



High Dose Vitamin D3 Improves Exercise Tolerance in Elderly Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: In addition to airflow limitation, peripheral muscle dysfunction is a limiting factor in physical performance of patients with chronic obstructive pulmonary disease (COPD). Any measure to improve global muscle function in COPD patients such as vitamin D replacement seems to enhance exercise tolerance of these patients.

Aim: The aim of present study was to study the effect of vitamin D replacement therapy on exercise tolerance of a group of stable COPD patients with vitamin D deficiency or insufficiency.

Methods: It was an experimental, unblinded open-label trial. A total number of 25 stable COPD patients were enrolled in the study in the period between March 2012 and OCT 2012 and received 50,000 IU vitamin D weekly for 4-8 weeks in addition to their standard medical therapy as before. They were also subdivided into two subgroups based on serum 25 hydroxy vitamin D, 25(OH)D (<10 ng/ml and 10-30 ng/ml). Pulmonary function tests, six-minute walk distance test (6MWD) were measured at baseline and three months after the enrollment.

Results: By the end of study, there was significant improvement in the distance walked during 6-minute walk test. This improvement was documented in both subgroups of patients. However, the perceived dyspnea during test did not differ from baseline value by the end of the study. Also, only patients with serum 25(OH) D, 10 -30 ng/ml showed the significant increase in their mean value of FEV1 by the end of the study.

Conclusion: Vitamin D replacement therapy is an effective measure to improve exercise tolerance of stable COPD patients with vitamin D deficiency or insufficiency

Keywords: Six-minute walk test; Vitamin D insufficiency; Exercise tolerance

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in First Second; 6MWD: Six-Minute Walk Distance

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by chronic irreversible airflow limitation. It is one of the major causes of morbidity and mortality in the elderly. Affected patients often experience reduced exercise tolerance and impaired quality of life [1]. It has been demonstrated that exercise capacity is a strong predictor of survival in these patients [2]. Adding pulmonary rehabilitation (PR) to optimal medical treatment is believed to improve exercise capacity and quality of life in COPD patients [3]. Rehabilitation programs include health education, chest physiotherapy training, skeletal and respiratory muscle training and psychological support. Exercise training is an essential component of pulmonary rehabilitation that leads to decreased ventilatory requirement at a given exercise load. It exerts its beneficial effect through physiological changes of leg muscle with no significant change in pulmonary function tests. Therefore, any comorbidity, negatively influencing global muscle function needs to be treated e.g.; vitamin deficiencies. Therefore, nutritional assessment would be a prerequisite for being enrolled in pulmonary rehabilitation programs [4]. Vitamin D insufficiency /deficiency is highly prevalent in COPD patients [5]. Disease-related symptoms such as dyspnea and limited physical activity, leading to decreased sun exposure, in addition, systemic nature of disease with anorexia and malnutrition are responsible for such a high prevalence. Muscle weakness is not uncommon in patients with advanced pulmonary disease. Global muscle

dysfunction in COPD patients has been the focus of investigations in recent years and there are documents that global muscle dysfunction is a better predictor of hospital readmission for exacerbation and better correlates with survival than pulmonary function tests [6]. Vitamin D insufficiency syndrome further compromises such muscle dysfunction even in normocalcemic patients [7]. There are reports that serum level of 25 hydroxy vitamin D is positively associated with exercise capacity in COPD patients [8]. It has been investigated that COPD patients with vitamin D deficiency who participate in outpatient pulmonary rehabilitation have more dropout rate than those with normal vitamin D reservoir. They have also poorer outcome in muscle training programs [9]. Therefore; it seems that vitamin D status needs to be evaluated to increase the yield of treatment including PR in COPD patients.

Six minute walk distance test is a simple measure to assess the exercise capacity of patients with cardiopulmonary diseases. During the test, the patient is asked to walk as much as possible within 6 minutes. It has been shown that it better predicts survival than measurements of air flow limitation in patients with severe COPD [10]. In another word,

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markers of airflow limitation such as FEV1 correlate with the degree of respiratory involvement of the disease, while 6 minute walk distance expresses the systemic nature of COPD.

This study was designed to evaluate the impact of vitamin D replacement on exercise capacity of elderly patients with COPD and vitamin D insufficiency/deficiency. The six minute walk distance test was used to assess the functional capacity and exercise tolerance of patients in our study.

Material and Methods

Study design and population

The study was an unblinded, open-label trial done in a group of Iranian COPD patients. Before commencing the study, we obtained medical ethics committee approval of Tehran University of Medical Sciences. All patients enrolled in the study indicated their consent by reading and signing the consent forms. We started the study in March 2012 and finished in the following October and recruited patients with COPD, based on GOLD diagnostic criteria [11], presenting to the outpatient pulmonary clinic of a university hospital. Venous blood samples were collected and serum levels of 25 hydroxy vitamin D, 25(OH) D, were measured using chemiluminescence immunoassay (CLIA). Patients with serum level of 25(OH) D below 30 ng/ml were selected. All patients received standard medical treatment for COPD including inhaled bronchodilators, inhaled steroids, and oxygen. Serum levels of 25(OH) D were used to categorize patients into deficient vitamin D (<10 ng/ml) and vitamin D insufficiency syndrome (10-30 ng/ml) groups [12]. However; there are controversies on vitamin D level as deficient status among different authors for example, some experts consider deficient status as serum 25(OH)D level below <20 ng/ml [13].

Inclusion criteria were stable COPD patients with vitamin D deficiency or insufficiency and age over 40 years whose pulmonary function tests had no significant change within previous three months.

Exclusion criteria were serum level of 25(OH) D more than 30 ng/ml, inability to perform 6- minute walk test due to musculoskeletal, neurologic disorders, aortic valve disease, heart failure syndromes, peripheral vascular disorders or ischemic heart disease. Patients with left ventricular ejection fraction less than 40 percent or systolic pulmonary artery pressure above 40 mmHg were also excluded. Exclusion criteria were expanded further into chronic kidney disease, urolithiasis, liver disease, parathyroid disorders, inflammatory bowel disease, mal absorption syndromes, convulsive disorders, active cancer, sarcoidosis and recent consumption of vitamin D and calcium supplements. As obesity decreases serum level of 25(OH) D, we excluded patients with BMI more than 30 [14]. We did not enroll the patients with history of hospital admission for COPD exacerbation within 2 weeks of study and excluded those who developed such exacerbation during the study time.

Patients underwent both pulmonary function testing and 6 minute walk test when being enrolled in the study. Then, they were treated for vitamin D deficiency/insufficiency syndrome and the tests were re measured three months apart from the baseline tests. The program details are summarized as follow:

Spirometry

Spirometry was performed using Ganzhorn, Germany, 2009, in the respiratory laboratory. The standard methods according to American Thoracic Society recommendation (ATS) were used to perform and

interpret the test [15]. Forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and FEV1/FVC were measured. FEV1 expressed as the percentage of predicted value was used to define the stage of COPD according to GOLD criteria [11]. But, the absolute number of FEV1 in litre was used to compare the degree of airflow limitation before and after vitamin D replacement.

Six-Minute walk test

The test was performed according to ATS guideline 2002 [16]. The patients were asked to walk as far as possible within 6 minutes turning around a 25- meter hospital corridor, marked each 3 meter interval. A specialized nurse supervised all the tests. The subjects rested 30 minutes before walking. Vital signs were recorded and in case of hemodynamic instability such as uncontrolled hypertension to 180/110 mmHg the test was not performed. If the patient was on supplemental oxygen therapy, the nurse carried the portable oxygen during the test. The distance was measured to the nearest meter and recorded. A visual analogue scale with verbal description called Borg scale was used to measure the perceived dyspnea. The patients were asked to rate their highest level of dyspnea perceived during the test by use of the given scale [17]. The walk tests before and after vitamin D replacement were performed in similar conditions and if the patient was receiving oxygen therapy, the oxygen flow was the same for two tests. The same trained nurse supervised all the tests that were performed around 2 hours after a light breakfast. Since, most musculoskeletal benefits of vitamin D replacement take several weeks to appear; the patients performed the second six –minute walk test at least three month after the first test [18]. The three month interval also weakened the effect of learning on test performance [19].

Vitamin D replacement protocol

Patients with vitamin D deficiency/insufficiency received 50,000 IU vitamin D orally once weekly for 4 to 8 weeks. Deficient patients also received 500mg elemental calcium orally on a daily basis if their urinary calcium excretion was less than 50 mg per day. As calcium carbonate tablets were the only available drug formulation for oral administration, and there was fear of rise in serum bicarbonate level by administering 1000-1200 mg elemental calcium and subsequent respiratory suppression, the patients received no more than 500 mg elemental calcium per day and urinary calcium excretion were measured monthly. Once excretion rate increased to more than 50 mg per day, oral calcium supplements were discontinued. Serum levels of 25(OH) D were assayed monthly. The goal of treatment was level equal or more than 30 ng/ml. When reaching the target, the treatment was switched to daily oral 800 IU vitamin D. All patients who were excluded but had vitamin D deficiency of insufficiency were treated accordingly.

Statistical analysis

Numerical values were presented as mean plus/minus (SD). Non-parametric Wilcoxon's test was used to analyze the paired data such as distance walked in 6MWD test, FEV1 and perceived dyspnea. Linear regression analysis was used to control for confounders. All statistical analysis was performed with SPSS version 18. P values less than 0.05 were considered to be significant.

Results

A total number of 25 COPD patients were enrolled in the study. The mean age was 63 ± 11.1 years, with a range of 42-83. Seventy six percent of patients were men and 24% were women. Table 1 illustrates general characteristics of participants. The mean serum level of 25 (OH) D was

14.05 ± ng/ml with a range of 5-30. Eleven patients (44%) were vitamin D deficient (25(OH) D<10 ng/ml) and fourteen (56%) patients were insufficient (10-30). Only three patients with vitamin D deficiency had stage IV COPD according to GOLD classification. Table 2 shows baseline and three months clinical data of participants irrespective of their vitamin D status (deficient or insufficient). The absolute value of FEV1 improved significantly three month after enrollment in the study (P<0.001). At the same time the distance walked during six minute walk test showed statistically significant increase (P<0.001). However, the perceived dyspnea rated by modified Borg scale did not show significant change (P=0.84). Mean serum level of 25(OH) D rose to more than 40 ng/ml but the difference did not reach significant value (P=0.002).

Table 3 shows baseline and three months clinical data of the two subgroup of patients regarding to their vitamin D status; vitamin D deficient and vitamin D insufficient subgroups.

By the end of the study, COPD patients irrespective of their vitamin D status (deficient or insufficient) showed statistically significant increase in mean six minute walk distance (6MWD)(P<0.05). The increase was more marked in insufficiency subgroup (P <0.001) than in deficient patients (P=0.003). Also, the mean value of FEV1 increased in both subgroups. However, the increase in patients with vitamin D deficiency did not reach statistically significant value (P=0.08), while the improvement was significant in vitamin D insufficiency subgroup (P=0.002).

Minimal clinically important difference (MCID) in the six minute walk test in patients with chronic pulmonary disease has been reported to be 54 m [20]. Eight patients (72.7%) in deficiency subgroup achieved the increase in six minute walk distance above MCID, while only five patients (35.7%) of the second subgroup achieved similar improvement. However, the difference between two subgroups was not statistically significant (P=0.06).

Serum level of 25(OH) D and daily urinary calcium excretion were measured monthly during the study. One month after enrollment, 80 percent of the patients had urinary calcium within the normal range (116 ± 4.1 mg/day). The remaining reached normal values by the

| Patient feature | Patient number |
|-----------------------|----------------|
| Age <65 years | 15 |
| Age >65 years | 10 |
| Male | 19 |
| Female | 6 |
| COPD stage 1 | 1 |
| COPD stage 2 | 8 |
| COPD stage 3 | 8 |
| COPD stage 4 | 8 |
| Smoker | 16 |
| Vitamin D< 10 ng/ml | 11 |
| Vitamin D 10-30 ng/ml | 14 |

Table 1: General characteristics of participants

| | Patients number | Baseline | Three months | P value |
|-------------------------------|-----------------|-------------|--------------|---------|
| FEV1(L) | 25 | 1.06 ± 0.63 | 1.16 ± 0.68 | <0.001 |
| 6-minute walk distance(m) | 25 | 238 ± 96.4 | 292.8 ± 97.8 | <0.001 |
| Perceived dyspnea(Borg scale) | 25 | 1.5 ± 0.5 | 1.5 ± 0.5 | 0.84 |
| Serum level of 25(OH)D(ng/ml) | 25 | 14.05 ± 9.5 | 62.7 ± 16 | 0.002 |

Table 2: Baseline and three months clinical data of FEV1, Six-minute walk test parameters and serum level of 25 (OH) D

| | Serum level of 25 (OH)D ng/ml | Patients number | Baseline | Three months | P value |
|----------------------------|-------------------------------|-----------------|---------------|---------------|---------|
| FEV1(L) | <10 | 11 | 0.85 ± 0.41 | 0.95 ± 0.40 | 0.08 |
| | 10-30 | 14 | 1.22 ± 0.74 | 1.33 ± 0.81 | 0.002 |
| 6-minute walk distance (m) | <10 | 11 | 201.8 ± 72.6 | 275 ± 80.7 | 0.003 |
| | 10-30 | 14 | 266.4 ± 106.2 | 306.7 ± 110.3 | 0.001 |

Table 3: Baseline and three months clinical data of FEV1 and six-minute walk distance in two subgroup of patients; vitamin D deficient and vitamin D insufficient subgroups

end of two months (133.1 ± 7.4 mg/day).Calcium supplements were discontinued by the time of normalization of urinary calcium excretion. By the end of three months all patients had serum levels of 25(OH) D more than 30 ng/ml with mean value of 62.7 ± 16 ng/ml.

Linear regression analysis showed that serum level of 25(OH) D (P <0.001, β=0.88) and FEV1 (P=0.04, β=0.13) by the end of study were independent factors affecting the distance walked at the three month test.

Discussion

The present study explored the effect of vitamin D replacement therapy in exercise capacity of COPD patients. Field tests are commonly used to evaluate exercise tolerance of patients with various cardio respiratory diseases. Six-minute walk (6MWT) and shuttle walking tests are commonly used with this aim as they are easy to perform and need minimal equipment. We utilized 6MW test and found that vitamin D supplementation significantly improved distance walked during 6MWT, signifying improvement in the exercise tolerance of COPD patients with vitamin D insufficiency/deficiency. Six minute walk test is a simplified exercise test assessing overall functional capacity of patients. It is influenced by many factors including cardio respiratory function, comorbid disorders, age, BMI, height, nutrition and peripheral muscle strength [10]. Lower limb muscle strength has been reported to have significant and positive relationship with the distance walked during 6MWT [21]. Peripheral muscle dysfunction is a well-known complication in COPD patients and vitamin D insufficiency that is common in COPD, contributes to its development. Therefore, it is prudent to assume that insufficient vitamin D store in COPD patients reduces their maximum distance walked during 6MWT .As a supportive evidence, Ringbaek et al., [9]. showed that COPD patients with vitamin D deficiency who undergo PR have poorer outcome in training programs compared with patients with enough vitamin D reservoir [9]. There is also a strong document stating vitamin D supplementation improves exercise capacity of COPD patients receiving pulmonary rehabilitation [22]. Vitamin D receptors exist on various organs including skeletal muscles. Vitamin D affects muscle metabolism in different pathways. For instance, after binding to its receptor, 1, 25(OH) D3 causes both voltage-dependent calcium channels and calcium-release-activated channels to be opened and facilitates calcium entry to the cells to initiate myosin and actin interaction and finally muscle contraction. Therefore, it is not surprising that vitamin D insufficiency causes proximal muscle weakness even in the presence of normocalcemia [23]. The exact mechanisms that vitamin D improves exercise tolerance in COPD patients are not known. Improvement in oxidative capacity of musculoskeletal tissues, reducing anaerobic threshold are areas of uncertainty that need to be addressed in future studies [18].

Yet, there are controversies about contribution of vitamin D deficiency to muscle dysfunction in COPD patients. Jackson et al. studied the correlation between vitamin D status , muscle strength and

quadriceps endurance in a group of COPD patients and reported no significant correlation, and attributed their finding to muscle resistance to vitamin D [24]. There are few studies evaluating the effect of vitamin D supplementation on six -minute walk test as a primary outcome in COPD patients. But in a double-blind randomized controlled trial in patients with heart failure, vitamin D supplementation did not improve exercise tolerance, muscle strength and six minute walk distance [25].

There are few reports investigating the contribution of vitamin D status to respiratory muscle strength in COPD patients. Also, there is little study to address the optimal level of 25 (OH) D in COPD patients to achieve maximum exercise capacity. Based on large cross-sectional data, when serum level of 25(OH) D increases from 9 ng/ml to 37 ng/ml, muscle strengths increases too and higher level of 25 (OH) D associated with better lower extremity function [26]. According to the statement of International osteoporosis Foundation in 2010, the target serum level of 25(OH) D of 30ng/ml should be maintained in all elderly patients [27]. In our study, the serum level of 25(OH) D after three months was correlated positively with distance walked during 6MW test at the end of study. All patients achieved serum level of 25(OH) D more than 30 ng/ by the end of the study with mean serum level of 62.7 ± 16 ng/ml. Similarly, the increase in 6MWD in insufficiency group was more than deficient patients by the end of the study. As mentioned, higher serum level of 25 (OH) D correlates with better skeletal muscle function and may enhance exercise tolerance. We treated our patients with almost the same regimen, irrespective of being insufficient or deficient in vitamin D that means 50,000 IU orally weekly for 4-8 weeks. Therefore, we assumed that the percentage of patients whose improvement in 6MWT was more than MCID would differ significantly in two subgroups but data analysis showed that was not the case. We attributed this finding to the small number of patients in each subgroup as the measured P value was only 0.06.

Patients with COPD often experience increased dyspnea during exercise that limits their exercise performance further. Ventilatory demands increase during exercise, and expiratory flow limitation causes progressive hyperinflation, so greater respiratory muscle activity is needed to overcome the increased elastic work at high lung volumes. The increased work of breathing translates into increased perception of dyspnea [28]. However, this exertional dyspnea might be in some part due to increased respiratory drive secondary to peripheral muscle dysfunction [29]. We assumed that vitamin D replacement would decrease perceived dyspnea during 6-minute walk distance test at least by improving peripheral muscle dysfunction. We used Borg category scale to rate the dyspnea. However, the mean Borg scale score during walk test before and after the intervention showed no significant improvement in perceived dyspnea while there was significant difference in distance before and after vitamin D replacement. The observed discrepancy between dyspnea score and the distance may be due to inability of elderly patients to discriminate easily between terms such as slight dyspnea and somewhat sever dyspnea (2 vs.4 score respectively). Based on the documentations by Muza et al., [30] psychometric measures such as visual analogue and Borg scale have good reproducibility but the proximity of verbal descriptors might be confusing and discouraging for patients with COPD. Therefore, rating dyspnea by Borg scale might not be highly sensitive [30,31].

Mean FEV1 value increased from baseline value at the three months in our study. But, the increase in deficient patients [25(OH) D<10 ng/ml] did not reach statistically significant value. However, in patients with vitamin D insufficiency; the increase in mean value of FEV1 was significant. Black et al., [32] surveyed the relationship between vitamin

D status and pulmonary function tests and showed men and women with serum level of 25(OH) D above 35ng/ml had FEV1 values 176 milliliter more than their matched controls [32]. However, Lehouk et al., [33] showed that high dose vitamin D administration to COPD patients with vitamin D insufficiency did not affect the FEV1 or the time to first exacerbation [33]. Also in a randomized clinical trial, severe COPD patients did not show any significant change in their physical performance or respiratory health status despite receiving 2000 vitamin D daily for 6 weeks [34]. In Hertfordshire Cohort Study, UK, the investigators did not find any significant relationship between serum 25(OH) D and FEV1 in COPD patients [35]. In addition Kunisaki et al., [36] showed that vitamin D status has no relationship with short term response of FEV1 to inhaled steroid [36]. The observed increase in mean FEV1 in the patients with vitamin D insufficiency in our study may not reflect the positive effect of vitamin supplementation on lung function test but may rather signify the seasonal and biologic variations of lung function tests in COPD patients.

There were limitations in our study. First; we did not study the effect of vitamin D replacement on end expiratory volume, inspiratory capacity and static dynamic hyperinflation during exercise. We did not measure muscle strength and quadriceps endurance before and after vitamin D supplementation. We did not follow patients beyond three months to evaluate their physical performance. Also, the number of matched COPD patients with sufficient vitamin D status was very small in our pulmonary clinic so we had no control group. Lastly, the sample size was very small.

In conclusion, it is worthy to state that to optimize medical treatment of patients with COPD and increase their exercise tolerance, not only airflow limitation but also peripheral muscle weakness needs to be treated appropriately. Functional capacity of COPD patients would not improve unless their lower limb muscle becomes more efficient in energy consumption.

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