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Vitamin D_3 – does it correlate with exercise tolerance in stable COPD?

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Abstract

Background: Though the classic function of vitamin D_3 in skeletal health is established, but its new role has been discovered in tissues and organs other than bones. Vitamin D_3 deficiency has been found in patients with various morbid conditions, such as cardiovascular diseases, autoimmune diseases, infectious diseases, Diabetes mellitus and malignancies including respiratory ailments. **Objectives**: This cross sectional study was designed to evaluate the status of this fat soluble vitamin D_3 and its correlation with exercise tolerance in stable COPD patients. **Methods:** For this purpose, 47 male, smoker (>4 pack years), stable (who has not experienced any acute exacerbation, hospitalizations, urgent care visits, or changes in routine medications within 4 weeks prior to study), COPD patients (post bronchodilator $FEV_1/FVC<0.70$; duration >4 years) of >40 years of age, were selected from the Out Patient Department of National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka. For the assessment of vitamin D_3 status, their serum 25-hydroxy-cholecalciferol [25(OH)D], for exercise tolerance, 6 min walk distance [6MWD; by 6 min walk test], peripheral capillary oxygen saturation (SpO_2) [by pulse oximetry], level of dyspnea and fatigue [by Modified BORG scale], were measured. The data were expressed as percentage and mean ±SEM and were statistically analyzed by Pearson's correlation coefficient test, where $p<0.05$ was accepted as significant. **Results:** Out of 47 stable COPD patients, 46 (97.8%) were with serum 25(OH) D < 30 ng/ml. In addition, 6MWD was positively ($p\leq0.05$) and dyspnea ($p\leq0.001$) along with fatigue ($p\leq0.05$) score were negatively correlated with serum 25(OH)D level in these stable COPD patients. **Conclusion:** This study result concluded that, majority patients with stable COPD had D_3 deficiency and this D_3 deficiency showed significant correlation with decrement of exercise tolerance.

Keywords: COPD, Vitamin D_3, SpO_2, 6 Minute Walk Distance, Dyspnea, Fatigue, Modified BORG scale

Introduction

Vitamin D_3 is a seco steroid that promotes calcium absorption in the gut and maintains adequate calcium and phosphate concentrations in serum to enable normal mineralization of bone. Synthesis of this fat soluble vitamin is triggered endogenously when Ultraviolet B (UVB) radiation from sunlight strikes the skin. Sunlight exposure for only 20 minutes daily (within 10 am to 4 pm) on face and palm is enough for this vitamin synthesis[1].

However, several reviews have found high prevalence of vitamin D_3 deficiency (ranging from 6 to 36%) in apparently healthy population, even in countries with low latitude, where it was generally assumed that UVB radiation was adequate enough to prevent vitamin D_3 deficiency[2-4].The reasons behind this increased prevalence of D_3 deûciency might be scarce exposure to sunlight in proper time for adequate duration, indoor lifestyle and use of extensive sunscreen and decreased intake of D containing foods[5].

Deficiency of this sunshine vitamin is also common in patients with multiple chronic diseases, such as cancer, autoimmune diseases, cardiovascular disorders and respiratory ailments due to their morbidity and indoor life style pattern[6-9]. It has also been suggested that, patients with airflow limitation, especially chronic obstructive pulmonary disease (COPD) have a high prevalence of vitamin D deficiency, ranging from approximately 30% in mild COPD to over 75% in severe COPD[10-13]. Recently, Heideri et al. (2015) reported that a significant proportion of young COPD patients may have insufficient (20 to 29 ng/ml) serum 25(OH)D[14].

Along with progressive expiratory airflow limitation, these morbid patients of COPD also present with impaired exercise capacity which may be related to reduction in muscle strength[15]. Basically, exercise intolerance is a clinical hall mark of COPD patients associated with reduced quality of life. It is a complex clinical syndrome represented with reduced oxygen consumption during any physiological stimulation[16-18.] To assess this exercise intolerance, the 6 minute walk test (6MWT) is an easily administered, better tolerated and more reflective of activities of daily living walk tests[19]. This self paced test measures the distance in a period of 6 minutes (6 minute walk distance, 6MWD) to assess the sub-maximal level of functional capacity. In addition, oxygen saturation, dyspnea and fatigue measurement before and after the 6MWT, are indicators of percentage of hemoglobin saturated with oxygen, weakness of inspiratory muscles in voluntary hyperventilation, increased respiratory work load and impaired function of the inspiratory muscles[20].

Though the vitamin D_3 deficiency is common in different chronic diseases, but at present the volume of information regarding it, in COPD patients, is not enough for reaching any final conclusion.

Our aim was to evaluate the status of vitamin D_3 and exercise tolerance as well as their relationship in stable COPD patients with D_3 deficiency.

Methods

This cross sectional study was carried out in Department of Physiology of Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2017 to Feb 2018. For this, 47 stable (pulmonologist diagnosed patient, who did not have any acute exacerbation, hospitalization, urgent care visits or changes in routine medication within 4 weeks prior to study), male patients, with COPD (post bronchodilator FEV_1/ FVC<0.70 and FEV_1 <80% of predicted value) were selected from the Out Patient Department of National Institute of the Disease of Chest and Hospital, Dhaka[21-23]. The inclusion criteria were age (40 to 70 years)[23], duration of COPD (>1 year)[23], smoking status (active/passive smoker of cigarette/ birri/ hukkah/ pipe/ white leaves/ khoini/ multiple; ex smoker with H/O 0 to 8 quit

years; duration>4 pack years)[11], BMI (18.6 to 31 kg/m^2)[24]. In addition, any patient with H/O heart diseases, uncontrolled hypertension (systolic d" 140 mm of Hg and diastolice"90 mm of Hg)[25], liver diseases, endocrine disorders, malignancy, renal insufficiency (serum creatinine >1.36 mg/dl)[26], use of any drug known to affect vitamin D metabolism within 1 month prior to study, were excluded from our study. This study protocol was approved by Institutional Review Board of BSMMU. After the selection, the aim, benefit and procedure of study was explained to all patients and an informed written consent from each patient was obtained. Then a detailed family history along with medical history was taken and a thorough physical examination was done. All the information was recorded in a standard data sheet. In addition, their vitamin D_3 status [by serum 25-hydroxycholecalciferol] and exercise tolerance [by 6 minute walk distance (6MWD), peripheral capillary oxygen saturation (SpO_2) (by AccuMed^R CMS-50DL pulse oximeter), dyspnea with fatigue level (by Modified Borg Scale)], were measured. The data was expressed as frequency percentage and mean ± SEM. For statistical analysis, Pearson's correlation coefficient test was done by Graph Pad prism (Version 7). In the interpretation of results, ≤0.05 level of probability (p) was accepted as significant.

Results

The general characteristics of our patients are shown in Table I. In addition, the status of vitamin D_3 and exercise tolerance variables (6MWD, SpO_2, dyspnea score and fatigue score) of these patients are shown in Table II. Out of our 47 stable COPD patients, 46 (97.8%) [as assessed by serum 25(OH) D] were D_3 deficient (<30 ng/ml) (Figure 1).

Along with these, 6MWD showed significant positive (r=0.3175; p≤0.05) correlation and dyspnea (r=-0.6739; p≤0.001) and fatigue (r=-0.3697; p≤0.05) score showed significant negative correlation with serum 25(OH) D in the D_3 deficient patients. However, SpO_2 showed no correlation with serum 25(OH)D (Figure 2).

Table I: General characteristics of the COPD patients (n=47)

Variables	Mean ± SEM
Age (in years)	60.2±1.35 (40-81)
Duration of COPD (in years)	3.55±1.18 (2-5)
Duration of smoking (in pack years)	15.79±0.84 (4-30)
BMI (kg/m^2)	22.11±0.60 (16.15-26.07)

Values in parenthesis indicate ranges. Pack year=[number of cigarettes smoked per day/20] X number of years smoked; BMI=Body mass index. COPD=Chronic obstructed pulmonary disease

Table II: Study variables of the COPD patients (n=46)

Variables	Mean ± SEM
25(OH D (in ng/ml)	20.39±0.66 (14.50-29.80)
6MWD (in meter)	362.05±7.92 (310-420)
SpO_2 (in %)	96.09±0.16 (95-98)
Dyspnea (in score)	3.61±0.12 (2-4)
Fatigue (in score)	4.43±0.12 (3-5)

Values in parenthesis indicate ranges. Pack year=[number of cigarettes smoked per day/20] X number of years smoked; BMI=Body mass index. COPD=Chronic obstructed pulmonary disease.

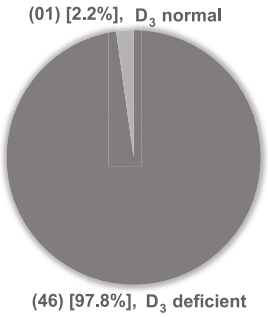

Figure 1: Frequency of D3 deficiency in stable COPD patients (n=47); Cut off value for D3 deficiency, serum 25(OH)D<30 ng/ml28.

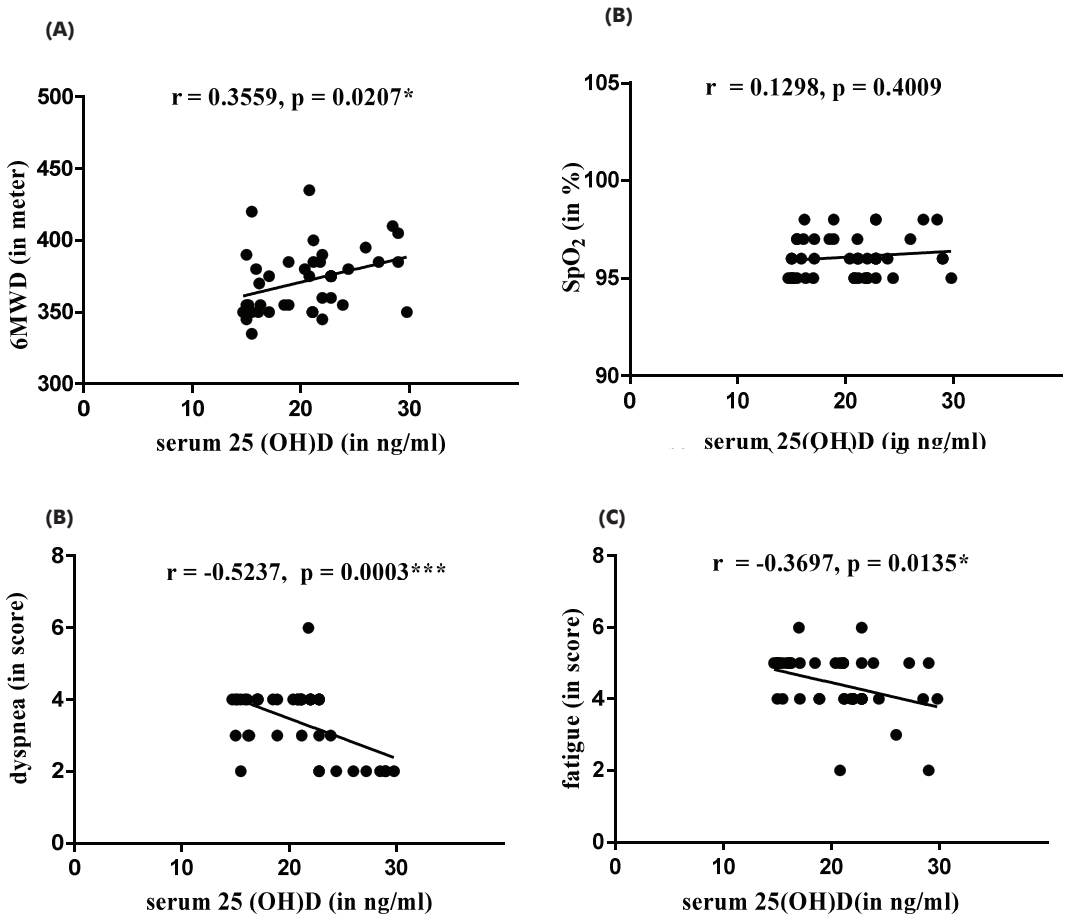

Figure 2: Correlation of 6MWD (A), SpO2 (B), dyspnea (C) and fatigue (D) with serum 25(OH)D in stable COPD patients. Statistical analysis was done by Pearson's correlation coefficient test. 6MWD=6 minute walk distance; 25(OH)D=25-hydroxycholecalciferol; SpO_2=Peripheral capillary oxygen saturation; * = significant ($p<0.05$); ***= significant ($p<0.001$)

Discussion

In the present study almost all the stable COPD patients were vitamin D_3 deficient as their serum 25(OH)D was below normal value[27]. This finding was supported by other investigators abroad[28-29]. It is very well known that initial step of vitamin D_3 synthesis in human is occurred in skin by conversion of provitamin D (7-dehydro-cholesterol) to previtamin D by exposure to Ultraviolet B (UVB) radiation[1]. As our elderly patients were with history of a long-standing heavy smoking, so their skin aging[30] as well as toxic effect of regular heavy smoke[11] might be attributed to their lower serum vitamin D_3 level. In addition, it has been suggested that, for proper UVB radiation the skin has to be exposed to sunlight of 10 am to 4 pm[1]. As our study subjects were with long-standing duration of COPD, so indoor staying at that specific day time due to chronic morbidity might be responsible for less exposure to sunlight and ultimately low serum vitamin D_3.

Moreover, the D_3 deficiency of our study patients was significantly correlated with different

variables of their exercise tolerance (6MWD, dyspnea score, fatigue score). These observations also agreed to other investigators[31-33]. It has been suggested that vitamin D_3 increases the serum Ca^{2+} level by increasing its intestinal absorption[34] which might contribute to muscle strength for exercise. Moreover, it has also been proposed that vitamin D receptor (VDR) protein might present in skeletal muscle cells[35-36], those specifically binds to 1,25 dihydroxycholecalciferol to activate several second messengers pathways. These phenomena might result in enhanced Ca^{2+} uptake in skeletal muscle cells both through voltage gated Ca^{2+} channels[37-38] and calcium release-activated calcium channels[39]. As a consequence, there might be increment in skeletal muscle contractile strength (both respiratory and peripheral). Furthermore, it has also been proposed that deficiency of 1, 25 $(OH)_2D$ decreases the serum PO_4^{3-} level by decreasing its intestinal absorption[33], which might cause decrement of skeletal muscle function. Moreover, 25(OH) D might directly influence the intracellular accumulation of inorganic PO_4^{3-} in the skeletal muscles to enhance their ATP content[40]. As our study patients were with vitamin D_3 deficiency, so the contractile strength of their respiratory and peripheral skeletal muscle might be reduced and ultimately showed significant correlation with different variables of exercise tolerance (positive with 6MWD and negative with dyspnea and fatigue).

Conclusion

Present study reveals that, vitamin D_3 deficiency in COPD patients showed significant correlation with decrement of exercise tolerance. Though in this study the sample size was very small and it could not be compared with any healthy control group, still this data may appraise the pulmonologists to give attention to vitamin D_3 status with exercise tolerance in stable COPD patients. Further trial with D_3 supplementation in this group of morbid patients is needed to elucidate its exact role.

Conflict of interest None

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