

## Article

### Article information:

Received: 24th March, 2020  
Accepted: 25 April, 2020  
DOI: <https://doi.org/10.3329/jbsp.v15i1.48112>

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### Cite this article:

Anjum S, Ali T, Bennoor KS, Hossain MA, Islam MS, Mahmud MB<sup>1</sup>, Hassan S, Nahar SB, Rosy SK, Sultana N, Akter K. Vitamin D<sub>3</sub> supplementation on plasma antioxidant enzymes in D<sub>3</sub> deficient patients with COPD - a randomized controlled trial.  
J Bangladesh Soc Physiol 2020;15(1): 23-32

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## Vitamin D<sub>3</sub> supplementation on plasma antioxidant enzymes in D<sub>3</sub> deficient patients with COPD - a randomized controlled trial

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### Abstract

**Background:** Free radical is a crucial factor for progression of COPD. Antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT) have been well known to reduce morbidity of chronic disease. Vitamin D<sub>3</sub> has antioxidant effect in human body. **Objectives:** To assess the effects of D<sub>3</sub> supplementation on plasma SOD and CAT levels in D<sub>3</sub> deficient COPD patients. **Method:** A double blinded placebo controlled randomized clinical trial was carried out on 30 vitamin D<sub>3</sub> deficient male, smoker and stable COPD patients of age >40 years. All the patients were randomly allocated to 'Study' (n=15) or 'Control' (n=15) and their baseline plasma SOD and CAT were measured. Study patients received 80,000 IU (2 oral capsules) of D<sub>3</sub> per week for first 13 weeks. Subsequently, after checking their serum 25(OH)D or Ca<sup>2+</sup>, they received 40,000 IU (1 oral capsule) of D<sub>3</sub> either per 1 week or per 2 weeks or per 6 weeks or no further supplementation for next 13 weeks. All the 'Control' patients received two oral capsules of placebo weekly for consecutive 26 weeks. Additionally, all patients of both groups were also advised to have sunlight exposure (within 11 to 14 hrs) at least for 5 to 15 minutes daily. After 26 weeks of follow up, both enzymes, serum 25(OH)D or Ca<sup>2+</sup> of all patients were measured by spectrophotometry. Data were analyzed by

paired sample and independent sample 't' test. **Results:** The baseline plasma SOD(14.80±3.86U/ml vs 11.95±4.03U/ml) and CAT (11.0±7.59U/ml vs 14.41±4.83U/ml) in study and control was almost similar (p>0.05). However, the mean SOD (18.98±2.98U/ml) and CAT (32.75±9.70U/ml) significantly increased (p<0.01; p<0.001) after 26 weeks of follow up only in 'Study' patients. In addition, both enzymes were significantly (p<0.001) higher in the D<sub>3</sub> supplemented patients than those of placebo treated patients after 26 weeks of follow up.

**Conclusion:** The present study reveals that vitamin D<sub>3</sub> supplementation increases the plasma antioxidant enzymes in D<sub>3</sub> deficient patients with COPD.

**Trial registration:** www.clinicaltrials.gov identifier NCT04011930

**Keywords:** COPD, Vitamin D<sub>3</sub>, Superoxide dismutase (SOD), Catalase (CAT)

## Introduction

One of the major causes of chronic morbidity and mortality throughout the world is Chronic obstructive pulmonary Disease (COPD).<sup>1</sup> It is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases<sup>1</sup>.

This respiratory ailment is currently fourth leading cause of death in the world but it is projected to be third leading cause of death by 2020<sup>1</sup>. In Bangladesh, prevalence of COPD among people greater than 40 years is 21.6% and overall prevalence in general population is 4.32%.<sup>2</sup>

Lungs are continuously exposed to free radicals originated from air pollution or cigarette smoke and excess oxidants can cause destruction of the lung.<sup>3-4</sup> Therefore, body antioxidants from different sources protect our body from the damaging effect of these exogenous or endogenous free radicals.<sup>5</sup> Several antioxidant enzymes in our body provide the first line defense by neutralizing these free radicals. Among these antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) are important for respiratory organs.<sup>6</sup> Previous studies reported decreased SOD and CAT activity in COPD patients compared to healthy control.<sup>7-8</sup>

Vitamin D<sub>3</sub> deficiency is a recent rising problem in general population throughout the world.<sup>9</sup> In respiratory health, vitamin D<sub>3</sub> deficiency has been shown to increase the risk of active tuberculosis<sup>10</sup> and upper respiratory tract infections.<sup>11</sup> It is believed that patients with COPD are at greater risk of vitamin D<sub>3</sub> deficiency.<sup>12</sup> In addition, research evidence indicate positive correlation between serum vitamin D<sub>3</sub> and erythrocyte SOD and CAT activity.<sup>13</sup> Furthermore, vitamin D<sub>3</sub> supplementation increased both (SOD and CAT) in diabetic mice<sup>14</sup>, hemodialysis patient<sup>15</sup>, preeclamptic women<sup>16</sup> as well as in vitamin D<sub>3</sub> deficient patients with stable asthma-COPD overlap patients.<sup>17</sup>

Nevertheless, the volume of information regarding the role of vitamin D<sub>3</sub> supplementation (as an antioxidant) on plasma antioxidant enzymes status is very scarce for any conclusive remarks.

Therefore, this study was designed to observe the effect of vitamin D<sub>3</sub> supplementation on plasma SOD and CAT level in vitamin D<sub>3</sub> deficient stable COPD patients.

## Method

*Study design, setting, time:*

This randomized double blinded placebo controlled trial was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib

Medical University (BSMMU) and National Institute of the Diseases of Chest and Hospital (NIDCH), Dhaka from March, 2019 to February, 2020. This clinical trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), ID: NCT04011930 and approved by Institutional Review Board of BSMMU.

#### *Study population:*

For this purpose, 30 (thirty) male, smoker, stable<sup>1</sup> patients with COPD of age  $\geq 40$  years were enrolled by purposive sampling. Diagnosis was done by pulmonologists through clinical, physical and radiological signs of chronic airway disease, usually with spirometric evidence of chronic airflow limitation (post bronchodilator FEV1/FVC $<0.7$ )<sup>1</sup>, but its absence did not absolutely exclude COPD. Duration of COPD (1 to 5 years), duration of smoking ( $>10$  pack years)<sup>18</sup>, body mass index (18.5 to 24.9 kg/m<sup>2</sup>)<sup>19</sup>, serum total calcium (8.5 to 10.5 mg/dl)<sup>20</sup>, serum inorganic phosphate (2.3 to 4.7 mg/dl)<sup>20</sup> and serum parathormone (10 to 65 pg/ml)<sup>20</sup> were inclusion criteria. In addition, patients with uncontrolled diabetes mellitus (fasting blood sugar  $\geq 7$  mmol/l and/or HbA1c  $\geq 7\%$ )<sup>21</sup>, uncontrolled systemic hypertension (systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg, with anti-hypertensive medication)<sup>22</sup>, dyslipidemia (total cholesterol  $\geq 240$  mg/dl and/ or HDL $<40$  mg/dl and/or LDL  $\geq 160$  mg/dl and/or triglyceride  $\geq 200$  mg/dl and/or with use of any lipid lowering drug)<sup>23</sup>, renal insufficiency (serum creatinine  $>1.36$  mg/dl)<sup>24</sup> 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, were excluded.

#### *Randomization:*

The final selection of vitamin D<sub>3</sub> deficient ACO patients (after screening) were done by principal investigator. Then a code was provided to each

of them (to hide their identity) and with the help of a computer-generated random table, all were randomly allocated into vitamin D supplemented group (n=26) or placebo treated group(n=25) (Figure 1). Both the randomization and blinding were done by a third party, not member of the research team. Neither the principal investigator nor the patients were aware about the grouping. Before the data analysis, grouping of the patient was disclosed.

#### *Intervention:*

Study patients received 80,000 IU (2 oral capsules) of vitamin D<sub>3</sub> per week for first 13 weeks. Detail of the dose schedule for D<sub>3</sub> supplementation for last 13 weeks<sup>25</sup> are shown in Table I. In this study design, all the 'Control' patients received two oral capsules of placebo weekly for consecutive 26 weeks. Additionally, all the patients of both groups were also advised to have sunlight exposure (within 11 am to 2 pm)<sup>26</sup> only for 5 to 15 minutes daily.<sup>27</sup> During the follow up after 13 weeks, if serum 25(OH)D level was found  $<10$  ng/ml (severely deficiency)<sup>25</sup> in any patient, then he was discarded (Figure 1) from the study (for ethical purpose). Ingredients of vitamin D<sub>3</sub> 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). Placebo was identical in all aspect to that of vitamin D<sub>3</sub> and ingredients of placebo were same as vitamin D<sub>3</sub> except Cholecalciferol. Vitamin D<sub>3</sub> and placebo capsules were prepared and supplied by Beximco Pharmaceuticals Limited, Bangladesh. After explaining the dose schedule and possible side effects of drug(vitamin D<sub>3</sub> or placebo) the patient consumed the first dose, given by the investigator and then followed the subsequent doses as instructed throughout the intervention period. Patients were advised to continue the standard pharmacological treatment

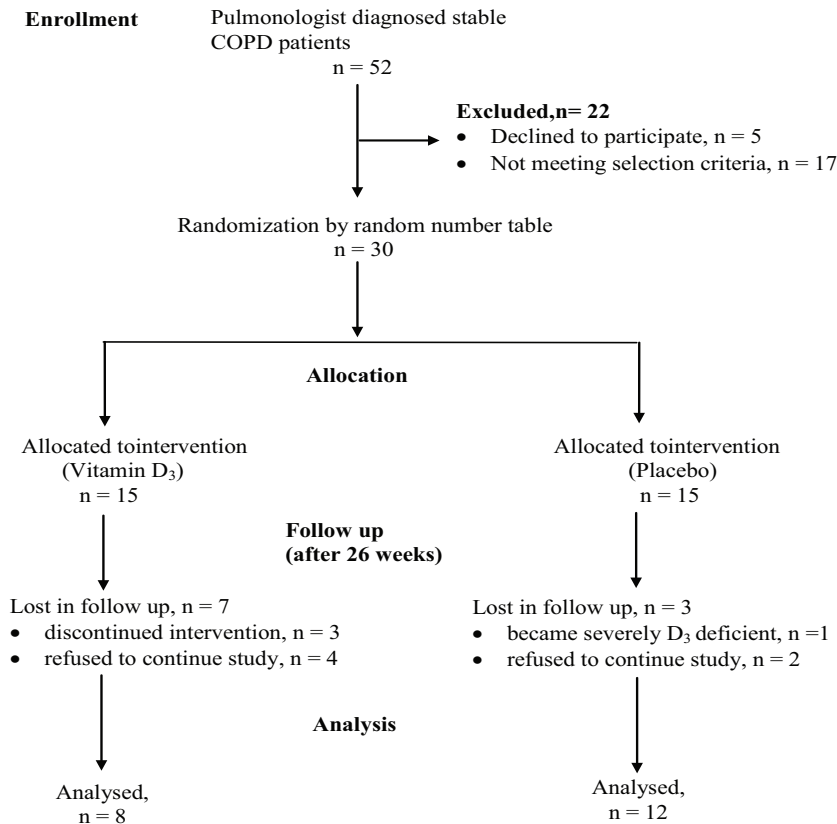
of COPD (according to GOLD criteria) throughout the intervention period.

#### Data collection.

An informed written consent was taken from each preliminarily selected patient and their serum 25(OH)D level was estimated. Patients with 25(OH)D level between 10-30 ng/ml was finally enrolled as vitamin D<sub>3</sub> deficient and. Before administration of vitamin D<sub>3</sub> or placebo the baseline plasma level of SOD and CAT of all patients were measured and at the end of 26 weeks follow up, both the enzyme levels and vitamin D<sub>3</sub> level of both groups were again measured.

Serum 25(OH)D was assessed by Chemiluminescent microparticle immunoassay (CMIA) method (Abbot Laboratory, Ireland). Plasma SOD and CAT enzyme levels were assessed by colorimetric method using SOD assay kit (Elabsience, USA) and CAT assay kit (Elabsience, USA).

**Statistical Analysis.** The data were expressed as mean±SD and the data were analyzed by SPSS (Version 20), and for statistical analysis, Shapiro-Wilk test, independent sample 't' test as well as paired sample 't' test were used as applicable. In the interpretation of results,  $p \leq 0.05$  was accepted as significant.



**Figure 1:** CONSORT (Consolidated Standards of Reporting Trials) diagram; COPD: Chronic obstructive pulmonary disease

## Results

A total of 30 patients were initially randomized and 20 of them ultimately completed the study (7 patients from study group and 3 patients from control groups were dropped out) (Figure 1).

Both the groups (with vitamin D<sub>3</sub> and placebo) at their baseline status were comparable, as there were no significant differences of the confounding variables (age, duration of COPD, duration of smoking, BMI, socioeconomic status, fasting

blood sugar, lung function Serum 25(OH)D, parathormone, total calcium, inorganic phosphate serum glycated hemoglobin, systolic and diastolic blood pressure) between them (Table II).

There was no significant difference in the baseline characteristics including antioxidant enzymes (SOD and CAT) between study and control groups (Figure 2). However, the mean plasma SOD ( $p \leq 0.01$ ) as well as CAT ( $p \leq 0.001$ ) significantly increased after 26 weeks of follow

**Table I:** D<sub>3</sub> supplementation schedule for D<sub>3</sub> deficient COPD patients<sup>25</sup>

### At 1<sup>st</sup> visit / at day 1:

Vitamin D<sub>3</sub> 80,000 IU (2 capsules of 40,000 IU) / week, for consecutive 13 weeks

### At 2<sup>nd</sup> visit / after 13 weeks:

If, Serum 25(OH)D and/or serum Ca <sup>2+</sup> =	Then, for next 13 weeks, dose 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) / week
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 weeks
50-80 ng/ml and/or 8.5-10.5 mg/dl		1 cap (40,000 IU) / 6 weeks
> 80 ng/ml and/or 8.5-10.5 mg/dl	stop taking drug and symptom analysis	no dose for further 13 weeks
>150 ng/ml and/or >10.5 mg/dl	close monitoring and ask for – <ul style="list-style-type: none"> <li>• feeling sick or being sick</li> <li>• poor appetite or loss of appetite</li> <li>• feeling very thirsty</li> <li>• passing urine often</li> <li>• constipation or diarrhea</li> <li>• abdominal pain</li> <li>• muscle weakness</li> <li>• pain</li> <li>• bone pain</li> <li>• feeling confused</li> <li>• feeling tired</li> </ul>	no dose for further 13 weeks

### At 3<sup>rd</sup> visit / after 26 weeks:

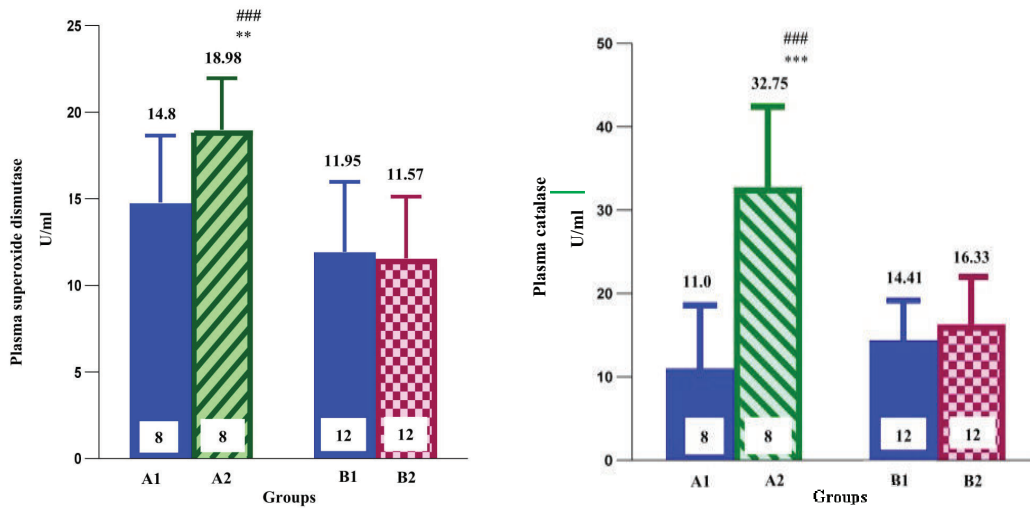
Patients were referred to pulmonologist and suggested to follow the above mentioned schedule

**Table II:** Baseline characteristics of COPD patient in both groups (N=30)

Characteristics	Study (n=15)	Control (n=15)	p value
Age (years)	61.73±8.31 (43-78)	58.13±7.97 (45-70)	0.23
Duration of COPD (years)	3.46±1.30 (1-5)	3.40±1.35 (1-5)	0.89
Duration of smoking (pack years)	15.54±4.66 (10-25)	16.70±5.50 (10-25)	0.53
Socioeconomic status (score)	2.00±0.00	2.00±0.00	1
Body mass index (kg/m <sup>2</sup> )	20.64±2.15 (17.84-24.90)	20.95±2.72 (16.90-24.90)	0.73
FEV1/FVC ratio (%)	55.60±9.85 (43-65)	55.33±8.78 (42-69)	0.93
FEV1 (% of predicted value)	44.07±14.97 (20.10-76.40)	48.35±16.37 (17.60-74.90)	0.46
Serum 25(OH)D (ng/ml)	19.44±4.05 (15-28)	20.08±4.94 (15-28.90)	0.93
Serum parathormone (pg/ml)	53.72±9.42 (31.30-64.80)	46.76±14.07 (18.10-65)	0.12
Serum total calcium (mg/dl)	9.26±0.21 (8.90-9.56)	9.35±0.34 (8.90-9.95)	0.37
Serum inorganic phosphate (mg/dl)	3.18±0.44 (2.39-3.90)	3.37±0.58 (2.25-4.30)	0.31
FBS (mmol/l)	5.63±1.08 (3.90-6.90)	5.52±0.85 (4-6.90)	0.75
Serum HbA1c (%)	6.56±0.50 (5.70-6.50)	6.40±0.39 (5.60-6.90)	0.34
Systolic blood pressure (mm Hg)	118.67±10.60 (100-140)	116.67±8.16 (100-130)	0.56
Diastolic blood pressure (mm Hg)	76.00±5.07 (70-80)	76.66±4.87 (70-80)	0.71

Data were expressed as mean±SD; Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t test; COPD: Chronic obstructive pulmonary disease; N: number of patients in both groups; A1: COPD patients with vitamin D<sub>3</sub> supplementation on day 1; B1: COPD patients with placebo supplementation on day 1; n: number of patients in each group; ns: non significant; Pack year: (number of cigarette smoked per day ÷ 20) X no. of year smoked; FEV1: forced expiratory volume in first second; FVC: forced vital capacity; 25(OH)D: serum 25-hydroxycholecalciferol; FBS: fasting blood sugar; HbA1c: glycated hemoglobin.





**Figure 2:** Antioxidant enzyme levels on pre and post intervention in both groups; Each bar symbolizes mean±SD of stable COPD patients; Study1: Patients with vitamin D<sub>3</sub> on day 1; Study2: Patients with vitamin D<sub>3</sub> after 26<sup>th</sup> week; Control1: Patients with placebo on day 1; Control2: Patients with placebo after 26<sup>th</sup> week; \*\*\*: p<0.001 in A1 vs A2; ###: p<0.001 in A2 vs B2; \*\*: p<0.01 in A1 vs A2.

up in comparison to their corresponding baseline level only in ‘Study’ patients. In addition, both of these enzymes were significantly ( $p \leq 0.001$ ) higher in the vitamin D<sub>3</sub> supplemented study patients than those of placebo treated control patients after 26 weeks of follow up (Figure 2).

### Discussion

The present study has been undertaken to observe the effects of vitamin D<sub>3</sub> supplementation on plasma antioxidant enzymes in vitamin D<sub>3</sub> deficient stable patients with COPD.

In this study, both the plasma SOD and CAT levels in the D<sub>3</sub> deficient stable male patients with COPD, at their baseline status, were almost similar to those reported by others<sup>13,15</sup>.

In this study, plasma SOD and CAT significantly increased in D<sub>3</sub> deficient patients with COPD after 26 weeks of vitamin D<sub>3</sub> administration in comparison to their baseline status. Similar observation in SOD and CAT level were found in erythrocytes of patients with atopic dermatitis after 60 days of vitamin D<sub>3</sub> supplementation<sup>13</sup>.

Moreover these antioxidant enzymes were found to be increased in serum after 8 weeks<sup>16</sup> as well as in plasma after 26 weeks<sup>17</sup> of vitamin D<sub>3</sub> supplementation in patients with preeclampsia and asthma-COPD overlap patients, respectively.

In addition, in the current study, after 26 weeks of follow up, SOD and CAT were significantly higher in plasma of our COPD patients with vitamin D<sub>3</sub> supplementation in comparison to that of patients with placebo. Similar observation was found in erythrocytes of atopic dermatitis patients on 60<sup>th</sup> day<sup>21</sup> in liver tissue of diabetic rats on 28<sup>th</sup> day<sup>28</sup>, in serum of preeclamptic pregnant women after 8 weeks<sup>16</sup> and in plasma of vitamin D<sub>3</sub> deficient asthma-COPD overlap patients on 26<sup>th</sup> week<sup>17</sup> after different dose schedule of vitamin D<sub>3</sub> supplementation.

Moreover, SOD was higher in plasma of neonates with hypoxic-ischemic encephalopathy on 5<sup>th</sup> day<sup>29</sup> in cardiac tissue of obese rat on 5<sup>th</sup> week<sup>30</sup> of vitamin D<sub>3</sub> supplementation.

In addition, CAT was also found higher in hippocampus of vitamin D<sub>3</sub> supplemented rats with multiple sclerosis on 21<sup>st</sup> day of follow up<sup>31</sup>.

From the present study, the exact cause of increment of SOD and CAT after vitamin D<sub>3</sub> supplementation in COPD patients is uncertain. However, being a steroid<sup>32</sup>through its genomic effect, vitamin D<sub>3</sub> might induce the mRNA gene expression of the antioxidant enzymes, SOD and CAT<sup>33-34</sup>through Sirtuin1 (SIRT1) expression<sup>35</sup>.

### Conclusion

The outcome of this trial reveals that vitamin D<sub>3</sub> supplementation increases the antioxidant enzymes in D<sub>3</sub> deficient COPD patients.

### Limitation

In this trial both of diabetes mellitus and hypertension were included which would cause oxidative stress, we intended to exclude the COPD patients with these two co-morbidities. But it could not be possible, due to patients unavailability and time constraint.

Therefore, similar study is recommended in nondiabetic as well as normotensive male COPD patients. In addition, other antioxidant enzymes should be assessed with different dose and follow up schedule of this fat soluble vitamin supplementation in D<sub>3</sub> deficient COPD patients to ascertain our findings.

**Conflict of interest** None

### Acknowledgement

This study was supported by an unrestricted educational grant from BeximcoPharmaceuticals Ltd. Bangladesh.

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