Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

Medicine

Correlation between Serum Vitamin D Levels and BODE Index in COPD Patients in A Tertiary Care Centre

Laxma Reddy S[1], Bhaskar K[2*], Vara Prasad K[3], Paramjyothi GK[4]
[1]Senior Resident, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, Telangana 500082, India
[2]Associate professor, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad Telangana 500082, India
[3]Junior Resident, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad Telangana 500082, India
[4]Professor and HOD, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad Telangana 500082, India

Original Research Article

***Corresponding author**
Bhaskar K

Article History
Received: 12.03.2018
Accepted: 25.03.2018
Published: 30.03.2018

DOI:
10.21276/sjams.2018.6.3.93

Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease and a major cause of disability and death all over the world. A multidimensional scale, the BODE index [BMI (B), degree of airflow obstruction (O), dyspnea as measured by the MRC dyspnea scale (D), and exercise capacity (E)] has been validated and proven to be useful in predicting two year mortality. Vitamin D deficiency is commonly seen in COPD patients. This study conducted in a tertiary care hospital has focused on the relationship between serum vitamin D levels and BODE index. A cross sectional observational study was performed at Nizam's Institute Of Medical sciences, a tertiary care hospital in Hyderabad, Telangana during the period of 2015-2017.This study included 104 COPD cases attending outpatient department of pulmonary medicine. Among 104 patients, 87 were males and 17 were females. The mean Vitamin D value of the study population was 20.77ng/ml (±11.74). Most of the patients (60%) had BODE index score < 5.The mean BODE index score decreased as the degree of vitamin D deficiency increases. Serum vitamin D deficiency is present in majority of COPD patients .It is more prevalent among patients with higher COPD GOLD Stages. There appears to be a positive correlation between serum vitamin D levels and post bronchodilator FEV1 (%). Vitamin D deficiency was found to be positively correlated with 6 minute walk distance. There is significant correlation between serum vitamin D deficiencies and BODE index.
Keywords: COPD, vitamin D, BODE index, BMI, FEV1, 6MWD, Dyspnea scale.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of disability and death all over the world. It is responsible for a huge social and economic burden for the health care infrastructure. COPD is the fourth leading cause of death in the world [1], represents an important public health challenge that is both preventable and treatable. According to World Health Organization estimates, 65 million people have moderate to severe COPD. More than 3 million people died of COPD in 2005 corresponding to 5% of all deaths globally [2].

According to the Global Obstructive Lung Disease (GOLD) guidelinesChronic Obstructive Pulmonary Disease (COPD) is defined as a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

There is no sufficient data estimating the prevalence of COPD in India, crude estimates suggest there are 30 million COPD patients in India [3]. COPD is a lung disease associated with significant and progressive irreversible airflow obstruction [4]. The strongest risk factor for COPD and an accelerated decline in adult lung function is cigarette smoking, and smoking cessation is known to slow the rate of decline of lung function [5,6,7]. Other factors that increase the burden of inhaled particulates and are associated with increased oxidative stress in the lungs including outdoor and indoor air pollution, and occupation[8,9],

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and a history of exposure to the above said risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context. Airflow limitation is best measured by Spirometry, a reproducible test of lung function. The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD.

Vitamin D plays a role in large number of biological processes, and that reduced levels of this hormone are implicated in a range of diseases. Vitamin D involved in the regulation of 3% of the human genome. Two genes containing the target sequence indicative of vitamin D regulation are those encoding LL-37 (cathelicidin) and hBD-2. These antimicrobial peptides are integral components of the innate immune system and act as natural antibiotics to help combat infection [10,11]. In 1922 Elmer V. McCollum identified an antirachitic substance in cod liver oil and called it Vitamin D [12]. Study of the physiological importance of vitamin D is a field which is expanding rapidly, with deficiencies of vitamin D giving an insight into many new roles. A recent meta-analysis of randomized controlled trials concluded that use of vitamin D supplements is associated with a decrease in total mortality rates [13]. Specifically in respiratory health, vitamin D deficiency has been shown to

- Increase the risk of upper respiratory tract infections and to decrease the forced expiratory Volume in 1 s (FEV_1) in asthma and wheezing disease [14]
- It also helps the remodeling of airways and reverses steroid resistance which are important Characteristics of COPD [15]

Interest in this area has grown further following the results of a large population survey in the United States, which observed a dose–response relationship between Vitamin D status and FEV_1 [16]. Higher vitamin D concentrations have been associated with better lung 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 NHANES II study[17].

Celli and colleagues evaluated 207 patients with COPD and identified 4 easily measured variables that predicted an elevated risk for death: BMI (B), degree of airflow obstruction (O), dyspnea as measured by the MRC dyspnea scale (D), and exercise capacity (E) as measured by the 6MWD test [18].These variables were used to construct a multidimensional scale, the BODE index, that ranged from 0 (least risk) to 10 (highest risk). Furthermore, in clinical studies comparing the BODE Index with FEV1, the BODE Index was shown to better assess progression of disease secondary to COPD exacerbations [19] and to be a significantly better predictor than the FEV1 for the risk for hospitalization due to exacerbations [20]. Therefore this study was performed to see the relationship between serum Vitamin D levels and BODE index.

METHODS

This cross sectional Observational study performed in the Department of Pulmonary Medicine, Department of Biochemistry, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, and Telangana. Total 104 stable COPD patients were recruited from ***1st January 2015 to 30th June 2016. Patients a***ged 35 years or more with history suggestive of COPD (cough with sputum production in chronic bronchitis and breathlessness in emphysema), and spirometry confirmed diagnosis of COPD as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, (only those patients who have a post bronchodilator FEV1/FVC ratio of less than 70%) were included.

EXCLUSION CRITERIA

- Current or past diagnosis of asthma (defined as an i ncrease in FEV1 >12% and > 200 mL above the ba seline value after administration of a bronchodilato r).
- Inability to complete the lung function test or 6-mi nutes walking distance (6MWD) test.
- All patients with insufficient mental capacity that p reclude obtaining an informed consent from them.
- Patients are excluded if they have TB, active cance, diabetes, hypertension, CAD, CKD and liver failur e.
- Patients who are on oral glucocorticoid therapy.

A detailed history of patient is taken & physical examination of each case done.Body mass index (BMI) calculation, Dyspnoea scoring according to modified medical research council (mMRC), 6 minute walk distance test was done and BODE index is calculated(Table 1).Hemogram,Serum vitamin D levels, Spirometry, Renal function tests, Liver function tests, Chest radiograph were done. Additional investigations may also be done depending on the patient's requirement.

Table-1: Calculation of BODE index

Parameters	Points on BODE index			
	0	1	2	3
FEV1(%of predicted)	≥65	50-64	36-49	≤35
Distance walked in 6 minutes(m)	≥350	250-349	150-249	≤150
Dyspnea scale score(mMRC)	0-1	2	3	4
Body mass index(BMI)	>21	<21		

SPSS statistics 17.0 version used for data analysis. Results were given as mean ± SD for data with normal distribution and variables that are not normally distributed will log-transformed (median and interquartile range [IQR]). The between-group differences calculated using a two-sided paired t-test or Chi-squared statistic where appropriate. To analyse relationships between variables, Student t test and simple regression performed. A p-value <0.05 will be considered statistically significant.

RESULTS

Total 104 stable COPD patients were recruited during study period.

87 were males and 17 were females of total 104 indicating male dominance (Table-2).

Table-2: Gender distribution of study population

Gender	Frequency(n)	Percentage
Male	87	83.6%
female	17	16.4%
Total	104	100%

Table-3: Age distribution of study population

Age(years)	Frequency(n)	Percentage
30-40	2	1.90%
40-50	10	9.61%
50-60	28	26.92%
60-70	46	44.2%
70-80	16	15.3%
>80	2	1.90%
TOTAL	104	100%

Age is ranged from 38 years to 91 years.Most of the patients were in age group between 60-70 years. About 60% patients were aged more than 60 years.

Mean BMI was 26.40 (±5.77) kg/m^2. Minimum BMI was 14.9 kg/m^2 and maximum BMI was 36.5 kg/m^2. Most of the population had normal BMI within the range of 18.5-25kg/m^2 (49.0%). 7 patients (6.7%) were obese with BMI >30 kg/m2 (Fig-1).

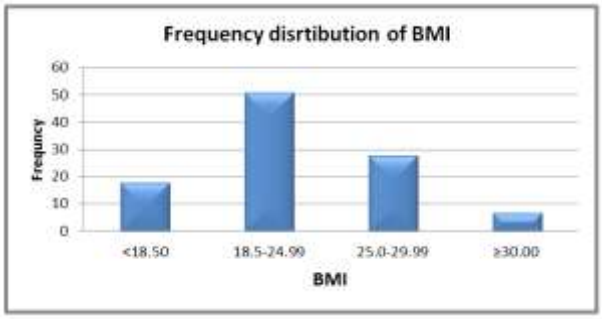

Fig-1: BMI status of study population

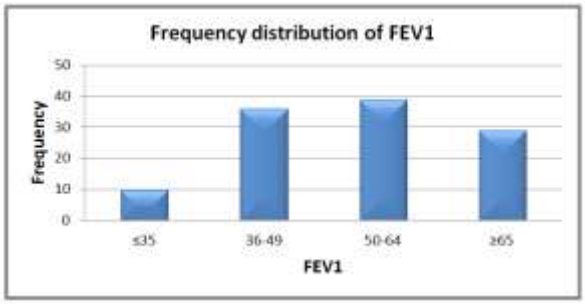

Fig-2: Distribution of study population as per FEV1

Majority of patients (71%) had FEV1 value between 36-64 (% of predicted). 27% of patients had FEV_1 of ≥65 (% of predicted).1% of patients had FEV_1 of ≤35 (% of predicted).

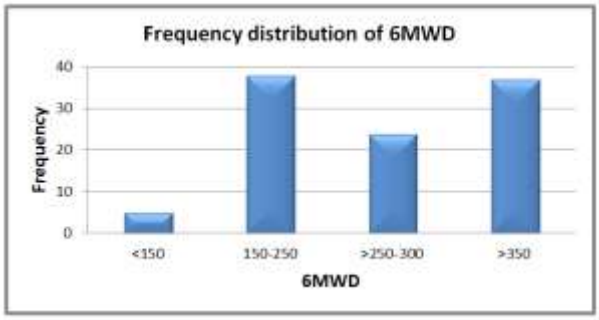

Fig-3: Frequency distribution of 6MWD

In 5 (4.80%) patients 6 minute walk distance was less than 150 meters. In 37 (35.57%) patients 6 minute walk distance was >350 meters. In most of patients (60.0%) 6 minute walk distance was between 150-350 meters.

Majority of patients had grade 3 mMRC breathlessness. None had grade 4 (Fig-4).

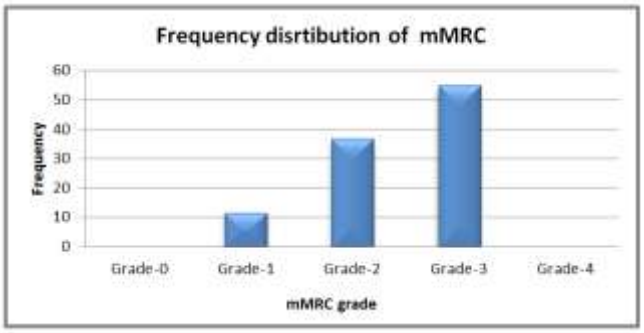

Fig-4: Frequency distribution of 6MWD

Table-4: Frequency distribution of vitamin D status

Vitamin D status	Frequency	Percentage
Sufficient (> 30 ng/ml)	32	30.7%
Deficiency (>10 to ≤30 ng/ml)	42	44.2%
Severe Deficiency (≤10 ng/ml)	26	25.0%
Total	104	100%

The mean Vitamin D value of the study population was 20.77 ng/ml (±11.74) .Minimum vitamin D levels was 5.6 ng/ml and maximum value was 43.9 ng/ml. Majority of the COPD patients were vitamin D deficient (69.2%).25.0 % was severely deficient of vitamin D.

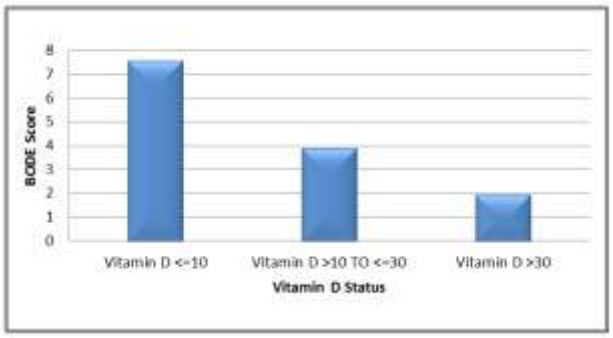

Fig-5: Vitamin D levels vs BODE score

BODE index score ranged from 0 to 9. Most of the patients (60) were had BODE index score < 5.The mean BODE index score increased as the degree of vitamin D deficiency increases. (7.57 ± 1.60>3.94 ± 2.10 >1.96 ±1.22)(P<0.001).

DISCUSSION

In this single institution based, observational cross sectional study, conducted for one and half year time period 104 COPD patients were recruited. Age ranged from 38 years to 91 years. Most of the study

population 64(60.0%) was above 60 years of age where 87(83.6%) patients were male and 17(16.4%) participants were female (Table 2&3).

Mean, minimum and Maximum BMI were 26.40 (±5.77) kg/m^2, 14.9 $kg/m^2$and 36.5 kg/m^2 respectively. Most of the population had normal BMI within the range of 18.5-25kg/m^2 (49.00%). 7 patients (6.72%) were obese with BMI>30 kg/m^2(Figure 1).

The mean Vitamin D value of the study population was 20.77 ng/ml (±11.74). Minimum vitamin D level was 5.6 ng/ml and Maximum value was 43.9 ng/ml. Majority of the COPD patients were vitamin D deficient (69.2%).25 % were severely deficient (Table 4).

Our study showed that both prevalence and severity of vitamin D deficiency in stable COPD patients increase as the disease severity progresses. Prevalence of serum vitamin D deficiency in GOLD Stage 1 was 30%, Stage 2 was 87.5%, and Stage 3 and 4 was 100%.

When compared to other studies, our study has higher prevalence of vitamin D deficiency. Similar analysis was done by Jansen's W. *et al*. [21] in 2010 showed 39%, 47%, 60% and 77% of patients deficient of vitamin D among GOLD stages 1, 2, 3 and 4 respectively and he concluded that vitamin D deficiency becomes more common as COPD GOLD stages become higher. We found the mean value of serum vitamin D decreases along with increase severity of COPD. The mean serum vitamin D level was 30.82 ng/ml among patient in GOLD Stage 1 and it was 10.05(±5.38) ng/ml in GOLD Stage 4.

Post bronchodilator FEV_1 (%) value, a measurement of severity of airway obstruction, decreases as the level of mean serum vitamin D become decreased. The mean FEV_1% was 83.15±11.53, 60.97±17.47, 30.71±7.96 amongst vitamin D sufficient, deficient and severe deficient groups respectively (Figure 2). We concluded that there is a positive correlation between serum vitamin D level and post bronchodilator FEV_1 (%) volumes (p <0.01).Similarly, Mohamad monandi *et al*. [22] measured the serum 25-hydroxyvitamin D (25-OHD) and post bronchodilator forced expiratory volume in 1s (FEV_1). The mean FEV_1 volume (L) in serum 25-OHD deficient COPD was lower than sufficient COPD (1.550±0.55 v/s 1.650±-0.58, p=0.45). Mean FEV_1 values increased from 1.55±0.55 L in patients with mean serum 25- OHD <20 ng/ml to 1.94±0.74 L in COPD patients with mean serum 25-OHD ± >40 ng/ml.

Similar study by Paresh Chandra Mohanta *et al.* [23], on correlating the serum vitamin D level and FEV_1% of predicted in stable COPD patients. In 25-OHD deficiency COPD cases FEV_1% of predicted was 28.10±6.17, in 25-OHD insufficiency cases was 35.92±8.03 and sufficiency cases was 46.10±11.99. There was very strong positive correlation present between, serum 25-OHD and FEV_1 % of predicted in stable COPD.

We studied the relationship between serum vitamin level and 6 minute walk distance,The mean 6 minutes walk distance decreased as the degree of vitamin D deficiency increases(343.0±73.22m> 280.66±89.22 m> 202.14 ±73.99m)(P <0.01)(Figure 3).Most of the study population had mMRC grade 4(Figure 4).

Finally we studied the correlation between serum vitamin D levels and BODE index. In our study BODE index score ranged from 0 to 9. Most of the patients (60) were having BODE index score < 5 .The mean BODE index score increased as the degree of vitamin D deficiency increases. (7.57 ± 1.60>3.94 ± 2.10 >1.96 ±1.22) (P<0.001)(Figure 5).

Balakrishnan Menon *et al*. [24] studied BODE index in sixty two COPD patients. Staging, severity and exacerbation rate were assessed. Vitamin D levels decreased with increased severity of disease. Mean levels in GOLD severity grade A was 41.02±14.12, in grade B was 31.57±12.49, in grade C was 17.63±8.51 and in grade D was 16.91±7.89. Vitamin D levels correlated negatively with GOLD severity grade (-0.406), BODE index (-0.408), CCQ (-0.495), exacerbation rate (-0.536) and GOLD staging (-0.369).

CONCLUSIONS

Our study demonstrated that serum vitamin D deficiency is present in majority of COPD patients .It is more prevalent among patients with higher COPD GOLD Stages. There appears to be a positive correlation between serum vitamin D levels and post bronchodilator FEV_1 (%). Vitamin D deficiency was found to be positively correlated with 6 minutes walk distance and Body mass index (BMI).There is significant correlation between serum vitamin D deficiencies and BODE index.

There is a need of research for supplementation of vitamin D in deficient COPD patients and improvement in respiratory, systemic parameters.

Limitations of this study include small sample size, conducted in a single center. Large sample size, prospective study with supplementation of vitamin D in those who are deficient and assessment of all parameters will provide adequate data to recommend routine assessment and supplementation of this vitamin in all patients.

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