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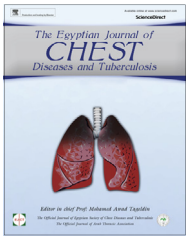

ORIGINAL ARTICLE

Effect of vitamin D replacement in chronic obstructive pulmonary disease patients with vitamin D deficiency

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KEYWORDS

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Abstract *Introduction:* Vitamin D deficiency is prevalent among patients with chronic obstructive pulmonary disease (COPD) and comes to be more frequent with increased disease severity. We aimed to assess the role of vitamin D supplementation in patients with severe COPD.

Patients and methods: We studied 30 patients with severe COPD and vitamin D deficiency. All patients received oral vitamin D3 50,000 IU once weekly for 8 weeks, followed by a daily dose of 800 IU thereafter. Pulmonary function tests, six minute walk test (6MWT), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), C-reactive protein (CRP), and serum vitamin D level were assessed at the start of the study and 1 year later. The frequency of exacerbations was recorded a year before and a year after vitamin D supplementation.

Results: The mean serum vitamin D level was 11.80 ± 2.40 ng/dl and reached 55.30 ± 5.65 ng/dl a year after vitamin D intake ($p < 0.001$). We found a significant improvement in dyspnea scale ($p < 0.003$), 6MWT ($p < 0.001$), MVV ($p < 0.001$), MIP ($p = 0.006$), MEP ($p < 0.001$), coupled with a decrease in disease exacerbations ($p < 0.001$) and CRP ($p < 0.001$) a year after vitamin D replacement. However, the FEV1 and FVC did not differ significantly.

Conclusion: Vitamin D replacement improved dyspnea, physical performance and decreased the frequency of exacerbation in severe COPD patients with vitamin D deficiency.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response of airways

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and the lungs to noxious particles or gases; exacerbation and comorbidities contribute to the overall severity in individual patients [1].

Patients with COPD are at high risk of vitamin D deficiency due to lower food intake, reduced synthesis with skin aging, lack of outdoor activity and sun exposure, increased catabolism by glucocorticoids, impaired activation because of renal dysfunction, and a lower storage capacity in muscles or fat due to wasting [2].

Vitamin D is a fat-soluble hormone precursor that plays an important role in bone metabolism and seems to have anti-inflammatory and immune-modulating properties. Vitamin D is present in 2 forms. Ergocalciferol, or vitamin D2, is present in plants and some fish. Cholecalciferol, or vitamin D3, is synthesized from 7-dehydrocholesterol in the skin by sunlight. The vitamin undergoes two consecutive hydroxylations, one in the liver to 25(OH)D (the inactive form of vitamin D) and the other in the kidneys to 1,25(OH)D, its active form, by the enzyme 1α hydroxylase [3,4].

Studies have demonstrated a role of vitamin D in enhanced eradication of intracellular pathogens like *Mycobacterium tuberculosis* [5], killing of a number of antibiotic-resistant bacteria, viruses and *Chlamydia* [6,7] and vitamin D deficiency may contribute to chronic respiratory infection and airway colonization [8]. Different lines of evidence also support a role of vitamin D in skeletal muscle health. Low levels of serum vitamin D (25-OHD) have been associated with reduced skeletal muscle strength and increased risk of falls while vitamin D supplementation improved balance and reduced falls by approximately 20% [9,10].

Vitamin D deficiency is prevalent among patients with COPD and comes to be more frequent with increased disease severity [11]. In participants with severe vitamin D deficiency at baseline, supplementation may reduce exacerbations [12]. According to a recent meta-analysis, the benefits of supplementation were only present when baseline 25-OHD levels are very low (<10 ng/ml) [13]. Nevertheless, because large cross-sectional data suggest that muscle strength continues to increase from 25-OHD levels of 9 ng/ml to 37 ng/ml [14], it can be speculated that the beneficial effects on the muscle are only seen when higher doses of supplementation are given [15].

In this study, we aimed to evaluate the effect of vitamin D supplementation on the symptoms, pulmonary function tests, respiratory muscle strength and physical performance in vitamin D deficient patients with severe COPD.

Patients and methods

The study design was prospective cohort pre-post study. Between March 2011 and February 2013, 30 COPD patients (26 male and 4 female, mean age 66.7 years) diagnosed as severe COPD were included. Severe disease was established according to GOLD criteria [1] (FEV1/FVC was <0.70 and post-bronchodilator FEV1 was $<50\%$ from predictive value). All patients had serum 25-OHD deficiency (levels <20 ng/ml). Patients accepted to participate by giving informed consent. The proposal of this study was approved by the Institutional Ethics Committee. All patients were subjected to a complete history taking, thorough clinical examination. Demographic data were systematically recorded. Dyspnea in daily life activity was assessed according to the Modified Medical Research Council (MMRC) dyspnea scale which spans from grade 0 through 4 as shown in Table 1.

Table 1 Modified Medical Research Council dyspnea scale.

Grade	Symptom
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Six minute walk test (6MWT)

The test measures the distance a patient can quickly walk on a flat, hard surface in a period of 6 min. The test was performed according to guidelines set by the American Thoracic Society [16]. In brief, the patient rested on a chair, located near the starting position, for 10 min before the test. No "warm-up" period before the test was given. The patient was instructed to walk as far as possible for 6 min and walk back and forth in a 30 m long, meter-by-meter marked hallway. The patient was informed that 6 min is a long time to walk, which means he would be exerting himself, probably get out of breath or become exhausted but he would be permitted to slow down, to stop, to rest as necessary or lean against the wall while resting, and resume walking as soon as he was able to. Pulse oximetry was attached. The baseline heart rate was measured and oxygen saturation (SpO_2) was recorded before and after the test. Upon completion of the test, dyspnea and fatigue level, number of laps, and additional distance covered were recorded. The total distance was then calculated.

Pulmonary function tests (PFT)

Pulmonary function tests were performed using Jaegar® Type Masterscreen-PFT machine, VIASYS Healthcare GmbH, CareFusion Corporation, Hoechberg, Germany. Forced expiratory volume in 1 s (FEV1), maximum voluntary ventilation (MVV), forced vital capacity (FVC), forced expiratory flow (FEF25), forced expiratory flow (FEF50), and forced expiratory flow (FEF75) were recorded.

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)

Measurement of MIP and MEP required mechanical pressure gauge connected to mouthpiece. The device contained a small hole of 1 mm diameter and 20–30 mm in length which allowed air leak to prevent the patient from generating pressure by cheek muscles as described previously [17].

For MIP, a new rubber mouthpiece with flanges was placed on the device. The patient was instructed to seal his/her lips firmly around the mouthpiece and to exhale slowly and

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completely then to pull in hard. The patient maintained an inspiratory pressure for 1.5 s and sustained the largest negative pressure for at least 1 s. Regarding MEP, a new rubber mouthpiece with flanges was also placed. The patient was instructed to inhale completely to total lung capacity then push the mouthpiece against his/her lips and teeth as hard as possible. The patient maintained expiratory pressure for 1.5 s and sustained the largest positive pressure for at least 1 s. In both MIP and MEP, the patient was allowed to rest for 1 min and then repeat the test 5 times. The goal was for the variability among measurements to be less than 10 cmH_2O [18].

Serum vitamin D

Serum samples were centrifuged, aliquoted and stored at −70 °C until analysis. Quantitative determination of serum 25-OHD was performed using Chemiluminescent Immunoassay technology (25-hydroxyvitamin D total assay, Cobas® e-analyzer, Roche Diagnostics, Mannheim, Germany). The concentration of each sample was calculated automatically either in ng/ml or nmol/L using the conversion factors (nmol/L × 0.40 = ng/ml and ng/ml × 2.50 = nmol/L).

Frequency of COPD exacerbation

The frequency of exacerbations a year before and a year after vitamin D supplementation was recorded. Exacerbation was defined as acute events in COPD patients beyond day to day variation and needed change of treatments [1].

Vitamin D supplementation

All patients received oral vitamin D3 50,000 IU once weekly for 8 weeks, followed by a daily dose of 800 IU thereafter. Serum vitamin D level was measured a year after the start of vitamin D supplementation. The previous parameters were re-assessed a year after vitamin D replacement.

Statistical analysis

IBM SPSS statistics version 21 (IBM® SPSS® New York, U.S.A) was used to analyze the data. Categorical variables were expressed as numbers and percentages and continuous variables as mean ± standard deviation. Fisher exact test was used to detect significant difference between categorical variables. Differences in means were compared using *t*-test. A *p*-value of <0.05 was considered statistically significant.

Results

Of 30 severe COPD patients with vitamin D deficiency, 26 (86.7%) were from urban areas and 4 (13.3) from rural areas. Mean smoking index was (48.4 ± 8.1) pack-year. The demographic characteristics of the study patients are shown in Table 2.

A significant improvement in MMRC dyspnea scale (2.20 ± .81 *vs.* 1.77 ± .57, $p = 0.003$), 6MWT (93.57 ± 13.48 *vs.* 113.23 ± 10.03, $p < 0.001$), and frequency of exacerbation (1.80 ± 0.81 *vs.* 1.03 ± 0.57, $p < 0.001$) was noticed 1 year after vitamin D replacement. CRP was significantly reduced (23.67 ± 18.91 *vs.* 13.00 ± 14.59, $p < 0.001$) (Table 3). In the meantime, the MIP (−75.87 ± 8.81 *vs.* −82.13 ± 7.99, $p = 0.006$), MEP (78.43 ± 7.13 *vs.* 86.27 ± 6.63, $p < 0.001$), and MMV (43.13 ± 8.60 *vs.* 51.40 ± 8.35, $p < 0.001$) showed a significant improvement.

Table 2 Demographic characteristics of the study patients.

Variable	
Age in years (mean ± SD)	66.7 ± 8.5
Gender	
Male, no. (%)	26 (86.7)
Female, no. (%)	4 (13.3)
Residency	
Rural, no. (%)	4 (13.3)
Urban, no. (%)	26 (86.7)
Smoking, pack-year (mean ± SD)	48.4 ± 8.1

Note: SD: standard deviation.

The mean percent predicted FEV1 in our COPD patients was 38.27 ± 6.32, and FVC 60.53 ± 4.36 before vitamin D supplementation. The FEV1, FVC and forced expiratory flows did not differ significantly a year after vitamin D replacement (Table 4).

Discussion

We have found a significant improvement of dyspnea, respiratory muscle strength and physical performance without parallel improvement in pulmonary function tests like FEV1 and FVC after supplementation of vitamin D over 1 year.

In the literature, a survey of 14,091 people ⩾20 years of age who had undergone spirometry, and in whom serum 25-OHD levels had been measured, found a strong relationship between serum concentrations of 25-OHD, FEV1, and FVC [19]. The investigators attributed this in a number of ways in which vitamin D might influence tissue remodeling and repair. These included the inhibition of matrix metalloproteinases which are involved in the digestion of extracellular matrix [20] and the effects on the proliferation of fibroblasts and synthesis of collagen [21].

Monadi and colleagues [22] studied the relationship between various COPD patients' groups classified on the basis of serum 25-OHD concentration and FEV. The researchers found that mean FEV1 volumes increased with higher serum 25-OHD concentrations. However, the mean FEV1 differences among groups did not reach to a statistically significant level. It is noteworthy that only 11% of their patients were vitamin D deficient and the proportion of those with severe COPD (GOLD stages 3 and 4) were only 2.5%, and 1.3% respectively.

In our study, we could argue why we could not find a significant improvement in pulmonary function like FEV1, FVC and flows after supplementation of vitamin D. The study was conducted on patients who were mostly elderly with established severe COPD and probably had different confounders, which could not allow them to benefit from the effect of vitamin D on tissue remodeling and repair.

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Table 3 Vitamin D level, dyspnea, 6MWT, CRP and frequency of COPD exacerbation before and after vitamin D replacement.

	Before vitamin D Mean ± SD	After vitamin D Mean ± SD	*p*-Value
Vitamin D (nmol/L)	11.80 ± 2.40	55.30 ± 5.65	<0.001*
Dyspnea scale	2.20 ± .81	1.77 ± .57	0.003*
6MWT (meters)	93.57 ± 13.48	113.23 ± 10.03	<0.001*
CRP (U/L)	23.67 ± 18.91	13.00 ± 14.59	<0.001*
Exacerbation/year (no.)	1.80 ± 0.81	1.03 ± 0.57	<0.001*

* Significant *p*-value.

Table 4 Pulmonary function tests, MIP and MEP before and after vitamin D replacement.

	Before vitamin D Mean ± SD	After vitamin D Mean ± SD	*p*-Value
FEV1 (% predicted)	38.27 ± 6.32	38.98 ± 6.50	0.670
FVC (% predicted)	60.53 ± 4.36	63.03 ± 4.79	0.074
FEF25 (% predicted)	44.50 ± 5.98	45.77 ± 6.33	0.111
FEF50 (% predicted)	39.40 ± 5.09	39.98 ± 5.34	0.659
FEF75 (% predicted)	30.63 ± 7.44	31.40 ± 7.12	0.446
MVV	43.13 ± 8.60	51.40 ± 8.35	0.001*
MIP	−75.87 ± 8.81	−82.13 ± 7.99	0.006*
MEP	78.43 ± 7.13	86.27 ± 6.63	<0.001*

Note: FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF: forced expiratory flow; MVV: maximum voluntary ventilation; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure.
* Significant *p*-value.

On the other hand, the 6MWT improved significantly. This test generally evaluates the global and integrated responses of all the systems involved during exercise including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism [16].

The effects of vitamin D on musculoskeletal, physiological and neurophysiological function have been published in a number of studies [23–26]. Bischoff-Ferrari and colleagues [14] found that ambulatory persons (⩾60 years) with vitamin D concentration 40–94 nmol/L had a better musculoskeletal function in the lower extremities than at a concentration of <40 nmol/L. Likewise, Menant et al. [23] found the associations between vitamin D insufficiency and impairments of physiological and neuropsychological function that predispose older people to fall. Bjerk et al. [24] reported an improvement in physical performance, inspiratory muscle strength and maximal oxygen uptake with vitamin D supplementation.

Romme et al. [25] studied 151 COPD patients of whom 87 patients had vitamin D deficiency. Plasma 25hydroxy vitamin D (25-OHD) concentration was positively associated with bone density and exercise capacity as measured by 6MWT. However, it was not associated with quadriceps muscle strength. The researchers concluded that the majority of COPD patients had vitamin D deficiency.

In contrast, Bjerk et al. [24] randomized 63 COPD patients to daily cholecalciferol (2000 IU) or placebo for 6 weeks and found that among patients with severe COPD, 2000 IU of daily vitamin D for 6 weeks almost normalized the level of 25-(OH) D and when compared with placebo, the short-term vitamin D supplementation had no noticeable effect on a simple measure of physical performance.

Our analysis revealed a significant decrease of CRP with vitamin D replenishment. Several studies elucidated the anti-inflammatory effects of vitamin D [27–29]. Moreno et al. [26] reported that calcitriol [1,25(OH)2D3] regulates the expression of several genes involved in prostaglandin (PG) metabolism and signaling, thereby reducing the levels and biological activity of PGs. Nonn et al. [27] found that calcitriol up-regulates the expression of mitogen-activated protein kinase phosphatase-5 (MKP-5) resulting in reduction of the level of expression of pro-inflammatory cytokines. Studies that employed cDNA microarrays to examine changes in gene expression in cancer cells treated with calcitriol or its analogs identified many novel calcitriol target genes, some of which could be important molecular mediators of its potent anti-inflammatory effects [28,29].

In our study, exacerbation decreased significantly after vitamin D replacement. This finding differs in a way from reports of other investigators [12,30,31]. For example, Lehouck et al. [12] found that the median time to first exacerbation did not differ significantly between the studied groups, nor did exacerbation rates, FEV1, hospitalization, quality of life, and death. However, a post hoc analysis in 30 participants with severe vitamin D deficiency (serum 25-(OH) D level <10 ng/ml at baseline) showed a significant reduction of exacerbations in the vitamin D group.

Similarly, other studies have found neither baseline serum 25(OH) D levels were predictive of subsequent acute exacerbation in severe COPD [29] nor low levels were associated with frequent exacerbation or increased susceptibility to worsening by human rhinovirus [31].

In conclusion, vitamin D replacement in vitamin D deficient COPD patient may improve dyspnea, exercise capacity,

and reduce the frequency of exacerbations. Further studies on a larger number of patients are recommended.

Conflict of interest

None declared.

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