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Original Article

Evaluation of Vitamin-D Level in Patients of Chronic Obstructive Pulmonary Disease (COPD) and Its Clinical Correlation

Bal Kishan Gupta*, Shyam Lal Meena, Meghraj Saini***, Hardeva Ram Nehara**, Makkhan Lal Saini***, Jigyasa Gupta******

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Abstract

Introduction: Data on vitamin D status in COPD in Indian population are limited while those comparing with GOLD stages, frequency of AECOPD, hospitalization and smoking status are lacking. *Aim:* To evaluate vitamin-D levels in patients of COPD and its clinical correlation. *Materials and Methods:* A total of 100 patients of COPD (post-bronchodilator FEV1/ FVC <0.70) with age e"40 years (82 male and 18 female) were studied. Serum vitamin D levels were measured by ELISA and clinically analyzed for Age, sex, BMI, smoking status, FEV_1%predicted, FEV_1 volume, FVC, FEV_1/FVC ratio, GOLD stages, frequency of AECOPD and hospitalization during the previous year. *Results:* Prevalence of vitamin-D deficiency and insufficiency were 42% and 31% respectively among COPD patients. We found positive correlation of Vitamin-D levels to FEV1% predicted (r =0.891; P<0.0001), FVC (r = 0.859; P<0.0001) and FEV_1/FVC (r =0.637; P <0.0001). The mean vitamin-D levels were not statistically significantly different in relation to age, gender, BMI and residence but were significantly lower in current smokers (P <0.0001) and significantly decreased with increasing frequency of AECOPD (P<0.0001). The mean vitamin-D levels of frequent exacerbators was lower than nonfrequent exacerbators (P= <0.0001) and it was also lower in hospitalized patients for AECOPD as compared to not hospitalized (P= <0.0001). Lower levels of vitamin-D was found with increased severity (GOLD stages) of COPD (P<0.0001). *Conclusions:* COPD is associated with a significantly low level of vitamin-D which was independent to patient's age, gender, BMI and residence but dependent on current smoking. The lower level of vitamin-D is associated with severity of COPD, increased frequency of AECOPD and increased risk for hospitalization. The relationship between lung functions and levels of vitamin D is almost linear.

Keywords: Vitamin-D; COPD; AECOPD; Frequent Exacerbator; Current Smoking; GOLD Stage.

Introduction

Vitamin D deficiency is a new emerging global health threat, although we have limited data in India but it is now recognized that Indians are having high prevalence of vitamin D deficiency because of modernization and change in life style, high melanin content in skin, clothing habits (Burqa, Pardah), atmospheric pollution and change in food habits etc [1]. Role of vitamin D is not limited to calcium homeostasis and bone mineral metabolism but now it is recognized to subserve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth, and immunomodulation [2]. Recent studies has shown that vitamin-D deficiency is associated with increased risk of chronic diseases like cancer, autoimmune diseases, infectious diseases, cardiovascular diseases and chronic lung diseases [3].

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Global Burden of Disease studies has estimated that COPD is the third leading cause of death worldwide [1].

Author's Affiliation: *Senior Professor, In-charge Medical ICU, **Assistant Professor ***Senior Resident, ****Intern, Department of Medicine, S.P. Medical College & PBM Hospital, Bikaner, Rajasthan, India.

Reprint Request: Bal Kishan Gupta, Prem Kutir, Opposite DRM Office, S.P. Medical College & PBM Hospital, Hospital Road, Bikaner - 334003 Rajasthan, India.
E-mail: bkgbkn@rediffmail.com

Tobacco smoke is the major risk factor for COPD worldwide, although inhaled noxious particles and gasses may also contribute. In addition, other pathobiological processes probably contribute, as the disease continues to progress in a substantial proportion of patients, even after cessation of inhalation of the offending agent. Such processes may include genetic and epigenetically determined responses, an imbalance of proteinases and antiproteinases, an abnormal interaction between environment and microbiome [4]. Patients with advanced COPD frequently have vitamin D deficiency, Factors that explain this include the alteration of the cutaneous synthesis of vitamin D due to age and the toxic effects of tobacco, low exposure to sunlight, increased catabolism of vitamin D by glucocorticoids, its sequestration in adipocytes, reduced intestinal absorption and poor hepatic and renal activation of vitamin D precursors [3]. Vitamin-D deficient patients with COPD have greater predisposition to respiratory infections and COPD exacerbations [5]. Airway remodeling which is the most characteristic pathogenic hallmark of COPD can be affected by vitamin-D deficiency [6].

Data on vitamin D status in COPD in Indian population are limited while those comparing vitamin D with GOLD stages, frequency of acute exacerbation of COPD (AECOPD), hospitalization and smoking status are lacking. Therefore this study was planned to evaluate levels of vitamin D in COPD patients.

Material and Methods

This study was conducted on consecutive 100 cases (82 male and 18 female) of COPD presented at pulmonary clinic in the Department of Medicine, S.P. Medical College, P.B.M and Associated group of Hospitals, Bikaner, India during the period of January 2015 to December 2015. Prior approval of ethics committee was taken for this study. Informed consent was taken. Inclusion criteria were age ≥40 yrs, post bronchodilator ratio of FEV1/FVC < 0.70. Exclusion criteria were co-morbid conditions like presence of tuberculosis, pleural effusion, congestive heart failure, primary pulmonary hypertension, pulmonary emboli, restrictive airway disease, diabetes mellitus, ischemic heart disease, thyroid disorders, malignancy or any other chronic illness, current treatment with vitamins and dietary supplements and lack of availability of data on exacerbations/hospitalization the year previous to the inclusion in the study. Patients who have not given consent to participate in the study been not included.

All patients were evaluated as per Performa. Patients were classified according to smoking status [7]. Age, gender, body mass index (BMI), pulmonary function test indices (FEV_1%predicted, FEV_1 volume, FVC, FEV_1/FVC ratio), severity of COPD according to GOLD stages (Global Initiative for Chronic Obstructive Lung Disease) [8], frequency of AECOPD, frequent exacerbators (≥2 AECOPD/year) [9] and hospitalization during the previous year were recorded for associations with vitamin-D level. Serum vitamin-D levels were measured by Enzyme Linked Fluorescent Assay technique. Patients were categorized on the basis of serum vitamin D levels as Deficient <20 ng/ml, Insufficient 20-29.9 ng/ml and Sufficient ≥30 ng/ml.

Statistical analysis was performed with Graph pad prism v 6.0. Unpaired T-test, ANOVA was used to compare difference in the level of continuous variables between 2 groups and more than 2 groups respectively. Linear regression analyses were performed to analyse the correlation between vitamin-D deficiency and lung function indices, P value of <0.05 was taken as significant and <0.0001 highly significant.

Results

Epidemiological and clinical profile of the patients is shown in table-1. Mean age of males and females was 61.90±11.93 & 58.22±12.12 yrs respectively. BMI of males and females was 21.62±0.37 kg/m^2 and 23.18±1.02 kg/m^2 respectively. Majority of the patients were present smokers (52%) and belonged to GOLD stage II (36%) and GOLD stage III (29%). Prevalence of hospitalization in last year for AECOPD was 47% and AECOPD ≥2 times in last year were 40%. Mean FEV_1 (% predicted) of all patients was 61.22±12.03, mean FVC (L) was 1.990 ± 0.648 and mean FEV_1/FVC was 0.563± 0.098. Post bronchodilator FEV_1 (% predicted) was low among males (51.70±21.33) as compared to females (65.56±24.06).

Comparison of mean value of Pulmonary Function Test (PFT) indices in relation to vitamin-D level is shown in table-2. Prevalence of vitamin-D deficiency and insufficiency were 42% and 31% respectively among COPD patients. Mean FEV_1 (%predicted) in vitamin-D deficient patients was significantly lower than vitamin-D insufficient and vitamin-D sufficient patients (34.74±11.08 vs 57.16±12.67 & 81.04±12.47; P= <0.0001). Mean FVC (L) in vitamin-D deficient

patients was significantly lower than vitamin-D insufficient and vitamin-D sufficient patients (1.429±0.356 vs 2.079±0.367 & 2.079±0.367; P= <0.0001). Mean FEV_1/FVC in vitamin-D deficient patients was significantly lower than vitamin-D insufficient and vitamin-D sufficient patients (0.502±0.101 vs 0.575±0.071 & 0.644±0.043;P= <0.0001). Mean FEV_1 volume in vitamin-D deficient patients was significantly lower than vitamin-D sufficient patients (0.708±0.153 vs 1.787±0.237; P= <0.0001). Mean FEV_1 value increased from 0.708±0.153 L in vitamin-D deficient patients to 1.195±0.205 L in vitamin-D insufficient patients. We also found positive correlation of Vitamin-D to FEV1% predicted as shown in Table 3.

Comparison of mean value of vitamin-D level in relation to different patient's characteristics is shown in Table 4. The mean vitamin-D levels were not statistically significantly different in relation to age, gender, BMI and residence. The mean vitamin-D level was significantly lower in current smokers than former smokers & never smokers (20.24±5.96 vs 26.51±7.93 & 29.52±7.26; P= <0.0001). The mean vitamin-D level of patients 29.79 ± 5.41, 24.05 ± 6.30, 18.12 ± 3.33 and 10.73 ± 3.67 with 0 AECOPD, 1 AECOPD, 2 AECOPD and 3 AECOPD respectively (P= <0.0001). The mean vitamin-D level of frequent exacerbators was lower than nonfrequent exacerbators (17.02±4.27 vs 24.05±6.30; P= <0.0001). The mean vitamin-D level of hospitalized patients for AECOPD was lower than not hospitalized for AECOPD (17.23±4.00 vs 28.42±4.88; P= <0.0001). The vitamin-D level in relation to GOLD stages were: stage I (33.78±3.81), stage II (27.03±5.26), stage III (19.16±2.63) and stage IV (13.46±2.90) statistically

Table 1: Epidemiological & clinical characteristics

Variables	All patients (N=100)	Male (N=82)	Female (N=18)
Age(yrs) (mean ±SD)	61.24 ± 11.99	61.90 ± 11.93	58.22 ± 12.12
BMI(kg/m²) (mean ± SD)	21.90 ± 3.61	21.62 ± 0.37	23.18 ± 1.02
Smoking status			
Present smokers n (%)	52(52%)	51(62.2%)	1(5.5%)
Past smokers n (%)	31(31%)	27(32.9%)	4(22.2%)
Never smokers n (%)	17(17%)	4(4.8%)	13(72.2%)
GOLD Class n(%)			
I (mild COPD)	18(18%)	10(12.1%)	8(44.4%)
II (moderate COPD)	36(36%)	32(39%)	4(22.2%)
III (severe COPD)	29(29%)	24(29.2%)	5(27.7%)
IV(very severe COPD)	17(17%)	16(19.5%)	1(5.5%)
Medication for COPD n (%)			
None	38(38%)	31(37.8%)	9(50%)
LAMA	38(38%)	30(36.5%)	8(44.4%)
LABA	62(62%)	53(64.6%)	9(50%)
Inhaled steroid	61(61%)	52(63.4%)	9(50%)
Frequent exacerbators n (%)	40(40 %)	34(41.4 %)	6(33.3 %)
Hospitalized for AECOPD in the last yr, n(%)	47(47%)	39(47.5 %)	8(44.4%)
Post bronchodilator			
FEV1(%pred),mean ± SD	61.22 ± 12.03	51.70 ± 21.33	65.56 ± 24.06
FVC (L), mean ± SD	1.990 ± 0.648	2.057 ± 0.634	1.681 ± 0.639
FEV1/FVC, mean ± SD	0.563 ± 0.098	0.548 ± 0.100	0.632 ± 0.046

FEV_1: Forced expiratory volume in 1 second, FVC: Force vital capacity, ICS: Inhaled Cortico Steroids, LAMA: Long Acting Muscarinic Antagonist, LABA: Long Acting β_2 Agonist

Table 2: Comparison of mean value of PFT indices in relation to vitamin-D levels

Parameters	Vitamin-D level (NG/ml)			P- value (ANOVA)
	<20 (n=42)	20-29.9 (n=31)	≥30 (n=27)	
FEV_1 (%predicted)	34.74±11.08	57.16±12.67	81.04±12.47	<0.0001
FVC(L)	1.429±0.356	2.079±0.367	2.079±0.367	<0.0001
FEV_1/FVC	0.502±0.101	0.575±0.071	0.644±0.043	<0.0001
FEV_1(L)	0.708±0.153	1.195±0.205	1.787±0.237	<0.0001

Table 3: Correlation between vitamin-D and PFT indices

Correlation with Vitamin-D	r-value	P-value
FEV_1 (% predicted)	0.891	< 0.0001
FVC (L)	0.859	< 0.0001
FEV_1 / FVC	0.637	< 0.0001

Table 4: Comparison of mean value of vitamin-D level in relation to different patient's characteristics

Characteristics	No. of patients	Mean value of vitamin-D	P-value
Gender			
Male	82	23.55±7.76	0.565
female	18	24.72±7.99	
Age			
40-60	53	24.55±7.59	
61-80	41	22.39±8.04	0.298
>80	06	26.25±7.10	
BMI (kg/m^2)			
<18.5	22	23.82±8.39	
18.5-24.99	59	23.73±7.68	
25-29.99	17	23.90±8.03	0.998
≥30	02	23.00±7.07	
Residence			
Rural	88	23.45±7.52	0.281
Urban	12	26.04±9.48	
Smoking status			
Current(present)	52	20.24±5.96	
Former(past)	31	26.51±7.93	<0.0001
Never	17	29.52±7.26	
Frequency of AECOPD			
0	44	29.79±5.41	
1	16	24.05±6.30	<0.0001
2	34	18.12±3.33	
3	06	10.73±3.67	
Frequent v/s non frequent exacerbators			
Frequent exacerbators	40	17.02±4.27	<0.0001
Non frequent exacerbators	16	24.05±6.30	
Hospitalization for AECOPD			
Yes	47	17.23±4.00	
No	09	28.42±4.88	<0.0001
GOLD stage			
I	18	33.78±3.81	
II	36	27.03±5.26	<0.0001
III	29	19.16±2.63	
IV	17	13.46±2.90	

highly significant (P= <0.0001).

Discussion

We observed high prevalence of COPD in males as compared to females in contrast to previous studies [10] probably because of the high prevalence of smoking and frequent exposure to pollution due to outdoor activity in males as compared to females in our area. We also observed younger age of COPD patients as compared to observations made by the previous workers [10] this may be because of poor nutrition, health unawareness in our patients.

In our study, prevalence of vitamin-D deficiency was 42% , lower than observation made by Jung JY et al [11] but higher than a study performed by Azza Farag Said [12]. Increased prevalence of vitamin D deficiency in our cases may be because of alteration of the cutaneous synthesis of vitamin D due to age and the toxic effects of tobacco, low exposure to sunlight, high content of melanin in skin, increased catabolism of vitamin D by glucocorticoids, its sequestration in adipocytes, reduced intestinal absorption and poor hepatic and renal activation of vitamin D precursors [1].

Our study indicate a positive correlation of

vitamin-D level with FEV1(% predicted), FVC and FEV_1/FVC similar to previous studies [12,13]. However, Cohort study reported by Shaheen et al in an older adult UK population did not show a positive correlation between serum 25(OH)D concentrations and lung function in spirometrically defined COPD patients [14].

We did not observed statistically significant difference of vitamin-D levels between males and females (P=0.565) similar to a study done by Andrei Malinovschi et al [10]. However, we found lower mean levels of vitamin-D in males as compared to females in contrast to a study done by Evgeni Mekov et al [15]. This may be because our study included large number of males with high prevalence of smoking and smoking reduce synthesis of vitamin-D in the skin, they were suffered from more severe COPD and more steroid use for severe COPD and also may be because of females were more exposed to early sun light because of habit to pray to rising sun.

Although we did not observed statistically significant difference of vitamin-D levels in relation to BMI (P-value 0.998) similar to Andrei Malinovschi et al [10], however, we found lower levels of vitamin-D in obese (BMI>30) as compared to normal BMI patients (23.00±7.07 vs 23.73±7.68), similarly observed by Persson LJ et al. [16] but Shah Sanket et al. concluded that low BMI was associated with high prevalence of Vitamin D deficiency because of Malnutrition and decreased skin thickness with decreased metabolism of vitamin D [17].

Our study observed significant difference of the mean value of vitamin-D level among present (current) smokers, past(former) and never smokers (P= <0.0001) similarly to Evgeni Mekov et al who also observed that hypovitaminosis-D was more prevalent in current smokers (87.5%) but mean value of vitamin D in current smokers, former smokers and never smokers did not differ significantly (p = 0.667) [15]. Possible explanation of reduced level of vitamin-D in current smokers could be alteration of the cutaneous synthesis of vitamin D by the toxic effects of tobacco [3].

We observed significant difference of vitamin-D levels with numbers of AECOPD (P=<0.0001) as observed by previous workers [10,18,19]. However Puhan MA et al [20] did not found relationship between vitamin D and an increased incidence of exacerbations, however, in this study patients taking vitamin D supplements were not excluded, and exacerbations were not adjudicated centrally, which may have blurred an association. We also observed significant difference of vitamin-D levels (17.02±4.27 vs 24.05±6.30; P=<0.0001) in frequent exacerbators and non-frequent exacerbators similar to previous study [11]. Lehouck A et al also performed a randomized trial, who found that high dose vitamin D supplementation has been found to decrease AECOPD number, but only in patients with severe deficiency [5].

Our study observed significant difference of vitamin-D levels (P= <0.0001) in patients who were hospitalized as compared to who were not hospitalized for AECOPD in last year before the measurement of vitamin-D level. Zasloff M. also concluded that Insufficient vitamin D levels contribute to respiratory infections and colonization of the respiratory system especially in patients with COPD which further increases the frequency of hospitalization, and accelerates progression of COPD [21].

Our study indicate strong relationship (P<0.0001) of severity of COPD with lower levels of vitamin-D. Similarly, Janssens W et al. also observed, from GOLD 2 onwards 25-OHD levels differed significantly from those of healthy smokers (P<0.0001) [22]. However, vitamin D levels were not related to the GOLD-COPD class in a study performed by Andrei Malinovschi et al. [10]. This could simply be due to the fact that the size of such study was too small.

Conclusion

Our study concludes that COPD is associated with a significantly low level of vitamin-D which was independent to patients' age, gender, BMI and residence but dependent on current smoking. The lower level of vitamin-D is associated with severity of COPD, increased frequency of AECOPD and increased risk for hospitalization. The relationship between lung functions and levels of vitamin D is almost linear. The findings of our study suggest that awareness of serum vitamin-D level in patients with COPD is important. Further studies are required to validate the importance of vitamin-D levels in COPD patients by comparing with control normal healthy subjects and by doing intervention in the form of supplementation of vitamin-D in COPD subjects.

Declaration

Authors Contribution

Designed the study: BKG. Drafted the manuscript: BKG, SLM and JG. Approved the final version to be published: BKG. Carried out clinical assessment, data

collection and review of literature: BKG, SLM, MS, HRN,MLS and JG. Evaluated and analyzed laboratory data and their interpretation: BKG, SLM and MS. All authors read and approved the final manuscript. Guarantors of the paper: BKG and SLM.

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Competing Interest: None declared

Ethical Approval

A prior approval has been taken from the Institutional Ethics Committee to carry out this work, and an informed consent was obtained from the subjects enrolled in this study.

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