Vitamin D and chronic obstructive pulmonary disease

Azza Farag Said a,*, Emad Allam Abd-Elnaeem b

a Chest Diseases Department, Minia University, Egypt
b Clinical Pathology Department, Minia University, Egypt

Received 22 August 2014; accepted 30 November 2014
Available online 5 January 2015

Abstract Background: Evidence is increasing that suggests an expanded role of vitamin D in health outcomes apart from its classic actions on the bone and calcium homeostasis. Vitamin D deficiency has been associated with some chronic respiratory illnesses; one of them is chronic obstructive pulmonary disease (COPD).

Objective: This study was designed to detect vitamin D level among stable COPD patients. The effect of vitamin D supplements (200,000 IU monthly for 6 months) with regular therapy of COPD on COPD outcomes was also evaluated.

Patients and methods: Pulmonary function test (PFT), COPD assessment test (CAT), 6 min walk test (6MWT), serum 25-hydroxyvitamin D (25-OHD) and ionized calcium were performed on 61 COPD patients (50 males and 11 females, mean age 61.1 years). PFT and clinical assessment were carried out at the start and completion of 6 month treatment among those with vitamin D deficiency. Twenty healthy age-matched and sex matched volunteers were also studied as a control group.

Results: The distribution of vitamin D status including vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency was 16.4%, 34.4% and 49.2% respectively among COPD patients. There was no significant improvement of 6MWT, CAT score and PFT among those treated with vitamin D supplements in addition to standard therapy of COPD.

Conclusion: Low serum level of vitamin D was less common among COPD patients than other studies and correlates with severity of COPD. 6 month supplementation of standard treatment with 200,000 IU monthly of vitamin D did not provide additional clinical benefit among COPD patients.

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D can be sourced in the diet from foods such as fortified dairy products and cereals, oily fish and fish liver oils [1]. Synthesized or dietary vitamin D, from the skin and the gut, respectively, are hydroxylated in the liver to form 25-hydroxyvitamin D [25-OHD] through the action of cytochrome P450 enzymes, which is converted to the biologically active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], in the kidney and other tissues by the 1α-hydroxylase [2].

The concentration of 25-hydroxyvitamin D in blood is regarded as the best indicator of vitamin D status, because it is quantitatively related to the supply of vitamin D over the weeks preceding blood sample collection. The concentration of 25-OHD reflects the supply of vitamin D from both the diet and from cutaneous synthesis under the influence of solar ultraviolet light [3].

Conventionally, vitamin D is known for its actions in bone mineralization and calcium homeostasis. Some studies have highlighted the role of vitamin D, vitamin D receptor (VDR) in regulation of several genes involved in inflammation, immunity, cellular proliferation, differentiation, and apoptosis. So, vitamin D may play a role in multiple chronic diseases such as cancer, autoimmune diseases, infections, and cardiovascular disorders [4,5].

Vitamin D may also have a role in several diseases involving the respiratory system such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and respiratory infections. These studies have demonstrated a high prevalence of vitamin D deficiency in their participants [6–9]. Patients with chronic obstructive pulmonary disease have a high prevalence of vitamin D deficiency, ranging from approximately 30% in mild COPD to over 75% in severe COPD [9–11]. Particularly for COPD, vitamin D deficiency may enhance chronic airway and systemic inflammation, reduce bacterial clearance, and increase the risk for infectious exacerbations at the same time [12].

Some intervention studies are being undertaken to study the impact of adequate vitamin D supplementation in chronic diseases. COPD is a candidate disease for which vitamin D supplementation might be beneficial. Epidemiological studies revealed a dose-dependent association between serum 25-OHD levels and pulmonary function so that adequate vitamin D supplementation may extend beyond its protection against osteoporotic fractures. In line with the novel insights into the immune function of vitamin D, it is tempting to speculate that vitamin D may down-regulate the inflammatory immune response in the airways while boosting innate immune defense against different microorganisms. Apart from its effects on osteoporosis, vitamin D may also interfere with other comorbidities of COPD such as skeletal muscle weakness, cardiovascular disease, and cancer. Because respiratory treatments in COPD fail to reverse disease progression, interventional trials that may exploit the broader potential of vitamin D are warranted [12].

Aim of the work

We undertook this study to assess serum level of vitamin D among patients with stable COPD. In addition the role of supplementation of vitamin D (200,000 IU cholecalciferol per month for 6 months) among COPD patients with vitamin D deficiency plus standard therapy of COPD on exercise capacity, clinical response and spirometry was assessed.

Patients and methods

Sixty-one cases of stable COPD were recruited from those attending the outpatient chest clinic at Minia University hospital from January 2011 to December 2013. The study also included 20 healthy controls.

This study was approved by the ethics committee of Faculty of Medicine, Minia University and consent was obtained from patients and controls.

Patients were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition (postbronchodiator FEV1/FVC ratio <0.7). Stable COPD was defined by the lack of hospitalizations, urgent care visits, antibiotics, or changes in medications within 4 weeks prior to study. Patients were excluded if they had a past history of TB, asthma, active cancer, diabetes, hypertension, ischemic heart disease, chronic kidney disease, liver failure, history of upper or lower respiratory tract infections or use of oral steroid within 1 month prior to study, as all these conditions are associated with a low serum level of vitamin D [4].

All the patients and healthy controls had been subjected to the following:

- Full detailed history taking including (age, sex, smoking status, patient’s medications, CAT score and GOLD stage).
- Clinical examination, body mass index (BMI), and 6 min walk test were also determined and 6 min walk distance (6MWD) was detected.
- Local chest examination.
- Investigations included:
  1. Plain chest X-ray (PA view).
  2. Complete blood count was done by automated cell counter (Sysmex KX 21N, Cole, Japan).
  3. The liver, renal function tests and random blood sugar were determined using Flexor 200ELI, Tech, France apparatus.
  4. Serum ionized calcium (Ca) was determined by ion selective electrode (AVL, USA).
  5. Electrocardiogram (ECG).
  6. Pulmonary function tests (PFTs) using 2130 spirometer (Vmax, Sensormedics, USA), which was calibrated daily. Patient’s maximum effort had been used in performing the test so as to avoid any expected error in diagnosis. Results were obtained for forced vital capacity (FVC), forced expiratory volume in 1st second (FEV1), and FEV1/FVC percentage. Subjects who had FEV1/FVC <70% underwent post–bronchodilator spirometry test, 20 min following 2 puffs of salbutamol 200 mcg.
  7. Blood samples were collected, centrifuged within 2 h of sampling, and the serum was frozen and stored at −40 °C until analyzed for measurement of serum 25-hydroxyvitamin D (25-OHD) by enzyme immunoassay kits supplied by Immunodiagnostic AG, Germany.
- This test kit is a competitive protein binding assay for the measurement of 25-OH Vit D. It is based on competition of 25-OH Vit D present in the sample with 25-OH Vit D tracer, for the binding pocket of vitamin D binding protein (VDBP, Gc-globulin). Since all circulating 25-OH Vit D is bound to VDBP in vivo, samples have to be precipitated with precipitation reagent to extract the analyte.

- 25-OH Vit D present in the sample competes with the tracer, coated on the well for the specific binding site of the binding protein and the VDBP-antibody is bound to the vitamin binding protein. Hence, with increasing concentrations of 25-OH Vit D in the sample, the amount of binding protein immobilized to the well via the tracer, is reduced. After a washing step to remove unbound components, the quantitation of VDBP is achieved by incubation with a host specific peroxidase labeled antibody using TMB (tetramethylbenzidine) as enzyme substrate. An acidic stopping solution is then added to stop the reaction. The color converts to yellow. The intensity of the yellow color is indirectly proportional to the concentrations of 25-OH Vit D in the sample.

According to Endocrine Society Clinical Practice Guidelines, vitamin D deficiency is defined by most experts [13–15] as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter), a level of 25-hydroxyvitamin D of 21–29 ng per milliliter (52–72 nmol per liter) can be considered to indicate an insufficiency of vitamin D, and a level of 25–29 ng per milliliter (50 nmol per liter). A level of 25-hydroxyvitamin D (group B) was re-assessed among 10 patients who received vitamin D supplements to detect if any of them developed hypercalcemia. Serum ionized calcium level at the end of 6 months was re-assessed among 10 patients who received vitamin D supplements to detect if any of them developed hypercalcemia. According to this level of vitamin D, 61 COPD patients were divided into the following groups:

Group (A): Included 31 COPD patients who had an impaired vitamin D level, 10 of them had vitamin D deficiency and 21 had vitamin D insufficiency.
Group (B): Included 30 COPD patients with a sufficient level of vitamin D.
Control group (group C): Included 20 apparently healthy individuals matched in age and sex with the other 2 groups and their serum level of 25-OHD was > 30 ng/ml.

Those with vitamin D deficiency received their usual treatment of COPD supplemented with a high-dose of vitamin D (cholecalciferol 200,000 IU ampoule) intramuscular injection every 4 weeks for 6 months. The outcome parameters used for the study after 6 months were spirometry, 6MWT and CAT score. Serum ionized calcium level at the end of 6 months was re-assessed among 10 patients who received vitamin D supplements to detect if any of them developed hypercalcemia as a sign of vitamin D overdose. None of these patients developed hypercalcemia.

**Statistical analysis**

Data entry and analysis were all done using the software SPSS version 13. Quantitative data were presented by mean and standard deviation; qualitative data were presented as frequency distribution. A one way ANOVA, Student’s t-test, correlation and chi square tests were used. Correlation was done using Pearson correlation. A value of $P < 0.05$ was considered to be statistically significant.

**Results**

*Table 1* shows the general characteristics of all studied groups, it was found that there was a significant difference in smoking and mean pack-year among COPD patients (groups A & B) and the control group (group C) ($P = 0.03$ and 0.01 respectively). Considering BMI, there was no significant difference in BMI among all of the COPD patients and healthy controls ($P = 0.7$). There was a significant difference in 6MWD, post-bronchodilator values of FVC%, FEV1% and FEV1/FVC among COPD patients and the control group ($P = 0.001$). Besides, FVC% predicted and FEV1% predicted were significantly lower in the group A than the group B ($P = 0.01$ and 0.03 respectively). It was found that those with impaired vitamin D level (group A) had a significantly higher CAT score and GOLD stage than those with sufficient level of vitamin D (group B) ($P = 0.004$ and 0.04 respectively).

*Fig. 1* shows mean 25-hydroxyvitamin D and ionized calcium levels among the studied groups. It was found that 10 COPD patients out of 31 in the group A had vitamin D deficiency with a mean value of 12.0 ± 4.5 ng/ml and the remaining 21 had vitamin D insufficiency with a mean value of 24.4 ± 3.7 ng/ml. The difference of 25-OHD mean value between the group A (20.4 ± 6.6) and both of the group B (47.1 ± 18.8) and group C (44.4 ± 9.1) was significant ($P = 0.001$). In addition, the mean value of serum ionized calcium was significantly lower among the group A (0.79 ± 0.1) versus groups B and C (0.9 ± 0.1 & 1.1 ± 0.05 respectively) ($P = 0.01$).

It was found that there was a significant positive correlation between serum 25-OHD and FVC% predicted, FEV1% predicted, FEV1/FVC and GOLD stage and a negative correlation with CAT score among patients with COPD. On the other hand, there was no correlation between both of clinical variables and pulmonary function test among the control group (*Table 2* and *Fig. 2*).

*Table 3* shows that in spite of minor improvement in CAT score, 6MWD, FVC% predicted and FEV1% predicted, this improvement was not statistically significant ($P > 0.05$ in all of them).

**Discussion**

Vitamin D deficiency is more common than previously thought. The Centers for Disease Control and Prevention has reported that the percentage of adults achieving vitamin D sufficiency as defined by 25-OHD of at least 30 ng/mL has declined from about 60% in 1988–1994 to approximately 30% in 2001–2004 in whites and from about 10% to approximately 5% in African Americans during this same time. So hypovitaminosis D is as an important public health problem in the United States and worldwide [16].

Few studies have assessed the relevance of vitamin D deficiency in COPD by measuring serum levels of 25-hydroxyvitamin D which is the principal circulating vitamin D metabolite and recognized as the best short-term biomarker of total exposure to vitamin D [17].
Table 1 Descriptive data of the studied groups.

<table>
<thead>
<tr>
<th>Character</th>
<th>Group A No. = 31</th>
<th>Group B No. = 30</th>
<th>Group C No. = 20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>59.9 ± 8.1</td>
<td>62.3 ± 7.2</td>
<td>56.1 ± 8.17</td>
<td>0.075</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (74.2%)</td>
<td>27 (90%)</td>
<td>16 (80%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Female</td>
<td>8 (25.8%)</td>
<td>3 (10%)</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>10 (32.3%)</td>
<td>10 (33.3%)</td>
<td>4 (20%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>12 (38.7%)</td>
<td>16 (53.3%)</td>
<td>5 (25%)</td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>9 (29%)</td>
<td>4 (13.3%)</td>
<td>11 (55%)</td>
<td></td>
</tr>
<tr>
<td>Pack-year</td>
<td>21 ± 4.5</td>
<td>28.8 ± 10.2</td>
<td>16.2 ± 4.7</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 ± 4.9</td>
<td>23.2 ± 4.1</td>
<td>23.8 ± 1.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS + short acting B2 agonist</td>
<td>19 (61.3%)</td>
<td>17 (56.7%)</td>
<td>–</td>
<td>0.4</td>
</tr>
<tr>
<td>Short acting B2 agonist</td>
<td>6 (19.5%)</td>
<td>0</td>
<td>–</td>
<td>0.004</td>
</tr>
<tr>
<td>Long acting B2 agonist</td>
<td>3 (9.6%)</td>
<td>0</td>
<td>–</td>
<td>0.04</td>
</tr>
<tr>
<td>Theophylline + short acting B2 agonist</td>
<td>3 (9.6%)</td>
<td>13 (43.3%)</td>
<td>–</td>
<td>0.001</td>
</tr>
<tr>
<td>6MWD (meter)</td>
<td>266.8 ± 93.8</td>
<td>272.4 ± 133.1</td>
<td>384.7 ± 53.1</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC% pred.</td>
<td>56.1 ± 17.9</td>
<td>68.6 ± 10.5</td>
<td>85.1 ± 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV1% pred.</td>
<td>33.7 ± 10.8</td>
<td>40.8 ± 13.6</td>
<td>83.1 ± 3.7</td>
<td>0.001</td>
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<tr>
<td>FEV1/FVC</td>
<td>46.7 ± 12.7</td>
<td>50.7 ± 8.3</td>
<td>74.7 ± 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>CAT score</td>
<td>26.2 ± 5.1</td>
<td>22.6 ± 4.4</td>
<td>–</td>
<td>0.004</td>
</tr>
<tr>
<td>GOLD stage</td>
<td>3.1 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Data are represented as number and percentages or mean ± SD, P < 0.05 = significant.
ICS = inhaled corticosteroids.

Figure 1 Serum level of 25-OHD and ionized calcium among all the studied groups.

Table 2 Correlation coefficient between serum 25-OHD and clinical data among all of the studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>COPD groups</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>r</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>COPD groups</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.01</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.01</td>
<td>0.6</td>
</tr>
<tr>
<td>6MWD</td>
<td>0.10</td>
<td>0.4</td>
</tr>
<tr>
<td>FVC% pred.</td>
<td>0.61</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV1% pred.</td>
<td>0.79</td>
<td>0.008</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.61</td>
<td>0.001</td>
</tr>
<tr>
<td>GOLD stage</td>
<td>0.80</td>
<td>0.05</td>
</tr>
<tr>
<td>CAT score</td>
<td>-0.24</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Figure 2 Correlation coefficient between serum 25-OHD and FVC% predicted among COPD patients.

Table 3 Comparison of clinical variables and pulmonary function test before and after 6 months of vitamin D supplements among patients with vitamin D deficiency.

<table>
<thead>
<tr>
<th>Character</th>
<th>Before therapy</th>
<th>After therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT score</td>
<td>25.5 ± 6.4</td>
<td>24.9 ± 7.7</td>
<td>0.08</td>
</tr>
<tr>
<td>6MWD</td>
<td>260.4 ± 116.4</td>
<td>284.8 ± 71.4</td>
<td>0.3</td>
</tr>
<tr>
<td>FEV1% pred.</td>
<td>32.4 ± 14.1</td>
<td>33.5 ± 17.2</td>
<td>0.1</td>
</tr>
<tr>
<td>FVC% pred.</td>
<td>55.9 ± 10.4</td>
<td>56.4 ± 15.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>
The present study was designed to detect firstly, vitamin D level among stable COPD patients. It was found that vitamin D was impaired among 50.8% of the studied COPD patients, 16.4% of them had vitamin D deficiency and 34.4% had vitamin D insufficiency.

Forli et al. [18] reported that in a small sample of patients with advanced COPD awaiting lung transplantation, the majority (> 50%) suffered from vitamin D deficiency (25-OHD < 20 ng/ml). In an outpatient study on patients with COPD in Denmark, 68% of the participants had osteoporosis or osteopenia [19].

The cause of lower percentage of vitamin D deficiency in our study than these reported studies could be attributed to the fact that most of the studied patients with vitamin D deficiency are farmers exposed to the sun most of the day and milk and cheese are main constituents of daily foods.

Impaired vitamin D in COPD can be due to that patients with COPD suffered from reduction of outdoor activity, a reduced capacity of aging skin for vitamin D synthesis, a lower food intake, increased glucocorticoids-induced catabolism, impaired activation as a consequence of renal dysfunction, and a lower storage capacity in muscle and fat due to wasting [12]. Franco et al. [20] found that patients with COPD, even without chronic use of systemic glucocorticoids, have increased risk for osteoporosis and low levels of vitamin D, which is correlated with the severity of disease.

Regarding correlation of vitamin D with other clinical variables, the present study showed that serum 25-OHD correlated significantly in a positive direction with pulmonary function test parameters among COPD patients, while there was no correlation among healthy controls. On the other hand, 25-OHD correlated negatively with CAT score. This finding was in accordance with Janssens et al. [9] who found that 25-OHD serum levels were correlated significantly with FEV1 in the COPD subgroup (r = 0.28, P < 0.0001) with no correlation with FEV1 in the subgroup of healthy controls. EL-Shafeey and EL-Srougy [21] found also that a significant correlation was found between serum 25-OHD and FEV1 (r = 0.896, P = 0.001).

However, another study reported by Shaheen et al. [22] in an older adult UK population (the Hertfordshire Cohort study) did not show a positive correlation between serum 25(OH)D concentrations and lung function in spirometrically defined COPD patients. This study concluded that vitamin D is not an important determinant of adult lung function in COPD.

The mechanisms by which vitamin D levels might affect lung function are unclear. Potential explanations could depend on the calcemic effects of vitamin D. The vital capacity and total lung capacity were found to decline with an increasing number of thoracic vertebral fractures as a direct consequence of vitamin D deficiency [23]. Kyphosis related to osteoporosis caused limitation in rib mobility and inspiratory muscle function and correlated with a reduction in FEV1 and FVC [24]. The altered properties of the thoracic skeleton could result in failure of the respiratory muscles contributing to the pathophysiology of COPD.

An important systemic consequence of COPD is muscle weakness, and this is associated with an increased risk of mortality.

Vitamin D plays a role in influencing skeletal muscle function, with deficiency resulting in muscle weakness, and VDRs are present in the muscles [25]. It has been reported that polymorphisms in the VDR can influence muscle weakness in both healthy individuals and patients with COPD [26], suggesting that the VDR has a significant influence on one of the important complications of this disease.

Vitamin D may also interact with stress, tobacco smoke, and air pollutants through an oxidative/antioxidative imbalance, influencing lung inflammation and consequently lung function [27].

Chronic obstructive pulmonary disease is a progressive and disabling disorder. Unfortunately, the treatment, mostly comprising bronchodilators of different groups, is entirely symptomatic. Findings of some epidemiological observations demonstrating benefits with dietary supplements and some vitamins have therefore raised the hope of managing COPD with an additional approach to currently available therapy [28–31].

Vitamin D therapy in COPD is an intriguing consideration. Given that vitamin D is inexpensive and safe, it would be a desirable treatment option if proven to be effective [32]. In addition to preserving skeletal health, vitamin D may have other health benefits, including improving both respiratory muscle and skeletal muscle function.

Vitamin D may play a beneficial role in improving the innate immune system against chronic respiratory infections by up-regulating specific antimicrobial peptides (human cathelicidin antimicrobial peptide (hCAP-18)) [33]. In addition, a meta-analysis of randomized controlled trials concluded that use of vitamin D supplements is associated with a decrease in total mortality rates [34].

The second aim of the present study was to evaluate the effect of vitamin D supplements in addition to the regular therapy among COPD patients. Unfortunately, pulmonary function test, exercise capacity as evidenced by 6MWD, and CAT score did not improve significantly after 6 months among COPD patients who took vitamin D supplements. This lack of clinical improvement could be attributed to the fact that, the studied COPD patients who took vitamin D supplements had a severe airflow limitation as their mean post-bronchodilator FEV1% predicted was 33.7 ± 10.8, in addition their CAT score was > 10 and they had a severe COPD stage (GOLD stage = 3.1 ± 0.6). Intervention in the earlier stages of COPD might therefore be more effective, which is consistent with the idea that such milder stages are also more sensitive to disease modification [35].

There are limited studies on the use of vitamin D supplements in COPD patients, one study [36] evaluated a monthly dose of 100,000 IU of vitamin D for 1 year in addition to regular therapy among COPD patients and they found that addition of vitamin D did not reduce the time to first exacerbation or the rate of exacerbations in patients with moderate to very severe COPD. Secondary outcomes in the same study, such as FEV1, quality of life, and death, were also not affected. However, a post hoc analysis in 30 participants with severe vitamin D deficiency (serum 25-[OH]D levels < 10 ng/mL) at baseline showed a significant reduction in exacerbations in the vitamin D group (rate ratio, 0.57 [CI, 0.33–0.98]; P = 0.042).

In conclusion, our study revealed that hypovitaminosis D was less common than western studies among stable COPD patients. We also found a direct relationship between serum level of vitamin D and pulmonary function test parameters. The long term use of vitamin D supplements in addition to
usual treatment of COPD had no significant effects on COPD outcomes.

We recommend further studies to assess vitamin D level among a bigger number of COPD patients and to judge on the use of vitamin D supplements on a large sample size than the current one. Finally, we recommend comparing COPD outcomes in vitamin D sufficient patients who take usual treatment of COPD versus those with vitamin D deficiency and on vitamin D supplements to detect the usual progress of the disease.

Conflict of interest

Both authors approved on the conception and design of the study. The authors report no conflicts of interest. The authors alone are responsible for the contents and writing of the paper. None of the authors had a financial support for this paper.

References

