Does vitamin D deficiency worsen the clinical and functional parameters of stable chronic obstructive pulmonary disease patients?

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Introduction There is not much data about the effect of deficient vitamin D on stable chronic obstructive pulmonary disease (COPD) patients and its relation to the disease severity.

Objective The aim was to measure the serum level of 25-hydroxy (OH) vitamin D in stable COPD patients, and to assess its relation to COPD severity and functional parameters.

Patients and methods A prospective study that was carried out at Chest Department, Kasr El-Aini Hospital, Cairo University. It was carried out on 70 male individuals: 50 stable COPD patients and 20 healthy individuals. All persons were subjected to history taking, clinical examination, 6 min walk test (6MWT), spirometry, and measurement of 25(OH) vitamin D serum level.

Results Our results showed a deficiency of vitamin D in 37 (74%) of the COPD patients. It showed a significant lower level of 25(OH) vitamin D in COPD cases who were severe and very severe, compared with those who were mild and moderate ones (P=0.017). There was also a positive significant correlation between vitamin D level and 6 min walk distance, basal oxygen saturation, post-6MWT oxygen saturation, and forced expiratory volume in the first second predicted, and an inverse correlation with basal heart rate and post-6MWT heart rate.

Conclusion The study highlights the value of measurement of vitamin D level in COPD, as a potential therapeutic agent. Vitamin D serum level showed low values in COPD cases compared with healthy ones and was correlated significantly to forced expiratory volume in the first second predicted.

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Introduction

Vitamin D: a fat-soluble hormone that maintains the health of bone and its integrity, besides it has an anti-inflammatory effect. The vitamin undergoes hydroxylation first in the liver to 25(OH) vitamin D and then in the kidneys to change to the active form 1,25 (OH) vitamin D [1].

The actions of vitamin D are regulated through specific receptors that are located in most of the cells in the human body [2].

Vitamin D is commonly lower in chronic obstructive pulmonary disease (COPD) especially in severe stages of the disease [3]. Also, vitamin D deficiency may predispose to chronic airway and chest infection [4] and reduced skeletal muscle strength [5].

Up till now, no one could swear if deficiency of vitamin D is a result of COPD or it may be involved in its pathogenesis. So, it is an attractive concern to study as vitamin D deficiency is accused of being an etiology of systemic inflammation.

In this study, the primary goal we aimed was to measure the level of vitamin D serum in stable COPD patients, and its relation to COPD severity. The secondary goal is to determine the correlation of vitamin D serum level with 6 min walk test (6MWT) parameters including 6 min walk distance, oxygen saturation data, heart rate data, and the clinical parameters.

Patients and methods

A prospective study which was done for measuring serum level of 25 (OH) vitamin D in patients with stable COPD who were diagnosed on the basis of clinical data followed by measuring postbronchodilator forced expiratory volume in the first second (FEV_1%) predicted according to GOLD guidelines [6]. The study was conducted at Chest Department, Kasr El-Aini Hospital, Cairo University during the period from April 2016 to October 2016. It was carried out on 70 male individuals: 50 stable COPD patients who were

recruited from the outpatients' chest clinic and 20 healthy individuals as a control group.

Exclusion criteria

Patients were excluded from the study if they have a history of COPD exacerbation in the last month or evidence of congestive heart failure, diabetes mellitus, neurological disease, renal failure, and liver cell failure based on clinical and laboratory data.

The Ethics Committee of Faculty of Medicine, Cairo University approved the study and all the patients have signed a written consent.

All the enrolled persons were submitted for the following:

(1) Complete history and clinical exploration.
(2) Routine labs, for example, complete blood count, serum sodium, serum potassium, liver and kidney functions, and blood sugar.
(3) Chest radiograph.
(4) Calculation of BMI.
(5) Spirometry (postbronchodilator spirometry in the COPD group). It was performed according to the guidelines [7] using spirometry: Flow-volume loop-ZAN 100 program (nSpire Health, Germany). Data were obtained as percent predicted values for FEV_1, forced vital capacity (FVC), maximum expiratory flow (MEF) 25–75%, and FEV_1/FVC%. Participants who had FEV_1/FVC less than 70% underwent postbronchodilator spirometry test, 20 min following two puffs of salbutamol 200 μg. COPD grading according to the severity of airflow limitation was as follows: GOLD 1 (mild) FEV_1 greater than or equal to 80% predicted, GOLD 2 (moderate) 50% greater than or equal to FEV_1 less than 80% predicted, GOLD 3 (severe) 30% greater than or equal to FEV_1 less than 50% predicted, GOLD 4 (very severe) FEV_1 less than 30% predicted [6].
(6) 6MWT was done on the basis of the American Society Guidelines (ATS) [8]. Recording of the 6 min walk distance, and both oxygen saturation and heart rate data using pulse oximetry were done. Heart rate was measured at the end of the test and at 1-min recovery, the difference between the two being defined as heart rate recovery (HRR). Abnormal HRR was defined as a recovery of less than or equal to 12 beats in the first minute post-6 MWT.
(7) Quantification of 25(OH) vitamin D serum level: 5 ml venous blood was withdrawn from cubital vein under sterile conditions; the whole blood sample was centrifuged at 3000*g* for 10 min to separate plasma. Separated plasma was stored at −20°C (grossly hemolyzed and lipemic samples were discarded). Serum level of 25(OH) vitamin D was measured by enzyme-linked immunosorbent assay (ELISA) (DRG International Inc., Springfield, New Jersey, USA) according to manufacturer's instructions.

Insufficiency of vitamin D is determined as a 25(OH) vitamin D serum level of 20–29 ng/ml, while deficiency of it is determined as a 25(OH) vitamin D serum level smaller than 20 ng/ml [9].

Statistical methods

A sample size of 40 (20 cases and 20 control individuals) was sufficient to detect a power of 80% and a significance level of 5%. On the basis of the Said and Abd-Elnaeem [10] study, the mean value of vitamin D level in COPD was 20.4 ng/ml and SD was 6.6, while in healthy control the mean was 44.4 ng/ml and SD was 9.1. Sample size estimation was performed using the Power and Sample size (PS) program (IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA).

Data were analyzed using the SPSS (Statistical Package for the Social Sciences) version 24. Mean, SD, median, minimum, and maximum were used in quantitative data, while frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric Kruskal–Wallis and Mann–Whitney tests [11].

χ^2-Test was used for comparing categorical data. When the expected frequency is less than 5, we use the exact test instead [12].

Spearman's correlation coefficient was used for correlation between quantitative variables [13]. The value was judged as statistically significant when the *P* value is less than 0.05.

Results

Table 1 shows statistical analysis of the demographic data, clinical parameters among the diagnosed COPD cases, and the control group. All the COPD patients and control individuals were men; COPD patients' age ranged from 40 to 76 years with a mean of 57.18 ±9.03 years.

There was no significant difference statistically between COPD patients and normal individuals in

Table 1 Statistical analysis of the demographic data, clinical parameters among chronic obstructive pulmonary disease cases and control group

	Groups				
	Cases (*N*=50)		Control (*N*=20)		
	Mean±SD	Median (minimum–maximum)	Mean±SD	Median (minimum–maximum)	*P* value*
Clinical data					
Age (years)	57.18±9.03	58.00 (40.00–76.00)	53.10±4.61	53.00 (46.00–60.00)	0.07
Smoking index (pack/year)	40.88±24.65	35.00 (8.00–150.00)			<0.001
BMI (weight/height^2)	25.97±5.06	26.00 (16.00–39.00)	27.40±3.91	27.50 (19.00–35.00)	0.221
Dyspnea grade by mMRC	2.46±.50	2.00 (2.00–3.00)			<0.001
Six-minute walk test data					
Distance of 6MWT (m)	296.00±65.47	300.00 (150.00–420.00)	492.75±26.33	495.00 (450.00–540.00)	<0.001
SO_2 before 6MWT (%)	95.04±4.48	96.00 (72.00–98.00)	98.00±.79	98.00 (97.00–99.00)	< 0.001
SO_2 after 6MWT (%)	93.02±6.74	95.50 (63.00–98.00)	97.00±.86	97.00 (96.00–99.00)	< 0.001
Exercise desaturation (%)	2.02±2.57	1.00 (0.00–12.00)	1.00±.65	1.00 (0.00–2.00)	0.093
SO_2 after 1 min (%)	94.26±5.48	96.00 (71.00–98.00)	97.40±.88	97.00 (96.00–99.00)	<0.001
Heart rate (basal) (bpm)	87.58±12.63	88.50 (64.00–115.00)	80.00±6.36	81.00 (69.00–90.00)	0.011
Heart rate (at the end) (bpm)	104.74±14.36	106.50 (74.00–135.00)	100.25±7.43	101.00 (88.0–115.00)	0.114
Heart rate (after 1 min) (bpm)	93.40±13.70	93.00 (67.00–129.00)	84.10±7.22	85.00 (70.00–96.00)	0.004
Heart rate recovery	11.34±6.94	9.50 (2.00–34.00)	16.15±5.26	15.50 (6.00–26.00)	0.003

mMRC, modified Medical Research Council; 6MWT, 6 min walk test, SO_2, oxygen saturation; bpm, beat per minute. *P<0.05, significant.

the mean BMI (25.97±5.06, 27.40±3.91, respectively; P=0.221).

Our data showed significant statistical difference between patients with COPD and normal individuals in the distance of 6MWT (mean=296.00 ±65.47 meter for COPD patients and mean=492.75 ±26.33 meter for normal individuals). There was also statistically significant difference as regards oxygen saturation before 6MWT, after 6MWT, and after 1 min (mean=95.04±4.48, 93.02±6.74, 94.26±5.48, respectively for COPD patients and mean=98±0.79, 97±0.86, 97.40±0.88 for normal individuals).

As regard the heart rate data, basal heart rate and heart rate after 1 min were significantly higher among COPD cases compared with controls (mean=87.58 ±12.63, 93.40±13.70 for COPD patients and mean=80±6.36, 84.10±7.22 for normal individuals). There was significant lower HRR among COPD patients compared with healthy individuals (11.34 ±6.94 vs 16.15±5.26, P=0.003).

According to the results of spirometry, the study included 50 COPD patients: two patients were mild, 15 patients were moderate, 20 patients were diagnosed as severe, and 13 patients as very severe COPD.

COPD patients showed significantly lower FEV_1/FVC, FEV_1%, and MEF 25–75% values compared with the control group with mean=56.72±8.09, 43.96 ±18.94, 24.94±13.39 for COPD patients and mean=82.30±4.86, 81.00±5.91, 70.15±6.89)for normal individuals (Table 2).

Vitamin D serum level decreased significantly in COPD patients in comparison to healthy individuals (mean=17.16±6.27, 57.05±14.76, respectively; P<0.001) (Table 2 and Fig. 1). Vitamin D deficiency was found in 37 (74%) of the COPD patients. A lower level of vitamin D was observed in severe and very severe COPD patients (Table 3).

Table 4 shows the correlation between 25(OH) vitamin D serum level in relation to the clinical and functional parameters of COPD patients.

We found significant correlation between vitamin D serum level and age, smoking index, and dyspnea grade by mMRC (P=0.016, 0.041 and 0.020, respectively), but there was no significant correlation between vitamin D serum level and BMI (P=0.664).

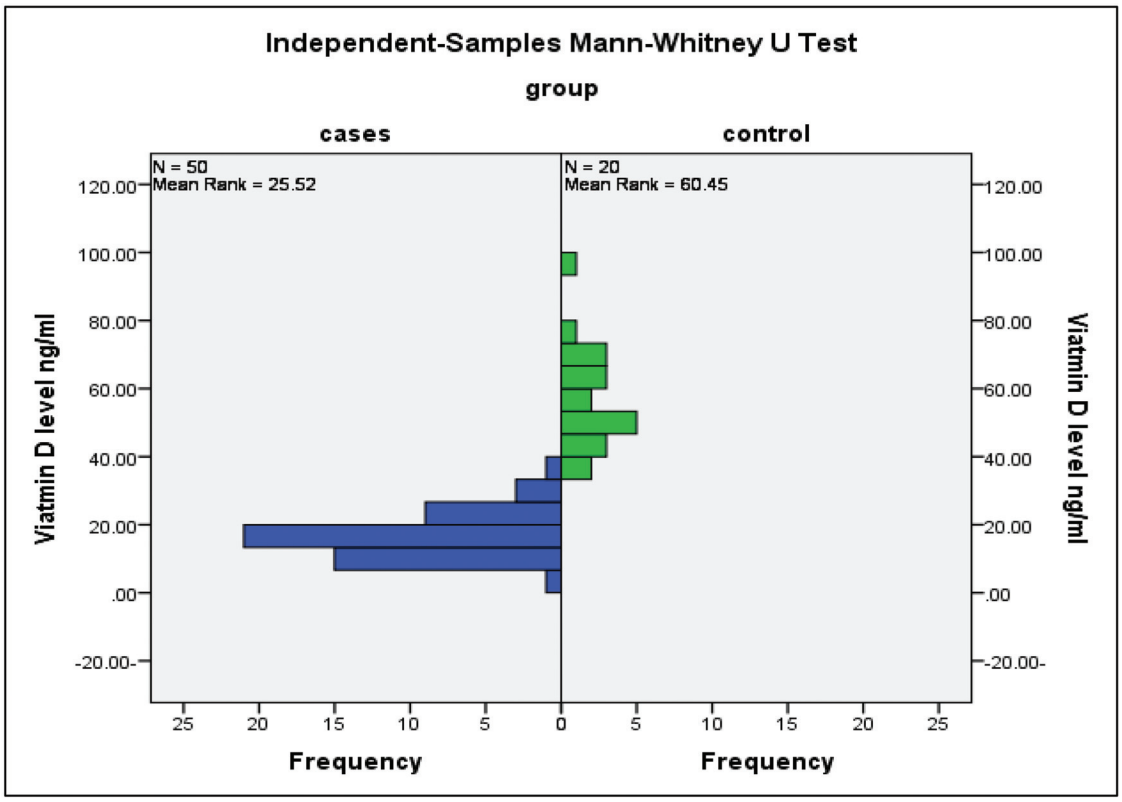
There was significant positive correlation between vitamin D serum level and distance of 6MWT in meters, basal saturation, saturation after 6MWT, and saturation after 1 min (P=0.036, 0.031, 0.048, and 0.040, respectively). There was significant inverse correlation between vitamin D serum level and basal heart rate and heart rate after 1 min (P=0.045 and 0.028, respectively), but no significant correlation found between vitamin D serum level and HRR (P=0.598).

Table 2 Statistical analysis of the functional data, and vitamin D level among chronic obstructive pulmonary disease cases and control group

	Groups				
	Cases (*N*=50)		Control (*N*=20)		
	Mean±SD	Median (minimum–maximum)	Mean±SD	Median (minimum–maximum)	*P* value*
Spirometry data					
FEV_1/FVC%	56.72±8.09	57.50 (38.00–68.00)	82.30±4.86	83.00 (74.00–92.00)	<0.001
FEV_1% predicted	43.96±18.94	37.50 (14.00–85.00)	81.00±5.91	81.50 (70.00–89.00)	<0.001
FVC% predicted	58.88±23.19	57.50 (18.00–111.00)	94.05±5.41	95.50 (84.00–101.00)	<0.001
MEF 25–75% predicted	24.94±13.39	21.50 (7.00–57.00)	70.15±6.89	69.50 (60.00–80)	<0.001
COPD severity [*n* (%)]					
Mild		2 (4)			
Moderate		15 (30)			
Severe		20 (40)			
Very severe		13 (26)			
Vitamin D level (ng/ml)					
	17.16±6.27	15.70 (6.30–38.40)	57.05±14.76	53.65 (37.50–94.20)	<0.001
Vitamin D status [*n* (%)]					
Sufficient		2 (4)		20 (100)	<0.001
Insufficient		11 (22)			
Deficient		37 (74)			

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MEF, maximum expiratory flow. *P<0.05, significant.

Figure 1



Statistical analysis of serum level of vitamin D among chronic obstructive pulmonary disease cases and control group.

There was statistical significance between vitamin D serum level and percent predicted FEV_1% (Fig. 2) and FVC% (P=0.030 and 0.008, respectively).

Discussion

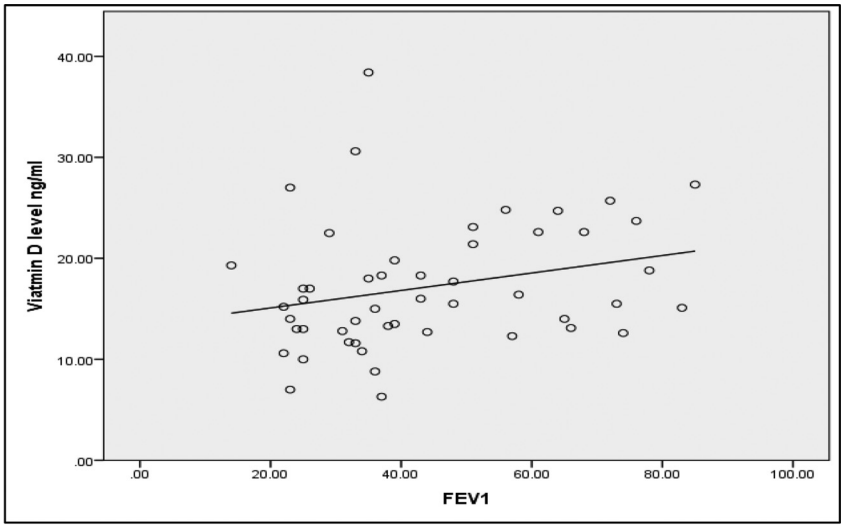
COPD is a preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar

Table 3 Serum level of 25(OH) vitamin D and chronic obstructive pulmonary disease severity

	Groups				
	Mild and moderate COPD (*N*=17)		Severe and very severe COPD (*N*=33)		
Serum level of vitamin D (ng/ml)	Mean±SD	Median (minimum–maximum)	Mean±SD	Median (minimum–maximum)	*P* value*
	19.63±5.15	21.40 (12.30–27.30)	15.89±6.48	15.00 (6.30–38.40)	0.017

*$P<0.05$, significant.

Figure 2



Correlation between serum vitamin D level and forced expiratory volume in the first second % predicted.

abnormalities usually caused by the following: significant exposure to noxious particles or gases [6].

Multiple factors contribute to low vitamin D level in COPD patients including lower dietary intake, decreased synthesis, increased catabolism by glucocorticoids, defective activation, and a decreased storage capacity because of muscle wasting [2].

In the current study, we found that vitamin D serum level was much more decreased in COPD patients than control individuals (mean=17.16±6.27 and median=15.70, mean=57.05±14.76, median=53.65, $P<0.001$, respectively) (Table 2, Fig. 1).

This finding was in agreement with many studies as that of Franco *et al.* [14], Hughes *et al.* [15], Berg *et al.* [16], and Said and Abd-Elnaeem [10], who all found a significant lower serum vitamin D level in COPD than control individuals. However, Persson *et al.* [17] found that vitamin D deficiency was high in both COPD and control individuals but after correcting data with age, smoking, BMI, season, and comorbidities, it was clarified that vitamin D deficiency was higher in COPD patients when compared with control ones.

There was significant inverse correlation between serum level of vitamin D and age (*P*=0.016), smoking index (*P*=0.041), and dyspnea (*P*=0.020) (Table 4).

6MWT is an important clinical test and is used as a predictor of mortality in different pulmonary diseases.

It was found that vitamin D serum level was correlated significantly with a distance of 6MWT in meters, basal saturation, saturation after 6MWT and saturation after 1 min (*P*=0.036, 0.031, 0.048, and 0.040, respectively) (Table 4).

It worth noting that resting heart rate is an important marker of the sympathetic activity and an important risk factor for all cardiovascular diseases in patients with heart disease [18] and in healthy humans [19]. The study demonstrated that COPD patients had a higher resting heart rate compared with healthy individuals that was in agreement with the finding of Jensen *et al.* [20]. Also, it was found that the basal heart rate and heart rate after 1 min were inversely correlated with serum vitamin D level. Much more studies are needed to figure out the influence of supplementation of vitamin D on improving heart rate parameters of COPD patients.

Regarding spirometric findings (Table 4, Fig. 2), there was statistical significance between vitamin D serum

Table 4 Correlation between serum level of 25(OH) vitamin D and clinical and functional parameters of the chronic obstructive pulmonary disease group

	Vitamin D level (ng/ml)
Clinical data	
Age (years)	
Correlation coefficient	–0.341–
P value	0.016
Smoking index (pack/year)	
Correlation coefficient	–0.290–
P value	0.041
BMI (weight/height^2)	
Correlation coefficient	–0.063–
P value	0.664
Dyspnea grade by mMRC	
Correlation coefficient	–0.328–
P value	0.020
6 min walk test data	
Distance of 6MWT (m)	
Correlation coefficient	0.297
P value	0.036
Basal SO_2 (%) 6MWT	
Correlation coefficient	0.305
P value	0.031
SO_2 (%) after 6MWT	
Correlation coefficient	0.281
P value	0.048
Exercise desaturation (%)	
Correlation coefficient	–0.157–
P value	0.275
SO_2 (%) after 1 min	
Correlation coefficient	0.292
P value	0.040
Basal heart rate (bpm)	
Correlation coefficient	–0.285–
P value	0.045
Heart rate at the end (bpm)	
Correlation coefficient	–0.254–
P value	0.075
Heart rate after 1 min (bpm)	
Correlation coefficient	–0.311–
P value	0.028
Heart rate recovery	
Correlation coefficient	0.076
P value	0.598
Spirometry data	
FEV_1/FVC%	
Correlation coefficient	–0.008–
P value	0.956
FEV_1% predicted	
Correlation coefficient	0.307
P value	0.030
FVC% predicted	
Correlation coefficient	0.369
P value	0.008
MEF 25–75% predicted	
Correlation coefficient	0.239
P value	0.095

6MWT, 6 min walk test; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MEF, maximum expiratory flow; mMRC, modified Medical Research Council; SO_2, oxygen saturation; bpm, beat per minute. *$P<0.05$, significant. There is no upper limit for the correlation coefficient.

level and FEV_1% and FVC% (P=0.030 and 0.008, respectively) which is in agreement with Said and Abd-Elnaeem [10] and Persson *et al.* [17] who found that there was a significant association between vitamin D levels and FEV_1% predicted in COPD patients. This finding was also in agreement with Janssens *et al.* [3] and El-Shafey *et al.* [21].

The mean of vitamin D serum level in mild and moderate COPD patients was 19.63±5.15, while in severe and very severe COPD patients it was 15.89 ±6.48 with statistically significant difference (P=0.017) (Table 3). These data go with a recent meta-analysis and systemic review by Zhu *et al.* [22] on 21 previous studies that included 4818 patients having COPD and 7175 controls concluded that lower levels of vitamin D were affiliated with increased risk of COPD. They also showed that patients with severe and very severe COPD based on GOLD were associated with lower levels of serum vitamin D compared with those with moderate COPD. Our results, which showed that vitamin D serum levels were directly related to the degree of COPD severity and low levels of vitamin D, were associated with the degree of airway obstruction as demonstrated by the correlation between FEV_1% and vitamin D and even more when categorized as COPD groups based on GOLD criteria.

Limitation of the study

The main limitation of our study is that the lack of assessment of dietary intake, an important correctable factor, may contribute to vitamin D deficiency in COPD patients.

Further studies are needed to evaluate the effects of supplementation of vitamin D on different clinical and functional parameters in COPD patients.

Conclusion

This study further supports that COPD patients are more prone to deficiency of vitamin D particularly those with advanced disease and the elderly ones.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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