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A Comparative Study for Evaluation of Relation between Vitamin D Deficiency and Chronic Obstructive Pulmonary Disease

Sreyas Sharma[1],Vinod Joshi[2], Narendra Khippal [3], Shubhra Jain [4]
[1]*Resident Doctor, Institute of Respiratory diseases, SMS medical college, Jaipur*
[2]*Senior Professor, Institute of Respiratory diseases, SMS medical college, Jaipur*
[3] *Senior Professor, Institute of Respiratory diseases, SMS medical college, Jaipur*
[4] *Assistant Professor, Institute of Respiratory diseases, SMS medical college, Jaipur*

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I. Introduction

Chronic Obstructive Pulmonary Disease is 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[1].

It is the result of complex interplay of long term cumulative exposure to noxious gases and particles, combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during childhood[2,3,4]. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries outdoor, occupational and indoor air pollution (resulting from the burning of wood and other biomass fuels) are major COPD risk factors[5,6].

It is currently the fourth leading cause of death in the world[1] but is projected to be third leading cause of death by 2020. More than 3 million people died of COPD in 2012. COPD represent an important public health challenge that is both preventable and treatable. Many people suffer from this disease for years and die prematurely from it and its complications. Globally the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and ageing of the population[7].

COPD is now considered to be a systemic disorder with multisystem involvement. COPD is usually associated with other co-morbidities which may have significant impact on the prognosis of the patient[8]. Co-morbidities like Hypertension, osteoporosis, dyslipidaemia, diabetes, ischemic heart disease, chronic renal failure, heart failure, Anaemia, and polycythemia have been found to be associated with COPD[9, 10]. Osteoporosis a major co-morbidity in COPD, is often under-diagnosed, and is associated with poor health status and prognosis. It is a well-known fact that vitamin D plays a major role in maintaining skeletal integrity. There has been increasing evidence in role of vitamin D in increasing risk of chronic diseases like cancer, autoimmune diseases, infectious diseases and cardiovascular diseases. Role of vitamin D in respiratory diseases is still needed to be addressed. However literature shows that lower levels of vitamin D was associated with reduction of lung function which was assessed by FEV1 and FVC in normal subjects. Vitamin D deficiency occurs frequently in COPD and correlates with severity of COPD[8].

But whether vitamin D deficiency has higher prevalence in COPD patients compared to general population is not well documented in India. In addition, level of vitamin D in various combined COPD assessment stage have not been studied. It is therefore important to compare levels of vitamin D in COPD patients and healthy controls, and to further evaluate the associations between important COPD characteristics to levels of vitamin D, including the variables combined assessment stage, pack year and body mass index[8].

II. Aims And Objectives

AIM: To study the relation between Vitamin D Deficiency and Chronic Obstructive Pulmonary Disease.
OBJECTIVES:
1. To compare levels of vitamin D in COPD patients and controls.
2. Further evaluate the association between Vitamin D and COPD characteristics including combined assessment stage, pack year and body mass index.

III. Material & Methods

A case control study was conducted during the time period of July 2018 to June 2019 among 200 subjects with COPD. Sample size was derived after discussion with statistician with licensed software nMaster version 1.0. Patients who were suspected to have COPD on clinical history and met the criteria for COPD according to GOLD criteria 2018 were included as cases in the study. Smoking was expressed as pack years. Age, gender and season matched controls without any conditions directly related to Vitamin D deficiency was taken as controls. Exclusion criteria include individuals with age > 65 years, BMI >30, Chronic kidney disease, History of small bowel resection, Cholestatic liver disease, Granulomatous disorder, individuals on treatment with Phenytoin, Phenobarbital, Carbamazepine, Isoniazid, Rifampin, Tenofovir, Efavirenz and individuals already on Vitamin D supplementation. All subjects underwent history taking, physical examination, questionnaire for Modified Medical Research Council Dyspnea scale, COPD Assessment Test, pulmonary function tests and blood test for Vitamin D levels. The study protocol was approved by the ethics committee of the Institution and informed consent was obtained prior to study entry.

PULMONARY FUNCTION TEST

Pulmonary function testing was done in all patients. Forced vital capacity (FVC), forced expiratory volume (FEV1) and FEV1/FVC were measured using spirometry. Post bronchodilator reversibility testing using 400 μg of salbutamol was done to exclude patients with bronchial asthma.

Measurement of 25-hydroxyvitamin D

A 4 ml of serum samples in BD Vacutainer was collected and processed in biochemistry lab at SMS hospital with chemiluminescence method by COBAS analyser. Patients were then classified based on their vitamin D levels into deficient, insufficient and normal when vitamin D levels are <20 ng/ml, 20-30 ng/ml, >30 ng/ml.

Statistical Analysis

Data analysis and interpretation was done with IBM SPSS Statistics v 20.0. Odds ratio was calculated with 95% confidence interval to compare the status of vitamin D with age and gender matched control. Categorical variables were expressed in number and percentage and were analysed using Fisher's-exact test and Chi-square test. P<0.05 was taken as significant.

IV. Results

A total of 400 study subjects took part in this case control study. Of these 200 individuals fulfilling the inclusion criteria were designated as cases and 200 Age, gender and season matched individuals without any conditions directly related to Vitamin D deficiency were taken as controls. Base line characteristics of both cases and controls are shown in [Table/Fig-1].

	CASES	CONTROLS
Number	200	200
Male	118 (59%)	82 (41%)
Female	118 (59%)	82 (41%)
Mean AGE	58.04±6.17 yr	56.055±6.44 yr
Smoker	182 (91%)	110 (55%)
BMI		
<18.5	48 (24%)	10 (5%)
18.5-24.9	146 (73%)	172 (86%)
≥25.0	6 (3%)	18 (9%)
Vitamin D		
<20ngm/ml	171 (85.5%)	118 (59%)
≥20ngm/ml	29 (14.5%)	82 (41%)
Mean value	14.5595 ± 4.89	18.308 ± 6.94

Base line characteristics [Table-1]

These subjects were ranging from 45 to 69 years of age.The mean age of cases and controls was 58.04±6.17 yr and 56.055±6.44 respectively. Majority of the study subjects were males (59%), whereas females comprised 41% of the study population. Majority of the subjects were smokers in both the study groups. The mean Serum vitamin D values were 14.5595 ± 4.89 and 18.308 ± 6.94 in case and control groups respectively. A Positive correlation was found between BMI and serum vitamin D levels[Pearson correlation=0.836; Sig. (2-tailed)= 0.001]. It was found that subjects with lower BMI had lower vitamin D values. Subjects with more pack years of smoking had lower vitamin D values and this correlation was found to be statistically significant [Pearson Correlation= -0.844; Sig. (2-tailed) = 0.001]. A positive correlation was found between FEV1/FVC

ratio and Serum Vitamin D. Subjects with lower FEV1/FVC ratio had lower vitamin D values [Pearson correlation= 0.987; Sig. (2-tailed) = 0.001]. Study subjects with higher CAT scores had lower Vitamin D values [Pearson correlation= -0.898; Sig.(2-tailed)= 0.001). Grade D COPD subjects had lower vitamin D values as compared to Grade A subjects [Pearson correlation= -0.959; Sig. (2-tailed)= 0.001). Study subjects with higher grading on dyspnea scale had lower levels of vitamin D values [Pearson correlation= -0.929; Sig.(2-tailed)= 0.001). Study subjects with higher severity of airflow obstruction had lower Vitamin D values. A negative co-relation was found between number of exacerbations [Pearson correlation= -0.886; Sig.(2-tailed)= 0.001),hospitalizations[Pearson correlation= -0.954; Sig.(2-tailed)= 0.001) and Serum vitamin D values. Study subjects with multiple exacerbations or hospitalizations had lower vitamin D values as compared to those without. A negative correlation was also found between co-morbidities and vitamin D values [Pearson correlation= -0.992; Sig.(2-tailed)= 0.001). Study subjects with either single or multiple co-morbidities had lower vitamin D values as compared to those without co-morbidities.

V. Discussion

COPD, the fourth leading cause of death in the world represents an important public health challenge that can be managed by both preventable and treatable measures.

It was observed that age range of study population was between 45-69 years, with 68 subjects [27 cases (13.5%) and 51 controls (25.5%)] between 45-50 years; 84 subjects [41 cases (20.5%) and 43 controls (21.5)] between 51-55 years; 112 subjects [58 cases (29%) and 54 controls (27%)] between 56-60 years; 80 subjects [46 cases (23%) and 34 controls (17%)] between 61-65 years and 46 subjects [28 cases(14%) and 18 controls (9%)].The mean age of cases and controls was 58.04±6.17 yr and 56.055±6.44 respectively. There are two similar studies one by Sanket S et.al.[8] and the other by Persson LJP et.al. [11]. Our study had similar age distribution as the study done by Sanket S et.al.[8] which also had a mean age of 56.93 (±8.6) years whereas study carried out by Persson et al. [11], had a mean age of 63.5±9.8 years. Patients between 55-65 years formed the maximum number of subjects in the case group, mainly because of the longer duration of smoking and repeated respiratory tract infections, which would have compromised their quality of life. Subjects having age more than 69 years were excluded from the study as old age is a proven risk factor for Vitamin D deficiency. This explains the difference in mean age compared to study done by Persson LJP et.al. [11], wherein elderly patients were not excluded from the study.

In our study majority of the study subjects were males (59%) like the other two studies [Sanket S et.al.[8] (93% were male subjects) and Pearson et al., (60% were males). The BOLD data showed prevalence of COPD among men 11.8% and among women 8.5%[12]. This observation agrees with the fact that COPD is common in males and greater in older age groups. This observation corresponds to other similar studies. Curkendall SM et al. observed that COPD is common in older population and is more prevalent in those aged more than 75 years. Another study in the Latin American project showed that COPD risk increases steeply with age, with the highest prevalence among those over 60 years[13].

In our study, the mean Serum vitamin D values were **14.5595 ± 4.89** and **18.308 ± 6.94** in case and control groups respectively. Case group had lower vitamin D values as compared to control group and this was found to be statistically significant with a P-Value of **0.00001**.These observations were similar to meta analysis conducted by Zhu M et al. [14] which showed that lower serum vitamin D levels were found in COPD patients than in controls (SMD: -0.69, 95% CI: -1.00, -0.38, P<0.001), especially in severe COPD (SMD: -0.87, 95% CI: -1.51, -0.22, P=0.001) and COPD exacerbation (SMD: -0.43, 95% CI: -0.70, -0.15, P=0.002). They found that vitamin D deficiency was associated with increased risk of COPD (OR: 1.77, 95% CI: 1.18, 2.64, P=0.006) and with COPD severity (OR: 2.83, 95% CI: 2.00, 4.00, P<0.001) but not with COPD exacerbation (OR: 1.17, 95% CI: 0.86, 1.59, P=0.326). They also concluded that serum vitamin D levels were inversely associated with COPD risk, severity, and exacerbation. Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not with COPD exacerbation.

In our study mean BMI values for case group (20.2675 ± 2.21) were found to be slightly lower as compared to the control group (21.3095 ± 2.38). This finding was statistically significant with a P-value of 0.00001. And a positive correlation was found between BMI and serum vitamin D levels[Pearson correlation=0.836; Sig. (2-tailed)= 0.001]. It was found that study subjects with lower BMI had lower vitamin D values. These findings were similar to a study done by Sanket S et.al.[8] who found that lower BMI was significantly associated with higher number of vitamin D deficient patients. Fisher's exact test 7.58 with degree of freedom 2 and p-value = 0.023. Malnutrition and decreased skin thickness with decreased metabolism of Vitamin D explains the finding. In previous study by Persson LJP et.al. [11], obesity was also defined as a risk factor of Vitamin D deficiency but similar observation could not be made out in our study.

In our study majority of the study subjects were smokers [91% subjects in the case group and 55% in the control group]. Subjects with higher pack years of smoking had lower vitamin D values and this correlation was found to be statistically significant [Pearson Correlation= -0.844; Sig. (2-tailed) = 0.001].These

observations were similar to those by Sanket S et.al. [8] who concluded that smoking is a known risk factor for vitamin D deficiency and the chances of having vitamin D deficiency are higher with increased pack year of smoking. The results were comparable with the study by Cutillas-Marco E [15]. Cigarette smoke decreases the production of the active form of vitamin D (1,25-dihydroxy vitamin D) in lung epithelial cells [16]. Cigarette smoke may affect expression levels of the vitamin D receptor[17]. Vitamin D has immunomodulatory and anti-inflammatory effects. TNF-α, a key cytokine implicated in lung destruction of COPD, is down-regulated by vitamin D[18].There was an observation by Levent Erkan et al that acute exacerbation COPD was common among exsmokers and smokers than non-smoker[19]. An additional study from JAPAN by Loveridge B et al. provide evidence that prevalence of COPD is appreciably higher in smokers and ex smokers than in non smokers.

In our study the mean values of FEV1/FVC among case and control group were found to be 46.5174 ± 8.49 and 83.8606 ± 7.21 respectively. Significant correlation of spirometric values was found among both the study groups with a P-Value of 0.00001. A positive correlation was found between FEV1/FVC ratio and Serum Vitamin D. It was found that subjects with lower FeV1/FVC ratio had lower Vitamin D values. [Pearson correlation= 0.987; Sig. (2-tailed)= 0.001] . These findings were similar to the study by Mishra et al. [20], they did a hospital-based case–control study among persons >40 years old demonstrated a positive linear relation between serum concentration of Vitamin D and lung function, after controlling for confounders such as age, sex, body mass index, and smoking-matched participants[20].

In our study 19 subjects had CAT scores less than 10, 52 subjects had CAT scores between 10-20, 80 subjects had CAT scores between 21-30 and 49 subjects had CAT scores between 31-40. We observed that study subjects with higher CAT scores had lower Vitamin D values [Pearson correlation= -0.898; Sig.(2-tailed)= 0.001). We categorized the subjects on the basis of COPD Grades and found that 17(8.5%) study subjects had Grade A, 59(29.5%) had Grade B, 2(1%) had Grade C and 122(61%) had Grade D COPD. We found that study subjects with Grade D COPD had lower vitamin D values [Pearson correlation= -0.959; Sig.(2-tailed)= 0.001). In our case group out of 200 subjects,19(9.5%) subjects were found to have Grade I mMRC, 52(26%) were found to have Grade II mMRC, 80(40%) were found to have Grade III mMRC and 49(24.5%) were found to have Grade IV mMRC. We observed that study subjects with higher grading on dyspnea scale had lower levels of vitamin D [Pearson correlation= -0.929; Sig.(2-tailed)= 0.001).

Study subjects in the case group were also categorized on the basis of severity of airflow obstruction. 17(8.5%) subjects were found to have mild obstruction, 54(27%) were found to have moderate obstruction, 59(29.5%) were found to have severe obstruction and 70(35%) were found to have very severe obstruction. We observed that study subjects with lower Vitamin D values had higher severity of obstruction.

In our study out of 200 subjects in case group, 28 (14%) had no exacerbation, 50 (25%) had single exacerbation and 122 (61%) had multiple exacerbations in last one year whereas 108 (54%) study subjects had no hospitalization, 59 (29.5%) had single hospitalization and 33 (16.5%) had multiple hospitalizations in last one year. A negative co-relation was found between number of exacerbations [Pearson correlation= -0.886; Sig.(2-tailed)= 0.001),hospitalizations[Pearson correlation= -0.954; Sig.(2-tailed)= 0.001) and Serum vitamin D values. Study subjects with multiple exacerbations or hospitalizations had lower vitamin D values as compared to those without. A negative correlation was also found between co-morbidities and vitamin D values[Pearson correlation= -0.992; Sig.(2-tailed)= 0.001). Study subjects with either single or multiple co-morbidities had lower vitamin D values as compared to those without co-morbidities.

Our findings were similar to previous studies, such as Persson LJP et. al.[11] who observed that COPD patients had an increased risk for vitamin D deficiency compared to controls after adjustment for seasonality, age, smoking and BMI. Variables associated with lower 25(OH)D levels in COPD patients were obesity (=26.63), current smoking (=24.02), GOLD stage III- IV (=24.71, =25.64), and depression (=23.29). Summertime decreased the risk of vitamin D deficiency (OR = 0.22). they concluded that COPD was associated with an increased risk of vitamin D deficiency, and important disease characteristics were significantly related to 25(OH)D levels. Michela Bellocchia et al. [21] found that the number of exacerbations in COPD was related to vitamin D level (p=0.046). Vitamin D supplementation was associated with a significant increase in 25-OHD (from 11.46±0.81 to 29.6±1.57 ng/ml, t=9.8,p<0.001), a decrease in the number of exacerbations (from 1.98±0.144 to 0.75±0.118, t=8.07, p<0.001) and of hospitalizations (from 0.39±0.093 to 0.160±0.072, t=2.887,p=0.006). The increase of 25-OHD was closely related with the decrease in acute exacerbation (r=0.49,p=0.002), They suggested that in COPD patients, 25-OHD deficiency is frequent and favors exacerbations and hospitalization for the disease. This hypothesis is supported by significant decrease in acute exacerbations and hospitalizations observed after vitamin D replenishment[8].Martineau AR et al. [22] showed that vitamin D3 was protective against moderate or severe exacerbation in participants with baseline serum 25-hydroxyvitamin D concentrations of less than 50 nmol/L (0·57, 0·35–0·92, p=0·021), but not in those with baseline 25-hydroxyvitamin D levels of at least 50 nmol/L (1·45, 0·81–2·62, p=0·21; p=0·021 for interaction between allocation and baseline serum 25-hydroxyvitamin D status). Baseline vitamin D status did not modify the effect of the intervention on risk of upper respiratory infection (p interaction=0·41). They suggested that

correction of vitamin D deficiency in patients with COPD reduces the risk of moderate or severe exacerbation. Vitamin D3 compared with placebo did not affect time to first moderate or severe exacerbation (adjusted hazard ratio 0·86, 95% CI 0·60–1·24, p=0·42) or time to first upper respiratory infection (0·95, 0·69–1·31, p=0·75) [21]. Sanket S et al.[8] showed that COPD patients had an increased risk for vitamin D deficiency compared to controls after adjustment for age and gender(OR =2.687 (1.40,5.13)). Variables associated with lower 25(OH) D levels in COPD patients were higher pack year (p=0.001), current smoking status (p=0.026), Low BMI (p=0.02), and GOLD stage III- IV (p=0.001). They concluded that COPD was associated with an increased risk of vitamin D deficiency, and there was a significant association between vitamin D levels and Combined COPD stage severity. Also, a higher pack year and a low BMI are associated with lower levels of vitamin D.[8] A systematic review and meta-analysis of individual participant data from three randomized controlled trials by Jolliffe et al. [23] concluded that Vitamin D supplementation safely and substantially reduced the rate of moderate-to-severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels. They also supported the strategy of routinely testing vitamin D status in patients with COPD who experience exacerbations and offering supplementation to those with circulating 25(OH)D concentrations of less than 25 nmol/L. Hassan A. Shabanaa et al. [24] showed that Vitamin D was significantly lower in patients with AECOPD than control group (mean: 39.5±32.5 vs. 56.3±43.7 nmol/l, P value< 0.05). Vitamin D insufficiency (25–75 nmol/l) was significantly higher in patients with AECOPD than controls [115 (56.09%) patients vs. 51 (34%) controls, P value <0.05], dyspnea score (mMRC) was higher in deficiency group (70.1% having two or more mMRC score) compared in insufficiency and sufficiency groups (51.3 and 51.5%, respectively). Patients with mild and moderate COPD (forced expiratory volume in first second >50%) showed higher 25(OH)D (69.4±23.1) than patients with severe and very severe COPD. The relationship is linear with lung function, disease severity groups and with previous exacerbation rate. Severe exacerbations requiring hospital admission and lengthy hospital stay were demonstrated in patients with low vitamin D[24].

The estimated risk for vitamin D deficiency was shown to be higher in COPD patients compared to controls. In COPD patients, there was a significant association between vitamin D levels and Combined COPD stage severity. These results are comparable with the study done by Pearson et al.,Sanket S et.al. In the NHANES III study, Black et al., found a dose- response relationship between 25(OH)D and both FEV1 and FVC, but no correlation with airway obstruction defined as a change in FEV1/FVC ratio [25]. However, in a recent study on COPD patients by Janssens et al., a strong relationship was found between GOLD stage and vitamin D deficiency suggesting a relationship with airway obstruction[26]. A similar association between 25(OH)D and FEV1 has been reported in adults with asthma. These studies suggest towards a strong association between COPD and vitamin D[27].

Possible explanations for the increased prevalence of vitamin D deficiency in COPD include reduced capacity of aging skin to synthesize vitamin D, poor diet and low storage capacity of fat due to associated wasting[14]. Conversely, vitamin D deficiency also affects lung function by various mechanisms. Innate and adaptive immune systems are implicated in the pathogenesis of COPD[28]. Role of vitamin D in adaptive immunity is demonstrated by the fact that cells of adaptive immune system express receptor for vitamin D and require it for their optimal functioning[14]. Vitamin D has been shown to affect maturation of dendritic and TH1 cell[29]. The ability of 1,25(OH)2D to increase expression of antimicrobial peptides, and to decrease the expression of pro-inflammatory cytokines partly explains the association between vitamin D and increased susceptibility to respiratory infections[30]. All these lead to an increased rate of FEV1 decline[30]. In addition to these, vitamin D has been shown to be involved in tissue remodelling via fibroblast proliferation and collagen synthesis, and modulation of matrix metalloproteinase (MMP) levels[31]. Also, undiagnosed osteoporosis leads to vertebral compression, reduced rib cage mobility and hence a decline in pulmonary function[32].

There is no defined or standardized range for normal serum vitamin D value. As was observed in this study that majority of the controls were found to have their vitamin D values less than <30 ng/ml, which has been taken as reference of sufficiency in some previous studies. There is a need for further studies involving normal healthy children and adults to define the normal range of vitamin D values on the basis of age, sex, BMI.

VI. Limitations

This was a single centre case control study. Although diet might be the minimal contributor to vitamin D status, lack of data on dietary intake is a limitation of study. Although vitamin D levels were found to be lower in patients with more severe disease with more co-morbidities, exacerbation and hospitalizations but whether Vitamin D can itself serve as a marker for severity of COPD is a question that need to be addressed in future studies.

VII. Conclusion

The present study suggests that COPD patient with low BMI, increased pack years of smoking, presence of co-morbidities, increasing severity with multiple exacerbations and hospitalizations have lower

levels of serum vitamin D. These results provide an improved understanding of vitamin D deficiency in COPD development and progression.

Awareness of association between serum vitamin D and COPD in clinical practice may benefit disease outcomes.

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