Section: Respiratory Medicine

Original Research Article

VITAMIN D STATUS AND ASSOCIATION WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION: A CROSS-SECTIONAL STUDY

Dhiraj Kumar[1], Yatin Mehta[2], Prabhat Kumar[3], Lalit Singh[4], Mohd Tariq[2]

[1]Junior Resident, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India
[2]Assistant Professor, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India
[3]Senior Resident, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India
[4]Professor and Head, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

Received : 22/05/2024
Received in revised form : 10/07/2024
Accepted : 28/07/2024

Keywords:
COPD, Exacerbation, vitamin D, Cross sectional study

Corresponding Author:
Dr. Yatin Mehta
Email: yatin.mehta1989@gmail.com

DOI: 10.47009/jamp.2024.6.4.57

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (4); 278-283

Abstract

Background: The objective of this study was to establish a correlation between serum 25 (OH) vitamin D levels and the severity of disease in patients with chronic obstructive pulmonary disease exacerbation (COPD). Additionally, the study aimed to assess other factors associated with the levels of serum 25 (OH) vitamin D in COPD patients. **Materials and Methods:** Based on convenient sampling, 56 COPD patients who presented to the department with acute exacerbation of COPD between 2022 and 2023 were screened and included in the study. A 3 ml blood sample was taken from each patient to measure the serum concentration of 25(OH) vitamin D and sent to the lab. **Result:** A comprehensive examination was conducted on a total of 37 patients. Among the 37 patients, 33 were male and the average age was 63 years. The average Vitamin D level in the population was 27 ng/ml, with 3 individuals having a history of smoking. **Conclusion:** The findings of our study demonstrate a close correlation between airway obstruction and levels of 25(OH) vitamin D, which are almost identical. Based on our observations, we determined that the majority of patients with Chronic Obstructive Pulmonary Disease (COPD) were males. Multiple studies, including our own, have demonstrated a correlation between reduced lung function, decreased exercise capacity, and lower levels of serum 25(OH)Vitamin D.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) ranks as the third most common cause of death globally,[1]posing a significant threat to public health. The GOLD report has further defined exacerbations as "an event characterized by dyspnoea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnoea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways." Chronic obstructive pulmonary disease (COPD) is a common cause of mortality and morbidity globally. COPD exacerbations are associated with significant morbidity, mortality, impaired quality of life and costs.[2] Patients with chronic obstructive pulmonary disease (COPD) experience a gradual decline in lung function, decreased exercise capacity, frequent exacerbations of the disease, and the emergence of additional health conditions outside of the lungs, such as osteoporosis, infection, and cardiovascular disease.[3]

Vitamin D is conventionally recognised for its functions in maintaining bone health and regulating the balance of calcium and phosphorus.[4]However, vitamin D is not just a vitamin. It is widely acknowledged as a pleiotropic prohormone, with its receptor (vitamin D receptor [VDR] being distributed ubiquitously.[5]Vitamin D, as an immunomodulatory agent, can enhance innate immune responses during infection and also regulate adaptive immune responses.[6]Furthermore, vitamin D is associated with the growth and division of cells, the specialisation of cells into different types, programmed cell death, and the binding of cells to one another.[7] The primary source of vitamin D is the skin, which produces it when exposed to sunlight. The remaining amount can be acquired through dietary intake or by taking supplements.[8]Epidemiological studies have documented that vitamin D deficiency is a significant global health concern.[9]Vitamin D

ISSN (O): 2687-5365; ISSN (P): 2753-6556

deficiency can be the underlying cause of a wide range of diseases, such as autoimmune diseases, allergy diseases, endocrine and metabolic disorders, cancer, infections, and cardiovascular disorders.[10,11] Several studies have suggested a potential connection between vitamin D and COPD, specifically focusing on the association between the two.[12-14]However, the conclusion was inconclusive. Two meta-analyses investigating the roles of vitamin D in chronic obstructive pulmonary disease (COPD) have been conducted.[15,16]However, the studies were insufficient in terms of article quantity were inaccurate in data extraction; combined vitamin D levels from serum and plasma; included participants who were taking vitamin D supplements; or failed to analyse the sources of significant variability. Thus, we conducted an additional comprehensive analysis and meta-analysis to elucidate the functions of vitamin D in chronic obstructive pulmonary disease (COPD).This study investigated the correlations between circulating 25(OH)D levels and the likelihood, intensity, and worsening of COPD.

MATERIALS AND METHODS

The present cross-sectional study was carried out in the Department of Pulmonary Medicine, SRMS IMS, Bhojipura, Bareilly, after approval by the Institutional Ethics Committee. Based on convenient sampling, 56 COPD patients who presented to the department with acute exacerbation of COPD between 2022 and 2023 were screened and included in the study. To ensure the validity of findings, we excluded patients with respiratory conditions other than COPD such as asthma, interstitial lung disease etc.; patients who were taking medicines that could potentially affect serum Vitamin D concentration (corticosteroids, calcium supplements, phosphorus, or Vitamin D supplements) immunocompromised patients; those with underlying renal, cardiovascular or liver diseases; those with metabolic syndrome, electrolyte imbalances, cancers or any diseases associated with Vitamin D metabolism and absorption.

Detailed history along with the socio-demographic details was recorded, vitals measured and complete physical examination was done. Acute exacerbation of COPD was considered if there was a sudden increase in dyspnea cough exacerbation and sputum disposal that led to hospitalization. Investigations were carried out as per the requirement. A 3 ml blood sample was taken from each patient to measure the serum concentration of 25(OH) VIT D and sent to the lab. The patients were considered fit to be discharged if they achieved a sufficient improvement in dyspnea and oxygen saturation, were clinically stable, and did not need continuous oxygen therapy.

All data was entered in MS Excel and analysed using SPSS 25.0 (trial version). Results were expressed as the means and standard deviation or as numbers and percentages. Statistical analysis was done by applying ANOVA test and student “t” test. The level of significance was fixed at 95%. P-value < 0.05 was considered statistically significant.

RESULTS

Out of the screened patients, we identified 56 individuals who satisfied the specified inclusion and exclusion criteria. Out of the total of 56 patients, 10 patients declined to take part in this study. Out of the remaining participants, 4 individuals were excluded due to their inability to undergo spirometry testing as a result of restricted mouth opening caused by conditions such as fibrosis or carcinoma. 1 patient was excluded due to their refusal to provide a blood sample. Among the remaining patients, 4 were excluded from further analysis due to incomplete data. A comprehensive examination was conducted on a total of 37 patients. Among the 37 patients, 33 were male and the average age was 63 years. The average Vitamin D level in the population was 27 ng/ml, with 3 individuals having a history of smoking.

General Characteristics: The results were presented using the mean values plus or minus the standard deviations. The average FEV1 % predicted in our study was 50.88%, and the average serum 25(OH) Vitamin D level was 27.86±16.47ng/ml [Table 1].The mean age at presentation was 63.84±9.86 years. Among the 37 patients, the majority (28) were classified in GOLD stage 2 and 3. The average 25(OH) vitamin D level was highest (59.33 ng/ml) among patients in stage 1. The majority of patients (56.8%) were former smokers, while only 10.8% of patients were non-smokers. The average number of pack years was 29.81±15.60.

Age Category: [Table 2] Our study found that the average 25(OH) vitamin D level was lower in older patients (aged over 70 years) compared to younger patients (aged under 69 years). Nevertheless, there was no statistically significant variation in 25(OH) vitamin D levels among different age groups, as indicated by a p value of 0.083.

COPD Severity: [Table 3] The average Vitamin D level was found to be highest among patients with stage 1 COPD, and as the severity of the disease increased, the Vitamin D level decreased. Patients with Stage 4 COPD exhibited the most diminished levels of serum 25(OH) vitamin D. A negative correlation existed between the severity of COPD and the levels of vitamin D. The statistical significance of the distribution of mean serum 25(OH) vitamin D according to disease severity was highly pronounced. The p-value is 0.001.

mMRC dyspnea grade: Among the 37 patients, the majority were classified in mMRC grade 2 and 3. The average 25(OH) vitamin D level was highest among patients in Grade 1 (52 ng/ml). As the mMRC score increased, the 25(OH) vitamin D level decreased. The average serum 25 (OH) vitamin D

ISSN (O): 2687-5365; ISSN (P): 2753-6556

levels were significantly lower (13 ng/ml) in patients with grade 4 COPD. A strong negative correlation was observed between the mMRC Dyspnoea grade and the 25(OH) vitamin D level, with a statistically significant p-value of 0.001.

The mean levels of vitamin 25 (OH) D in the GOLD group were divided based on disease symptoms and risk. Out of the 37 patients in our study, the majority, specifically 21 patients, belonged to GOLD group A, while 12 patients were classified under group B. The average 25(OH) vitamin D level was highest among patients in group A, and then followed by patients in group C. Group D patients exhibited the lowest incidence. A strong negative correlation was observed between the GOLD group and the level of 25(OH) vitamin D, with a statistically significant p value of 0.001. Put simply, individuals experiencing more severe symptoms exhibited lower levels of 25(OH) vitamin D compared to those with milder symptoms.

Pack years: We conducted a study to compare the average 25(OH) vitamin D level based on the number of pack years. The majority of patients (19) had accumulated over 30 pack years, while a smaller group (n=12) had accumulated 20-29 pack years. The patients with 10-19 and 20-29 pack years had the highest mean 25(OH) vitamin D level. It had the lowest occurrence rate among the patients who had smoked more than 30 pack years. A statistically significant negative correlation was observed between the number of pack years and the level of 25(OH) vitamin D. The value of P is 0.015.

Our study focused on comparing the mean 25(OH) vitamin D levels based on the use of ICS therapy. Among the 37 patients, 19 were receiving inhaled corticosteroids (ICS). The 25(OH) vitamin D level was lower in patients receiving ICS and higher in patients not receiving ICS. A statistically significant difference was observed in the 25(OH) vitamin D level among COPD patients based on ICS therapy (P=0.001). The majority of patients in the ICS therapy group exhibited moderate to severe chronic obstructive pulmonary disease (COPD).

Table 1: Characteristics of the patients with COPD.

Characteristic	Mean/Number
Total Number of Patients(n)	37
Age in Years(Mean)	63.84±9.86
Male:Female (Ratio)	66:8
Pack Year(Mean)	29.81±15.60
Vitamin D Level[Mean(ng/ml)]	27.86±16.47
mMRC# (Mean)	2.57±0.49
FEV1%Predicted (Mean)	50.88±16.30
Smoking Status [n (%)]	
Current Smoker(n)	12(32.4%)
Ex-Smoker(n)	21(56.8%)
Non-Smoker(n)	4(10.8%)
COPD Severity [n (%)]	
Mild	3(8.1%)
Moderate	12(32.4%)
Severe	16(43.2%)
Very Severe	6(16.2%)

*BMI – Body mass index, mMRC – Modified medical research council, COPD – Chronic obstructive pulmonary disease.

Table 2: Mean serum 25(OH) vitamin D levels in different age group in COPD patients.

		Vitamin D level(ng/ml)		ANOVA 'F' Value	Significance 'p' value
Age Group (in years)	Number	MEAN	SD		
40-59	8	31.06	17.85	2.313	0.083
60-69	17	31.30	16.40		
70-79	8	19.94	14.18		
>80	4	23.14	13.54		

Table3: Characteristics of patients according to GOLD staging

Characteristic	Gold Staging				F Value	P Value
	Stage1n-3	Stage2n-12	Stage3n-16	Stage4n-6		
	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
Age in Years	55.17±8.68	63.29±10.06	63.63±8.51	69.83±10.70	3.347	0.024
Pack Year	24.33±8.21	23.67±14.05	30.97±15.44	41.75±15.57	4.434	0.007
mMRC	1.00±0.00	2.13±0.33	3.09±0.73	3.58±0.90	32.688	0.001
BMI	22.83±4.11	18.79±4.89	18.91±4.36	18.09±3.86	1.663	0.183
Vitamin D Level (ng/ml)	59.33±15.51	36.17±10.35	22.25±10.98	10.50±4.10	37.558	0.001

Table 4: Mean Vitamin D level according to MMRC Dyspnea grade among COPD patients.

Mmrc Dyspnea grade		Vitamin D level (ng/ml)		ANOVA 'F' Value	Significance 'p' value
	Number	MEAN	SD		
Grade1	5	52.00	19.69		

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Grade2	11	35.91	10.69	29.938	0.001
Grade3	13	22.31	10.18		
Grade4	8	13.18	6.03		

Table 5: Comparison of mean Vitamin D level according to GOLD group among COPD patients.

		Vitamin D level(ng/ml)			
Gold B groups	**Number**	**MEAN**	**SD**	**ANOVA'F' Value**	**Significance 'p' Value**
Group A	3	59.33	15.51	39.260	0.001
Group B	12	36.17	10.35		
Group C	1	45.00	24.04		
Group D	21	17.81	8.74		

Table 6: Comparison of mean Vitamin D level according to Pack Year among COPD patients

		Vitamin D level(ng/ml)		ANOVA'F' Value	Significance 'p' Value
Pack year	**Number**	**MEAN**	**SD**		
0-9	4	28.75	9.43	3.740	0.015
10-19	2	35.60	7.43		
20-29	12	35.17	18.11		
>30	19	22.24	15.60		

Table 7: Comparison of mean Vitamin D level according to ICS Therapy among COPD patients

		Vitamin D level (ng/ml)		Student 't' Test value	Significance 'p' Value
ICS Therapy	**Number**	**MEAN**	**SD**		
Yes	19	21.47	13.20	3.717	0.001
No	18	34.61	17.05		

DISCUSSION

The objective of this study was to establish a correlation between serum 25 (OH) vitamin D levels and the severity of disease in patients with chronic obstructive pulmonary disease (COPD). Additionally, the study aimed to assess other factors associated with the levels of serum 25 (OH) vitamin D in COPD patients.

The severity of COPD was assessed based on the mean FEV1% predicted, which was found to be 50.88%. Additionally, the mean 25 (OH) vitamin D level was measured at 27.86ng/ml, which is below the normal range of >30 ng/ml. Over the past few years, researchers have observed a deficiency of 25 (OH) vitamin D in patients experiencing a decline in lung function.[17] In the NHANES III study, Black et. al discovered a negative correlation between blood levels of 25(OH) vitamin D and FEV1 and FVC in the healthy general population.[18]

In 2010, Janssens et. al. conducted a study on individuals who were former smokers and had COPD, as well as individuals who were former smokers with normal lung function. The purpose of the study was to investigate the relationship between serum 25(OH) vitamin D levels and COPD, as well as the vitamin D receptor gene. The average FEV1% predicted was 61±27% and the average 25(OH) vitamin D level was 19.9±8.2 ng/ml. The study's authors determined that there is a high prevalence of 25(OH) vitamin D deficiency in individuals with COPD, and this deficiency is associated with the severity of the disease in individuals who used to smoke and have COPD.[19] Kunisaki et al. conducted a secondary analysis of data from North America in 2011 and observed a parallel trend.

A large cohort study of 973 patients with severe COPD indicated lower levels of 25(OH) vitamin D, with a mean level of 25.7ng/ml.[20] In our study, we examined patients who had been diagnosed with COPD. Our main objective was to establish a connection between the severity of COPD and the levels of 25(OH) vitamin D. The results of our study indicate a very similar relationship between airway obstruction and 25(OH) vitamin D levels. The findings of our study in the Indian context align with the research conducted by Janseens et al., Kunisaki KM et al., and Cilingir BM et al.These studies collectively offer compelling evidence supporting the correlation between decreased levels of serum 25 (OH) vitamin D and the deterioration of lung functions in patients with COPD. They also suggest the importance of maintaining optimal levels of serum 25(OH) vitamin D in COPD patients.[19,20-35]

Age Groups: Our study found that the average 25 (OH) vitamin D level was lower in patients over the age of 70 compared to patients under the age of 69. Nevertheless, there was no statistically significant variation in 25(OH) vitamin D levels among different age groups, as indicated by a p-value of 0.083. Previous research has characterized 25(OH) vitamin D deficiency as a prevalent occurrence among older populations.[21,22] Prior Studies by Jindal et al (2001), Mahesh et al (2009) and Parasuramalu et al (2014)suggested that the prevalence of COPD increases with age, which in turn may lead to decreased mobility and sun exposure.[23-25] Furthermore, the diminished consumption of 25(OH) vitamin D in patients with COPD, especially in the elderly, can account for our observed results.[26]

mMRC stands for modified Medical Research Council. A statistically significant negative correlation was observed between the mMRC Dyspnoea grade and the 25(OH) vitamin D level, with a p-value of 0.001. In a randomized control

ISSN (O): 2687-5365; ISSN (P): 2753-6556

trial conducted by Sanjari Metal.in in 2015, the study examined the effects of treatment with 25 (OH) vitamin D. The researchers calculated and compared the MMRC scores before and after treatment in different groups. They found a significant difference (p<0.001) between the group receiving calcitriol and the group receiving placebo.[27] Similarly, Rezk et al observed a substantial enhancement (p-0.003) in the Mmrc dyspnoea scale one year after administering 25(OH) vitamin D replacement.[28]

The GOLD group classification was based on the differentiation of disease symptoms and risk factors. A statistically significant negative correlation was observed between the GOLD group and the 25 (OH) vitamin D level, with a p-value of 0.001. Put simply, individuals experiencing more severe symptoms exhibited lower levels of 25 (OH) vitamin D compared to those with milder symptoms. A study conducted by Kocabas A et al. in 2013 from Turkey found that the likelihood of 25 (OH) vitamin D deficiency was 4.83 times higher in GOLD group D compared to GOLD group A.[29] This supports the notion that there is a similar outcome to previous research.

Our study involved comparing the mean 25 (OH) vitamin D level based on the Pack Year. A statistically significant negative correlation was observed between the number of pack years and the level of 25 (OH) vitamin D (P=0.015). The earlier study,[30] has described a negative correlation between smoking status and the decline in lung function.

In 2016, Sanket S et al discovered that there was a greater likelihood of experiencing a deficiency in 25 (OH) vitamin D with an increase in the number of pack years of smoking.[31] A study conducted by Cutillas et al in 2012 also yielded a comparable result.[32]

Our study involved comparing the average 25(OH) vitamin D level based on the use of ICS therapy. The 25(OH) vitamin D level was lower in patients receiving ICS and higher in patients not receiving ICS. A statistically significant difference was observed in the 25(OH) vitamin D level among COPD patients based on ICS therapy (P=0.001). The majority of patients in the ICS therapy group exhibited moderate to severe chronic obstructive pulmonary disease (COPD). In 2011, Gupta A et al. discovered that the utilization of inhaled corticosteroids in individuals with asthma was linked to a deficiency of 25(OH) vitamin D.[34]

Summary - Serum 25 (OH) Vitamin D levels are an effective and appropriate method for evaluating systemic vitamin D levels. The objective of this study was to establish a correlation between serum 25(OH) vitamin D levels and the severity of disease in patients with chronic obstructive pulmonary disease (COPD). Additionally, the study aimed to assess other factors that are associated with serum 25(OH) vitamin D levels in COPD patients. Based on our observations, we determined that the predominant demographic of patients with COPD was male. Lower levels of serum 25(0H) vitamin D were linked to increased airway obstruction. The average levels of serum 25 (OH) Vitamin D were found to be lower in older patients compared to younger patients, and were also associated with GOLD group D rather than GOLD group A. Reduced levels of serum 25 (OH) vitamin D were linked to higher pack years, more frequent exacerbations in the self-declared previous year, lower socioeconomic status, and the use of inhaled corticosteroids in patients.

CONCLUSION

In our study, we included patients who had been diagnosed with COPD. Our primary objective was to establish a correlation between the severity of COPD and the levels of 25(OH) vitamin D. The findings of our study demonstrate an almost similar trend between declining lung function and deficiency of 25(OH) vitamin D levels. Based on our observations, we determined that the majority of patients with Chronic Obstructive Pulmonary Disease (COPD) were males and smokers. Multiple studies, including our own, have demonstrated a correlation between reduced lung function, decreased exercise capacity, and lower levels of serum 25(OH) Vitamin D. Collectively, our study findings, along with previous research, indicate a robust correlation between reduced levels of serum 25(OH) vitamin D and deteriorating lung function in individuals with COPD. Therefore, it is recommended to maintain optimal serum 25(OH) vitamin D levels in COPD patients. Future well-designed clinical trials are necessary to evaluate the impact of vitamin D supplementation on the decline in lung function, exercise limitations, morbidity and mortality in patients with COPD.

REFERENCES

1. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. European Respiratory Journal. 2006 Feb 1;27(2):397-412.
2. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report: Gold Executive Summary. American Journal of Respiratory and Critical Care Medicine [Internet]. 2023 Apr 1 [cited 2024 Mar 27];207(7):819–37. Available from: https://www.atsjournals.org/doi/full/10.1164/rccm.202301-0106PP doi:10.1164/rccm.202301-0106pp
3. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. European respiratory journal. 2009 May 1;33(5):1165-85.
4. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. The Lancet. 2014 Jan 11;383(9912):146-55.
5. Hollis BW, Wagner CL. The role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes. The Journal of Clinical Endocrinology & Metabolism. 2013 Dec 1;98(12):4619-28.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

6. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013 Jul 5;5(7):2502-21.
7. Samuel S, Sitrin MD. Vitamin D's role in cell proliferation and differentiation. Nutrition reviews. 2008 Oct 1;66(suppl_2):S116-24.
8. Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. Advances in Nutrition. 2011 May;2(3):244-53.
9. Edwards MH, Cole ZA, Harvey NC, Cooper C. The global epidemiology of vitamin D status. J Aging Res Clin Prac. 2014;3(3):148-58.
10. Adams JS, Hewison M. Update in vitamin D. The Journal of Clinical Endocrinology & Metabolism. 2010 Feb 1;95(2):471-8.
11. HolickMF.VitaminDdeficiency.NEnglJMed.2007;357:266–281.
12. Baldrick FR, Elborn JS, Woodside JV, Treacy K, Bradley J, Schock B, Ennis M, Dollin K, McGinty A, Young IS, McKinley MC. Vitamin D status in chronic obstructive pulmonary disease. Proceedings of the Nutrition Society. 2012;71(OCE2).
13. Shaheen SO, Martineau AR. Vitamin D and chronic obstructive pulmonary disease: justified optimism or false hope?. American journal of respiratory and critical care medicine. 2012 Feb 1;185(3):239-41.
14. Foong RE, Zosky GR. Vitamin D deficiency and the lung: disease initiator or disease modifier?. Nutrients. 2013 Jul 26;5(8):2880-900.
15. Zhang LL, Gong J, Liu CT. Vitamin D with asthma and COPD: notafalsehope?Asystematicreviewandmeta-analysis.GenetMolRes.2014;13(3):7607–7616.
16. ZhuB,XiaoC,ZhengZ.VitaminDdeficiencyisassociatedwiththeseverityofCOPD:asystematicreviewandmeta-analysis.IntJChronObstruct Pulmon Dis. 2015;10:1907–1916.
17. Persson LJ, Aanerud M, Hiemstra PS, Hardie JA, Bakke PS, Eagan TM. Chronic obstructive pulmonary disease is associated with low levels of vitamin D.PLoSOne.2012;7(6):e38934.doi:10.1371/journal.pone. 0038934.Epub 2012 Jun 21.
18. BlackPN,ScraggR.Relationshipbetweenserum25-hydroxyvitamin d and pulmonary function in the third national healthandnutritionexaminationsurvey. Chest. 2005 Dec;128(6):3792-8.
19. Janssens W, Lehouck A, Carremans C, Bouillon R, Mathieu C, Decramer M. Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. AmJRespirCrit CareMed.2009 Apr15;179(8):630-6.doi: 10.1164/rccm.200810-1576PP. Epub 2009 Jan 22.
20. 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 Feb; 37(2):238-43.doi:10.1183/09031936.00146509. Epub2010Jul1.
21. VanderWielenRP,LowikMR,vandenBergH,de Groot LC, Haller J.Serum vitamin D concentrations amongelderlypeople.EuropeLancert,2005;346:207-210.
22. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001 Aug; 22(4):477-501.
23. Jindal SK, Aggarwal AN, Chaudhry K, Chhabra SK,D'SouzaGA,GuptaD,KatiyarSK, KumarR, Shah B, Vijayan VK; Asthma Epidemiology Study Group. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci. 2006 Jan-Mar; 48(1):23-9.
24. Mahesh PA, Jayaraj BS, Prahlad ST, Chaya SK, Prabhakar AK, Agarwal AN, Jindal SK. Validation of a structured questionnaire for COPD and prevalence of COPD in rural area of Mysore: A pilot study. Lung India.2009Jul;26(3):63-9.doi:10.4103/09702113.53226.
25. Parasuramalu BG, Huliraj N, Prashanth Kumar SP; Gangaboraiah,RameshMasthiNR, SrinivasaBabu CR. Prevalence of chronic obstructive pulmonary diseaseand its association with tobacco smoking and environmental tobacco smoke exposure among rural population.IndianJPublicHealth.2014Jan-Mar;58(1): 45-9. doi: 10.4103/0019-557X.128166.
26. J. De Batlle, I. Romieu, J.M. Antó, M. Mendez, E. Rodríguez, E. Balcells. PAC-COPD Study Group: Dietary habits of firstly admitted Spanish COPD patients. Respir Med. 2009;103:1904-1910.
27. Sanjari M, Soltani A. The effect of vitamin D on COPDexacerbation. JDiabetesMetabDisord.2015;15 (1):33.
28. Rezk A. effect of vitamin D replacement in COPD. EJCDT. 2015; 64.2.
29. Kocabaş A, Karagüzel G, Imir N, Yavuzer U, Akçurin S. Effects of vitamin D receptor gene polymorphisms on susceptibility to disease and bone mineral density in Turkish patients with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2010 Dec; 23 (12):1289-97.
30. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH. Cutting edge: 1, 25- dihydroxyvitamin D3 is a direct inducer ofantimicrobial peptide gene expression. J Immunol. 2004 Sep; 54: 64-9.
31. Sanket S. Relation between vitamin d deficiency andseverityofCOPD.JClinDiag2016.10(1);oc16-9. 173 (5):2909-12.
32. Cutillas-Marco E, Fuertes-Prosper A, Grant WB, Morales-Suárez-Varela M. Vitamin D deficiency in South Europe: effect of smoking and aging. PhotodermatolPhotoimmunolPhotomed. 2012 Jun; 28(3):159-61. doi: 10.1111/j.1600-0781.2012. 00649.x.
33. Moberg M, Vestbo J. prognostic value of CRP and Vitamin D in severe COPD. The scientific World Journal2014:140736,7.dx.doi.org/10.1155/2014/140736.
34. Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, HunninghakeGM,FornoE,LaskeyD,SylviaJS,Hollis BW, Weiss ST, Litonjua AA. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica.AmJ Respir CritCareMed. 2009 May1;179 (9): 765-71.doi:10.1164/rccm.200808-1361OC.Epub2009Jan29.
35. Cilingir BM, Gunbatar H. Relationship between COPD and levels of vitamin D. Dicle medical journal. 2015:42 (2):158-165.

ISSN (O): 2687-5365; ISSN (P): 2753-6556