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DOES VITAMIN D3 SUPPLEMENTATION IMPROVE VENTILATORY FUNCTION OF VITAMIN D DEFICIENT COPD PATIENTS? - A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Vitamin D is important for bone mineralization and lung tissue remodeling. Vitamin D deficiency may therefore influence lung health and its supplementation may help improve conditions like chronic obstruction pulmonary disease (COPD). **Aim**: The aim of the study was to evaluate the effects of vitamin D3 supplementation on ventilatory function in vitamin D3 deficient patients with COPD. **Materials and Method:** A double blinded randomized controlled trial was carried out on 40 vitamin D3 deficient [serum vitamin D (25(OH)D] <30 ng/ml], male, smoker (>4 pack years), stable COPD (post bronchodilator FEV1/FVC<0.70) patients (age 40 to 80 years), and randomly allocated as study (n=20) and control (n=20). Their baseline ventilatory function (FVC, FEV1, FEV1/FVC%, PEFR, FEF 25-75) were measured. Then oral capsules of vitamin D3 [80,000 IU /week for 13 weeks, followed by 40,000 IU per one to six weeks for further 13 weeks, according to serum 25(OH)D and calcium levels] and placebo were provided to 'Study' and 'Control' patients, respectively, for consecutive 26 weeks.Additionally, all patients of both groups were also advised to have sunlight exposure (within 11 to 14 hours) at least for 5 to 15 minutes daily and follow up was done at the end of 26th week, and all the ventilatory variables were again measured. Results were expressed as mean±SD and percentage. The data were statistically analyzed by SPSS (Version 16), using independent sample 't' test and paired student's 't' test, where $p \leq 0.05$ level was accepted as significant. **Results:** None of ventilatory variables were improved, in our vitamin D3-supplemented patients than those with placebo after 26 weeks of follow up. **Conclusion:** Vitamin D3 supplementation cannot improve ventilatory variables in vitamin D3 deficient stable patients of COPD.

Trial registration: www.clinicaltrials.gov identifier NCT03781895

Keywords: COPD, Vitamin D3, FVC, FEV1, FEV1/FVC%.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major causes of chronic morbidity and mortality throughout the world[1].COPD is a multicomponent disease, comprising emphysema in the lung parenchyma, large central airway inflammation and mucociliary dysfunction, bronchiolitis and small airway structural changes[2].

On the basis of different variables, the prevalence of COPD ranged from 2.1% to 26.1%[3] in different countries. Furthermore, 90% of COPD deaths occur in low and middle income countries[4].

COPD, are preventable and treatable, yet once developed the disease along with its comorbidities cannot be cured. However, their progression and exacerbation of morbidity can be attenuated. Besides using standard treatment, now a days different nontherapeutic supplements on different lung diseases are taking hold.

It has also been suggested that, patients with COPD have a high prevalence of vitamin D deficiency, ranging from approximately 30% in mild COPD to over 75% in severe COPD [5-8].

Vitamin D is important in bone mineralization and lung tissue remodeling[9,10]. The prevalence of vitamin D deficiency has been increasing in the general population in recent decades [11]due to decreased sun exposure with a limited dietary contribution.Vitamin D may have role in several diseases involving the respiratory system. Recently Heideri et al. reported that a significant proportion of young COPD patients may have insufficient (20 to 29 ng/ml) serum 25(OH)D[12]. They also found a statistically significant positive relationship between serum 25(OH)D and FEV1 in this group of patients. It has also been suggested that, patients with COPD have a high prevalence of vitamin D deficiency, ranging from approximately 30% in mild COPD to over 75% in severe COPD [5-8].However, the present volume of information concerning the effect of vitamin D3 administration in COPD patients is not adequate for outstretching any final conclusion.

Therefore, on the basis of this background the present study has been designed to assess the effects of Vitamin D3 on the spirometric lung function status in vitamin D3 deficient patients with stable COPD and draw attention of the pulmonologists about the effects of this fat soluble vitamin.

MATERIALS AND METHOD

Study design, settings and time

This randomized double blinded placebo-controlled trial was carried out in the Department of Physiology, Bangladesh Medical University (BMU) and National Institute of the Diseases of Chest and Hospital (NIDCH), Dhaka from March, 2017 to February, 2018.This clinical trial was registered at www.clinicaltrials.gov, ID: NCT03781895 and approved by Institutional Review Board of BMU.

Study population

For this purpose, 40 (forty) vitamin D3 deficient (serum25-hydroxycholecalciferol <30ng/ml)[13], male, smoker, stable patients with COPD[14] of age 40 to 80 years were selected by pulmonologists through clinical findings of chronic airway disease, usually with spirometric evidence of chronic airflow limitation (post bronchodilator FEV1/FVC<0.7)[15].

The inclusion criteria were duration of COPD (1 to 5 years), duration of smoking (>10 pack years)[6], body mass index (18.5 to 24.9 kg/m^2)[16], serum total calcium (8.5 to 10.5 mg/dl)[17], serum inorganic phosphate (2.3 to 4.7 mg/dl)[18] and serum parathormone (10 to 65 pg/ml)[17].

In addition, patients with uncontrolled diabetes mellitus (fasting blood sugar ≥7 mmol/l and/or HbA1c ≥7%)[18], uncontrolled systemic hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, with anti-hypertensive medication)[19], 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)[20], renal insufficiency (serum creatinine>1.36 mg/dl)[21] 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 D3 deficient COPD 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=20) or placebo treated group (n=20) (Figure1).

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 per week for first 13 weeks. Detail of the dose schedule for vitamin D3 supplementation for last 13 weeks[13] are shown in Table 1. Whereas, all the 'Control' patients received two oral capsulesof placebo weekly for consecutive 26 weeks. Additionally, all the patients of both groups were also advised to have sunlight exposure (within 11am to 4pm) only for 20 minutes daily[22]. On the other hand, if serum 25(OH) D was <10 ng /ml (severely deficient)[13] of any patient, then he was dropped out (Figure 1) from the study (for ethical purpose). After 26th week of follow up, both the lung function and exercise tolerance variables were again measured. Ingredients of vitamin D3 capsules were cholecalciferol (40,000 IU), microcrystalline cellulose (58.1 gm), butylated hydroxy toluene (0.2 mg), magnesium stearate (3 mg), gelatin capsule shell (1mg).

Ingredients of placebo were same as vitamin D3 except Cholecalciferol (prepared by a certain local pharmaceutical company of Bangladesh). After explaining the dose schedule and possible side effects of drug (vitamin D3 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)[1].

Data collection

An informed written consent was taken from eachpreliminarily selected patient and his serum 25(OH) D was estimated. When serum 25(OH) D was <30ng/ml (vitamin D3deficiency) but >10 ng/ml[13], then he was finally selectedand randomly assigned as 'Study' (n=20) or 'Control' (n=20) patient (Figure 1). The baseline value of lung function and exercise tolarence variables of all patients were measured. Serum 25(OH) D was assessed by Chemiluminescent microparticle immunoassay (CMIA) method (Abbot Laboratory, Ireland). Lung functions were assessed by spirometry.

Statistical Analysis

The results were expressed as mean ± SD and the data were analyzed by SPSS (Version 16), and for statistical analysis, independent sample 't' test as well as paired student's 't' test was used. In the interpretation of results, $p \leq 0.05$ was accepted as significant.

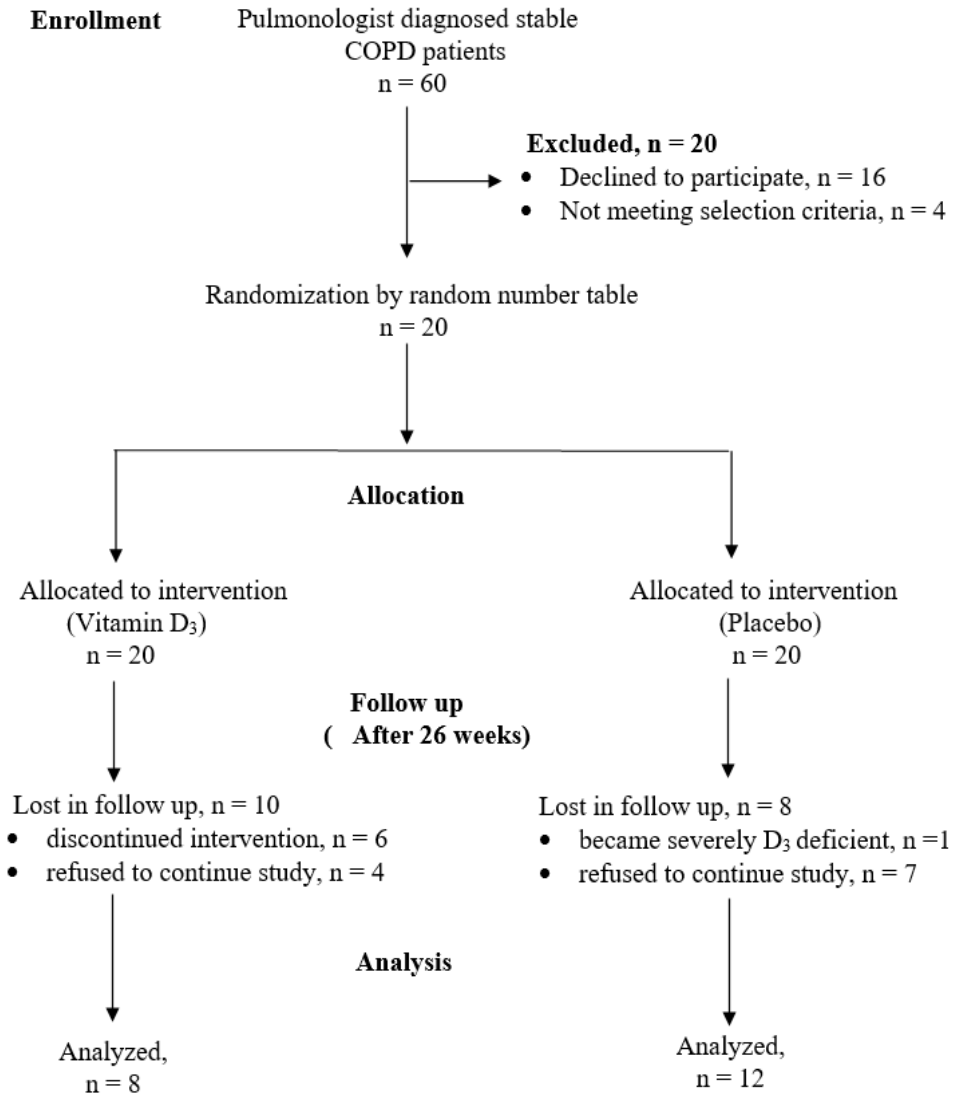

Figure 1: CONSORT (Consolidated Standards of Reporting Trials) diagram; COPD: Chronic obstructive pulmonary disease

RESULTS

A total of 40 patients were initially randomized and 22 of them ultimately completed the study (10 in vitamin D3 group and 8 in placebo group were dropped out). There was no significant difference in the baseline characteristics between vitamin D3 supplemented and placebo groups (Table2). However, after 26 weeks of their follow up, none of the ventilatory variables were improved in comparison to their base line values and in comparison to those with placebo (Figure 2).

Table 1: Vitamin D3 Supplementation schedule for vitamin D3 deficient COPD patients

At 1st visit / at day 1:

Vitamin D 380,000 IU (2 capsules of 40,000 IU) / week, for consecutive 13 weeks

At 2nd visit/after13weeks:

If, serum 25 (OH)D and/or serum Ca^{2+} =	**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
60-80 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 & 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 2: Baseline characteristics of COPD patients in both groups (N=22)

Parameters	Placebo group (n=30)	Vitamin D3group (n=30)
Age (years)	57.66±10.90	60.13±9.75
Duration of COPD (years)	3.53±0.81	3.63±0.80
Duration of smoking (pack years)	16.28±5.72	14.62±4.46
Body Mass Index (kg/m2)	21.75±3.01	22.51±3.34
Mid Upper Arm	26.93±3.43	26.73±2.88
Circumference (cm)	116±7.23	116±7.23
Systolic blood pressure (mm of Hg)	75.33±7.76	75.33±7.76
Diastolic blood pressure (mm of Hg)	83.02±16.97	86.80±17.93
FEV1/FVC (%)	58.22±21.93	62.88±21.11
FEV1 (% of PV)	45.95±16.28	44.89±12.33
25-hydroxcholecalciferol (ng/ml) serum	19.58±3.79	19.20±4.44
parathormone (pg/ml)	49.93±10.92	53.29±9.28
Total calcium (mg/dl)	9.39±0.4	9.15±0.33
Inorganic Phosphate (mg/dl)	3.27±0.39	3.15±0.63
Fasting blood sugar (mmol/l)	5.14±0.77	5.09±0.79
Glycosylated hemoglobin (%)	6.12±0.49	6.14±0.44

Data were expressed as mean ± SD; Statistical analysis was done by independent sample t test; n: number of subjects; Packyear: (number of cigarette smoked perday÷20) X no. of year smoked; FEV1:Forced expiratory volume in 1st second; FVC: Forced Vital Capacity; PV: Predicted Value.

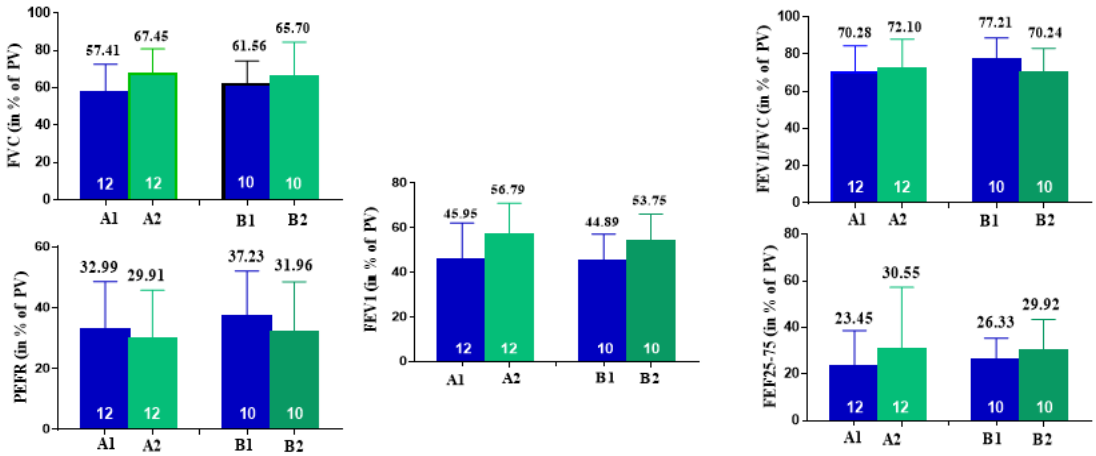

Figure 2: Ventilatory functions in two groups of stable COPD. Each bar symbolizes mean±SD; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1st second; PEFR: Peak expiratory flow rate; FEF25-75: Forced expiratory flow in the middle half of FVC; % of PV= Percentage of predicted value; Each bar symbolizes mean±SD; A1 = Patients with placebo on day 1; A2=Patients with placebo on 26th week; B 1 = Patients with vitamin D on day 1; B 2 = Patients with vitamin D3 on 26th week.

DISCUSSION

The present study has been undertaken to observe the effects of vitamin D3 administration on lung functions in male stable COPD patients. In the present study, all the variables in all the vitamin D3 deficient male COPD patients, at their baseline status, were almost similar to those reported by other investigators of different countries[12,23-26].

In the present study, ventilatory function variables (FVC, FEV1, FEV1/FVC ratio, PEFR, FEF 25-75) were not improved in vitamin D3 deficient COPD patients with vitamin D3 supplementation. Similar observation was reported in FVC[24,25,27], FEV1[12,24,27], FEV1/FVC ratio[27], PEFR[27], and FEF 25-75[24] after different dose and duration schedules of vitamin D3 supplementation.

However, it has been proposed that smoking causes inflammation and oxidative stress as well as increment of protease activity leading to lung tissue destruction[28]. This might be the cause of the severe decrement of ventilatory variables in our heavy smokers COPD patients. Though, vitamin D could minimize these processes by inhibiting matrix metalloprotease[29] as well as inhibiting fibroblast proliferation and collagen synthesis[30], but the present dose and duration schedule of vitamin D3 supplementation might not be able to reverse the lung tissue alteration in our study patients and could not improve the ventilatory variables significantly. Our study had limitations. One was the small sample size and the other was short follow up period. Moreover, this study was not confounded by an over estimation of the effectiveness of an intervention.

CONCLUSION

The results of the present study conclude that, 26 weeks supplementation of vitamin D3 do not improve ventilatory functions in vitamin D3 deficient stable COPD patients. Further multicenter trials on both male and female patients are recommended.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICAL APPROVAL

The protocol for this study was approved by the Institutional Review Board of Bangladesh Medical University.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. 2019.. Available from: https://www.google.com/search?q=gold+2019+pdf&oq=gold&aqs [(Accessed on 29 March2019)]

2. Agusti AG. COPD, a multicomponent disease: implications for management. Respir Med. 2005 ;99(6):670-82. doi: 10.1016/j.rmed.2004.11.006.

3. Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC Med. 2011;9:7. doi: 10.1186/1741-7015-9-7.

4. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet. 1997;349(9063):1436-42. doi: 10.1016/S0140-6736(96)07495-8.

5. 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. doi: 10.1378/chest.128.6.3792.

6. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010;65(3):215-20. doi: 10.1136/thx.2009.120659.

7. Ferrari M, Schenk K, Papadopoulou C, Ferrari P, DalleCarbonare L, Bertoldo F. Serum 25-hydroxy vitamin D and exercise capacity in COPD. Thorax. 2011;66(6):544-5. doi: 10.1136/thx.2010.152785.

8. Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE. Vitamin D status and longitudinal lung function decline in the Lung Health Study. Eur Respir J. 201;37(2):238-43. doi: 10.1183/09031936.00146509.

9. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology. 23rd ed. New York: McGraw-Hill Company; 2012. 375-388p

10. Hall JE. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone, and teeth .In: Guyton and Hall Textbook of medical physiology. 13th ed. India (New Delhi): Elsevier.;2016.1001-1016 p.

11. Caballero A, Torres-Duque CA, Jaramillo C, Bolívar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). Chest. 2008;133(2):343-9. doi: 10.1378/chest.07-1361.

12. Heidari B, Monadi M, Asgharpour M, Firouzjahi A, Tilaki KH, Monadi M. Efficiency of supplemental vitamin D in patients with chronic obstructive pulmonary disease. J Adv Med Med Res. 2014:3031-41. doi: 10.9734/BJMMR/2014/8373

13. Vitamin D Council. I tested my vitamin D level. What do my results mean? 2019: Available from: https://www.vitamindcouncil.org/i-tested-myvitamin-d-level-what-do-my-results-mean/ [(Accessed on 25 March 2019)]

14. Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD). Diagnosis and initial treatment of asthma, COPD and asthma COPD overlap. 2017.Available from:https://ginasthma.org/wp-content/uploads/2019/04/wms GINA- [(Accessed on 19 April 2018)]

15. Fabricius P, Løkke A, Marott JL, Vestbo J, Lange P. Prevalence of COPD in Copenhagen. Respir Med. 2011;105(3):410-7. doi: 10.1016/j.rmed.2010.09.019.

16. World Health Organization. Regional office for the Western Pacific. The Asia pacific perspective: redefining obesity and its treatment .WHO. 2000. Available from: https://apps.who.int/iris/handle/10665/206936 [(Accessed on 29 March 2019)].

17. Risteli J, Winter WE, Kleerrekoper M, Risteli L. Bone and mineral metabolism. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz textbook of clinical chemistry and molecular diagnostics.5th ed. USA: Saunders Elsevier; 2012.1733-1806 p

18. American Diabetes Association. Classification anddiagnosis of diabetes mellitus: standards of medicalcare in diabetes-2018. Diabetes Care. 2018; 41(Suppl 1):s13-s27. doi: 10.2337/dc18-S002

19. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al.Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012 ;125(1):e2-e220. doi: 10.1161/CIR.0b013e31823ac046.

20. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486.

21. Walker SW. Laboratory reference ranges. In: Walker BR, Colledge NR, Ralston SH, Penman ID, editors. Davidson's principles and practice of medicine. 22nd ed. Edinburg, Churchill Livingstone: Elsvier. 2014.1307-12 p.

22. 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.

23. Monadi M, Firouzjahi A, Hosseini A, Javadian Y, Sharbatdaran M, Heidari B. Serum C-reactive protein in asthma and its ability in predicting asthma control, a case-control study. Caspian J Intern Med. 2016;7(1):37-42.

24. Moosavi SAJ, Shoushtari MH. The Effects of Vitamin D Supplementation on Pulmonary Function of Chronic Obstructive Pulmonary Disease Patients, before and after Clinical Trial. Diseases. 2015;3(4):253-259. doi: 10.3390/diseases3040253.

25. Rafiq R, Aleva FE, Schrumpf JA, Heijdra YF, Taube C, Daniels JM, et al. Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol. BMC Pulm Med. 2015 ;15:106. doi: 10.1186/s12890-015-0101-4.

26. Rezk NASA, Aly NYA, Hewidy AAH. Effect of vitamin D replacement in chronic obstructive

pulmonary disease patients with vitamin D deficiency. Egypt J Chest Dis Tuberc 2015;64(2):353-7. doi: 10.1016/j.ejcdt.2015.01.002

27. Said AF, Abd-Elnaeem EA. Vitamin D and chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc.2015;64(1):67-73. doi: 10.1016/j.ejcdt.2014.11.033

28. Hammer TR, Fischer K, Mueller M, Hoefer D. Effects of cigarette smoke residues from textiles on fibroblasts, neurocytes and zebrafish embryos and nicotine permeation through human skin. Int J Hyg Environ Health 2011;214(5):384-91. doi: 10.1016/j.ijheh.2011.04.007

29. Koli K, Keski-Oja J. 1aa, 25-Dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. Cell Growth and Differentiation-Pub Am AssocCancer Res 2000;11(4):221.

30. Dobak J, Grzybowski J, Liu F-T, Landon B, Dobke M. 1, 25-Dihydroxyvitamin D3 increases collagen production in dermal fibroblasts. J. Dermatol. Sci 1994;8(1):18-24. doi: 10.1016/0923-1811(94)90316-6