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Vitamin D3 supplementation on lung functions and exercise tolerance in D3 deficient asthma COPD overlap syndrome patients - A randomized controlled trial

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Abstract

Background: Vitamin D3 supplementation showed significant improvement in lung functions and exercise tolerance in both of asthma and COPD patients. **Objectives:** To evaluate the effects of vitamin D3 supplementation on lung functions and exercise tolerance in D3 deficient, stable patients with ACO. **Methods:** A double blinded randomized placebo controlled trial was carried out on 60 (sixty) D3 deficient [serum 25-hydroxycholecalciferol, 25(OH)D<30 ng/ml], male, smoker, stable ACO patients of age 40 to 80 year, selected according to selection criteria. After the final selection, all the patients were randomly allocated as 'Study' (n=30) or 'Control' (n=30) and their baseline spirometric lung functions (FVC, FEV1, FEV1/FVC ratio, PEFR, FEF25-75) and exercise tolerance represented by 6Minute Walk Distance (6MWD), peripheral capillary oxygen saturation (SpO2) at rest, SpO2 after 6MWT, dyspnea scale and fatigue scale variables were measured. All the 'Study' patients received 80,000 IU (2 oral capsules) of vitamin D3 per week for first 13 weeks. Subsequently, according to their serum 25(OH)D or calcium, they got 40,000 IU (1 oral capsule) of D3 per 1 week or per 2 weeks or per 6 weeks or no further supplementation, for following 13 weeks. Whereas, all the 'Control' patients received two oral

capsules of placebo weekly for consecutive 26 weeks. After 26 weeks of follow up, spirometric lung functions and exercise tolerance variables were again measured and compared with their corresponding baseline value. Data were analyzed by independent and paired sample t test, where $p \leq 0.05$ was accepted as significant. **Results:** There was significant improvement in 6MWD ($p<0.05$), SpO2 after 6MWT ($p<0.001$), dyspnea scale ($p<0.001$) and fatigue scale ($p<0.001$), in patients with vitamin D3 supplementation in comparison to those of placebo on 26th week of follow up. However, there was no improvement in ventilatory variables in the D3 supplemented group in comparison to those of placebo group. **Conclusion:** The present study reveals that vitamin D3 supplementation improves exercise tolerance but not ventilatory variables in vitamin D3 deficient stable ACO patients. Further multi centered trials with different dose as well as duration schedule on both male and female ACO patients are recommended.

Keywords: Asthma COPD overlap, vitamin D3, lung functions, SpO2, 6 Minute walk distance, modified Borg scale

Introduction

Chronic obstructive pulmonary disease (COPD) and bronchial asthma both are common airway diseases contributing to mortality and morbidity worldwide[1]. About one out of four COPD patients has asthmatic features consisting of wheezing, airway hyperresponsiveness or atopy.[2] Again, asthma patients may have fixed airway obstruction over time.[3] In 2017, a joint project of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended the term 'asthma-COPD overlap (ACO)' for the patients present with features of both asthma and COPD.[4]

The prevalence rate of ACO has been estimated 15 to 55.5% worldwide.[5] However, in Bangladesh, prevalence of ACO has been estimated about 11.6%.[6]

To provide a quick, acceptable, repeatable and reproducible lung function data, spirometry is a safe and practical procedure.[1] The ventilatory function of the lung (FVC, FEV1, FEV1/FVC ratio, PEFR, FEF25-75, FEF25, FEF50 and FEF75) can be assessed by spirometry.[7]

In addition to change in ventilatory functions patients with respiratory diseases may have reduced exercise tolerance.[8] For the assessment of exercise tolerance 6 minute walk test (6MWT) is one of the practical and simple manovaure.[9] The primary variable of this test is the distance walked in a period of 6 minute (6MWD) and the secondary variables are peripheral capillary oxygen saturation (SpO2), dyspnea scale and fatigue scale.[10]

Despite the fact that all of the obstructive airway diseases (ACO/ COPD/ Asthma) are preventable and treatable, but once developed along with their comorbidities those respiratory ailments cannot be restored. Presently, the role of different vitamin supplements on various lung diseases are ongoing.[11-13]

The classical role of vitamin D in bone mineralization and calcium homeostasis is now

well established.[14] However, its various non-classical roles such as cancer prevention[15], autoimmune disease[16], hypertension[17], cardiovascular disorder[18], and inflammatory diseases[19] were also investigated.

In respiratory health, several studies reported positive associations between vitamin D and asthma.[20-22] Studies also found positive correlations between 25- hydroxy cholecalciferol [25(OH)D] level and ventilatory variables in COPD patients.[23] In addition,vitamin D concentration was positively associated with exercise capacity in COPD patients.[24] However, Odler et al. found positive correlation between serum 25(OH)D and ventilatory function of lung in ACO patients.[25]

Furthermore, in patients with bronchial asthma, significant improvement in FEV1 was shown after 50,000 IU /day of vitamin D for consecutive 3 months.[26] In addition, in D3 deficient COPD patients 50,000 IU/week vitamin D for 8 weeks followed by 800 IU /day for 1 year did significant improvement in exercise tolerance.[27] Most remarkably, a very recent study with 80000 IU/ week vitamin D supplementation for consecutive 3 months showed significant improvement in FVC and exercise tolerance in D3 deficient stable COPD patients.[28]

In recent years, ACO has gained much attention and have extensively reviewed worldwide. As patients with ACO seem to be at risk for a poor outcome, high risk of exacerbations, it is of utmost importance to perform more research on ACO. Various studies have shown that vitamin D3 supplementation improved lung functions and exercise tolerance in both asthma and COPD patients. However, as far as we searched no data was found published on D3 supplementation on ventilatory lung function or exercise tolerance in patients with ACO.

Therefore, on the basis of this background, the study was designed to observe the effects of vitamin D3 supplementation on the lung ventilatory function parameters and exercise tolerance in D3 deficient, stable patients with ACO.

Methods

Study design and setting

This double blinded randomized controlled trial (RCT) was done in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March, 2018 to August, 2019. The study design involving the human subjects followed the ethical rule of Helsinki[29] and ethicaly approved by the Institutional Review Board of BSMMU.

Study sparticipants

For this study, 60 (sixty) male, stable (diagnosed patient with no acute exacerbation, hospitalization, emergency medical visits or changes in routine medication within 4 weeks prior to study)[1] patients with ACO were selected from the Out Patient Department of National Institute of Diseases of the Chest and Hospital, Dhaka. Pulmonologists diagnosed ACO patients by clinical, physical and radiological signs of chronic airway disease(commonly with spirometric evidence of chronic airflow limitation, i.e. post bronchodilator FEV1/FVC<0.7)[4], but its absence did not exclude ACO entirely. The diagnosis was eventually confirmed by 'tick box' approach proposed by GINA and GOLD jointcommittee. Patients were included in terms of age (40 to 80 years), vitamin D3 deficient (serum 25(OH)D <30 ng/ml)[30], duration of ACO (1 to 5 years)[31], smoker (>10 pack years)[32], body mass index (18.6 to 24.9 kg/m^2)[33], mid upper arm circumference (>25.1 cm)[34], serum total calcium (8.5 to 10.5 mg/dl)[35], serum inorganic phosphate (2.3 to 4.7 mg/dl)[35] and serum parathormone (10 to 65 pg/ml)[35].

Exclusion criteria

In addition, patients were excluded if there was uncontrolled systemic hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg in antihypertensive medication)[36], uncontrolled diabetes mellitus (fasting blood sugar ≥7 mmol/l and/or HbA1c ≥6.5%)[37], dyslipidemia (total cholesterol ≥240 mg/dl and/or HDL ≤40 mg/dl and/or LDL ≥160 mg/dl and/or triglyceride ≥200 mg/dl and/or with use of any lipid-lowering drug)[38], renal insufficiency (serum creatinine >1.36 mg/dl)[39] as well as history of any pulmonary, liver, endocrine or cardiac disease, malignancy or with consumption of any drug known to affect vitamin D metabolism (phenytoin, carbamazepine, clotrimazole, rifampicin, nifedipine, spironolactone) within 1 month prior to study.

Sampling and Data collection

After taking an informed written consent from a preliminarily selected patient, his serum 25(OH)D was estimated. If it was <30 ng/ml (D3 deficiency) but >10 ng/ml[30], final selection was done and was randomly assigned as 'Study' (n=30) or 'Control' (n=30) patient (Figure-1). The baseline study variables (FVC, FEV_1, FEV_1/FVC ratio, PEFR, FEF 25-75, 6 MWD, SpO2 at rest, SpO2 after 6 MWT, dyspnea scaleand fatigue scale) of all subjects of both the groups were assessed.

Intervention

Then along with the standard pharmacological treatment of ACO (according to GOLD criteria), 'Study' patients received 80,000 IU (2 capsules) of vitamin D3 per week for first 13 weeks. Detail of the dose schedule for D3 supplementation for last 13weeks[37] are shown in Table I. Whereas, all 'Control' patients received two oral capsules of placebo weekly for consecutive 26 weeks. In addition, all the patients of both groups were advised to be exposed to sunlight (between 11 am and 2 pm) only for 20 minutes a day[40]. On the other hand, if serum 25(OH)D became <10 ng/ml (severely deficient)[30] of any patient on 13th week, then he was dropped out (Figure 1) from the study (for ethical purpose). After 26th week of follow up, all the spimetric measures as well as exercise tolerance measures were again assessed.

Preparation of vitamin D3 and placebo capsules

All capsules were prepared and supplied by Beximco Pharmaceuticals Limited, Bangladesh. Ingredients of vitamin D3 capsules were cholecalciferol (40,000 IU), microcrystalline cellulose (58.1 gm), butylatedhydroxy toluene (0.2 mg), magnesium stearate (3 mg), gelatin capsule shell (1 mg). Ingredients of placebo except for Cholecalciferol were same as vitamin D3.

Assessment of serum vitamin D3: Chemiluminescent microparticle immunoassay (CMIA) method (Abbot Laboratory, Ireland) was used for the assessment of serum 25(OH)D.

Assessment of study variables: For the assessment of lung function, spirometery[41] was performed with a portable digital spirometer (Pony FX, Italy). In addition, for the assessment of exercise tolerance variables, 6 minute walk test (6MWT) was done according to American Thoracic Society (ATS) guidelines (2002)[9] and dyspnea as well as fatigue score were measured by Modified Borg Scale.[42,43] In addition, peripheral capillary oxygen saturation (SpO2) was recorded by a portable pulse oximeter[44] (YK-88 LED, China).

Statistical Analysis

The results were expressed as mean±SD and the data were statistically analyzed by SPSS (Version 16), using independent sample 't' test (between two groups) as well as paired Student's 't' test (between paired groups before and after intervention). In the interpretation of results, ≤0.05 level of probability (p) was accepted as significant.

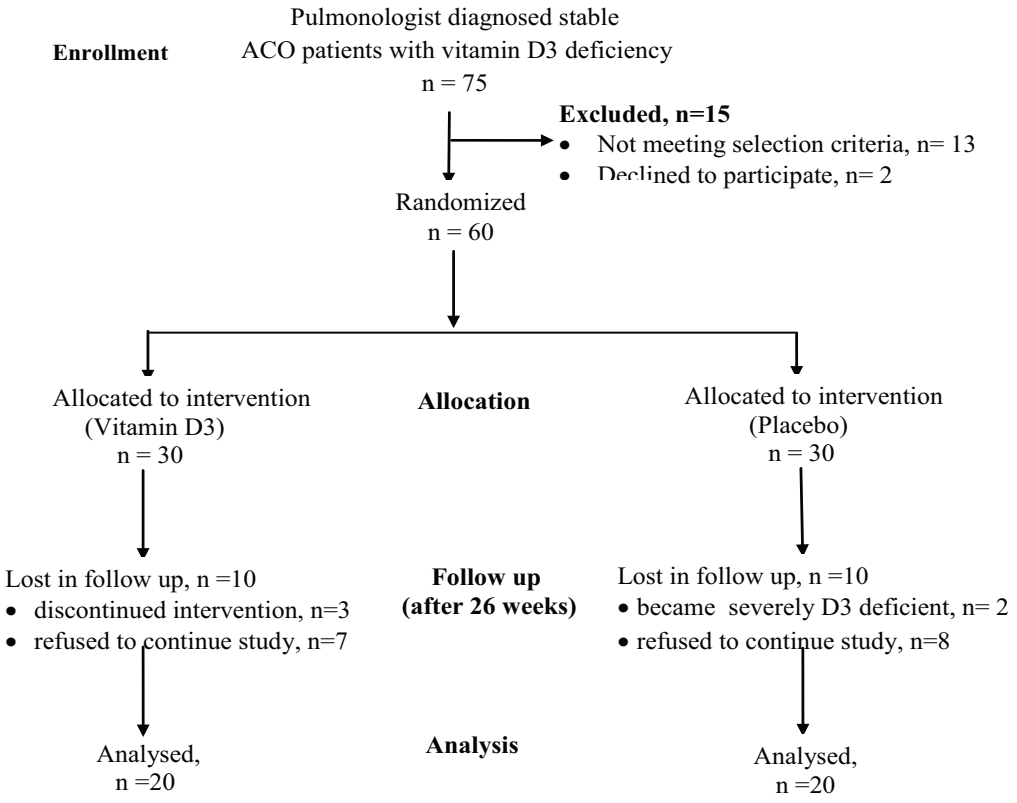

Figure 1: *CONSORT (Consolidated Standards of Reporting Trials) diagram; ACO: Asthma COPD Overlap*

Results

A total of 60 patients were initially randomized and 40 of them ultimately completed the study (20 in each group was dropped out). No significant difference was observed in the baseline characteristics between vitamin D3 supplemented and placebo group (Table 2). FVC, FEV1, FEV1/FVC ratio, PEFR and FEF25-75 were almost similar in the study and control groups at baseline (Table II). However, the mean values were increased in both study and control patients on 26th week of their follow up in comparison to their corresponding baseline values, though none of them were statistically significant (Figure 2). Moreover, the values were higher in vitamin D3 supplemented group than that of placebo, though their difference was not statistically significant (Figure 2).

Exercise tolerance variables: In the present study, the exercise tolerance variables were almost similar in study and control patients at baseline (Table II). However, a statistically significant improvement were noticed in 6MWD ($p<0.01$), SpO2 at rest as well as after 6MWT ($p<0.001$), dyspnea scale ($p<0.001$) and fatigue scale ($p<0.001$), in study patients after 26 weeks of vitamin D3 supplementation than those of corresponding baseline values (Figure 3). In addition, the mean of 6MWD ($p<0.05$), SpO2 after 6MWT ($p<0.01$), dyspnea score ($p<0.001$), fatigue score ($p<0.001$) was significantly higher in D3 supplemented patients than those of placebo treated patients on 26th week of follow up (Figure 3).

Table I: D_3 Supplementation schedule for D3 deficient ACO patients[30]

At 1st visit / at day 1:
Vitamin D3 80,000 IU (2 capsules of 40,000 IU) / wk, for consecutive 13 weeks

At 2nd visit / after 13 weeks:

If, *serum 25 (OH)D and/or serum Ca^{2+} =*	*Then,* *for next 13 weeks, dose schedule was -*	*So,* *for next 13 weeks, dose schedule was -*
30-40 ng/ml and/or 8.5-10.5 mg/dl	4600 IU/day	4600 IU X 7 = 32,200 IU / 7 days = 1 cap (40,000 IU) / wk
40-50 ng/ml and/or 8.5-10.5 mg/dl	3000 IU/day	3000 X 15 = 45,000 IU / 15 days = 1 cap (40,000 IU) / 2 wks
60-80 ng/ml and/or 8.5-10.5 mg/dl		1 cap (40,000 IU) / 6wks
> 80 ng/ml and/or 8.5-10.5 mg/dl	stop taking drug & symptom analysis	no dose for further 13 weeks
>150 ng/ml and/or >10.5 mg/dl	close monitoring and ask for – • feeling sick or being sick, • poor appetite or loss of appetite, • feeling very thirsty, • passing urine often, • constipation or diarrhea, • abdominal pain, • muscle weakness and pain, • bone pain • feeling confused,feeling tired.	no dose for further 13 weeks

At 3rd visit / after 26 weeks:
Patients were referred to pulmonologist and suggested to follow the above mentioned schedule

Table II : Baseline characteristics of ACO patients in both groups (n=60)

Characteristics	Vitamin D3 Supplemented pts (n=30)	Placebo treated pts (n=30)	p value
Age (years)	60.13±9.75 (41-78)	57.66±10.90 (40-72)	0.26
Duration of ACO (years)	3.63±0.80 (1-5)	3.53±0.81 (1-5)	0.69
Duration of smoking (pack years)	14.62±4.46 (10-25)	16.28±5.72 (10-30)	0.23
Body Mass Index (kg/m^2)	22.51±3.34 (19.59-24.9)	21.75±3.01 (18.56-24.9)	0.73
MUAC (cm)	26.73±2.88 (26-34)	26.93±3.43 (26-35)	0.53

Table II : *Cont'd*

Characteristics	Vitamin D3 Supplemented pts (n=30)	Placebo treated pts (n=30)	p value
Serum 25(OH)D (ng/ml)	19.20±4.44 (10.2-18.2)	19.58±3.79 (13.4-27.2)	0.34
Serum parathormone (pg/ml)	53.29±9.28 (31.3-64.8)	49.93±10.92 (18.1-64)	0
Serum calcium (mg/dl)	9.15±0.33 (8.56-10)	9.39±0.4 (8.5-9.95)	0.16
Inorganic Phosphate (mg/dl)	3.15±0.63 (2.33-4.35)	3.27±0.39 (2.3-4.12)	0.32
FBS (mmol/l)	5.09±0.79 (5.60-6.80)	5.14±0.77 (5.70-6.90)	0.74
Serum HbA1c (%)	6.14±0.44 (5.80-6.90)	6.12±0.49 (5.90-6.80)	0.54
Systolic blood pressure (mmHg)	117.33±6.19 (100-140)	118.67±8.67 (100-130)	0.56
Diastolic blood pressure (mmHg)	80.33±6.68 (70-80)	81.05±6.66 (70-80)	0.71
FVC (% of PV)	76.09±19.45 (50.39-115.36)	77.93±21.19 (47.76-118.76)	0.62
FEV1 (% of PV)	62.88±21.11 (26.62-87.98)	58.22±21.93 (24.18-85.19)	0.25
FEV1/FVC ratio (%)	86.80±17.93 (53.85-100.00)	83.02±16.97 (42.11-110.00)	0.43
PEFR (% of PV)	46.73±17.36 (18.08-93.94)	41.64±16.97 (14.81-83.84)	0.34
FEF 25-75(% of PV)	43.73±26.05 (12.58-97.59)	40.58±23.79 (6.82-97.51)	0.58
6 MWD (meter)	361.83 ±43.49 (270.00-435.00)	359.83±36.02 (300.00-420.00)	0.83
SpO2 (at rest) (%)	97.03±0.71 (96.00-98.00)	96.80±0.81 (96.00-98.00)	0.23
SpO2 (After 6MWT) (%)	95.80±0.67 (95.00-97.00)	95.46±0.57 (95.00-97.00)	0.07
Dyspnea scale (Borg score)	3.56±0.89 (1.00-5.00)	3.60±1.03 (1.00-5.00)	0.88
Fatigue scale (Borg score)	3.96±1.03 (1.00-5.00)	4.13±1.04 (1.00-6.00)	0.37

Data were expressed as mean±SD; values in perentheses indicate ranges;Statistical analysis was done by Independent sample t test;ns: non significant; n = number of subjects; Pack year: (number of cigarette smoked per day ÷ 20) X no. of year smoked; 25(OH)D: serum 25-hydroxycholecaciferol; FBS: fasting blood sugar; HbA1c: glycated hemoglobin;FVC: Forced vital capacity; PV: Predicted value;FEV1: Forced expiratory volume in 1st second; PEFR: Peak expiratory flow rate; FEF25-75: Forced expiratory flow in the middle half of FVC;6MWD: 6 minute walk distance; SpO2:Peripheral capillary oxygen saturation; MUAC: Mid upper arm circumference

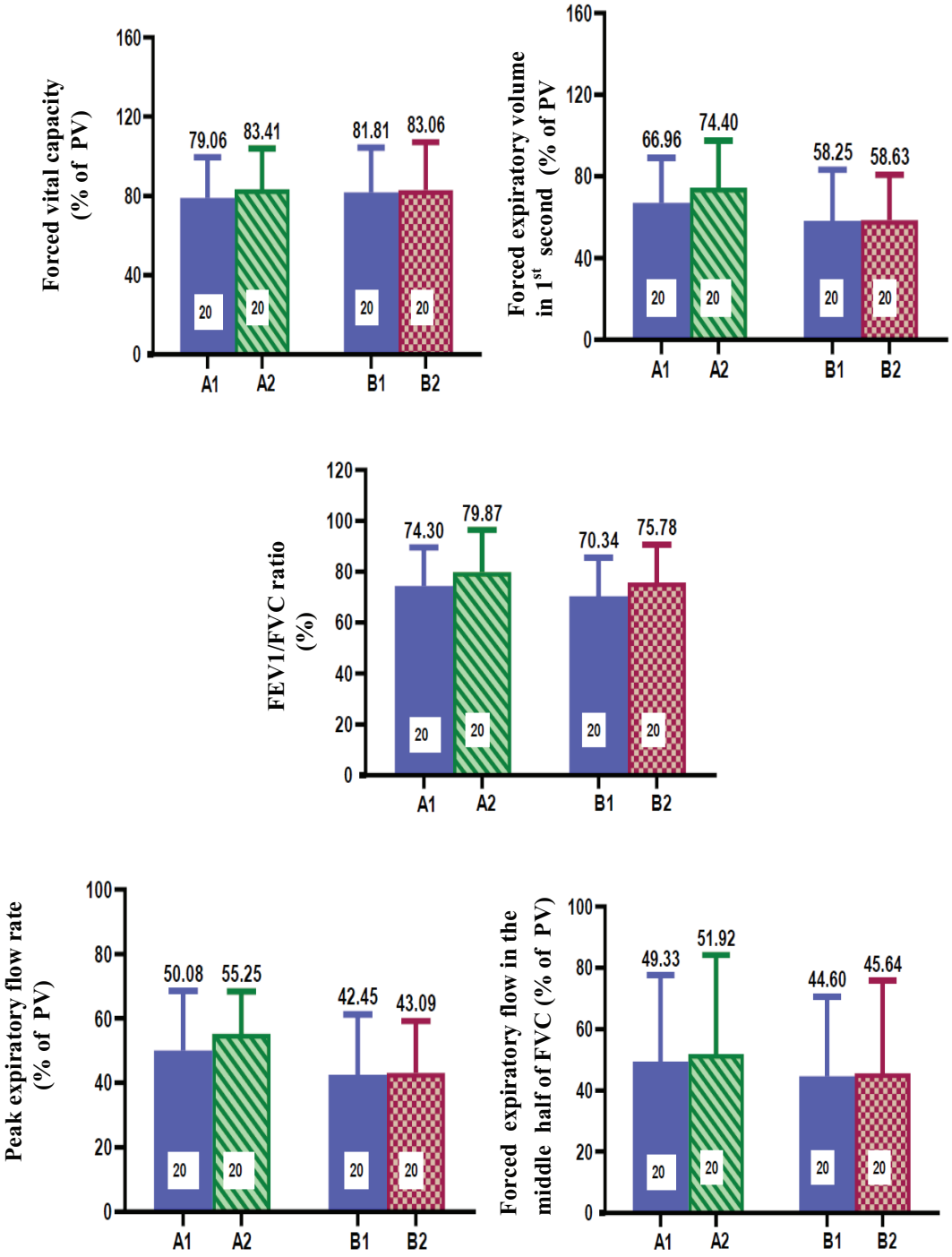

Figure 2: Ventilatory variables on pre and post intervention in both groups. Each bar symbolizes mean ±SD of 20 patients. A1: Patients with vitamin D3 on day 1; A2: Patients with vitamin D3 on 26th week; B1: Patients with placebo on day 1; B2: Patients with placebo on 26th week; PV: Predicted value

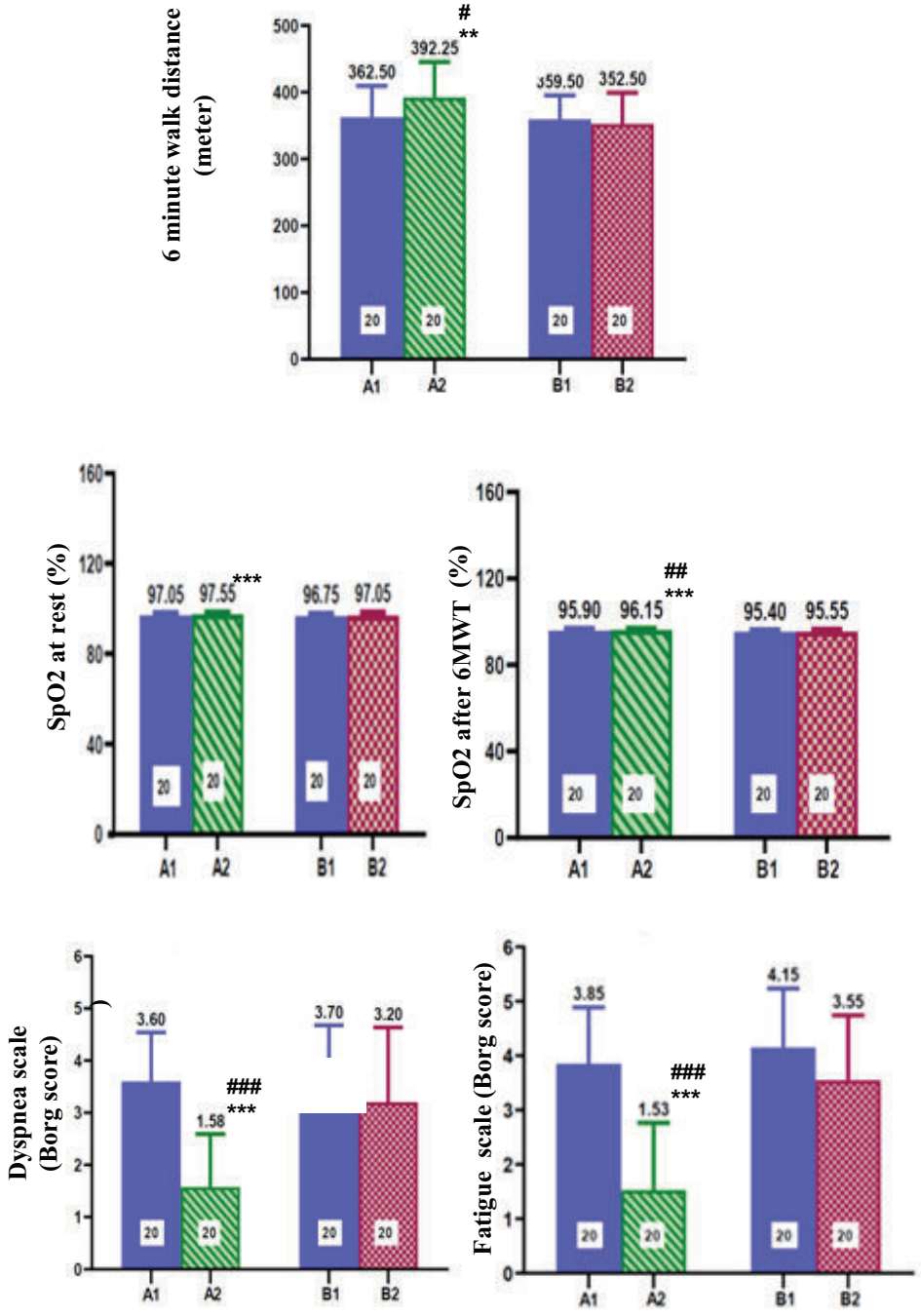

Figure 3: Exercise tolerance variables on pre and post intervention in both groups. Each bar symbolizes mean ±SD of 20 patients. A1: Patients with vitamin D3 on day 1; A2: Patients with vitamin D3 on 26th week; B1: Patients with placebo on day 1; B2: Patients with placebo on 26th week. ***: p<0.001 in A1 vs A2; ###: in A2 vs B2; **: p<0.01 in A1 vs A2; ##: p<0.01 in A2 vs B2; #: p<0.05 in A2 vs B2; 6MWT : 6 minute walk test; SpO2:Peripheral capillary oxygen saturation

Discussion

The present study has been carried out to observe the effects of vitamin D3 supplementation on lung functions and exercise tolerance in male stable ACO patients.

In the present study, D3 supplementation could not improve lung function variables in D3 deficient ACO patients. Similar results were reported in COPD patients as well as in asthma[45-49]after different dose schedules and duration of vitamin D3 supplementation. It is very well known that smoking causes inflammation and oxidative stress as well as increment of protease activity leading to lung tissue destruction[50]. This might be the cause of the severe decrement of lung function variables in our heavily smoker (Table 2) ACO patients. Though, vitamin D could minimize these processes by inhibiting matrix metalloprotease[51] as well as inhibiting fibroblast proliferation and collagen synthesis[52], but the present dose and duration schedule of D3 supplementation might not be able to reverse the lung tissue destruction our study patients and could not improve the lung function significantly.

On the contrary, the 6MWD was significantly improved in our ACO patients with vitamin D3 supplementation. Though no similar observation was available in D3 deficient ACO patients for comparison but, in COPD patients, similar type of significant improvement of this variable was reported by different researchers after different dose and duration schedules of D3[28,53,54]. Again, SpO2 both at rest and after 6MWT were significantly improved in the ACO patients with vitamin D3 supplementation. Similar results were observed in COPD patients, in a placebo controlled trial of 3 months duration with D3[27].

In addition, in our patients of study group, dyspnea scale and fatigue scale after 6MWT were also significantly improved which were supported by 3 month[27] as well as 6 month[28] trial on COPD patients with D3 supplementation. It is now recognized that vitamin D3 enhances intestinal absorption of Ca^{2+}, thus increasing serum Ca^{2+} level which could increase muscle strength[55]. In addition, vitamin D3 might bind with vitamin D receptor (VDR) protein present in skeletal muscle cells[56] which might lead to an increased Ca^{2+} uptake in skeletal muscle cells[57,58]. As a result, there might be increase in strength of skeletal muscle (both respiratory and peripheral) in our ACO patients. Moreover, it has also been suggested that vitamin D3 increases the serum PO_4^{3-} level by enhancing its intestinal absorption[59] which might increase in skeletal muscle function. Moreover, this vitamin might directly affect the intracellular accumulation of inorganic PO_4^{3-} in the respiratory and peripheral skeletal muscles to increase their ATP content[60]. These mechanism might improve all the exercise tolerance variables of our ACO patients with vitamin D3 supplementation.

Conclusion

The results of the present study concluded that, 26 weeks supplementation of vitamin D3 could improve exercise tolerance but not lung function in D3 deficient stable ACO patients. Further multicentered trials with different dose as well as duration schedule on both male and female ACO patients are recommended.

Registration of clinical trial: This Clinical Trial registration was done with Clinical trials.gov PRS system ID NCT03880734 where full protocol can be accessed.

Conflict of interest: None

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