Serum Vitamin D levels in Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Lower serum 25 (0H) Vitamin D is associated with decreased lung function in healthy population and various lung disease. Information on the relationship of levels of serum 25 (OH) Vitamin D with severity of Chronic Obstructive Pulmonary Disease (COPD) is important in standardizing the treatment, in planning appropriate follow up and improving quality of life. This study also warranted further trial to assess the effect of serum 25 (OH) vitamin D on morbidity and mortality in COPD patients. **Material and Methods:** It was a prospective (observational), cross-sectional study which included all patients with Chronic Obstructive Pulmonary Disease (COPD) attended the Department of Pulmonary Medicine, People's College of Medical Sciences & RC, Bhopal, over a period of 1 year 6 months. **Results:** The mean serum 25 (OH) vitamin D level in COPD patients was 27.86±16.47 ng/ml. There was no significant difference in serum 25 (OH) vitamin D between patients in different age groups. The serum 25 (OH) vitamin D levels varied significantly between different GOLD stages and different mMRC dyspnea grades. The patient who had a history of admission for twice or more in the past 1 year had a lower mean serum 25 (OH) vitamin D level as compared to patient with just one or no hospitalization in the past. **Conclusion:** Decrease serum 25(0H) vitamin D levels were associated with increase airway obstruction.

Keywords: Chronic Obstructive Pulmonary Disease (COPD), mMRC, FEV1%, Serum 25 (OH) vitamin D, Acute Exacerbation, pack years, socioeconomic, 6 minute walk test.

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Introduction

The role of 25(OH) vitamin D in preserving skeletal integrity is well known. However, it has become evident that 25(OH) vitamin D deficiency is associated with increased risk of chronic diseases like cancer, autoimmune diseases, infectious diseases, cardio-vascular diseases and respiratory diseases [1].

Previous studies strongly suggest that 25(OH) vitamin D deficiency may be a risk factor for respiratory disease such as development of respiratory infections [2] and increasing asthmatic symptoms or asthma in childhood [3], [4]. National Health and Nutrition Examination Survey [NHANES-3] on general population (n=14076)

in the United States suggest that lower levels of 25(OH) vitamin D were associated with a reduced level of lung function measured by forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) [5]. Recent studies show that a substantial proportion of patients with chronic obstructive pulmonary disease have decreased 25(OH) vitamin D levels (<20 ng/mL) [1], [6], [7]. In one study of 262 COPD patients FEV1, body mass index (BMI), season of blood sampling and gene variants in the 25(OH) vitamin D binding gene were found to be significantly associated with 25(OH) vitamin D deficiency [1].

Obstructive lung disease by the year 2030 is expected to rank among the top five chronic diseases in term of global mortality and morbidity [8]. Deficiency of serum

25 (OH) vitamin D in COPD patients is highly prevalent but correlation between serum 25(OH) vitamin D levels and severity of COPD is not yet well documented. It is reasonable to compare the levels of 25(OH) vitamin D with severity of COPD. In this current study we aimed to assess the association between level of serum 25(OH) vitamin D and severity of COPD. We also aimed to examine possible interaction by different variable such as 6 minute walk test, FEV1, mMRC grading, exacerbations frequency, Socioeconomic Status and body mass index. We hypothesized that low 25(OH) vitamin D level would be associated with increase severity of COPD and lower lung function.

Material and Methods

Study Population: All Patients with confirmed diagnosis of Chronic Obstructive Pulmonary Disease (COPD) presenting to the Department of Pulmonary Medicine, Peoples hospital and RC, Bhopal, who fulfill the study criteria were selected prospectively over a period of 1 year 6 months (November 2014 to April 2016). This was a prospective, cross-sectional study with sample size of 112 patients.

Procedure for Sampling: All the patients age 40 and above presenting to pulmonary medicine department, who fulfilled the COPD diagnostic criteria [8] according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) were evaluated during a single visit that included a medical interview, physical examination, 6-MWT, BMI, CXR, ECG, laboratory test for 25(OH) vitamin D and spirometry.

Exclusion criteria were: (1) Patient of Obstructive Lung Disease other than COPD, (2) Patient of associated lung disease. e.g. presence of pulmonary infection, active pulmonary tuberculosis, pleural effusion, pulmonary emboli, pulmonary hypertension, (3) Concurrent reason for worsening of COPD symptoms; e.g. congestive heart failure, acute myocardial infarction, (4) Contraindication or inability to perform required tests, (5) Conditions associated with 25(OH) vitamin D metabolism, absorption e.g. hyperparathyroidism. (6) Use of medications for three or more consecutive months, which may interfere in 25(OH) vitamin D metabolism e.g. 25(OH) vitamin D supplements, thiazide diuretics, phenytoin, (7) Uncooperative patients or unwilling to give informed written consent.

Sample selection and data collection: Medical history was obtained through a questionnaire applied by a single investigator. Data obtained included age, gender, smoking history, previous history of exacerbations, socioeconomic history, BMI, uses of inhaled corticosteroid, season and dyspnea scale (mMRC). Smoking history was determined as current smoker, ex-smoke and never smoked. Smoking intensity, expressed in pack-years which were number of cigarette packs per day per year of smoking. Patients who had stopped smoking less than 6 months prior to the evaluation were considered to have a current smoking history. In our study we have considered one cigarette equal to one bidi. Exacerbations history was based on participant response to question: '' Did you had less than two episode of exacerbations in previous year '' (yes or no).

Here acute exacerbation was defined to patients as increased or new onset of more than one of the following: cough, expectorant, dyspnea, wheeze, chest tightness for at least 3 days and requiring hospitalization, antibiotics or systemic corticosteroids. Socioeconomic history was according to updated BG Prasad socioeconomic classification 2014 [10]. Inhaled corticosteroids data was based on questioner: '' Have you in the past six month, used inhaled corticosteroid, consistently for more than two month ''. Seasons were classified according to seasons of blood sample collection.{Winter (Dec-March), Summer (Apr-June), Monsoon (July-Sep), Post monsoon (Oct-Nov)} [11].

Modified Medical Research Council (mMRC) dyspnea scale was used according to guidelines to grade severity of dyspnea [12]. Blood sample for serum 25 (OH) vitamin D measurements were collected by trained heath care worker and processed without delay. Serum 25 (OH) vitamin D level were measured by a fully automated antibody-based CHEMILUMINESCENCE (CLIA) assay. Serum 25 (OH) vitamin D level were the best marker of body vitamin D status (13).

We categorized according to widely used biological reference range, which was defined as deficiency as serum 25-(OH)D <20ng/ml, insufficiency between 20ng/ml to 29ng/ml, sufficient between 30 to 100ng/ml and toxic above 100ng/ml (14). Spirometry was done by trained professional at screening station using Schiller sensors SP-260, also recommendations and criteria from the American Thoracic Society (ATS) were applied and followed. Schiller sensors SP-260 work on pneumotachometer method, was a complained with

ATS 1994 standards. Instrument and biological quality control was conducted periodically via trained staff for quality assurance. Tests were performed in sitting position before and 20 minutes after 2.5 mg Salbutamol given via nebulizer with a nose clip. Three to four trials were given. Best of all trial were included where expiration continued for >6 s with acceptable flow/volume loop. FEV1 and FEV1/FVC parameter were used to diagnose COPD, whereas FEV1% predicted were used in study for severity of COPD assessment. GOLD grouping [8] and GOLD severity staging [8] were done according to guideline. 6 Minute Walk (6MTW) Tests were performed according to standardized approach of ATS guidelines [15]. Limitation, contraindication, safety issues and quality assurance of the test was consider as priority.

Statistical Analysis: Statistical analysis was done using Statistical Package of Social Science (SPSS Version 20; Chicago Inc., USA). Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Quantitative variables were compared using mean values and qualitative variables using proportions. Significance level was fixed at $P < 0.05$.

Results

We screened patients from November 2014 to April 2016 in the Department of Pulmonary Medicine, Peoples Hospital, Bhopal and found 112 patients met these inclusion and exclusion criteria. Among 112 patients 21 patients refused to participate in this study. From remaining, 7 were excluded because some of them were unable to perform spirometry due to restricted mouth opening (fibrosis, carcinoma) and others were unable to perform 6MWT (2 DVT, 1 Lower limb amputation). We excluded 2 patients as they did not allow us to draw blood sample. Out of remaining 82 patients 8 patients were excluded from further analysis due to missing data. Final analysis was done on 74 patients. Out of 74 patients 66 were males and mean age was 63 years. Mean Vitamin D level among population was 27 ng/ml and 6 were having positive smoking history.

Table-1: Characteristic of the patients with COPD.

Characteristic	MEAN or Number
Total Number of Patients (n)	74
Age in Years(Mean)	63.84±9.86
Male:Female (Ratio)	66:8
Pack Year, (Mean)	29.81±15.60
Vitamin D Level, [Mean (ng/ml)]	27.86±16.47
mMRC # (Mean)	2.57±0.49
6 Min Walk test (meter)	228.96±151.61
FEV1% Predicted (Mean)	50.88±16.30
Smoking Status, [n(%)]	
Current Smoker (n)	24(32.4%)
Ex-Smoker (n)	42(56.8%)
Non-Smoker (n)	8(10.8%)
COPD^Severity [n(%)]	
Mild	6(8.1%)
Moderate	24(32.4%)
Severe	32(43.2%)
Very Severe	12(16.2%)

*BMI – Body mass index, #mMRC – Modified medical research council, ^COPD – Chronic obstructive pulmonary disease.

General Characteristics: Results were expressed using means ± standard deviations. In our study, the mean FEV1 % predicted was 50.88% and mean serum 25 (OH) Vitamin D level was 27.86±16.47 ng/ml (Table 1). Mean age at

presentation was 63.84±9.86 years. Out of 74 patients, most (56) patients were in GOLD stage 2 & 3. Mean 25(OH) vitamin D level was highest (59.33 ng/ml) among stage1 patients. Majority of patients (56.8%) were ex-smoker and only 10.8% patients were non-smoker. The mean pack years were 29.81±15.60.

Table- 2: Mean serum 25 (OH) vitamin D levels in different age group in COPD patients.

Age Groups (Year)	Number	Vitamin D level(ng/ml)		ANOVA 'F' Value	Significance 'p' Value
		MEAN	SD		
40-59 year	17	31.06	17.85	2.313	0.083
60-69 year	33	31.30	16.40		
70-79 year	17	19.94	14.18		
>80 year	7	23.14	13.54		

Age group: (Table 2) In our study, Mean 25(OH) vitamin D level was lower among older patients (>70 years) than younger patients (<69years). However, there was statistically no significant difference in 25(OH) vitamin D levels according to different age groups with a p value of 0.083.

Table-3: Characteristics of patients according to GOLD staging.

Characteristic	Gold Staging				F Value	pValue
	Stage 1 n-6	Stage 2 n-24	Stage 3 n-32	Stage 4 n-12		
	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
Age in Years	55.17±8.68	63.29±10.06	63.63±8.51	69.83±10.70	3.347	0.024
Pack Year	24.33±8.21	23.67±14.05	30.97±15.44	41.75±15.57	4.434	0.007
mMRC	1.00±0.00	2.13±0.33	3.09±0.73	3.58±0.90	32.688	0.001
BMI	22.83±4.11	18.79±4.89	18.91±4.36	18.09±3.86	1.663	0.183
6 Min Walk test (Meter)	515.00±65.65	347.71±69.80	147.81±73.54	64.83±34.91	101.077	0.001
Vitamin D Level (ng/ml)	59.33±15.51	36.17±10.35	22.25±10.98	10.50±4.10	37.558	0.001

COPD Severity: (Table 3) Mean Vitamin D level was highest among stage1 COPD patients and as severity increased, vitamin D level decreased. Stage 4 COPD patients had the lowest serum 25(OH) vitamin D levels. There was a negative correlation between COPD severity and vitamin D levels. The distribution of mean serum 25(OH) vitamin D according to severity of disease was statistically highly significant. (p=0.001)

Table- 4: mean vitamin D level according to mMRC Dyspnea grade among COPD patients.

mMRC Dyspnea grade	Number	Vitamin D level(ng/ml)		ANOVA 'F' Value	Significance 'p' Value
		MEAN	SD		
Grade 1	9	52.00	19.69	29.938	0.001
Grade 2	22	35.91	10.69		
Grade 3	26	22.31	10.18		
Grade 4	17	13.18	6.03		

mMRC dyspnea grade: Out of 74 patients, most of the patients were in mMRC grade 2 and 3. Mean 25(OH) vitamin D level was highest among Grade 1 patients (52 ng/ml), with increasing mMRC, 25(OH) vitamin D level decreased. Mean serum 25 (OH) vitamin D levels was lest (13 ng/ml) among grade 4 COPD patients. There was statistically highly significant negative correlation found between mMRC Dyspnoea grade and 25(OH) vitamin D level with p value of 0.001.

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Table- 5: Comparison of mean vitamin D level according to GOLD group among COPD patients.

Gold groups	Number	Vitamin D level(ng/ml)		ANOVA 'F' Value	Significance 'p' Value
		MEAN	SD		
Group A	6	59.33	15.51	39.260	0.001
Group B	24	36.17	10.35		
Group C	2	45.00	24.04		
Group D	42	17.81	8.74		

Mean vitamin 25 (OH) D levels: GOLD group were divided according to disease symptoms and risk. In our study out of 74 patients, maximum 42 were in GOLD group A and 24 were in group B. Mean 25(OH) vitamin D level was highest among group A patients followed by group C patients. It was seen least among group D patients. There was statistically highly significant negative correlation found between GOLD group and 25(OH) vitamin D level with a p value of 0.001. In another words, patients with more severe symptoms had lower 25(OH) vitamin D levels than those with less symptoms.

Table- 6: Comparison of mean vitamin D level according to Pack Year among COPD patients

Pack year	Number	Vitamin D level(ng/ml)		ANOVA 'F' Value	Significance 'p' Value
		MEAN	SD		
0-9	8	28.75	9.43	3.740	0.015
10-19	5	35.60	7.43		
20-29	23	35.17	18.11		
>30	38	22.24	15.60		

Pack years: On comparing mean 25(OH) vitamin D level according to Pack Year in our study. Most (38) of the patients were having more than 30 pack years followed by 20-29 pack years (n-23). Mean 25(OH) vitamin D level was highest among the patients who had 10-19 & 20-29 pack years. It was least among the patients who had more than 30 pack year. There was statistically significant negative correlation found between pack year and 25(OH) vitamin D level. (P=0.015).

Table- 7: Comparison of mean vitamin D level according to 6 Minute Walk Test among COPD patients

6 MWT	Number	Vitamin D level (ng/ml)		ANOVA 'F' Value	Significance 'p' Value
		MEAN	SD		
>400 meter	13	49.62	17.03	35.166	0.001
399-300 meter	11	40.09	8.54		
299-200 meter	8	30.00	11.25		
199-100 meter	27	21.11	6.26		
<99 meter	15	11.07	5.35		

6 minute walk test: Out of 74 patients, maximum 27 were in 100-199 meter group. As 6 minute walk test value decreased, 25(OH) vitamin D level also decreased. It was highest among those patients in whom 6 MWT value was above 400 meter and it was minimum among those patients in whom 6 MWT value was below 99 meter. There was statistically highly significant positive correlation between 6 MWT value and 25 (OH) vitamin D level (P=0.001).

Table- 8: Comparison of mean vitamin D level according to ICS Therapy among COPD patients.

ICS Therapy	Number	Vitamin D level (ng/ml)		Student 't' Test value	Significance 'p' Value
		MEAN	SD		
Yes	38	21.47	13.20	3.717	0.001
NO	36	34.61	17.05		

ICS therapy: On comparing mean 25(OH) vitamin D level according to ICS in our study. Out of 74 patients, 38 were on ICS. The 25(OH) vitamin D level was less among patients on ICS and higher among patients without ICS. There was statistically highly significant difference found in 25(OH) vitamin D level according to ICS therapy among COPD patients (P=0.001). Most of the patients in ICS therapy group had moderate to severe COPD.

Discussion

The purpose of this study was to find correlation between serum 25 (OH) vitamin D levels and severity of disease in COPD patients and also to evaluate other factors associated with levels of serum 25 (OH) vitamin D levels in COPD patients.

Severity of COPD: In our study, the mean FEV1% predicted was 50.88% and the mean 25 (OH) vitamin D level was 27.86ng/ml (Normal>30 ng/ml). In past few years, deficiency of 25 (OH) vitamin D was observed in patients with declining lung functions [1]. In the NHANES III study, Black et. al found a negative co relationship between 25(OH) vitamin D levels in blood and FEV1 and FVC in healthy general population [5].

However, Janssens et. al. in 2010 did a study on ex-smoker COPD patients and ex-smoker with normal lung function to find link between serum 25(OH) vitamin D levels with COPD and vitamin d receptor gene. The mean FEV1% predicted was 61±27% and mean 25 (OH) vitamin D was 19.9±8.2 ng/ml. Authors from this study concluded that 25(OH) vitamin D deficiency occurs frequently in COPD and correlates with severity of disease in ex-smoker COPD [16]. A parallel trend was observed in 2011 by Kunisaki et al. in secondary analysis of data from North America.

Where large cohort study of 973 severe COPD patients suggested lower levels of 25(OH) vitamin D with mean levels of 25.7ng/ml [17]. Our study, which included diagnosed COPD patients and where our primary aim was to correlate severity of COPD with 25(OH) vitamin D levels shows a nearly identical relationship between airways obstruction and 25(OH) vitamin D levels. Outcome from our study in Indian scenario, support studies by Janseens et al., Kunisaki KM et al., and Cilingir BM et al. Together these studies provide strong

evidence for the relationship between lower serum 25 (OH) vitamin D levels and decline lung functions in COPD patients and suggest to maintain optimal serum 25(OH) vitamin D levels in patients with COPD [16, 17, 30].

Age Groups: In our study, Mean 25 (OH) vitamin D level was lower among older patients (>70 years) than younger patients (<69years). However, there was statistically no significant difference in 25 (OH) vitamin D levels according to different age groups with a p value of 0.083. Previous studies have described 25(OH) vitamin D deficiency as a common phenomenon in elderly populations. [18, 19]. Prior Studies by Jindal et al (2001), Mahesh et al (2009) and Parasuramalu et al (2014) suggested that the prevalence of COPD increases with age, which in turn may lead to decreased mobility and sun exposure [20,21,22]. Also, reduced dietary intake of 25(OH) vitamin D in COPD patients particularly in elderly can explain our outcome [23].

mMRC: There was statistically highly significant negative correlation found between mMRC Dyspnoea grade and 25 (OH) vitamin D level with p value of 0.001. Recently in a randomized control trial by Sanjari M et al. in 2015, the difference between before and after treatment with 25 (OH) vitamin D was seen, MMRC was calculated and compared between groups, significant (p < 0.001) difference was observed between calcitriol group vs. Placebo [31]. Similarly, Rezk et al noted a significant improvement (p-0.003) in MMRC dyspnoea scale, 1 year after 25(OH) vitamin D replacement [24].

GOLD group: GOLD groups were divided according to disease symptoms and risk. There was statistically highly significant negative correlation found between

GOLD group and 25 (OH) vitamin D level with a p value of 0.001. In another words, patients with more severe symptoms had lower 25 (OH) vitamin D levels than those with less symptoms. Similar outcome was observed in a study by Kocabas A et al. in 2013 from Turkey, suggesting that the possibility of 25 (OH) vitamin D deficiency increased 4.83 times in GOLD group D, when compared to GOLD group A [25].

Pack year: On comparing mean 25 (OH) vitamin D level according to Pack Year in our study. There was statistically significant negative correlation found between pack year and 25 (OH) vitamin D level (P=0.015). Negative correlation of smoking status and lung function decline has been describe earlier [26].

Sanket S et al in 2016 also found that the chance of having 25 (OH) vitamin D deficiency was higher with increased pack year of smoking [27]. There was a similar outcome from a study by Cutillas et al in 2012 [7].

6MWT: As 6 minute walk test value decreased, 25 (OH) vitamin D level also decreased. It was highest among those patients in whom 6 MWT value was above 400 meter and it was minimum among those patients in whom 6 MWT value was below 99 meter. There was statistically highly significant positive correlation between 6 MWT value and 25 (OH) vitamin D level (P=0.001). Similarly Moberg et al. in his study reported that 6 min walking distance has significant positive relation with 25(OH) vitamin D level ($p = 0.01$) [32].

ICS therapy: On comparing mean 25(OH) vitamin D level according to ICS in our study. The 25(OH) vitamin D level was less among patients on ICS and higher among patients without ICS. There was statistically highly significant difference found in 25(OH) vitamin D level according to ICS therapy among COPD patients (P=0.001). Most of the patients in ICS therapy group had moderate to severe COPD. Gupta A et al. in 2011 found that use of inhaled corticosteroid in patients with asthma was associated with 25(OH) vitamin D deficiency [28].

Summary- Serum 25 (OH) Vitamin D levels are efficient and suitable method for assessment of systemic vitamin D levels. The purpose of this study was to find correlation between serum 25(OH) vitamin D levels and severity of disease in COPD patients also to evaluate other factors associated with serum 25(OH) vitamin D

levels in COPD patients. From the observations we concluded that the majority of COPD patients were males. Decrease serum 25(0H) vitamin D levels were associated with increase airway obstruction, Mean serum 25 (OH) Vitamin D levels were lower in older patients than younger and related to GOLD group D as compared to GOLD group A. Decrease serum 25 (OH) vitamin D were associated with increased pack years, increased frequency of exacerbation in self declared previous year, lower socioeconomic status and in patients on inhaled corticosteroids.

Conclusion

In our study, we included diagnosed COPD patients and our primary aim was to correlate severity of COPD with 25(OH) vitamin D levels. The results of ours study shows a nearly identical relationship between airways obstruction and 25(OH) vitamin D levels. From the observations we concluded that the majority of COPD patients were males. As proved by many studies in ours also the exercise capacity decreased with decreased lung functions and decreased serum 25 (OH) Vitamin D levels. Taken together, the results of our study and the older ones we can conclude that there is a strong relationship between lower serum 25(OH) vitamin D levels and declining lung functions in COPD patients and suggest to maintain optimal serum 25(OH) vitamin D levels in patients with COPD. Future appropriately designed clinical trials are warranted to assess the effect of supplementation of vitamin D on decline in lung function, exercise limitation, morbidity and mortality in patients of COPD.

Limitation- The limitation of the current study was its small sample size and It was also a observational type of study. Large number of baseline data recorded, strictly followed inclusion criteria and use of recommended state of the art machine for measurement of serum 25 (OH) vitamin d levels were the strength of this study.

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