Vitamin D₃ – does it correlate with exercise tolerance in stable COPD?

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Abstract

Background: Though the classic function of vitamin D₃ in skeletal health is established, its new role has been discovered in tissues and organs other than bones. Vitamin D₃ 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 D₃ 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 FEV₁/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 D₃ status, their serum 25-hydroxycholecalciferol [25(OH)D], for exercise tolerance, 6 min walk distance [6MWD; by 6 min walk test], peripheral capillary oxygen saturation (SpO₂) [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≤0.05) and dyspnea (p≤0.001) along with fatigue (p≤0.05) 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 D₃ deficiency and this D₃ deficiency showed significant correlation with decrement of exercise tolerance.

Keywords: COPD, Vitamin D₃, SpO₂, 6 Minute Walk Distance, Dyspnea, Fatigue, Modified BORG scale
Vitamin D₃ – correlation with exercise tolerance in COPD

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Introduction

Vitamin D₃ 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. However, several reviews have found high prevalence of vitamin D₃ 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 D₃ deficiency. The reasons behind this increased prevalence of D₃ deficiency 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.

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. 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. 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.

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. Basically, exercise intolerance is a clinical hallmark of COPD patients associated with reduced quality of life. It is a complex clinical syndrome represented with reduced oxygen consumption during any physiological stimulation. 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. 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.

Though the vitamin D₃ 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 D₃ and exercise tolerance as well as their relationship in stable COPD patients with D₃ 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 FEV₁/FVC<0.70 and FEV₁<80% of predicted value) were selected from the Out Patient Department of National Institute of the Disease of Chest and Hospital, Dhaka. The inclusion criteria were age (40 to 70 years), duration of COPD (>1 year), 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)\(^\text{11}\), BMI (18.6 to 31 kg/m\(^2\))\(^\text{24}\). In addition, any patient with H/O heart diseases, uncontrolled hypertension (systolic d” 140 mm of Hg and diastolice”90 mm of Hg)\(^\text{25}\), liver diseases, endocrine disorders, malignancy, renal insufficiency (serum creatinine >1.36 mg/dl)\(^\text{26}\), 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\(^\text{R}\) 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.
Discussion
In the present study, almost all the stable COPD patients were vitamin D₃ deficient as their serum 25(OH)D was below normal value. This finding was supported by other investigators abroad. It is very well known that initial step of vitamin D₃ synthesis in human is occurred in skin by conversion of provitamin D (7-dehydrocholesterol) to previtamin D by exposure to Ultraviolet B (UVB) radiation. As our elderly patients were with history of a long-standing heavy smoking, so their skin aging as well as toxic effect of regular heavy smoke might be attributed to their lower serum vitamin D₃ 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. 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 D₃.

Moreover, the D₃ deficiency of our study patients was significantly correlated with different exercise tolerance in COPD.

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; SpO₂ = Peripheral capillary oxygen saturation; * = significant (p<0.05); *** = significant (p<0.001)
variables of their exercise tolerance (6MWD, dyspnea score, fatigue score). These observations also agreed to other investigators\textsuperscript{31-33}. It has been suggested that vitamin D\textsubscript{3} increases the serum Ca\textsuperscript{2+} level by increasing its intestinal absorption\textsuperscript{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\textsuperscript{35-36}, those specifically binds to 1,25 dihydroxycholecalciferol to activate several second messengers pathways. These phenomena might result in enhanced Ca\textsuperscript{2+} uptake in skeletal muscle cells both through voltage gated Ca\textsuperscript{2+} channels\textsuperscript{37-38} and calcium release-activated calcium channels\textsuperscript{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)\textsubscript{2}D decreases the serum PO\textsubscript{4}\textsuperscript{3-} level by decreasing its intestinal absorption\textsuperscript{33}, which might cause decrement of skeletal muscle function. Moreover, 25(OH) D might directly influence the intracellular accumulation of inorganic PO\textsubscript{4}\textsuperscript{3-} in the skeletal muscles to enhance their ATP content\textsuperscript{40}. As our study patients were with vitamin D\textsubscript{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\textsubscript{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\textsubscript{3} status with exercise tolerance in stable COPD patients. Further trial with D\textsubscript{3} supplementation in this group of morbid patients is needed to elucidate its exact role.

**Conflict of interest** None

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**References**

1. Harinarayan CV, Holick MF, Prasad UV, Vani PS, Himabindu G. Vitamin D status and sun exposure in India. Dermatoendocrinol 2013;5(1):130-41. doi: 10.4161/derm.23873

2. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J, IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int November 2009;20(11):1807-20.

3. Wahl DA, Cooper C, Ebeling PR, Eggersdorfer M, Hilger J, Hoffmann K, Josse R, Kanis JA, Mithal A, Pierroz DD, Stenmark J, Stöcklin E, Dawson-Hughes B. A global representation of vitamin D status in healthy populations. Arch Osteoporos 2012;7(1-2):155-72.

4. Schoor NV, Lips P. Worldwide Vitamin D Status. In: Fedman D, Pike JW, Bonillon R, Giovannucci E, Goltzman D, Hewison M, editors. Vitamin D: Volume 2: Health, Disease and Therapeutics. 4th ed. London: Elsevier Inc;2018.15-40p.

5. Reilly JJ, Silverman EK, Shapiro SD. Chronic obstructive pulmonary disease. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison’s principles of internal medicine. 16th edition. McGraw–Hill Professional;2004.1547-60p.

6. Holick MF. Vitamin D Deficiency. N Engl J Med 2007;357(3): 266-81.

7. Lappe JM, Gustafson DT, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85(6):1586–91. doi.org/10.1093/ajcn/85.6.1586.

8. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87(4):1080S–6S.
9. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappe DL, Muhlestein JB, Intermountain Heart Collaborative (IHC) Study Group. Relation of Vitamin D Deficiency to Cardiovascular Risk Factors, Disease Status, and Incident Events in a General Healthcare Population. Author links open overlay panel. Am J Cardiol 2010;106(7):963-8.

10. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest 2005;128(6):3792-8.

11. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buyssschaert I, Coolen J, Mathieu C, Decramer M, Lambrechts S. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax 2010;65(3):215-20.

12. Ferrari M, Schenk K, Papadopoulou C, Ferrari P, Dalle Carbonare L, Bertoldo F. Serum 25-hydroxyvitamin D and exercise capacity in COPD. Thorax 2011;66(6):544-5.

13. Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE. Vitamin D status and longitudinal lung function decline in the Lung Health Study. Eur Respir J 2011;37(2):238-43.

14. Heidari B, Javadian Y, Monadi M, Dankob Y, Firouzjahi A. Vitamin D status and distribution in patients with chronic obstructive pulmonary disease versus healthy controls. Caspian J Intern Med 2015;6(2):93-7.

15. Forli L, Bjortuft O, Boe J. Vitamin D status in relation to nutritional depletion and muscle function in patients with advanced pulmonary disease. Exp Lung Res 2009; 35(6):524-38.

16. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989;262(17):2395-401.

17. Mancini DI, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991; 83(3):778-6.

18. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, DeFina L, Willis B. Physical fitness and risk for heart failure and coronary artery disease. Circ Heart Fail 2013;6(4):627-34.

19. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119(1):256-70.

20. Schutz SL. Oxygen saturation monitoring by pulse oximetry. In: Lynn-Mchale DJ, Carlcon KK, editors. AACC procedure manual for critical care, 4th ed. Philadelphia: WB Saunders; 2001.101-7p.

21. Said AF, Abd-Elnaeem EA. Vitamin D and chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc 2015;64(1):67-73.

22. Hall JE. Guyton and Hall text book of medical physiology. Chapter 37, Pulmonary ventilation; 13th ed. India (New delhi): Elsevier; 2016.465-72p.

23. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://www.goldcopd.org/
pulmonary disease is associated with low levels of vitamin D. PLoS One 2012;7(6):e38934. doi.org/10.1371/journal.pone.0038934.

29. Janssens W, Mathieu C, Boonen S, Decramer M. Vitamin D deficiency and chronic obstructive pulmonary disease: A vicious circle. Vitam Horm 2011; 86:379-99. doi: 10.1016/B978-0-12-386960-9.00017-4.

30. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D. J Clin Invest 1985; 76:1536-8.

31. Jung HY, Kim YS, Kim SK, Kim HY, Oh YM, Lee SM, Seo JB, Lee SD, KOLD Study: Relationship of vitamin D status with lung function and exercise capacity in COPD. Respir Physiol 2015;205(5):782-89.

32. Kim C, Jung JY, Kim YS, Lee JS, Rhee CK, Lee JH, Lee JH, Kim TH, Lim SY, Sheen SS, Yoo KH, Seo JB, Oh YM, Lee SD, Park YB. Vitamin D deficiency is associated with rapid decline in exercise capacity in male patients with chronic obstructive pulmonary disease. Respiration 2016; 91(5):351-8.

33. Park YB, Kim C, Jung JY, Oh YM, Lee SD, Yoo KH. Vitamin D deficiency is associated with rapid decline in exercise capacity in male patients with COPD. Eur Respir J 2016;48:4181. doi: 10.1183/13993003.0303.

34. Hall JE. Guyton and Hall text book of medical physiology. Chapter 80, Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone, and teeth; 13th ed. India (New Delhi): Elsevier. 1001-6p.

35. Boland R, Norman A, Ritz E, Hasselbach W. Presence of a 1, 25-dihydroxy-vitamin D3 receptor in chick skeletal muscle myoblasts. Biochem Biophys Res Commun 1985;128(1):305-11.

36. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, Dick W. In situ detection of 1, 25-dihydroxy vitamin D receptor in human skeletal muscle tissue. Histochem J 2001;33(1):19-24.

37. Massheimer V, Fernandez LM, Boland R, de Boland AR. Regulation of Ca2+ uptake in skeletal muscle by 1, 25-dihydroxyvitamin D3: role of phosphorylation and calmodulin. Mol Cell Endocrinol 1992;84(1-2):15-22.

38. De Boland AR, Boland RL. Non-genomic signal transduction pathway of vitamin D in muscle. Cell Signal 1994;6(7):717-24.

39. Vazquez G, de Boland AR, Boland R. Stimulation of Ca²⁺Release-activated Ca²⁺channels as a potential mechanism involved in non-genomic 1,25(OH)₂-Vitamin D₃-induced Ca²⁺-entry in skeletal muscle cells. Biochem Biophys Res Commun 1997; 239(2):562-5.

40. Birge SJ, Haddad JG. 25-hydroxycalciferol stimulation of muscle metabolism. J Clin Invest 1975;56(5):1100-07.