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Research Article

Is There Relation Between 25(OH) Vitamin D and Chronic Obstructive Pulmonary Disease?

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Abstract

Background: Vitamin D level can affect pulmonary function in patient who have chronic obstructive pulmonary disease (COPD).
Objectives: There are few studies that assess this subject, so we investigate the relation of Vitamin D and COPD.
Materials and Methods: A case-control study was conducted among the patients referred to the pulmonology clinic of Shahid Beheshti hospital of Hamadan, in which 68 of patients were assigned into the case group with COPD and 68 patients into the control group. Both groups were evaluated for respiratory differences as clinical or laboratory and the blood level of vitamin D was measured.
Results: Of 136 evaluated participants with the mean age of 58.83 years old, 68 patients were studied as case group consisting of 2 females and 66 males. The results suggested that the serum level of vitamin D in COPD patients and control group patients were 22.22 ± 15.83 ng/mL and 27.47 ± 21.43 ng/mL, respectively. It was also found that there was a positive correlation between lung function and serum level of vitamin D in COPD. The greater the severity of COPD (forced expiratory volume in the first second [FEV1] lower level) was, the more the vitamin D deficiency was seen. It was also clarified that there was an indirect correlation between the serum level of vitamin D in COPD patients and body mass index (BMI).
Conclusions: Prevalence of vitamin D deficiency in COPD patients was more than that in control group patients. Due to the growing prevalence of vitamin D deficiency in such patients, any use of vitamin D maybe suggested.
Keywords: COPD, Vitamin D, FEV1, BMI, GOLD Criteria

Background

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death in human beings, and also millions of people around the world are suffering from it. Several risk factors have been discovered associated with COPD. Avoiding risk factors can slow down or stop the progression of COPD. Different factors have been identified that shows in patients with COPD, the pulmonary dysfunction could significantly affect the function of other organs of the body which in turn exacerbate dysfunction in COPD patients (1). These factors include tumor necrosis factor alpha (TNF-α) and a wide range of interleukins. There are some evidence of the effect of diet on forced expiratory volume in the first second (FEV1) and lung capacity (2,3). Recently, the serum levels of vitamin D in patients with COPD have been drawing attention as a factor which can be correlated with the degree of disability caused by COPD (4). Reduction of serum levels of vitamin D has an effect on so many diseases, including osteoporosis, hypertension (HTN), ischemic heart disease, type I diabetes and cancer (2,5-9). At the beginning, it was the increase in incidence of osteopenia and osteoporosis in patients with COPD that made scientists to discover this relationship (10). The new findings suggest that serum vitamin D levels can be directly related to the parameters of pulmonary function test (PFT) (11). These findings led scientists to better understand the pathophysiological role of vitamin D in the development of disability in patients with COPD. In addition to the receptors that vitamin D3 has in the digestive tract, glands, parathyroid glands, and bone cells, it plays multiple roles in the inflammatory system of the body. Vitamin D receptors can widely be found on monocytes, activated macrophages, dendritic cells, NK cells and T, B lymphocytes. The activation of vitamin D receptors on these cells has a strong anti-proliferative and immunomodulatory effect (12). Currently, lack of vitamin D is widely spreading among people which is related to the individuals' nutrition, lifestyle and behavioral changes (13).

Objectives

COPD is one of the common respiratory diseases in our country. Since the complications are very difficult for the patient to bear, it causes enormous cost to the country's health system, and also the fact that prevention is always better than cure for any disease, identifying the risk factors seems to be essential. Thus the current study was designed to investigate the correlation between vitamin D deficiency and the pathogenesis of COPD.

Subjects and Methods

Study Design and Settings

A case-control study was conducted on the individuals who had a stable COPD and referred to the Lung Clinic in Shahid Beheshti hospital of Hamadan-Iran, between March 2014 and February 2016.

Study Population

All the patients were initially examined by the execution of the project and were enrolled only if they were ill; otherwise they were excluded from the study. However, in order to confirm the diagnosis and determine the severity of pulmonary disease, the patients underwent spirometry with respect to the standards. The criteria of airway hyperresponsiveness and its reversible component were determined using standard methods. Severity of the disease was also divided into four stages according to the GOLD criteria (20). Inclusion criteria for the study group consisted of developing COPD, 18 to 75 years of age, not being pregnant, not using calcium and vitamin D in the past 3 months, no history of drug use, no history of malabsorption diseases, and no history of using drugs that affect the absorption and metabolism of vitamin D. The exclusion criteria for the study group included the patient's unwillingness to continue to cooperate; pregnancy, the patient's need to take drugs that affect the metabolism of vitamin D, and also developing other diseases that affect spirometry. The control group was selected from relatives of the patients with COPD. These people had no history of respiratory disease, as well as use of calcium and vitamin D in the past 3 months. After determining the case and control groups for the study and also after providing the written informed consent, the participants were enrolled. The patients were asked for medical history. Moreover, physical examination including measurement of height - weight and spirometry was performed on the participants. Demographic data, clinical findings, spirometric parameters and vitamin D test results were recorded for patients.

Paraclinical Measurements

Five cubic centimeter (cc) venous blood was taken to measure the level of 25-hydroxy vitamin D. Then, the serum was separated and stored at the temperature of -20°C in the laboratory. The test was conducted by enzyme-linked immunosorbent assay (ELISA) using Euroimmun kits. Spirometry with and without bronchodilator was done at the spirometry unit in the Shahid Behesti University by a technician using a device made in the German company *ZAN*. Height of the patients was measured using wall mounted stadiometer and their weight with a SOGA digital scale. The technicians were all blinded to the patients in both case and control groups and study protocols to prevent any bias when processing the samples and measurements.

Ethics Statement

The study was approved by the Ethics Committee of the Hamadan University of Medical Sciences. The study was conducted in accordance with the Declaration of Helsinki. All participants signed and filled out the informed consent form.

Statistics

Statistical analysis was done using SPSS version 18.0 software (SPSS Inc., Chicago, IL). The means of groups were compared using parametric or non-parametric tests according to 1-sample Kolmogorov–Smirnov (K-S) test for normal distribution. The distributional properties of continuous data were expressed as mean ± standard deviation (SD). The categorical data were presented by frequency and percentage. The relationship between quantitative variables was measured using the *t* test. Differences in categorical variables were analyzed using the chi-square test (linear by linear correlation). ANOVA test was used in order to evaluate the differences between vitamin D levels in 3 age categories. Finally, Pearson correlation coefficient was applied to identify the probable correlation between vitamin D levels and FEV1 levels. *P* value less than .05 was reported as statistically significant.

Results

This case-control study evaluated the study goals among 68 cases of COPD and 68 healthy individuals. Significance level or first type error was considered 0.05. The mean age of total study population, case and control groups, were 58.83, 63.01 ± 11.37 and 54.64 ± 12.72 respectively. The differences were statistically significant. Restriction method was used in order to match the age variable. Because of the wide range of age groups, to test the hypotheses of the study, this variable was categorized as: 23 to 39, 40 to 59, and 60 to 85 years of age. The most frequent age group was 60 to 85 years old (49.26%). In this study, 97.06% of attendees were men.

The overall vitamin D level was equal to 24.83 ng/mL. Although the mean of vitamin D level in the case group was lower than that in the control group, this difference was not statistically significant (Table 1). In other words, in general, there was no link between vitamin D levels and COPD.

Vitamin D levels were divided into 4 categories which showed those with deficient vitamin D level were the most frequent ones (44.12%). Vitamin D level less than 20 ng/mL was classified as deficiency of vitamin D (44.12%), 20 to 30 ng/mL as an insufficient level of vitamin D (29.41%), 30 to 100 as sufficient levels (25.74%), and over 100 ng/mL was considered as vitamin D intoxication (0.74%).

The results showed that there was no statistically significant relationship between categories of vitamin D and study case and control groups. Moreover, no significant difference was found between levels of vitamin D among different age groups; in other words, there was no relationship between age groups and vitamin D deficiency (Table 2).

Statistically, no difference was found between different levels of vitamin D among both sexes; so there was no relationship between gender and vitamin D deficiency. Although the mean level of vitamin D was higher among women than men, the difference was not statistically significant (P = .2).

Using variance analysis, it was found that the mean level of vitamin D in all 3 age groups were not statistically different (P = .07, F = 2.68).

In our study, the mean of body mass index (BMI) of the control group was higher than that of the case group, and this difference was statistically significant (P = .00). The mean BMI was equal to 22.45 ± 4.73 kg in the case group, whereas in the control group, it was equal to 25.01 ± 3.64 kg/m.

After the classification of BMI in the control and case groups, it was observed that BMI of individuals who suffered from COPD was less than that of healthy individuals. The differences were statistically significant. Vitamin D levels were not different among groups of classified BMI.

In this study, the FEV1/FVC ratio of all individuals in the case group was less than 0.7, and in the control group it was greater than 0.7. FEV1 was classified among the case group patients which showed that there was a positive relationship between FEV1 and vitamin D levels. This means that as FEV1 value increases, the level of vitamin D increases as well. The Pearson correlation coefficient was calculated to be 0.2; in other words, FEV1 value increases as the level of vitamin D increases, even though, the intensity is not great according to the Pearson correlation coefficient (Figure 1). The differences between the vitamin D levels and FEV1 categories were evaluated and the results were provided (Table 3).

Table 1. Vitamin D Levels in Study Groups

Groups	Mean ± SD	*P* Value [a]
Case	22.22 ± 15.83	.112
Control	27.42 ± 21.43	

Abbreviation: SD, standard deviation.
[a] *T* test was used to evaluate the statistical differences.

Discussion

The aim of this study was to evaluate serum levels of vitamin 25 (OH) D3 among those suffering from COPD compared to those who did not develop COPD. There is ample evidence that there is a relationship between deficiency of vitamin 25 (OH) D3 and chronic diseases such as different kinds of cancer, autoimmune disease, infectious disease, and cardiovascular disease (14-16). The mean serum level of vitamin D in men was 25.18 while the mean serum level of vitamin D in women was equal to 12.85; however, due to the small number of women participating in the study, correct interpretation

Table 2. Differences Between Demographic and Clinical Features of Study Groups and Vitamin D Levels

Variables		Vitamin D Levels				Total	*P* Value[a]
		Deficient	Insufficient	Sufficient	Intoxication		
Study groups, No. (%)	Case	32 (47.1)	19 (27.9)	17 (25.0)	0 (0.0)	68 (100)	.721
	Control	28 (41.2)	21 (30.9)	18 (26.4)	1 (1.5)	68 (100)	
	Total	60 (44.1)	40 (29.3)	35 (25.8)	1 (0.8)	136 (100)	
Age (y), No. (%)	23-39	6 (66.7)	3 (33.3)	0 (0)	0 (0)	9 (100)	.332
	40-59	30 (50.0)	16 (26.7)	14 (23.3)	0 (0)	60 (100)	
	60-85	24 (35.9)	21 (31.3)	21 (31.3)	1 (1.4)	67 (100)	
	Total	60 (44.1)	40 (29.4)	35 (25.8)	136 (100)	136 (100)	
Gender, No. (%)	Male	57 (43.1)	39 (29.5)	35 (26.5)	1 (0.8)	132 (100)	.570
	Female	3 (75.0)	1 (25.0)	0 (0)	0 (0)	4 (100)	
	Total	60 (44.1)	40 (29.4)	35 (25.8)	1 (0.4)	136 (100)	

[a] Chi-square test was used in order to assess the differences between above variables and vitamin D levels.

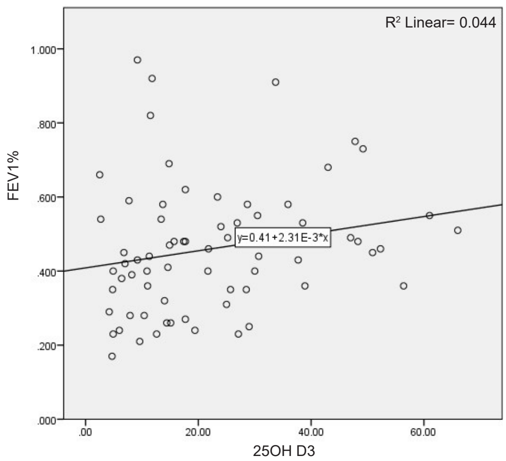

Figure 1. Correlation Between Vitamin D Levels and FEV1.

could not be provided. Comparison of the results of the current study with the results of a study conducted by Reiaszade et al in Tehran showed that serum levels of vitamin D in women were less than those in men; a result which was consistent with our result. It could be due to differences in lifestyle or the cover that women in the society need to wear (17). Today, more attention is paid to vitamin D deficiency and lung diseases, particularly COPD among chronic diseases (18). Previous studies have found that serum levels of vitamin 25-OHD are lower in people who suffer from COPD compared to healthy subjects (15,19). In addition, serum levels of vitamin D in healthy individuals or among individuals in the control groups were deficient (was in an insufficient level). People with COPD may be less exposed to the sun due to their disease; this has intensified lack of vitamin 25-OHD in their body. Another reason for low levels of vitamin D in patients with COPD is consumption of corticosteroids and also long-term oxygen therapy in these patients (20). Vitamin 25-(OH) D can be produced in the lungs; that is why COPD patients are at the risk of reduction of the desirable vitamin 25-OHD level (21,22).

In this study, BMI of the case group was equal to 22.45 while the anthropometry index in the control group was 25.01. This difference was statistically significant. The finding of the current study was consistent with that of Janssens et al (15) which showed a negative correlation between vitamin D levels and BMI. Our results showed that increasing the levels of vitamin 25-OHD results in the lung function improvement, so that there would be a positive correlation between levels of vitamins 25-OHD and FEV1 with a Pearson correlation coefficient of 0.2. The findings of this study were consistent with the findings of Monadi et al (23) which showed a dose-response relationship between level of vitamin 25-OHD and FEV1. In other words, in severe cases of COPD, vitamin D deficiency is more common (15). The mean age of the case group was greater than that of the control group, 63.01 and 54.64 respectively; this difference was statistically significant which indicates that risk of COPD disease increases with age. The current study was similar to the study of Janssens et al in that the mean age of participants with COPD was 66 years, while the control group had a mean age of 61 years, and this difference was statistically significant (10). Although the desired level of 25-hydroxy vitamin D is controversial among experts, in this study, any level lower than 20 ng/mL was considered as a vitamin deficiency which is an acceptable threshold level among most of the experts. In our study, 47.06% of participants with COPD had a vitamin level of less than 20 ng/mL, while in the control group, 41% showed a vitamin level below 20 ng/mL. It was not found any statistical relationship between vitamin D level and COPD in both control and case groups which can be affected by sample size or be due to the selected control group, but the difference was clinically significant (24). It is worth mentioning that epidemiological studies are usually encountered with some mistakes and errors. The current study might have a bias called volunteer bias which indicates that those who have been selected,

Table 3. Differences Between Various Vitamin D Levels and FEV1 and BMI

FEV1 Levels		Vitamin D Levels				Total	*P* Value [a]
		Deficient	Insufficient	Sufficient	Intoxication		
FEV1	Mild	3	0	1	0	4	.123
	Moderate	6	5	8	0	19	
	Sever	13	10	8	0	31	
	Very sever	10	4	0	0	14	
	Total	32	19	17	0	68	
BMI	Low	12	3	3	0	18	.790
	Normal	31	18	17	0	66	
	Overweight	16	15	14	1	46	
	Obese	1	4	1	0	6	
	Total	60	40	35	1	136	

Abbreviations: FEV1, forced expiratory volume in the first second; BMI, body mass index.
[a] Chi-Square test was used to assess the differences between variables.

possibly are not representative of the patients and healthy individuals in the society. The low number of women that participated in the study reduces the generalizability of study.

Finally, according to the results of this study, some suggestions are offered including: conducting studies with larger sample size to do more accurate investigation of the relationship between COPD and serum levels of vitamin D, the implementation of more robust epidemiological studies such as clinical trials or cohort clinical trials, and also taking into account other confounding variables such as smoking and seasonal changes in future studies.

Conclusions

Given the increasing prevalence of vitamin D deficiency and the important role of vitamin D in chronic diseases, especially obstructive pulmonary disease, the patients affected by this disease should be seriously assessed. The treatment of vitamin D deficiency in these patients is recommended until an optimal level of vitamin D could be achieved.

Authors' Contribution

Farshid Divani developed the concept and designed the study and supervised all stages of the process. Alireza Zahedi interpreted the output data, wrote the manuscript and supervised the study designing. Maryam Vasheghani interpreted the data and helped in clinical aspects of study. Mohammad Jafari lent technical support and conducted pathological studies. Jalal Poorolajal and Mohammad Faryadres helped in statistical and epidemiological aspects of the study.

Conflict of Interest Disclosures

All authors declare that there is no conflict of interests.

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