Does vitamin D deficiency worsen the clinical and functional parameters of stable chronic obstructive pulmonary disease patients?
Esmat A. Abd Elnabya, Samah S. Abd Elnaiem, Amira I. Mostafa, Dina Sabry, Mohamed K. Haswa

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.

Keywords: 6 min walk test, chronic obstructive pulmonary disease, forced expiratory volume in the first second predicted, vitamin D

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.
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 FEV1, forced vital capacity (FVC), maximum expiratory flow (MEF) 25–75%, and FEV1/FVC%.
   Participants who had FEV1/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) FEV1 greater than or equal to 80% predicted, GOLD 2 (moderate) 50% greater than or equal to FEV1 less than 80% predicted, GOLD 3 (severe) 30% greater than or equal to FEV1 less than 50% predicted, GOLD 4 (very severe) FEV1 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 3000g 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].

χ²-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) | P value* |
|-----------------------|--------------|----------------|----------|
|                       | Mean±SD      | Median (minimum–maximum) | Mean±SD      | Median (minimum–maximum) |          |
| **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/height²)  | 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±0.50    | 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   |
| SO₂ before 6MWT (%)   | 95.04±4.48   | 96.00 (72.00–98.00) | 98.00±7.97 | 98.00 (97.00–99.00) | <0.001   |
| SO₂ after 6MWT (%)    | 93.02±6.74   | 95.50 (63.00–98.00) | 97.00±8.86 | 97.00 (96.00–99.00) | <0.001   |
| Exercise desaturation (%) | 2.02±2.57 | 1.00 (0.00–12.00) | 1.00±0.65 | 1.00 (0.00–2.00) | 0.093    |
| SO₂ after 1 min (%)   | 94.26±5.48   | 96.00 (71.00–98.00) | 97.40±8.87 | 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 (88.00–115.00) | 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, SO₂, 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 FEV₁/FVC, FEV₁%, 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 0.200, 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=0.045 and 0.028, respectively), but no significant correlation found between vitamin D serum level and HRR (P=0.598).
There was statistical significance between vitamin D serum level and percent predicted FEV\textsubscript{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...
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 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) |
|                               | 19.63±5.15, 21.40 (12.30–27.30) | 15.89±6.48, 15.00 (6.30–38.40) |
| P value*                      | 0.017                         | 0.017                              |

*P < 0.05, significant.
level and FEV\textsubscript{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\textsubscript{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\textsubscript{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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1 Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci 2004; 29:664–673.

2 Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266–281.
3 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.
4 Zasloff M. Fighting infections with vitamin D. Nat Med 2006; 12:388–390.
5 Menant JC, Close JC, Delbaere K, Sturnieks DL, Trollor J, Sachdev PS, et al. Relationships between serum vitamin D levels, neuromuscular and neuropsychological function and falls in older men and women. Osteoporos Int 2012; 23:981–989.
6 This Executive Summary of the Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2017.
7 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319–338.
8 ATS Statement. Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166:111–117.
9 Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008; 87:1080–1096.
10 Said AF, Abd-Elnaeem EA. Vitamin D and chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc 2015; 64:67–73.
11 Chan YH. Biostatistics102: quantitative data – parametric & non-parametric tests. Singapore Med J 2003a; 44:391–396.
12 Chan YH. Biostatistics 103: qualitative data – tests of independence. Singapore Med J 2003b; 44:498–503.
13 Chan YH. Biostatistics 104: correlational analysis. Singapore Med J 2003c; 44:614–619.
14 Franco CB, Paz-Filho G, Gomes PE, Nascimento VB, Kulak CA, Boguszewski CL, et al. Chronic obstructive pulmonary disease is associated with osteoporosis and low levels of vitamin D. Osteoporos Int 2009; 20:1881–1887.
15 Hughes DA, Norton R. Vitamin D and respiratory health. Clin Exp Immunol 2009; 158:20–25.
16 Berg I, Hanson C, Sayles H, Romberger D, Nelson A, Meza J, et al. Vitamin D, vitamin D binding protein, lung function and structure in COPD. Respiratory medicine 2013; 107:1578–1588.
17 Persson LJF, Annerud M, Hiemstra PS, Hardie JA, Bakke PS, Eagan TML. Chronic obstructive pulmonary disease is associated with low levels of vitamin D. PLoS One 2012; 7:e38934.
18 Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005; 26:967–974.
19 Jensen MT, Marott JL, Jensen GB. Elevated resting heart rate is associated with greater risk of cardiovascular and all-cause mortality in current and former smokers. Int J Cardiol 2011; 151:148–154.
20 Jensen MT, Marott JL, Lange P, Vestbo J, Schnohr P, Nielsen OW, et al. Resting heart rate is a predictor of mortality in chronic obstructive pulmonary disease. Eur Respir J [Internet] 2013; 42:341–349. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23143550
21 El-Shafey BI, El-Srougy HA. Does serum 25 hydroxy vitamin D level play a role in COPD? Egypt J Tuberc Lung Dis 2014; 63:43–47.
22 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.