Vitamin D deficiency during chronic obstructive pulmonary disease exacerbations

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Background Vitamin D deficiency is widespread and associated with increased risk of chronic diseases. The relation between chronic obstructive pulmonary disease (COPD) and vitamin D is complex owing to comorbidities, which are affected by vitamin D. Patients with low vitamin D showed higher risk for exacerbations.

Aim The aim was to study the status of vitamin D in patients during exacerbation of chronic obstructive pulmonary disease (AECOPD).

Patients and methods The study included 205 patients presented with AECOPD and 150 controls. Patients and controls were subjected to full clinical history and examination, pulmonary function testing, and vitamin D [hydroxyvitamin D, 25(OH)D] examination by Liaison 25 OH Vitamin D assay (direct competitive chemiluminescence immunoassay, DiaSorin Inc, Stillwater, Minnesota, USA) in serum. Symptom scoring was done using modified Medical Research Council (mMRC) and combined assessment of Global Initiative for Chronic Obstructive Lung Disease COPD classification, with division into groups A, B, C, and D. Data related to severity of exacerbation, site of care, and hospital days were gathered.

Statistics Pearson's χ^2-test was used to compare the prevalence of categorical variables between patients with COPD and control groups. *t*-Test was used to compare differences in the levels of continuous variables between the two groups. R^2-test was used to measure how close the data are to be fitted in the regression line.

Results 25(OH)D was significantly lower in patients with AECOPD than control group (mean: 39.5±32.5 vs. 56.3±43.7 nmol/l, *P*? 0.05). Vitamin D insufficiency (25–75 nmol/l) was significantly higher in patients than controls [115 (56.09%) patients vs. 51 (34%) controls, $P<0.05$]. 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 (forced expiratory volume in first second <50%) (47.4±28.3), with *P* value less than 0.05. Patients required hospitalization showed lower levels of 25(OH)D compared with patients treated at home (23±14.9 and 52±22.1, respectively), with *P* value less than 0.05. Hospital days were higher in deficiency group (3.78±3.51 days) compared with insufficiency group (1.68±2.33 days) or sufficiency group (1.3±1.7 days), with *P* value less than 0.05.

Conclusion Vitamin D is low in patients with COPD during AECOPD. 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.

Egypt J Bronchol 2017 11:311–321

Egyptian Journal of Bronchology 2017 11:311–321

Keywords: chronic obstructive pulmonary disease, deficiency, exacerbation, vitamin D

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Received 22 April 2017 **Accepted** 9 July 2017

Introduction

Vitamin D sources originate from skin after exposure to ultraviolet rays, dietary resources, and supplementation [1]. Vitamin D plays a role in bone maintenance and calcium and phosphorous homeostasis, strengthens the innate immune responses upon infection, and regulates the adaptive immune responses [2]. Vitamin D deficiency is widespread worldwide and is associated with increased risk of cancer, autoimmune diseases, infectious diseases, and cardiovascular diseases [3]. Factors affecting vitamin D level include old age, female sex, habits of exposure to sun, dietary nature, and vitamin D supplementations [4]. Vitamin D deficiency role in chronic obstructive pulmonary disease (COPD) is not clear. Some studies linked vitamin D deficiency and COPD [5,6], without definite conclusion. COPD exacerbations affect the disease by symptom worsening and functional and clinical deterioration [7]. Vitamin D deficiency studies showed effect on asthma [8,9], COPD [10], and recurrent respiratory tract infections [11,12]. These studies highlighted the association between vitamin D deficiency and liability to infection, through influence on airway colonization [13] or alteration of airway remodeling [14]. These studies

 DOI: 10.4103/ejb.ejb_35_17

lack prospective clinical trials that study vitamin D during COPD exacerbations.

Aim

The aim was to explore the status of vitamin D in patients with COPD during exacerbation of chronic obstructive pulmonary disease (AECOPD).

Patients and methods

Ethics

Written consent was obtained from all patients and controls before inclusion in the study. The study design was approved by the institutional review board.

Participants

Patients with COPD exacerbation who were managed in either pulmonology clinic, Emergency Department, or Internal Medicine Clinic in four referral medical centers were selected for the study prospectively from January 2014 to June 2016. Overall, 205 patients with COPD with AECOPD and 150 controls attending the medicine clinic were selected for the study. All participants were studied for serum 25 hydroxyvitamin D [25(OH)D]. All of them were assessed for demographic data, smoking history, years since diagnosis of COPD, and medications used. All patients and controls were screened for comorbidities. Symptom scoring by modified Medical Research Council Dyspnea Scoring (mMRC) was done. Clinical examination included vital signs and BMI. Patients were further classified per WHO criteria into obese (30 kg/m^2 or more), overweight (25–29.9 kg/m^2), normal (18.5–24.9 kg/m^2), or underweight (<18.5 kg/m^2). Clinical assessment of severity of disease, years since diagnosis of COPD, previous exacerbations, and if there was previous admission owing to COPD exacerbation were recorded. Exacerbation history was defined as having respiratory symptoms treated with antibiotics and/or oral steroids and/or hospitalization in the last 12 months. Pulmonary function tests were retrieved from previous examination, and the ratio of forced expiratory volume in first second (FEV1)/forced vital capacity less than 70% was essential to diagnosis. FEV1% of predicted was recorded, and spirometry was repeated after recovery from exacerbation. Classification of COPD severity by FEV1% from predicted, symptom scoring by mMRC, and risk of exacerbation into group A, B, C and D. Division of patients with COPD into subgroups was done according to the current global initiative for obstructive lung disease (GOLD) classification 2015 [15]. Chest radiography and routine laboratory examinations were done to detect comorbid conditions including diabetes, hypertension, renal failure, and congestive heart failure. Site of care (home treatment, hospitalization, or intensive care) was determined per severity and recorded for each patient. Duration of hospitalization stay was recorded if any for patients who were hospitalized. Arterial blood gas analysis and categorization was recorded as normal blood gases, type I or type II respiratory failure.

The medical records of the patients were collected for retrieving the previous history including pulmonary function tests, previous exacerbations, and previous hospital admissions, and chronic medications used.

Inclusion criteria included all patients diagnosed with AECOPD with previous spirometry showing ratio of FEV1/forced vital capacity less than 70%, and smoking history of at least 10 pack-years. Exclusion criteria included enrollment in other studies, refusal to participate in the study, inability to undergo spirometry, presence of other pulmonary disorders including asthma bronchiectasis or lung fibrosis, renal impairment or failure, presence of osteoporosis, or treatment with vitamin D supplements.

Laboratory analysis

Vitamin D [25(OH)D] in serum was analyzed using the Liaison 25(OH) Vitamin D assay (direct competitive chemiluminescence immunoassay). Samples were stored at 2–8°C for less than 24 h if not tested immediately. Categorization of results per levels supplied by laboratory cutoff values was done into sufficient (<75 nmol/l), insufficient (25–75 nmol/l), and deficient (>25 nmol/l).

Statistical analysis

Pearson χ^2-test was used to compare the prevalence of categorical variables between patients with COPD and control groups (Table 1). *t*-Test was used to compare the differences in the levels of continuous variables between TWO groups (e.g. participants with vitamin D sufficiency and insufficiency and insufficiency and vitamin D deficiency based on laboratory cutoff values) in Table 2. R^2 was used to measure how close the data are to be fitted on the regression line. The study also measured the coefficient of determination or the coefficient of multiple determination for multiple regression. It was performed to analyze the relation between vitamin D status and demographics (age, BMI, mMRC, and smoking index). It was also

Table 1 Baseline characteristics of patients with exacerbation of chronic obstructive pulmonary disease and control group

Variables	COPD (*n*=205) [*n* (%)]	Controls (*n*=150) [*n* (%)]	*P* value
Age (mean±SD) (years)	63±9.3	59.5±8.6	0.07 (NS)
Sex			
Males	174 (84.87)	121 (80.66)	0.09 (NS)
Females	31 (15.12)	29 (19.33)	0.15 (NS)
Smoking history			
Never smoker	0 (0)	37 (24.66)	? 0.05
Ex-smoker	115 (56)	58 (38.66)	0.35 (NS)
Current smoker	90 (43.9)	55 (36.66)	0.27 (NS)
BMI (mean±SD) (kg/m^2)	32.3±8.4	33.8±7.3	0.18 (NS)
Comorbidities			
0	62 (30.24)	39 (26)	<0.05
1	63 (30.73)	45 (30)	0.24 (NS)
2	38 (18.53)	27 (18)	0.09 (NS)
3	42 (20.48)	41 (27.3)	<0.05
FEV1% (mean±SD)	49±12.7	74.13.9	? 0.05
mMRC (mean±SD)	2±1.2	1±1.5	? 0.05
GOLD classification			
GOLD A	18 (8.78)	–	
GOLD B	50 (24.39)	–	
GOLD C	71 (34.63)	–	
GOLD D	66 (32.19)	–	
Vitamin D (mean±SD) (nmol/l)	39.5±32.5	56.3±43.7	<0.05
Sufficiency	33 (16.09)	63 (42)	<0.05
Insufficiency	115 (56.09)	51 (34)	<0.05
Deficiency	57 (27.8)	36 (24)	0.09 (NS)
Site of care			
Home	134 (65.36)	–	
Ward	60 (29.26)	–	
ICU	11 (5.36)	–	
Respiratory failure			
Type I	15 (7.31)	–	
Type II	11 (5.36)	–	

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in first second; GOLD, global initiative for chronic obstructive lung disease classification available from: http://www.goldcopd.org/; mMRC, modified medical research council questionnaire. *P* values are according to Pearson's χ^2-test, where *P* value less than 0.05 is considered as statistically significant. *P* value is significant if less than 0.05, otherwise not significant.

performed to study the relation between vitamin D and severity of COPD disease as determined by COPD GOLD classification, postbronchodilator FEV1, previous exacerbations, and hospital stay days. *P* value less than 0.05 was assumed to indicate statistical significance of observed associations.

Results

Patient characteristics

Among 376 patients selected for the study, 171 patients were excluded owing to lack of follow-up or inability to perform spirometry after recovery from AECOPD, presence of other pulmonary disorders upon further radiological studies, renal impairment, or the current use of vitamin D supplements. The characteristics of the study population (205 patients and 150 controls) are shown in Table 1. The mean age was higher in the COPD group by 4.5 years but was statistically insignificant. Men were more than women in both COPD and control groups (84.8 and 80.6%, respectively). There was no significant difference in smoking index between current smokers and ex-smokers in both patient and control groups, but there were no never smokers in the patient group compared with the control group (24.66%). BMI was 32.3±8.4 in AECOPD group compared with 33.8±7.3 (*P*=0.18) in control group. Comorbidities were counted in patient group and control groups, and there is no statistical difference when there is one or two comorbidities, but COPD group showed higher percentage of 0 comorbidities [62 (30.24%)] compared with control group [39 (26%)], with *P* value less than 0.05. Control group contained higher percentage of participants with three comorbidities [41 (27.3%)], than COPD group [42 (20.48%)], with *P* value less than 0.05. The mean FEV1 in the COPD group was 49±12.7 compared with 74.13.9 in

Table 2 Serum levels of vitamin D [25(OH)D] in nmol/l in patients with chronic obstructive pulmonary disease and differences with age, sex, smoking status, and BMI.

	Age (years)			Sex		Smoking		BMI (kg/m^2)			
	<60 (*n*=70)	60–75 (*n*=109)	>75 (*n*=26)	Males (*n*=174)	Females (*n*=31)	Current smokers (*n*=89)	Ex-smokers (*n*=116)	<18.5	18.5–24.9	25–29.9	≥30
25 (OH)D (mean±SD) (nmol/l)	53.6±20.1	27.1±19.6	19±11.3	34.3±23.3	19.1±12.9	42.4±22.9	25.1±20.1	51.6±19.1	48.6±18.5	55.6±20.1	53.2±20.8
P value	<0.05		<0.05	<0.05		<0.05		0.13 (NS)		0.15 (NS)	

t-Test was used to compare differences between various groups, where *P* value is less than 0.05 is considered as statistically significant.

the control group ($P<0.05$). Dyspnea scoring through mMRC showed higher score in COPD group (2±1.2) compared with the control group (1±1.5) ($P<0.05$). Patients with COPD were categorized according to GOLD combined assessment classification into GOLD A [18 (8.78%)], GOLD B [50 (24.39%)], GOLD C [71 (34.63%)], and GOLD D [66 (32.19%)]. According to the site of care, 134 (65.36%) of patients with AECOPD were treated at home, 60 (29.26%) were admitted to ward, and 11 (5.36%) were admitted to ICU. In the admitted group, 15 (7.31%) were diagnosed with type I respiratory failure and 11 (5.36%) with type II respiratory failure.

Vitamin D status in chronic obstructive pulmonary disease exacerbation

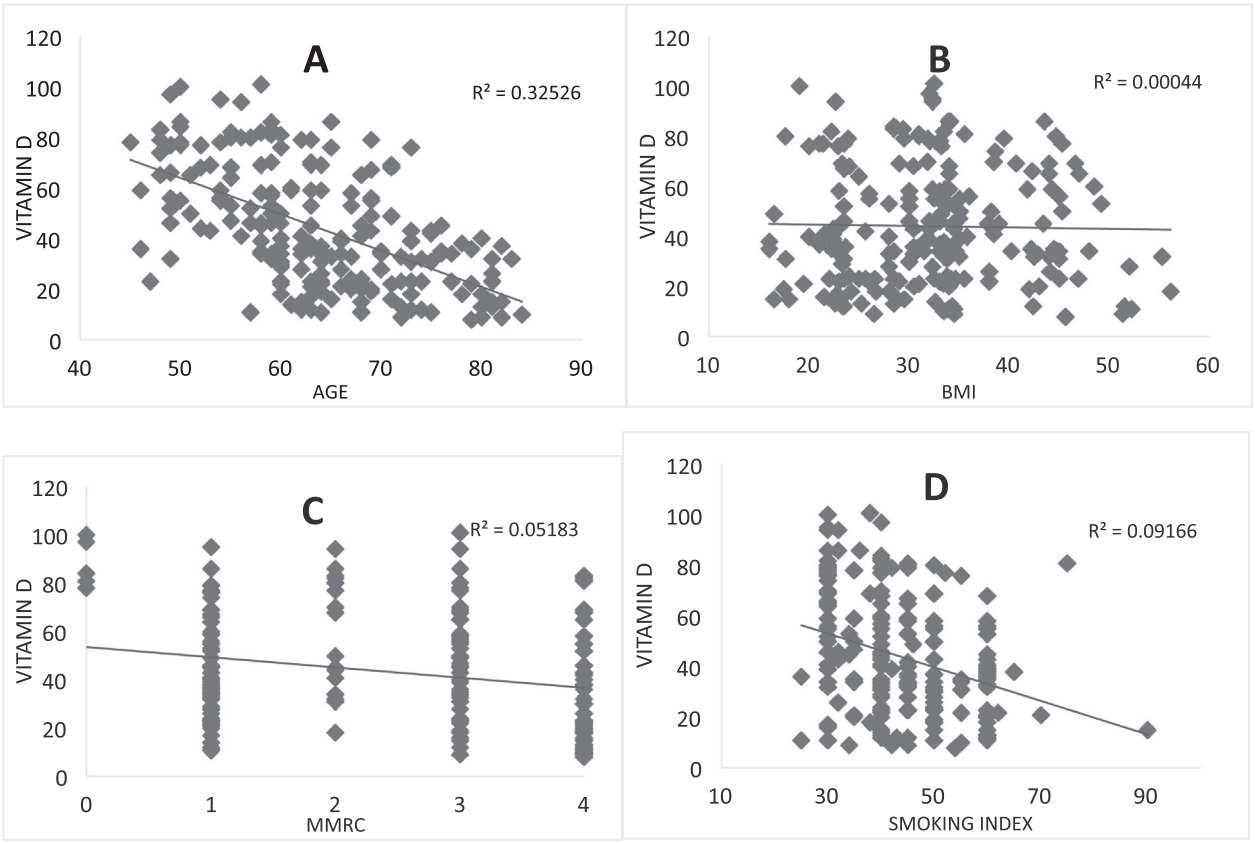
The mean 25(OH)D level in patients with COPD was 39.5±32.5 compared with 56.3±43.7 in control group. Classification of 25(OH)D was done according to its level into sufficiency (>75 nmol/l), insufficiency (25–75 nmol/l), and deficiency (<25 nmol/l). In COPD group, 33 (16.09%) had sufficient level compared with 63 (42%) in the control group ($P<0.05$); 115 (56.09%) patients with COPD had insufficient vitamin D compared with 51 (34%) in the control group ($P<0.05$); and vitamin D deficiency was found in 57 (27.8%) of patients with COPD and in 36 (24%) in control group (*P* is nonsignificant).

In patients with COPD, older age was associated with lower levels of 25(OH)D; it was 53.6±20.1 in patients more than 60 years ($n=70$), as compared with 27.1± 19.6 in patient with age between 60 and 75 years ($n=109$) and 19±11.3 in patients older than 75 years ($n=26$), with *P* value less than 0.05. Males ($n=174$) showed higher levels of 25(OH)D (34.3±23.3) than females ($n=31$, mean values 19.1±12.9) with *P* value less than 0.05. Ex-smokers ($n=116$) showed lower levels of 25(OH)D (25.1±20.1) than current smokers ($n=89$, 25.1±20.1, $P<0.05$). Body weight and BMI did not show differences between underweight, normal weight, overweight, and obese patients of statistical significance as shown in Table 2.

Figure 1 showed a linear relationship between vitamin D and age (Fig. 1a) and smoking index (Fig. 1d) with *P* value less than 0.05 but there was no relation between vitamin D and BMI (Fig. 1b) and dyspnea severity (Fig. 1c).

There were statistically lower levels of 25(OH)D (62.3 ±20.4) in GOLD group B compared with group A

Figure 1



Levels of vitamin D in nmol/l plotted against (a) age, (b) BMI, (c) mMRC, and (d) smoking index. $P<0.05$, significant.

Table 3 Serum levels of 25(OH)D in nmol/l and differences with GOLD combined assessment classification, forced expiratory volume in first second, hospitalization, and history of previous exacerbation

	GOLD combined assessment				FEV1		Hospitalization		History of exacerbation	
	A (*n*=18)	B (*n*=50)	C (*n*=71)	D (*n*=66)	>50 (*n*=82)	<50 (*n*=123)	None (*n*=135)	Yes (*n*=70)	0–1 (*n*=64)	2 or more (*n*=141)
Vitamin D (mean±SD) (nmol/l)	78.4±18.6	62.3±20.4	41.4±23.6	34.1±21.6	69.4±23.1	47.4±28.3	52±22.1	23±14.9	68±19.3	32.5±18.2
P value	<0.05		<0.05		<0.05		<0.05		<0.05	

FEV1, forced expiratory volume in first second; GOLD, global initiative for chronic obstructive pulmonary disease classification available from: http://www.goldcopd.org/. t-Test was used to compare differences between various groups, where *P* value is less than 0.05 is considered as statistically significant.

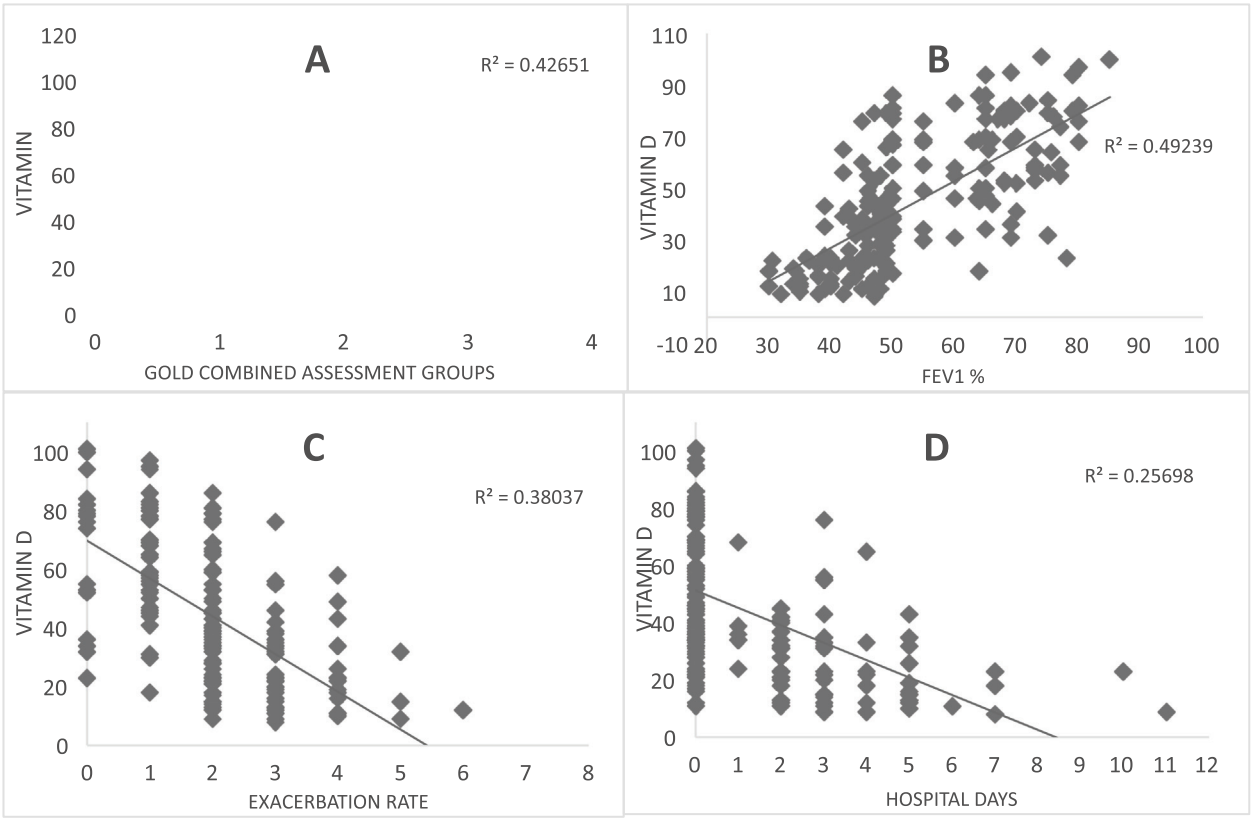
(78.4±18.6), with *P* value less than 0.05. The same was seen in group D (34.1±21.6) compared with group C (41.4±23.6), with *P* value less than 0.05. Patients with mild and moderate COPD (FEV1 >50%) showed higher 25(OH)D (69.4±23.1) than patients with severe and very severe COPD (FEV1<50%) (47.4± 28.3), with *P* value less than 0.05. Patients who required hospitalization showed lower levels of 25 (OH)D compared with patients treated at home (23±14.9 and 52±22.1, respectively) with *P* value less than 0.05. History of previous exacerbations as a risk for future exacerbations showed that patients with low risk (zero or one previous exacerbation) showed higher levels of 25(OH)D compared with higher risk group (two or more previous exacerbations) (68±19.3 vs. 32.5±18.2, respectively), with *P* value less than 0.05 as shown in Table 3.

Figure 2 showed a linear relationship between GOLD COPD combined assessment classification and vitamin D levels (2A) and FEV1 (Fig. 2b), previous number of exacerbations (Fig. 2c), and total hospitalization days (Fig. 2d).

25(OH)D in patients with chronic obstructive pulmonary disease

Table 4 shows the subdivision of patients with COPD by vitamin D status into sufficient (>75 nmol/l, *n*=33), insufficient (25–75 nmol/l, *n*=115), or deficient (<25 nmol/l, *n*=57). Patients with vitamin deficiency were

Figure 2



Levels of vitamin D in nmol/l plotted against (a) COPD GOLD groups (1=GOLD A, 2=GOLD B, 3=GOLD C, and 4=GOLD D), (b) against forced expiratory volume in first second (FEV1), (c) exacerbation rate, and (d) hospital days. $P<0.05$, significant.

older in age (68.9±7.76 years) compared with those with insufficiency (61.84±8.76 years) and sufficiency (55.31±6.57 years), with *P* value less than 0.05. None of females tested had sufficient vitamin D levels (>75 nmol/l), whereas 30 (100%) males had sufficient vitamin D levels. There were 104 (90.4%) males with insufficient vitamin D compared with 11 (9.56%) females, with *P* value less than 0.05. Deficiency of vitamin D was seen in 38 (65.68%) males compared with 20 (34.48%), with *P* value less than 0.05. Ex-smokers were higher in deficiency group (79.3%, *n*=46) compared with current smokers (28.6%, *n*=12). Insufficiency group also showed more ex-smokers (53.1%, *n*=61) compared with current smokers (46.9%, *n*=54). Current smokers in sufficiency group were higher than ex-smokers (2.72%, *n*=24, vs. 27.27%, *n*=9). Smoking index was higher in sufficiency group compared with insufficiency and deficiency groups(44.4±11.3, 41 ±10, and 36.6±9.7, respectively). There was no difference in BMI between sufficiency, insufficiency, and deficiency (28.3±7.2, 29.5±8.7, and 28.8±9.2, respectively). COPD years were higher in the deficiency group compared with insufficiency and sufficiency groups (13.52±7.2, 17.53±12.6, and 21.3 ±13.5, $P<0.05$). None of patients with COPD with sufficiency were in classified into group D but eight (24.2%) patients were into group A, 17 (51.5%) patients into group B and eight (24.2%) group C patients into group C; the insufficiency group showed 47 (40.8%) patients in group C compared with 10 (8.6%) patients in group A, 31 (26.9%) in group B and 27 (23.4%) in group D; and there were more patients in the deficiency group with group D COPD (39 patients, 68.4%) compared with groups A, B, and C [one (1.75%) patient, one (1.75%) patient, and 16 (28.6%) patients, respectively]. Dyspnea score (mMRC) was higher in deficiency group (70.1% having 2 or more mMRC score) compared with in insufficiency and sufficiency groups (51.3 and 51.5%, respectively), as shown in Table 4.

Patients with vitamin D deficiency showed high rate of previous exacerbation (2 or more exacerbations in the last year) [55 (96.49%) patients] compared with low rate of exacerbations (0 or 1 exacerbation) [two (3.50%) patients]. Previous high exacerbation rates were less in patients with vitamin D insufficiency [75 (65.21%) patients], and there were even less patients with high exacerbations in patients with vitamin D sufficiency [eight (24.24%) patients]. Home treatment was predominant in sufficiency and insufficiency

Table 4 Categorization of patients with chronic obstructive pulmonary disease based on vitamin D status of sufficient, insufficient, and deficient status

	Vitamin D sufficiency >75 nmol/l (*n*=33) [*n* (%)]	*P* value	Vitamin D insufficiency 25–75 nmol/l (*n*=115) [*n* (%)]	*P* value	Vitamin D deficiency <25 nmol/l (*n*=57) [*n* (%)]
Age (mean±SD) (years)	55.31±6.57	<0.05	61.84±8.76	<0.05	68.99±7.76
Sex					
Males	33 (100)	<0.05	104 (90.4)	<0.05	38 (65.51)
Females	0 (0)	<0.05	11 (9.56)	<0.05	20 (34.48)
Smoking					
Current	24 (72.72)	<0.05	54 (46.9)	<0.05	12 (28.68)
Ex-smoker	9 (27.27)	<0.05	61 (53.1)	<0.05	46 (79.31)
Smoking pack (mean±SD) (years)	36.65±9.7	<0.05	41.03±10.08	<0.05	44.42±11.34
Comorbidities					
DM	7 (21.21)	<0.05	59 (51.3)	<0.05	41 (70.68)
HTN	6 (18.18)	<0.05	52 (45.21)	<0.05	43 (74.13)
DSL	1 (3.03)	<0.05	20 (17.39)	0.09 (NS)	12 (20.68)
BMI (mean±SD) (kg/m^2)	28.32±7.24	0.051 (NS)	29.51±8.71	0.15 (NS)	28.88±9.21
COPD (mean±SD) (years)	13.52±7.2	<0.05	17.53±12.6	<0.05	21.3±13.5
GOLD combined assessment groups					
A	8 (24.24)	<0.05	10 (8.69)	<0.05	1 (1.75)
B	17 (51.51)	<0.05	31 (26.95)	<0.05	1 (1.75)
C	8 (24.24)	<0.05	47 (40.86)	<0.05	16 (28.07)
D	0 (0)	<0.05	27 (23.47)	<0.05	39 (68.42)
mMRC					
0–1	16 (48.48)	0.07 (NS)	56 (48.69)	<0.05	17 (29.82)
2 or more	17 (51.51)	0.09 (NS)	59 (51.30)	<0.05	40 (70.17)
FEV1% (mean±SD)	64.32±11.28	<0.05	53.03±10.60	<0.05	41.17±7.72
Previous exacerbations					
0–1	25 (75.75)	<0.05	40 (34.78)	<0.05	2 (3.50)
2 or more	8 (24.24)	<0.05	75 (65.21)	<0.05	55 (96.49)
Severity of exacerbation					
Home	32 (96.96%)	0.09 (NS)	85 (73.91)	<0.05	16 (28.07)
Hospital	1 (3.03)	<0.05	28 (24.34)	<0.05	32 (56.14)
ICU	0 (0)	<0.05	2 (1.73)	<0.05	9 (15.78)
Hospital (mean ±SD) (days)	1.3±1.7	<0.05	1.68±2.33	<0.05	3.78±3.51
Respiratory failure on admission					
Type I	0 (0)	<0.05	3 (2.6)	<0.05	12 (21.05)
Type II	0 (0)	<0.05	1 (0.8)	<0.05	10 (17.54)

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DSL, dyslipidemia; FEV1, forced expiratory volume in first second; GOLD, global initiative for chronic obstructive lung disease classification available from: http://www.goldcopd.org/; HTN, hypertension; ICU, intensive care unit, type I respiratory failure: hypoxemic respiratory failure, type II respiratory failure: hypercapnic respiratory failure; mMRC, modified medical research council questionnaire. *P* value is significant if less than 0.05, otherwise not significant.

groups [32 (96.96%) patients and 85 (73.91%) patients respectively, *P* is nonsignificant] compared with deficiency group, which showed higher hospitalization [41 (71.9%) patients in hospital including ICU vs. 16 (28.07%) patients treated at home $P<0.05$]. Hospital days were higher in deficiency group than in insufficiency or sufficiency groups (3.78±3.51 vs. 1.68±2.33 and 1.3±1.7 days, respectively). None of the patients in sufficiency group showed respiratory failure compared with four (3.4%) patients in insufficiency group [three (2.6%) patients with type I and one (0.8%) patient with type II] and 22 (38.5%) patients in deficiency group [12 (21.05%) patients with type I and 10 (17.54%) patients with type II), with *P* value less than 0.05.

Discussion

The main finding in this study is the lower levels of vitamin D seen during acute exacerbation of COPD compared with controls. AECOPD was defined as worsening or new symptoms from stable daily state that requires additional treatment [16]. Many published studies [17,18] have looked for a

relationship between vitamin D level and the risk of high exacerbations rate based on number and severity of previous exacerbations. This study, to our knowledge, is the first prospective study that provides information about the actual status of vitamin D during the different severities of exacerbation of COPD.

Vitamin D levels in patients with COPD were studied before, and many studies showed deficiency of vitamin D [10,19,20] among different groups of COPD, and many other studies indicated higher risk of COPD in vitamin D-deficient patients [21,22,23,24], indicating a causal and conditional relationship. Heulens *et al*. [25] in their experimental study on mice found that vitamin D deficiency resulted in increased pulmonary inflammatory mediators and acceleration and aggravation of development of COPD features.

Vitamin D has antimicrobial antibacterial and antiviral effects through different mechanisms, one of them is the control of activity of cathelicidin which is an antimicrobial polypeptide. Cathelicidin was shown to be active against mycobacteria and against other organisms causing COPD exacerbations including antibiotic resistant strains such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, chlamydia, and other groups of viruses [26,27,28]. Such mechanisms could be an explanation for the increased exacerbations and severity of exacerbation associated with low vitamin D in the groups studied.

In a very recent meta-analysis and systematic review of individual participant data in 2017 done by Martineau *et al*. [29], a significant protective benefit of vitamin D supplementation was seen in prevention of acute respiratory tract infections especially in patients with vitamin D deficiency. In the first published randomized control study [30] in 2012 on vitamin D supplementation on 182 patients with COPD, although there was improvement of the phagocytic action of monocytes in the vitamin D supplement group, it failed to show a significant reduction in the rate of exacerbation; however, this can be attributed to the small sample size in that RCT and being performed in a single center. Another limitation of this RCT study is being performed on patients with severe COPD already on maximum bronchodilator inhalational therapy, and the added therapeutic effect of vitamin will be difficult to obtain. In that study, although the time to first exacerbation did not differ between treated and control groups, the probability of exacerbation per patient-year was seen to decrease by 43% compared with control group without vitamin D supplementation.

In the primary analysis of our study, only 16% of patients with AECOPD showed sufficient levels of vitamin D compared with 42% in controls, whereas 56.09% of patients with AECOPD showed vitamin D insufficiency compared with 34% in the control group, despite there being no statistical significance in the percentage of deficiency in both groups (27.8% in AECOPD compared with 24% in control group). Zhu *et al*. [31] in their meta-analysis on 18 studies on vitamin D deficiency in COPD showed that serum levels of vitamin D were lower in patients with COPD, but an earlier meta-analysis done by Zhang *et al*. [32] collected eight studies on asthma and two studies only on COPD, and it did not show a statically significant difference of vitamin D serum levels in COPD and controls. They mentioned that the limitation to their meta-analysis is the low quality of studies collected and being designed as observational studies. In the analysis of our study, 172 (83.9%) patients during exacerbations showed either insufficient or deficient 25(OH)D levels, whereas deficiency and insufficiency were seen in 58% of the controls. Kunisaki *et al*.[17] in their original research, which was designed to study the effect of daily azithromycin on exacerbation rate in patients with severe COPD, did a secondary analysis on the baseline vitamin D status from blood samples taken at enrollment and observed their patients for subsequent AECOPD and concluded that in patients with severe COPD, baseline 25(OH)D levels are not predictive of subsequent AECOPD. Although their study included large number of participants (73 patients with COPD), limitations were seen including that the study design was based on baseline 25(OH)D and not on actual 25(OH)D at the time of exacerbation. The second limitation was exacerbation information was collected by phone calls or clinical visits for symptoms with duration of at least 3 days and requiring treatment with an antibiotic or systemic corticosteroid, which may underestimate or overestimate the actual exacerbation rates. Another limitation is that most of their patients had severe COPD and were less ambulant with insufficient exposure to sunlight, hence the expected with lower levels of 25(OH)D. Our study included 205 patients, which demonstrates a cross-section of patients with COPD with different level of severities. Moreover, blood samples were extracted at the same time of patient presentation with AECOPD, which reflects an accurate measurement of vitamin D during the exacerbation.

Low baseline levels of vitamin D levels and association with exacerbations of COPD and mortality were not proved in a study done in Dutch and Swiss primary care settings [33]. In contrast, an Italian retrospective cohort study on previous history of exacerbations and hospitalization and relation with vitamin D deficiency conducted by Malinovschi *et al.* [34] showed that exacerbation frequency and history of hospitalization was associated with more severe vitamin D deficiency.

A recent Bulgarian study by Mekov *et al.* [35] on the prevalence vitamin D deficiency in hospitalized patients with COPD exacerbation, showed high prevalence of vitamin D deficiency in admitted patients with AECOPD. Vitamin D deficiency was associated with longer hospital stay a low quality of life, and low lung function (FEV1 <50%), but low levels were not associated with different comorbidities. There are limitations in their study as they included hospitalized patients only, and patients on vitamin D supplements during enrollment were not excluded from the study. In our study, it was noticed that patients with frequent previous exacerbations were associated with lower levels of vitamin D, which reflects basically that higher risk for future exacerbations, or reflect the multifactorial nature of COPD disease, and vitamin D deficiency is only one factor.

A recent meta-analysis and systemic review done by Zhu *et al.* [18] on 21 previous studies that included including 4818 patients with COPD and 7175 controls showed that lower levels of vitamin were associated with increased COPD risk. They also showed that patients with severe and very severe COPD based on GOLD were associated with lower levels of vitamin D compared with those with moderate COPD, despite the association between low vitamin D levels and risk of exacerbation was not proved by their meta-analysis on three studies meeting the criteria. Our results, which showed that vitamin D levels were directly related to degree of COPD severity and low levels of vitamin D, were associated with the degree of airway obstruction as demonstrated by lower FEV1% in vitamin D deficiency and even more when categorized as COPD groups based on GOLD criteria as A, B, C, and D. Lower vitamin D levels were seen in group B compared with A, and also lower levels in group D compared with group C. Shaheen *et al.* [36] failed to show a direct relationship between low vitamin D and lung function in adults and in COPD but Monadi *et al.* [37] showed a direct relationship between lower levels of vitamin D and lower FEV1. Another recent study showed in patients with severe and very severe COPD that vitamin D supplementation was associated with decreased rate of exacerbation and improvement of FEV1 [38]. Moreover, our study showed inverse relation between the number of previous exacerbations and 25(OH)D, and in exacerbations that needed hospitalization, more hospitalization days were inversely related to vitamin D levels; this relationship was also has been demonstrated by other studies [34,35].

In their study on Danish general population including 12 041 individuals, Skaaby *et al.* [39] found that despite a higher rate of vitamin D deficiency was associated with COPD and mortality owing to COPD, there is no effect on its prevalence, suggesting that vitamin D deficiency is an outcome rather than a cause of COPD. This was also demonstrated in secondary analysis of our study which showed low vitamin D levels were associated with older age and female sex, and this may be related to either disease severity in elderly and in women in our study, or related to lack of exposure to sunlight and activity which is more common in elderly and women in our community. Although smoking pack-years did not show a significant difference between ex-smokers and current smokers in COPD and control, there was a significantly higher mean vitamin D level in current smokers compared which ex-smokers; it could be explained by more severe COPD diseases and older age seen in the ex-smoker group compared with the current smokers in the present study.

Vitamin D was not influenced by weight as measured by BMI in our study, as there was no difference between underweight, normal, overweight, or obese patients. This is in contrast to another study [40] which showed decreased circulatory level of vitamin D in obese people, which reflects the multifactorial effect of COPD disease and its relationship with vitamin D is not simple. Moreover, symptom score in our study measured by mMRC questionnaire did not show a statistical difference between low symptoms (0–1 score) and high symptoms (2 or more) in patients with sufficiency and insufficiency, but 70% of patients with vitamin D deficiency showed high symptoms compared with patients with insufficiency.

In the present study, COPD exacerbations seen in patients with sufficient 25(OH)D were in nature mild and did not require hospitalization, whereas in patients with insufficiency and deficiency, hospitalization and even ICU admissions were seen

in most patients; moreover, there was a linear relationship between vitamin D and hospital stay days, as the more hospital days were seen related to low vitamin D. Patients with type I or type II respiratory failure were seen more in patients with deficiency or insufficiency, which in turn suggests that vitamin D is a factor adding to the complexity of disease and aggravating the disease status.

The limitations of our study are that it did not include patients with COPD with no exacerbations to compare their vitamin D levels with patients with AECOPD, and our study did not focus on sunlight exposure. Another limitation is that we did not study the level of vitamin D after recovery from exacerbation to demonstrate any change from the level retrieved at exacerbation.

In conclusion, vitamin D is low in patients with COPD during AECOPD, and 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.

Acknowledgements

Hassan A. Shabana was responsible for design and conducting the research, collection of cases matching with inclusion criteria, collection of results, sending results for statistical analysis, analysis of results, and writing the discussion. Naser K. Abdelnaby was responsible for collection of cases matching with inclusion criteria, collection of results, and analysis of results. Moustafa S. Moustafa was responsible for collecting cases matching with inclusion criteria, collection of results, and analysis of results. Waleed R. Arafat was responsible for collecting cases matching with inclusion criteria, collection of results, and analysis of results.

This work studies the status of vitamin D during COPD exacerbations and whether it is affected by severity of COPD itself or the current severity of COPD exacerbation. The work is conducted in Chest Diseases Department Cairo University.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. *Adv Nutr* 2011; **2**:244–253.

2 Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients* 2013; **5**:2502–2521.

3 Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357**:266–281.

4 Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, *et al.* Global Vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009; **20**:1807–1820.

5 Shaheen SO, Martineau AR. Vitamin D and chronic obstructive pulmonary disease: justified optimism or false hope? *Am J Respir Crit Care Med* 2012; **185**:239–241.

6 Foong RE, Zosky GR. Vitamin D deficiency and the lung: disease initiator or disease modifier? *Nutrients* 2013; **5**:2880–2900.

7 Trigueros Carrero JA. How should we define and classify exacerbations in chronic obstructive pulmonary disease? *Expert Rev Respir Med* 2013; **7**:33–41.

8 Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. Vitamin D serum levels and markers of asthma control in Italian children. *J Pediatr* 2011; **158**:437–441.

9 Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009; **179**: 765–771.

10 Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, *et al.* Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010; **65**:215–220.

11 Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009; **169**:384–390.

12 Roth DE, Shah R, Black RE, Baqui AH. Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. *Acta Paediatr* 2010; **99**:389–393.

13 Zasloff M. Fighting infections with vitamin D. *Nat Med* 2006; **12**: 388–390.

14 Boyan BD, Wong KL, Fang M, Schwartz Z. 1α,25(OH)2D3 is an autocrine regulator of extracellular matrix turnover and growth factor release via ERp60 activated matrix vesicle metalloproteinases. *J Steroid Biochem Mol Biol* 2007; **103**:467–472.

15 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global strategy for the diagnosis, management and prevention of COPD*; 2015. Available at: http://www.goldcopd.org/ [Accessed 29 January 2016].

16 Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003; **41**:46s–53s.

17 Kunisaki KM, Niewoehner DE, Connett JE. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. *Am J Respir Crit Care Med* 2012; **185**: 286–290.

18 Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 2597–2607.

19 Persson LJ, Aanerud M, Hiemstra PS, Hardie JA, Bakke PS, Eagan TM. Chronic obstructive pulmonary disease is associated with low levels of vitamin D. *PLoS One* 2012; **7**:e38934.

20 Heidari B, Javadian Y, Monadi M, Dankob Y, Firouzjahi A. Vitamin D status and distribution in patients with chronic obstructive pulmonary disease versus healthy controls. *Caspian J Intern Med* 2015; **6**:93–97.

21 Said AF, Abd-Elnaeem EA. Vitamin D and chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc* 2015; **64**:67–73.

22 Zhang P, Luo H, Zhu YQ. Prevalence of vitamin D deficiency and impact on quality of life in patients with chronic obstructive pulmonary disease. *J Cent South Univ (Med Sci)* 2012; **37**:802–806.

23 Lu YX, Liu JF, Qin XF. The association between serum vitamin D and CAT scores in stable chronic obstructive pulmonary disease. *J Cummun Med* 2014; **12**:50–52.

24 Huang JH. Effects of vitamin D to the pulmonary function and living quality in COPD. *Jiangxi Med J* 2013; **48**:668–670.

25 Heulens N, Korf H, Cielen N, De Smidt E, Maes K, Gysemans C, *et al.* Vitamin D deficiency exacerbates COPD-like characteristics in the lungs of cigarette smoke-exposed mice. *Respir Res* 2015; **16**:110.

26 Pfeffer PE, Hawrylowicz CM. Vitamin D and lung disease. *Thorax* 2012; **67**:1018–1020.

27 Banerjee A, Panettieri R Jr. Vitamin D modulates airway smooth muscle function in COPD. *Curr Opin Pharmacol* 2012; **12**:266–274.

28 Hewison M. Antibacterial effects of vitamin D. *Nat Rev Endocrinol* 2011; **7**:337–345.

29 Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, *et al.* Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; **356**:i6583.

30 Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, *et al.* High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease. A randomized trial. *Ann Intern Med* 2012; **156**:105–114.

31 Zhu B, Xiao C, Zheng Z. Vitamin D deficiency is associated with the severity of COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015; **10**:1907–1916.

32 Zhang LL, Gong J, Liu CT. Vitamin D with asthma and COPD: not a false hope? A systematic review and meta-analysis. *Genet Mol Res* 2014; **13**:7607–7616.

33 Puhan MA, Siebeling L, Frei A, Zoller M, Bischoff-Ferrari H, Ter Riet G. No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD. *Chest* 2014; **145**:37–43.

34 Malinovschi A, Masoero M, Bellocchia M, Ciuffreda A, Solidoro P, Mattei A, *et al.* Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients. *Respir Res* 2014; **15**: 131.

35 Mekov E, Slavova Y, Tsakova A, Genova M, Kostadinov D, Minchev D, *et al.* Vitamin D Deficiency and Insufficiency in Hospitalized COPD Patients. *PloS ONE* 2015; **10**:e0129080.

36 Shaheen SO, Jameson KA, Robinson SM, Boucher BJ, Syddall HE, Sayer AA, *et al.* Relationship of vitamin D status to adult lung function and COPD. *Thorax* 2011; **66**:692–698.

37 Monadi M, Heidari B, Asgharpour M, Firouzjahi A, Ghazi Mirsaied MA. Relationship between serum vitamin D and forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD). *Caspian J Intern Med* 2012; **3**:451–455.

38 Zendedel A, Gholami M, Anbari K, Ghanadi K, Bachari EC, Azargon A. Effects of vitamin D intake on FEV1 and COPD exacerbation: a randomized clinical trial study. *Glob J Health Sci* 2015; **7**:243–248.

39 Skaaby T, Husemoen LL, Thuesen BH, Pisinger C, Jorgensen T, Fenger RV, *et al.* Vitamin D status and chronic obstructive pulmonary disease: a prospective general population study. *PLoS One* 2014; **9**:e90654.

40 Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; **72**: 690–693.