.059
• Female	37	23	

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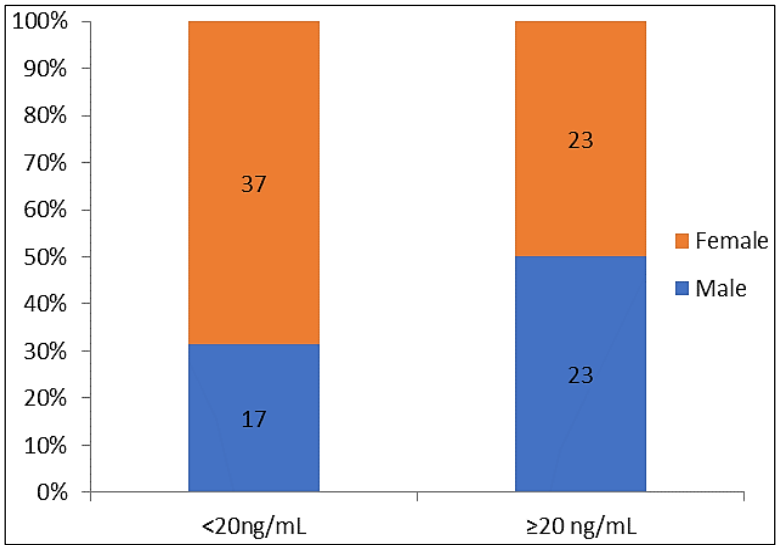
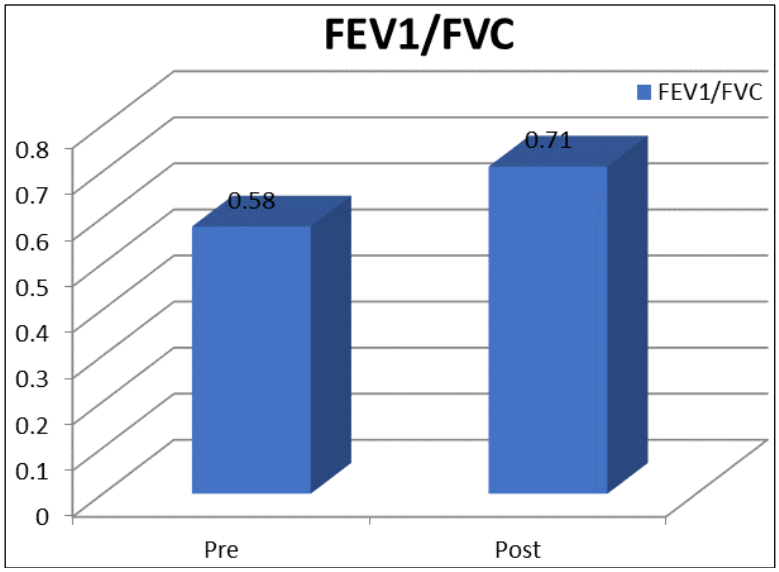


Graph 3:Bar chart of comparison of serum vitamin D levels among gender of study subjects

The measurements recorded are for FEV1/FVC pre and FEV1/FVC post. The mean FEV1/FVC pre value is 0.58 with a deviation of ±0.11, while the mean FEV1/FVC post value is 0.71 with a deviation of ±0.1. These measurements suggest obstructive pattern in spirometry.

Table 4: Mean FEV1/FVC ratio pre and post bronchodilation among study subjects.

Variable	DM(n=100)
FEV1/FVC pre	0.58±0.11
FEV1/FVC post	0.71±0.1



Graph 4: Bar chart of mean FEV1/FVC ratio pre and post bronchodilation among study subjects

The measured FVC pre bronchodilation has a mean value of 2.16 with a deviation of ±0.7, while FVC post bronchodilation has a mean value of 2.37 with a deviation of ±0.66. These measurements suggest significant increase in post bronchodilation FVC.

Table 5: Mean forced vital capacity pre and post bronchodilation among study subjects.

Variable	DM(n=100)
FVC pre	2.16±0.7
FVC post	2.37±0.66

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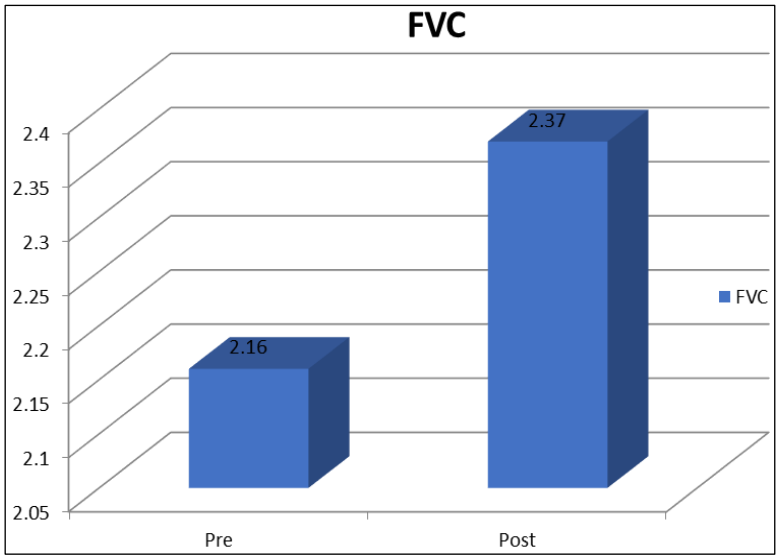
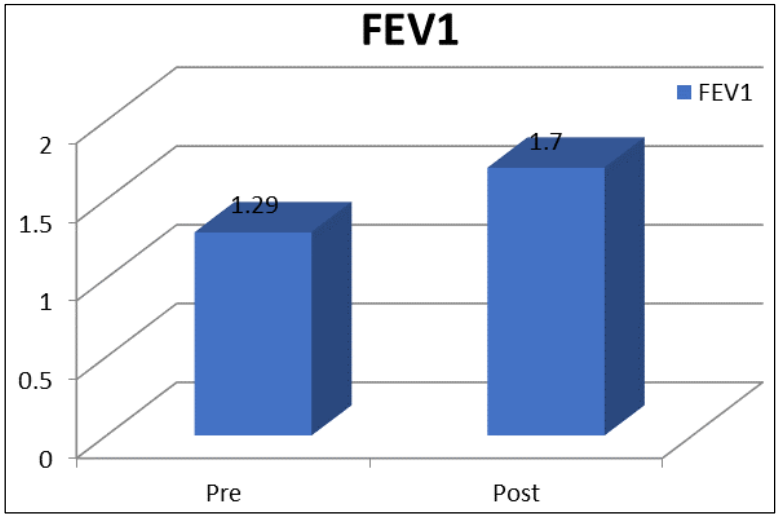


Graph 5: Bar chart of Mean forced vital capacity pre and post bronchodilation among study subjects

The measurements recorded are for FEV1 pre bronchodilation and FEV1 post bronchodilation. The mean FEV1 pre bronchodilation value is 1.29 with a deviation of ±0.47, while the mean FEV1 post bronchodilation value is 1.7 with a deviation of ±0.49. These measurements refer to forced expiratory volume at first second (FEV1) before and after giving bronchodilator nebulization which signifies these patients are asthmatics.

Table 6: Mean forced expiratory volume in 1st second pre and post bronchodilation among study subjects

Variable	DM(n=100)
FEV1 pre	1.29±0.47
FEV1 post	1.7±0.49



Graph 6: Bar graph of Mean forced expiratory volume in 1st second pre and post bronchodilation among study subjects

For Serum Vitamin D, the data is presented as 18 with a range of (11.98, 39.13). This likely indicates that the median serum vitamin D level is 18, with a range between 11.98 and 39.1 suggesting vitamin d deficiency and insufficiency among study subjects.

Table 7: Median serum Vitamin D levels among study subjects.

Variable	DM(n=100)
Serum Vitamin D*	18(11.98,39.13)

Values in mean±SD, *median(IQR)

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For AEC, the mean value is 571.49 with a standard deviation of ±268.73. This indicates an increase in absolute eosinophil count among the study subjects.

Table 8: Mean Absolute eosinophil count among study subjects

Variable	DM(n=100)
AEC	571.49±268.73

The data categorizes the severity of asthma into three levels: Mild, Moderate, and Severe. For each severity level, the number of individuals (n) and the corresponding percentage (%) are provided. Additionally, the serum vitamin D levels are reported for each severity category.

1. MILD ASTHMA

- 4 individuals (4% of the sample) are classified as having mild asthma.
- The median serum vitamin D level for this group is 71.65, with a range of 51.23 to 80.33.

2. MODERATE ASTHMA

- 31 individuals (31% of the sample) are categorized as having moderate asthma.
- The median serum vitamin D level for this group is 28.1, with a range of 14.05 to 51.4.

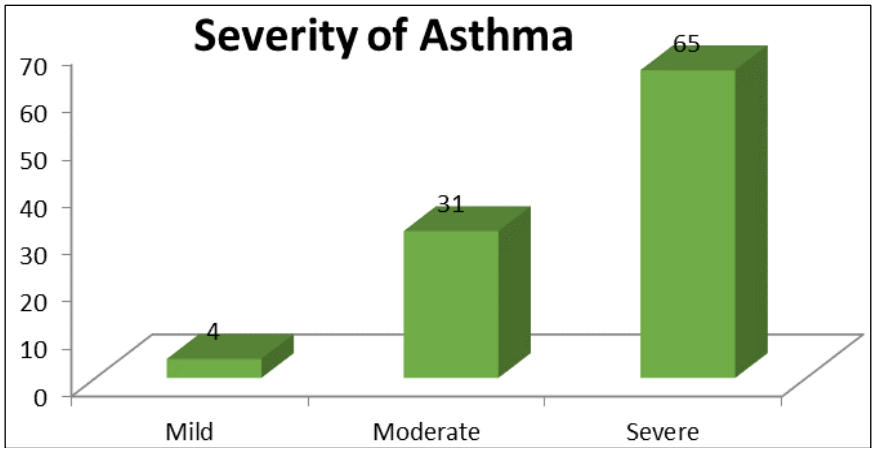
3. SEVERE ASTHMA

- 65 individuals (65% of the sample) are identified as having severe asthma.
- The median serum vitamin D level for this group is 14, with a range of 10.2 to 29.2 suggesting vitamin D deficiency.

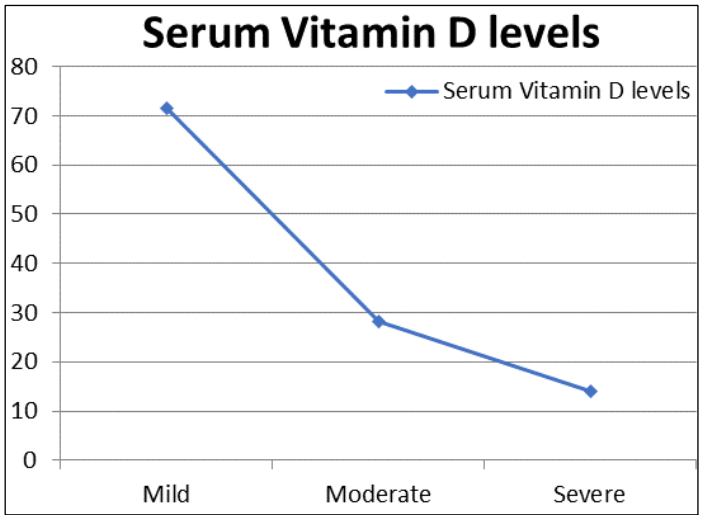
Table 9: Serum vitamin D levels in different subgroups of asthma

Severity of Asthma	n(%)	Serum Vitamin D*
Mild	4(4)	71.65(51.23,80.33)
Moderate	31(31)	28.1(14.05,51.4)
Severe	65(65)	14(10.2,29.2)

*Values as median(IQR)



Graph 9: Serum vitamin D levels in different subgroups of asthma



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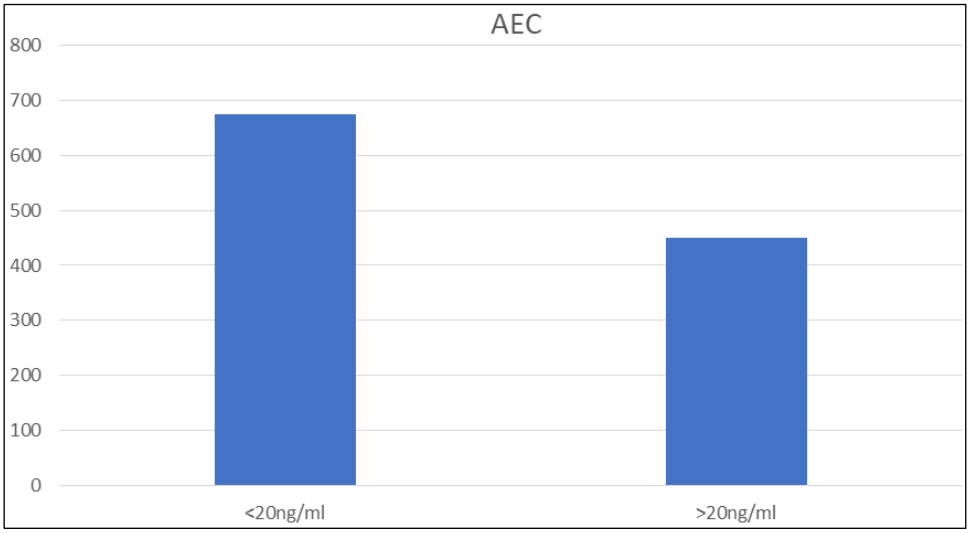
Asthmatic patients with vitamin d levels < 20ng/ml showed peripheral blood eosinophilia with mean value of 674.96 with a standard deviation of ±261.1 which is statistically significant with p value <0.001. This suggests that asthmatics with vitamin D deficiency showed increased absolute eosinophil count.

Table 10: Correlation between serum vitamin D levels and AEC

Variable	Vitamin D		p-value
	<20 ng/mL	≥20 ng/mL	
AEC	674.96±261.1	450.02±225.03	<0.001*



Graph 10:Bar chart of Correlation between serum vitamin D levels and AEC

DISCUSSION

Vitamin D has a significant impact on respiratory system as it can influence immunity and cell functions. The ability of lung epithelial cells to synthesize active Vitamin D by 1α hydroxylase and the presence of VDR polymorphisms support this. Studies have demonstrated an association between lower Vitamin D levels and many lung diseases including respiratory tract infections, rhinosinusitis, COPD, tuberculosis and bronchial asthma[18]. Many studies have linked Vitamin D deficiency with asthma exacerbations[19-21].

The present cross sectional study included 100 asthmatic subjects, diagnosed by performing spirometry. Patients were divided into groups based on severity of asthma as mild, moderate and severe. We had no patients presenting with life threatening disease. Serum Vitamin D levels and AEC were done for all patients.

Majority of the subjects belonged to the age group 21-40 years, with mean age being 39.9 ± 12.75 years. Studies by Li *et al.*[22], Sheb*let al.*[23]Korn*et al.*[20] had patients with a similar mean age. Some studies had a lower mean age of patients[24,25]. Many studies were also done in children [26-30].

There were 40 males and 60 females in the study population, Female patients were more than males, which is similar to other studies [22,29,30,31] and show that adult females have a higher tendency to develop asthma than males. When Vitamin D was measured among asthmatic male and female patients p value was < 0.059 which was not significant. Some studies also have found no difference between males and females [29].

Sun exposure is the major source of Vitamin D. Vitamin D metabolism is affected by various factors such as age, skin pigmentation, obesity and chronic illnesses. Sedentary lifestyle and dietary changes have caused increased prevalence of Vitamin D insufficiency and deficiency in the general population. In our study, Vitamin D deficiency was found in 54% of patients and vitamin D insufficiency in 16% of patients with bronchial asthma. It is in agreement with studies by Brehm*et al.*,[33], Searing *et al.*,[34], Felicia Montero-Arias *et al.*,[35], Stephanie Korn*et al.*,[36]. The low levels can be attributed to limited sunlight exposure due to outdoor activity limitation in patients with bronchial asthma.

Vitamin D protects against aeroallergen stimulated asthma by promotion of tolerogenic dendritic cells, enhanced regulatory T (Treg) cell action to suppress inappropriate Th2 responses, reduced IgE synthesis by B cells, increased IL-10 secretion and decreased mast cell activation. In nonallergic asthma, it modulates epithelial response to stimulation by producing a decoy blocker for IL-33, thus having an anti-inflammatory action. Vitamin D also decreases the synthesis of cytokines such as IL-17 which has distinct features in steroid resistant asthma [12]. Studies in children also showed similar results [37,38].

Severity of bronchial asthma was assessed and We observed that patients with mild asthma had median

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Vitamin D levels of 71.65(51.23,80.33)ng/ml, moderate asthma had 28.1(14.05,51.4)ng/ml and severe asthma had 14(10.2,29.2)ng/ml. Similarly, Korn*et al*.[20] observed that patients with mild asthma had mean Vitamin D level of 27.3 ng/ml, whereas moderate and severe asthma had mean levels of 26.5 ng/ml and 24.0 ng/ml with a significant p value (0.046). Kumar *et al*.[39] and Barday[40] also reported similar results, with the least Vitamin D levels in patients with severe asthma (p <0.001). Thus, Vitamin D levels can be a predictor of severity of asthma.

The Vitamin D levels differed significantly according to severity of the disease, with the least levels observed in severe asthma 14(10.2,29.2). This is in accordance to studies by Krishnan *et al*.[41] and Samrah*et al*.[24] who found a statistically significant relation between asthma severity, control and Vitamin D status. Korn*et al*.[20] reported that patients with severe asthma had 20% higher chances of being Vitamin D insufficient compared to mild or moderate disease and patients with uncontrolled asthma had 30% higher risk of being Vitamin D insufficient compared to well or partly controlled asthma.

The strong correlation between Vitamin D levels and asthma severity and control suggests an impact of its hormonal effects on the pathogenesis of bronchial asthma. Reduced Vitamin D levels are associated with increased expression of pro-inflammatory cytokines and thus, have pro inflammatory effects in asthma. Vitamin D has effects on airway remodeling through decreased smooth muscle hypertrophy and hyperplasia. It also complements the action of glucocorticoids and reduces steroid resistance. We hypothesize that there might be a dose-response relationship between Vitamin D levels and asthma severity and control. Severe asthma might be due to greater Vitamin D deficiency causing increased steroid resistance and thus, requirement of high dose of steroids for control of asthma. Lower Vitamin D levels might cause more inflammation and remodeling, leading to poorer asthma control.

Active form of Vitamin D has local immune effects in response to respiratory tract infections and might dampen the inflammation caused by them. It also reduces airway remodeling and improves steroid response, which are major risk factors for exacerbations. The present data showed that Vitamin D levels were negatively correlated with the number of exacerbations in the last one year. The lesser the Vitamin D levels, more were the number of exacerbations. Confino-Cohen *et al*.[32] found an inverse linear association between Vitamin D levels and the proportion of asthmatics with exacerbations. Brehm*et al*.[42] reported that Vitamin D was the strongest predictor of the number of hospitalizations in bronchial asthma. Studies by Samaha*et al*.[43], Gupta *et al*.158 and Solidoro*et al*.[44] also confirmed the same. Vitamin D reduces necrosis & also secondary release of cytotoxic granules from eosinophils in tissues[45]. In this study asthmatic patients with vitamin d deficiency showed raised peripheral blood eosinophils. The vitamin d concentration is inversely correlated with blood eosinophil count. Similar results were observed in study done by Hernández-Colín DD *et al*.which suggests VD concentration was inversely correlated with blood eosinophil count (*P* =.003, statistical power of 84%) and in this study When the median and mean concentration of eosinophils were compared between patients with asthma and VD <20 ng/ mL & patients with VD ≥20 ng/mL, there was a statistically significant difference, i.e., 359 eosinophils/mL vs. 240 eosinophils/μL respectively[46].

With this background, trials have started to see if supplementation of Vitamin D reduces the number of exacerbations of asthma[30,41,47,48].Vitamin D supplementation improved the quality of life[49] and control and severity of asthma in randomized control trials done by Menon*et al*.[50] and Tachimoto*et al*.[51].

A meta-analysis by Rajabbik*et al*.[52] also showed a possible association between low Vitamin D levels and incidence of asthma, which implied that supplementation might prevent asthma. Higher FEV_1, FVC and FEV_1/FVC and lower cytokine indices were observed when Vitamin D was supplemented. There was decreased asthma recurrence and re-hospitalization rate, suggesting Vitamin D supplementation increases asthma control rate and improves lung functions[37,44]. As Vitamin D deficiency in pregnancy is associated with increased incidence of respiratory infections and asthma in the newborn[54], supplementation during pregnancy might have beneficial effects on infant respiratory outcomes by modifying the immune system. These findings require randomized controlled trials to be conducted on a larger population to prove advantage and have a long way to go.

But, this study is in contradiction to Theusen*et al*.[53], who reported that Vitamin D levels are not related to development of allergy or asthma. A study by Esfandiar*et al*.[55] in 53 asthmatic children classified into mild, moderate and severe asthma, showed that although reduced Vitamin D levels were associated with asthma, it was not related to the severity or control of the disease. Studies by Meo*et al*.[56] and Yao *et al*.[57] showed that Vitamin D levels are not related to lung function impairment or FeNO. Devereux *et al*.[58] studied 80 asthmatic adults with 80 controls and found that Vitamin D levels are not related to asthma severity or control.

CONCLUSION

The following conclusion can be derived from this study

- Vitamin D deficiency was highly prevalent in patients with bronchial asthma.
- Vitamin D < 20 ng/ml was associated with increased severity of asthma
- Severe asthmatics with vitamin D < 20 ng/ml is associated with peripheral blood eosinophilia.

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Thus measuring serum levels of vitamin D could be considered in routine assessment of patients with bronchial asthma.

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