Original Article

Correlation of severity of chronic obstructive pulmonary disease with serum vitamin-D level

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Abstract

Context: The global scenario of illness is shifting from infectious diseases to non-communicable diseases, with chronic conditions such as heart diseases, stroke and Chronic Obstructive Pulmonary Disease (COPD) now being chief causes of death globally and more than 90% of deaths due to COPD occur in low and midline income countries.[1] Low serum vitamin D level is associated with various lung diseases and decreased lung function.[2] **Aims:** This study was designed to study the serum vitamin D level and its correlation with severity of COPD as assessed by spirometry, COPD assessment test (CAT) and exercise capacity and BMI of COPD patients. **Settings and Design:** Observational cross sectional study conducted on patients of COPD attending the outpatient department. **Materials and Methods:** One hundred sixty consecutive patients of COPD attending the outpatient Department were included in the study. Pack years, CAT score, 6 minute walk distance, post bronchodilator spirometry values and BMI was recorded along with complete history and physical examination. **Statistical Analysis Used:** Data analysis was done using IBM SPSS 23 software. Descriptive statistics, Independent sample *t* test, ANOVA and Pearson correlation were applied. **Results:** A significant positive correlation was found between FeV1% of predicted and serum Vitamin D level($r = 0.291$; $P < 0.001$). A negative correlation was found between serum Vitamin D level and severity of COPD as assessed by CAT score ($r = -0.355$; $P < 0.001$). Also, a significant positive correlation was found between vitamin D levels and exercise capacity as assessed by 6 minute walk test (6MsWT) ($r = 0.648$; $P < 0.001$). **Conclusions:** COPD patients with more severe disease tend to have lower serum Vitamin D levels. As it is an immunomodulator affecting various inflammatory pathways, it is imperative that we give due consideration to Vitamin D levels in managing patients of COPD.

Keywords: 6 minute walk test, body mass index, chronic obstructive pulmonary disease assessment test, forced expiratory volume in one second (FeV1), Global initiative for Obstructive Lung Diseases, pack years, smoking, Vitamin D

Introduction

According to *World Health Organisation (WHO)*, the global scenario of illness is shifting from infectious diseases to non-communicable diseases, with chronic conditions such as heart diseases, stroke and chronic obstructive pulmonary disease (COPD) now being chief causes of death globally.[1] COPD is 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 and gases.[2]

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The *Global Burden of Disease Study* reports a prevalence of *251 million* cases of COPD globally in 2016.[1] Globally, it is estimated that *3.17 million* deaths were caused by the disease in 2015 (that is, *5%* of all deaths globally in that year).[1] COPD is a leading cause of mortality, currently the *fifth* leading cause of mortality in the world.[3-5] COPD is a leading cause of mortality that will become third most cause of death by 2030.[6] According to *WHO* report, more than 90% of deaths due to COPD occur in low and midline income countries which worsen the condition more.

In India, the direct mean expenditure for a patient of COPD was assessed as Rs. *2,258 per year* and *Rs. 1,970* for the caregiver in the family.[7] This total amount is huge burden as seen for per capita income.

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Low serum vitamin D is associated by various lung diseases and present with decreased lung function, which is a hallmark of COPD.[8] More recently Vitamin D is being recognized not just as a vitamin but as a pleiotropic prohormone. The vitamin-D receptor (VDR) is widely distributed throughout the human body. Being an immunomodulator, vitamin-D cannot only enhance the innate immune response but also regulate adaptive immune responses.[9] Moreover, cell differentiation, apoptosis, intercellular adhesion, cell proliferation are associated with vitamin-D. COPD is associated with systemic inflammation and Vitamin D has a bearing on the pathogenesis of inflammation.

There are evidences that link a low vitamin D nutritional status to inflammatory processes seen in highly prevalent chronic illnesses including COPD, common cancers, autoimmune diseases, infectious, and cardiovascular diseases.[10] Vitamin D supplementation reduces the incidence of moderate or severe COPD exacerbation. This could be attributed to vitamin D mediated suppression of proinflammatory cytokines and chemokines such as IL 6 and CCL5, which are associated with pathogenesis of exacerbation.[11]

Vitamin D has an effect both on the pathogenesis as well as severity of COPD in multiple ways. Owing to its role in immunoregulation, vitamin D affects the frequency of occurrence of respiratory infections that trigger the acute exacerbation in COPD. Furthermore, Vitamin D deficiency may cause more severe exacerbations due to attenuated response to the causative pathogen, leading to an enhanced adaptive immune response with increased production of cytokines and aggravated bronchial inflammation.[12] Also, it causes inhibition of the proliferation of airway smooth muscle,[12] and may also affect tissue remodeling by collagen synthesis.[13]

Therefore, a cumulative study to assess the relation between serum vitamin-D level and severity of COPD is necessary. Correlation between serum vitamin-D levels and severity of COPD is not yet well documented.[14] Hence, it is useful to compare and analyse the level of vitamin-D with severity of COPD, as optimum Vitamin-D levels are important to treat COPD and to improve the quality of life.[15]

There are not much evidences of vitamin D correlation with COPD. One of the study reveals that 31–77% of patients with COPD have vitamin D deficiency and insufficiency.[15] Decreased serum 25 (0H) vitamin D levels were associated with increase airway obstruction.[14] Also, Vitamin D deficiency and insufficiency are more prevalent in female COPD patients.[15]

There is relatively limited data on bidi smoking and COPD and mostly from India where bidi smoking has remained popular.[16] In urban areas that are more polluted, smokers had more respiratory problems than non-smokers.[17] Bidi used as a means of tobacco smoking was clearly recognised as an important etiological factor.[18-21] For non-smokers, combustion and smoke of burning dried wood, animal dung is one of the factors of causing obstructions of respiratory tract.[16]

India is an agro-economy. According to *Census report*, about *68.84%* of people living in India belong to rural backward where economic activities performed are the primary leading people to be exposed to solar radiations as compared to that of other countries where secondary and tertiary are the leading activities. The different lifestyles of people in India demands for indigenous studies, best suited to Indian context. Studies done in rest of the world cannot be processed in India, as lifestyles, food habits, and duration, intensity, and exposure to solar-radiation are quite different, determining different Serum Vitamin-D level concentration. Vitamin-D concentration level may vary from place to place within the country and can also depend on the patient's day to day physical activities. Therefore, it is imperative that a study of vitamin D levels in the indigenous population in both the sexes be done to find the correlation of Vitamin D levels with disease severity in Indian population. Since, decreased exercise capacity, occurring in COPD patients can also be affected by the levels of Vitamin D, a correlation of 6-min walk test with Vitamin D levels is also studied. In this study we aim to assess the relation between serum Vitamin D level and spirometry, 6 Minute walk distance, CAT score and BMI in COPD patients.

Materials and Methods

Study design and population

Our study was an observational cross sectional study. We included 160 consecutive stable COPD patients attending the outpatient department over a period of 6 months.

Patient selection criteria

COPD was diagnosed based on history, physical examination and spirometric criteria in accordance with *Global Strategy for Diagnosis Management and Prevention of COPD, 2018 (GOLD Guidelines)*.[2] Patients with acute exacerbation of COPD, pneumonia, tuberculosis and other coexisting respiratory illness were not included in the study. Patients with coexisting cardiac illness, systemic hypertension, chronic renal disease, anaemia, hypoproteinemia, hyperparathyroidism, disease related to vitamin-D metabolism and absorption were also excluded. Uncooperative patient, unsocial and those unwilling to give informed written consent, physically challenged patients with walking disability and patients with very low intelligence quotient were not included.

Collection of data

Medical history of the patient was assessed through a detailed questionnaire designed for the study. This included age, sex, physical examination, living area/status, smoking history, information regarding his/her illness, duration, symptoms, any history of exacerbation, socioeconomic status, any drug used or inhaled corticosteroid use, any history of antibiotics or corticosteroids in the previous year and hospitalization history due to any pulmonary

symptoms in the last one year, COPD assessment test (CAT) score, dyspnoea scale (mMRC), 6 Minute Walk Distance, spirometry test and analysis of serum vitamin D level. Patients were classified as frequent exacerbates if they had more than one exacerbation or if there was any history of hospitalization due to an exacerbation in the previous one year. The patients were grouped as: smokers-patients who continue to smoke or have stopped smoking less than 6 months prior to the examination, ex-smokers-patients who stopped smoking more than 6 months prior to the examination and non-smokers-patients who never smoked or smoked less than 100 cigarettes in their life time. The number of bidi/cigarette consumed in terms of pack years was also recorded.

A series of questions under *COPD assessment test (CAT)* were asked to measure the impact of COPD on patient's life and how it change overtime.[22] On the behalf of CAT assessment, the patient was awarded score out of 40. Also, a simple measure of breathlessness such as *Modified Medical Research Council (mMRC)* questionnaire[23] was considered adequate for assessment of symptoms, as the *mMRC* relates well to other measure of health status[24] and predicts future mortality risk.[25,26] According to mMRC, total 5 grade from 0 to 4 are assigned to grade the dyspnoea. Study subjects were classified into *GOLDgroup ABCD* based on their CAT score and history of exacerbation.[2] Patient's height and weight was measured and then *Body Mass Index (BMI)* was calculated.[27] Height was measured in metres (m) and weight in kilograms (Kg) the BMI was recorded in universally expressed unit of kg/m^2. Patients were classified as underweight (BMI <18.5), normal (BMI 18.5-24.9) and overweight (BMI ≥25.0). Patients' Chest X Ray (PA view) was also analysed.

Pulmonary function test

The lung function was assessed by using *spirometry* by measuring the volume of air that the patients can expel out from the lungs after a maximal inspiration. Pre- and Post- values were recorded for FEV1 (% of predicted), FVC (% of predicted), FEV1/FVC% (of the patient) and the obstruction was classified as mild (FEV1 ≥ 80% predicted), moderate (50% ≤ FEV1 < 80% predicted), severe (30% ≤ FEV1 < 50% predicted) and very severe (FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure).[2]

Minute Walk Distance was calculated after asking the patient to walk on a long, hard, flat, horizontal surface without any hindrance for 6 minutes and the distance walked, heart rate, oxygen saturations were recorded. This test was conducted accordingly to *American Thoracic Society Guidelines*.[28]

Blood sample and analysis

A venous blood sample extracted from antecubital fossa of arm was collected from each patient. Analysis of serum vitamin D levels was done by quantitative chemiluminescent immunoassay (CLIA) method. Serum Vitamin D level less than 30 ng/ml was taken as Vitamin D deficiency. In addition, routine investigations like haemogram, blood sugar, lipid profile analysis were done.

An approval was taken from the Institutional Ethics Committee of the hospital to conduct the research.

Statistical analysis

All data collected, was analysed by using *IBM Statistical Package of Social Science SPSS* Version 23.0**.** Test for normality was done using descriptive statistics. Comparison of mean between groups was carried out using independent sample T-test (two tailed) and one-way ANOVA with LSD post hoc-test for significance. Test for correlation was done using Pearson correlation. Spearman correlation test was done for data that was not normally distributed.

Result

A total of 160 COPD patients were included in the study. 77.5% (n = 124) of them were males. The mean age of male patients was 57.18 ± 8.28 years. The mean age of female patients was 53.78 ± 7.81 years. 23.4% (n = 29) of males were smokers, 62.9% (n = 78) were ex-smokers and 13.7% (n = 17) were non- smokers. Among females 63.9% (n = 23) were smokers. 19.4% (n = 7) were ex-smokers and 16.7% (n = 6) were non-smokers. The mean number of pack years among smokers was 63.41 ± 37.61 and among ex-smokers was 41.25 ± 22.98. There are about 66% (105 of 160) of the total patients had Vitamin D deficiency (Serum level <30 ng/ml). According to GOLD 2018 criteria for spirometric severity of obstruction, 5.0% (n = 8) patients had mild obstruction, 40% (n = 64) patients had moderate obstruction, 30% (n = 48) patients had severe obstruction and 25.0% (n = 40) patients had very severe airflow obstruction on spirometry. The baseline patient characteristics are shown in Table 1. The mean Serum Vitamin D level in various subgroups of study participants are shown in Table 2.

Table 1: Patient characteristics

Patient characteristic	*n* (%)
Total patients	160 (100%)
Males	124 (77.5%)
Females	36 (22.5%)
Age (Total mean)	56.41±8.25
Males (mean)	57.18±8.28
Females (mean)	52.81±7.76
Pack years	
Smokers	63.41±37.61
Ex-smokers	41.24±22.98
Smoker	52 (32.5%)
Ex-smoker	85 (53.1%)
Non-smoker	23 (14.4%)
COPD stage	
GOLD A	16 (10.0%)
GOLD B	107 (66.9%)
GOLD C	9 (5.6%)
GOLD D	28 (17.5%)
Spirometric severity of airway obstruction	
Mild	8 (5.0%)
Moderate	64 (40.0%)
Severe	48 (30.0%)
Very severe	40 (25.0%)
Frequent exacerbators	37 (23.1%)

The mean 6-minute walk distance was 395.0 ± 24.31 m, 350.44 ± 81.50 m, 271.78 ± 118.60 m and 246.62 ± 97.79 m in patients with mild, moderate, severe and very severe obstruction respectively. The mean 6-minute walk distance of patients with mild obstruction was significantly higher than mean 6-minute walk distance of patients with severe obstruction (P = 0.001) and patients with very severe obstruction (p = 0.000). The mean 6-minute walk distance of patients with moderate obstruction was significantly higher than 6 min walk distance of patients with severe (p = 0.000) and very severe obstruction (p = 0.000). The mean 6 min walk distance was not significantly different between patients with mild and moderate obstruction (p = 0.221) and between patients with severe and very severe obstruction (p = 0.227) [Figure 1a].

Table 2: Mean serum Vitamin D level in various subgroups of COPD patients

Patient characteristic	Mean serum Vitamin D level	*n*	Statistics	*P*
All	25.168±10.19	160		
Sex			*t*=0.249	0.804
Male	25.28±10.21	124		
Female	24.79±10.29	36		
Smoking			*F*=0.768	0.466
Smoker	23.7±8.0	52		
Ex-smoker	25.88±9.65	85		
Non-smoker	25.80±15.48	23		
CAT			*t*=-2.234	0.027
<10	29.62±13.20	22		
≥10	24.46±9.50	138		
FeV1% predicted			*F*=5.449	0.001
FeV1% ≥80% (mild)	35.8±8.89	8		
50% ≤ FeV1<80% (moderate)	26.95±10.43	64		
30% ≤ FeV1<50% (severe)	23.19±9.35	48		
FeV1<30% (very severe)	22.56±9.41	40		
COPD Stage			*F*=2.348	0.075
GOLD A	31.49±12.2	16		
GOLD B	24.44±9.72	107		
GOLD C	23.96±12.49	9		
GOLD D	24.73±9.24	28		
BMI			*F*=5.98	0.004
<18.5 (underweight)	23.85±8.9	42		
18.5-25 (normal weight)	29.27±11.25	28		
>25 (overweight/obese)	16.95±3.8	8		

On classifying patients based on GOLD criteria of severity of disease as groups A, B, C and D, significant difference in mean 6 min walk distance was observed between groups A and B (post hoc test P = 0.003) while no significant difference in mean 6 min walk distance was observed between other groups [Figure 1b].

Interestingly, a significant positive correlation was found between Fev_1% predicted and 6-minute walk distance (r = 0.461, P = 0.00) [Figure 2].

The mean serum vitamin D level was 24.79 ± 10.07 in males and 26.23 ± 10.49 in females. The mean serum Vitamin D level was 36.2 ± 10.2, 27.58 ± 10.4, 22.49 ± 9.1 and 22.25 ± 8.9 in patients with mild, moderate, severe and very severe obstruction respectively. On applying one-way ANOVA, it was found that the mean serum Vitamin D level in patients with mild obstruction was significantly higher than patients with moderate (p = 0.017), severe (p = 0.001) and very severe obstruction (p = 0.001). The mean serum vitamin D level of moderate obstruction was also significantly higher than that of severe (p = 0.046) and very severe obstruction (p = 0.766) [Figure 3a].

A significant positive correlation was found between serum vitamin D level and FEV_1%in smokers (r 0.524, P = 0.000), and non-smokers (r = 0.750, P = 0.000). No such positive correlation was found among ex-smokers (r = 0.137, P = 0.212) [Figure 4].[4]

The mean serum vitamin D level was 23.7 ± 8.0 ng/ml in smokers, 25.88 ± 9.65 ng/ml in ex-smokers and 25.80 ± 15.48 ng/ml in non-smokers. The difference was not found to be statistically significant (ANOVA F = 2.144, P = 0.124). A significant positive correlation was found between serum Vitamin D level and 6 minute walk distance in smokers, ex-smokers and non-smokers, suggesting a relation between serum Vitamin D level and exercise capacity of COPD patients [Figure 5].

However, we did not find any significant difference between mean serum vitamin D levels of GOLD A, B, C and D groups ANOVA F = 2.348, P = 0.075 [Figure 3b]. Also, no significant difference in mean serum vitamin D level was found between patients with no

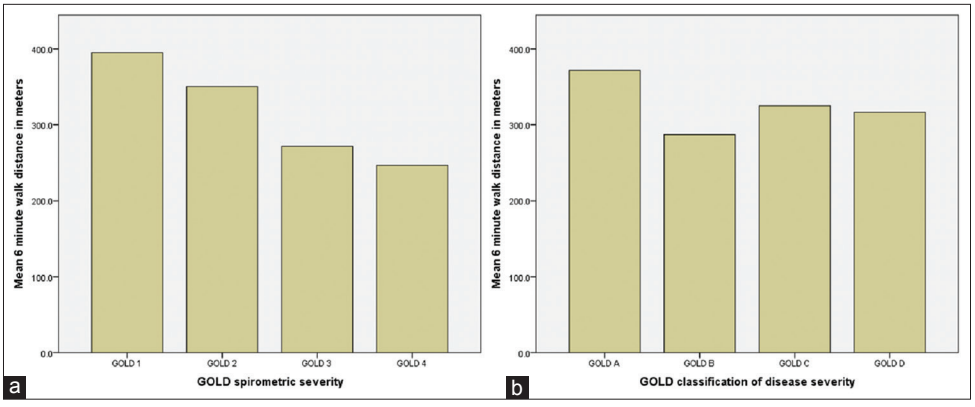

Figure 1: Comparison of mean six minute walk distance based on GOLD spirometric severity and disease severity (GOLD classification A, B, C, D)

exacerbation in previous year (25.774 ± 10.57 ng/ml) as compared to patients with frequent exacerbations (23.15 ± 8.67 ng/ml). (p = 0.126). A significant negative correlation was found between serum vitamin D level and COPD assessment test (CAT) score ($P < 0.001$) [Figure 6]. The mean serum Vitamin D level in patients with CAT score <10 was 29.62 ± 13.20 ng/ml while in patients with CAT score ≥10 it was 24.46 ± 9.50 ng/ml. This difference was found to be significant (t = -2.234 $P = 0.027$).

The mean serum vitamin D level in underweight patients was 24.05 ± 9.17 ng/ml, in patients with normal BMI was 28.86 ± 11.22 ng/ml, and in obese patients, it was 17.09 ± 3.97 ng/ml. vitamin D level of normal weight patient was significantly higher than that of patients who were underweight or overweight/obese.

The mean serum vitamin D level of smokers was 23.73 ± 8.02 ng/ml, ex-smokers 25.88 ± 9.65 ng/ml and that of non-smokers was 25.80 ± 15.48 ng/ml. No significant difference was observed. (F = 0.768; $P = 0.466$). A significant negative correlation was found between serum vitamin D level and pack years both among smokers and ex-smokers [Figure 7].

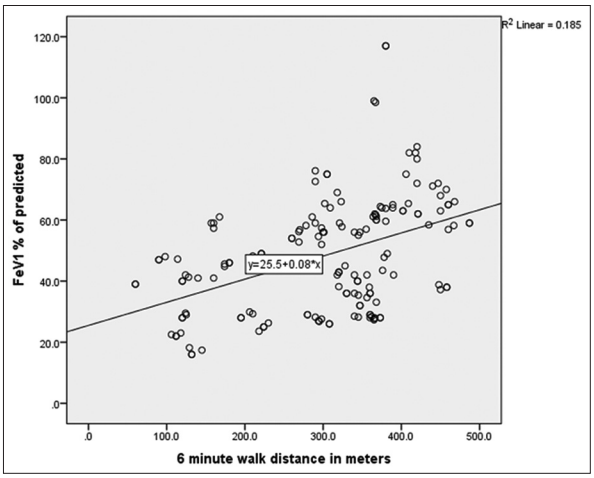

Figure 2: Scatter plot showing relation between Fev_1% predicted and 6-minute walk distance (r = 0.461, $P = 0.00$)

The mean serum vitamin D level in patients with infrequent exacerbation in previous yearwas 25.77 ± 10.57 ng/ml and in patients with frequent exacerbations it was 23.15 ± 8.67 ng/ml. The difference was not found to be statistically significant (p = 0.171).

The mean 6 minute walk distance (6MWD), Fev_1% of predicted and COPD assessment test (CAT) score was significantly higher in patients with no Vitamin D deficiency as compared to those with Vitamin D deficiency. There was no significant difference in age, body mass index and pack years between the two groups [Table 3]. Table 4 shows the coefficients of correlation of serum vitamin D level with FeV1%, CAT score, 6 MWD, body mass index and pack years.

Discussion

The purpose of this study was to assess the serum Vitamin-D levels, to determine COPD patients based on disease severity

Table 3: Clinical parameters in patients with and without Vitamin D deficiency

	Vitamin D deficient *n*=105	Vitamin D sufficient *n*=55	*P*
Age (years)	55.77±8.434	57.64±7.82	0.175
FeV1% of predicted	45.52±19.45	54.02±16.66	0.007
CAT score	19.27±6.9	15.85±4.84	0.001
Pack years	46.82±34.44	34.31±31.02	0.025
6 MWD (meters)	260.61±92.75	384.22±85.67	0.000
BMI (kg/m^2)	19.84±4.46	19.05±3.40	0.252

Table 4: Correlation of Vitamin D level with clinical parameters (All patients)

Parameter	Statistics	*P*
FeV1% of predicted	0.291	0.000
6 MWD (meters)	0.648	0.000
CAT score	-0.355	0.000
BMI (kg/m^2)	-0.073	0.356
Pack years		
Smokers: (*n*=52)	-0.545	0.000
Ex-Smokers: (*n*=85)	0.221	0.042

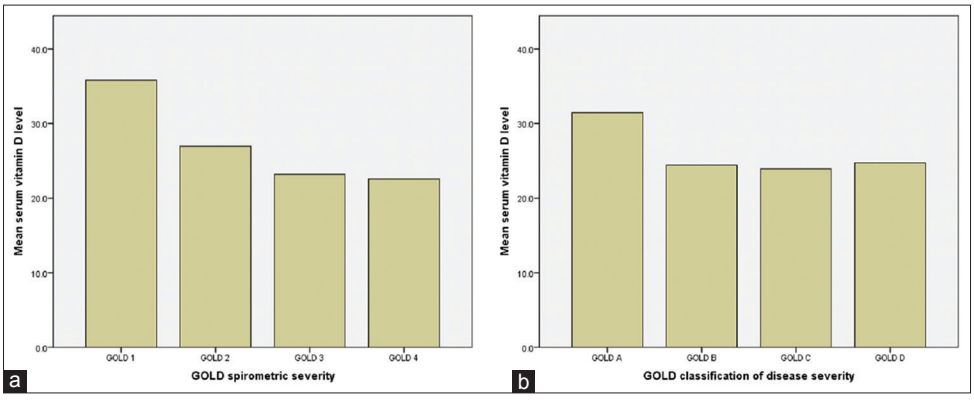

Figure 3: Comparison of mean serum vitamin D levels based on (a) GOLD spirometric severity and (b) disease severity (GOLD classification A, B, C, D)

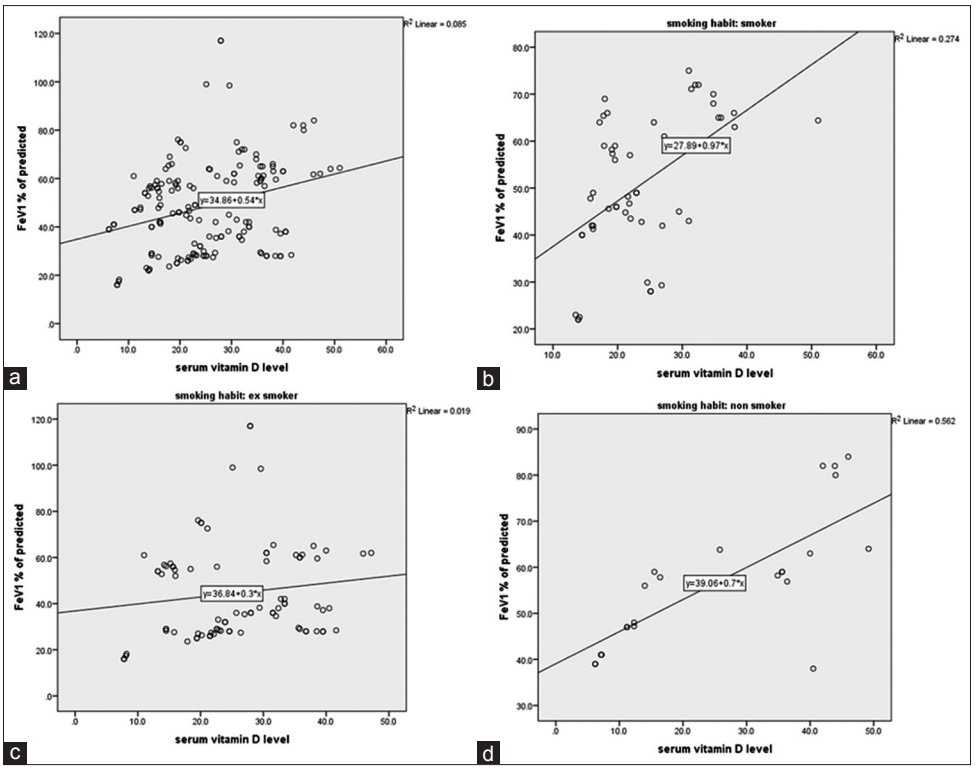

Figure 4: Scatter plot showing relation between mean vitamin D level and FEV1% of predicted (a) all patients, (b) smokers, (c) ex-smokers, (d) non-smokers

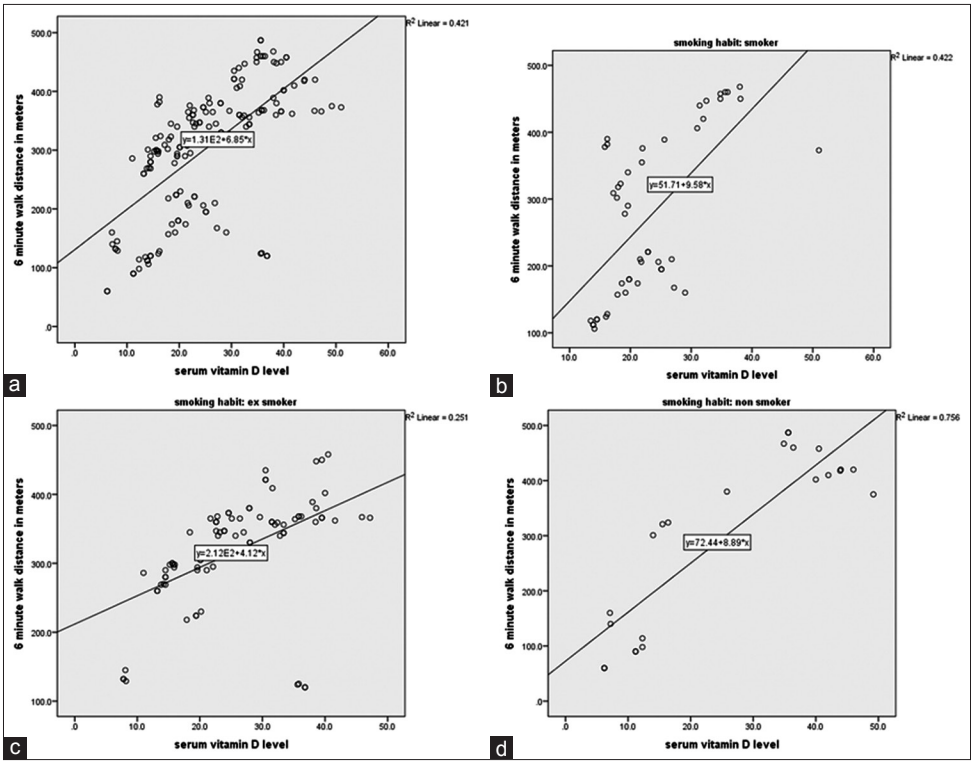

Figure 5: Scatter plot showing significant positive correlation between serum Vitamin D level and 6-minute walk distance (Spearman rho = 0.698, *P* = 0.00) in (a) all patients, (b) smokers, (c) ex-smokers and (d) non-smokers

and exercise capacity and to find out if there is any relation of serum vitamin-D level with severity of airway obstruction, exercise capacity, BMI, symptoms and quality of life and other relevant factors in COPD patients.

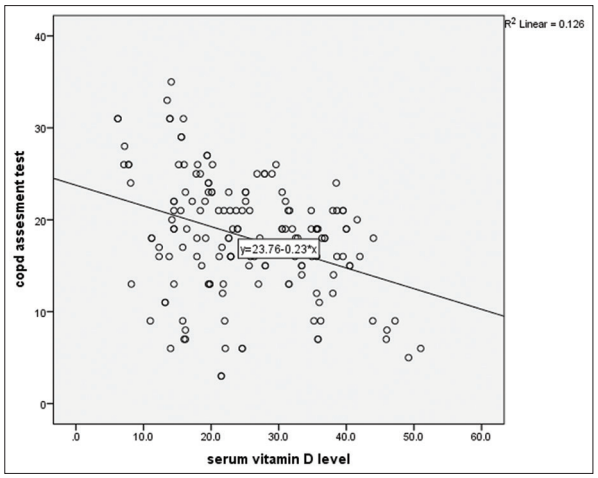

Figure 6: Scatter plot showing significant negative correlation between serum vitamin D level and COPD assessment test (CAT) score ($P < 0.001$)

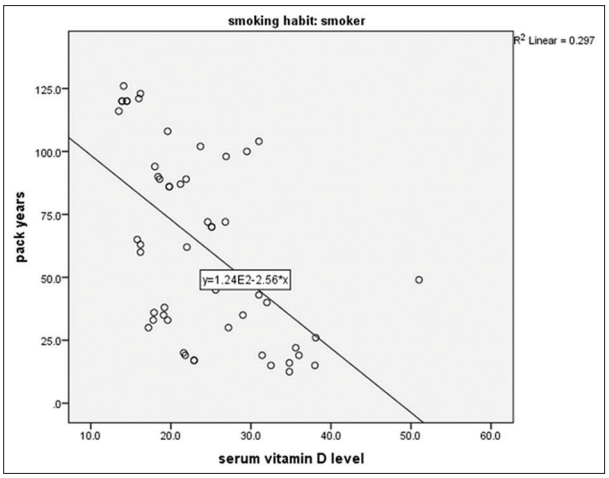

Figure 7: Scatter plot showing significant correlation between vitamin D level and pack years in smokers

In our study, the mean serum vitamin-D level was 24·79 ± 10·79 ng/ml in males and 26·23 ± 10·49 ng/ml in females. Min Zhu *et al.'* (2016) conducted a meta-analysis which confirmed that COPD patients had low serum vitamin-D levels than control subjects.[8] However, significant heterogeneity was found among the result of various studies included in the meta analysis. The factors responsible may include the geographical latitude where the study was conducted and the assay method used for measuring the serum vitamin-D. In our study also, we found COPD patients to be deficient of vitamin-D.

In our study, serum vitamin-D levels were significantly higher in patients with mild to moderate airway obstruction as compared to patients with severe to very severe obstruction. We found a significant positive correlation between serum vitamin-D level and FEV1 (% of predicted) in current smokers but not in COPD patients who have quit smoking. Our result was similar to that of Janssens *W, et al.,* which reported that in COPD patients, Vitamin-D levels correlate significantly with FEV1% and as many as 60% and 70% patients with GOLD stage 3 and 4 exhibit deficient Vitamin-D level with <20 ng/ml.[29] Another study has demonstrated an independent association of low FeV1% with serum Vitamin D level.[30] Angelico *et al.*, have also concluded that hypovitaminosis D is associated with lower baseline FeV1% and subsequently higher mortality.[31] Lee HM *et al.*, concluded that lower level of vitamin-D may be associated with further increase in total and cardiovascular disease mortality associated with COPD.[32] Lower serum vitamin-D levels in COPD patients with more severe airway obstruction may be explained by low physical activity and decreased exposure to sun due to lack of outdoor activity in such patients. Such patients tend to be more homebound and are usually not part of the working class. Such patients also tend to have poorer socio-economic status. Inadequate dietary intake of Vitamin-D may be another factor leading to deficiency of vitamin-D.

We also found significant positive correlation between serum vitamin-D and 6 minute walk distance in smokers, ex-smokers and non-smokers suggesting a relationship between serum vitamin-D level and exercise capacity of COPD patients. Statistically significant difference in mean 6 minute walk distance was found between patients with and without vitamin-D deficiency ($P < 0·001$). Thus patients without vitamin D deficiency were able to walk a longer distance. Similarly, other studies have also reported a significant positive correlation between vitamin-D level and 6 minute walk distance.[33] Low exercise capacity can be explained by poor musculoskeletal strength and cardio-pulmonary function. In addition to this, COPD patients known to have systematic inflammation leading to sarcopenia and muscles atrophy. Study has shown that muscle strength and quality of life are positively predicted by vitamin-D concentration independent of age, sex, and smoking status.[34] In addition to this, loss in exercise capacity can also be explained by the sarcopenia and loss of muscle strength as a consequence of Vitamin D deficiency.[34]

We also found significant negative correlation between serum vitamin-D level and CAT score, which is a measure of the patient's symptoms and impact of COPD on the patient's life. The mean CAT score in patients with Vitamin-D deficiency was significantly higher than mean CAT score of patients with no vitamin-D deficiency ($P = 0·001$) In a study by Zhang *P et al.*, it was found that vitamin-D level negatively correlate with CAT score in both stable COPD and acute exacerbation of COPD.[35] We also found that the mean serum Vitamin-D level in patients with low CAT score (<10) was 29.62 ± 13.2 ng/ml, while in patients with higher CAT score (≥10), it was 24.46 ± 9.50 ng/ml. This difference in mean serum Vitamin-D level in the two group was significant (p = 0.027). Thus, the patients who were less symptomatic had higher serum Vitamin D level.

The mean serum Vitamin D level of patients with normal weight was significantly higher than that of patients who were either

underweight or over weight. This is mainly explained by a possible lower intensity of systemic inflammation in patients with normal weight. Overweight or obese patients may be less mobile and less physically active and thus may have a less exposure to sunlight. Also, obesity associated inflammation itself may be a cause of low serum Vitamin-D level.

In a meta-analysis of multiple cohorts, it was found that higher BMI leads to a lower serum Vitamin-D level while any effect of low serum Vitamin-D level on increase in BMI are likely to be small.[36] In another study from Ethiopia, it was found that vitamin-D deficiency was significantly associated overweight and obese school children.[37]

In another study, it was found that COPD is associated with an increased risk of vitamin-D deficiency and there was significant association between vitamin-D levels and combined COPD stage severity. Also, higher pack years and low BMI are associated with lower level of vitamin-D.[38] We did not find any significant difference in mean serum vitamin-D level of smokers, and ex-smokers. However, a significant positive correlation was found between serum vitamin-D levels and pack years among smokers.

In our study, we did not find significant difference in serum vitamin-D levels among COPD patients who did not have frequent exacerbation as compared to patients having frequent exacerbation. However, all the patients included in the study were in stable phase of COPD and did not have any exacerbation at the time when they were included in the study.

There was significant statistical difference between mean number of pack years in patients with and without vitamin-D deficiency. This may suggest that vitamin-D deficiency has greater association with COPD as a disease itself as well as the amount of exposure to cigarette smoke.

We did not find any relationship between serum vitamin-D level and age of the patients. Studies by Jindal *et al.,* and Mahesh *et al.,* suggest that there is higher prevalence of COPD with increasing age which leads to decreased mobility and exposure of sun.[38,39] Moreover because of reduced functional capacity and sarcopenia associated with COPD, such patients have a suboptimal exposure to sun and consequently a greater predisposition to Vitamin D deficiency. Carson E. *et al.*, found a positive prediction of muscle strength and quality of life by serum Vitamin D level independent of age, sex and smoking status.[34] Decreased dietary intake in elderly can also lead to vitamin-D deficiency.[40] However, in our study, no correlation was found between age and serum vitamin-D level. This may be because of small sample size and short duration of study.

For most patients coming from rural India, the first point of healthcare contact is a primary health centre. It caters to majority of the health care needs in the community. Owing to high prevalence of COPD in the developing countries, it is one of the most common condition a primary care physician deals with. Vitamin D level has a bearing on immune response and airway remodelling. Flexeder C. *et al.*; found a positive correlation between volume related lung function parameters and vitamin D level even in individuals as young as fifteen years of age.[41] Approximately 90% of COPD related deaths occur in low income countries where nearly two-thirds of global COPD patients reside.[42] Thus a robust and effective primary healthcare system will be able to curb the huge healthcare related economic burden on the already meagre healthcare resources.

A comprehensive primary management of COPD will be able to reduce the huge morbidity and mortality associated with the disease thereby reducing hospitalisation and specialised care associated expenditure. It is suggested that there is a need for recommendations in national health policies for supplementation of Vitamin D in housebound patients.

Conclusion

Vitamin-D deficiency is quite ubiquitous in patients of COPD and the deficiency is more frequent in patients with more severe disease. Since, vitamin-D deficiency is frequently association with COPD and has an implication on the disease course and severity, a more comprehensive treatment approach keeping in view the implications of Vitamin-D deficiency, should be practiced. The drawback of our study is small sample size, certain confounding factors like osteoporosis, systemic hypertension and cardiovascular disease could not be excluded. Larger studies over a longer duration are required to find out a more accurate relationship between vitamin-D level and COPD.

Vitamin D deficiency is very common in patients of COPD and Vitamin D levels has a bearing on disease course, severity and health related quality of life. Therefore it is important to look for Vitamin D deficiency for a comprehensive management, a better patient outcome and enhanced quality of life in patients of COPD.

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Conflicts of interest

There are no conflicts of interest.

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