Immunopathologia Persa
http www.immunopathol.com
DOI:10.15171/ipp.2019.22

Administration of vitamin D to ameliorate dyspnea of chronic obstructive pulmonary disease patients: a randomized controlled trial

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Received 13 April 2019
Accepted 17 July 2019
Published online 2 September 2019

Keywords: Chronic obstructive pulmonary disease, Spirometry, Vitamin D, Immune system

Abstract

Introduction: As one of the most common causes of human morbidity and mortality, chronic obstructive pulmonary disease (COPD) affects millions around the world. Some evidences have already considered about association between serum levels of vitamin D and COPD.
Objectives: This study was aimed to evaluate the effects of vitamin D supplementation on COPD improvement.
Patients and Methods: This study was designed as a randomized controlled trial. Forty COPD patients with vitamin D deficiency were enrolled into two groups; cases group who administered vitamin D and control group who received placebo. The severity of dyspnea and spirometric indices were analyzed in both groups. Values were presented as mean and standard deviation (SD) and differences were considered significant at the level of $P<0.05$.
Results: Spirometric indices did not show significant differences before and after vitamin D administration (P>0.05). Dyspnea severity was significantly improved after receiving vitamin D supplementation in comparison with placebo consumption (P=0.03).
Conclusion: Spirometric indices were not affected during vitamin D supplementation therapy but it showed a significantly positive effect on the curing of dyspnea. Therefore, adjuvant therapy of COPD using vitamin D supplementation is recommended to better handling of dyspnea in COPD cases.
Trial Registration: Registration of trial protocol has been approved in Iranian registry of clinical trials (identifier: IRCT2017042919554N12; http://www.irct.ir/trial/17481, ethical code# ZUMS.REC.1395.202).

Citation: Ghodrati S, Ezzatpanah A, Asadi-Khiavi M, Alian Samakkah S, Esmaeilzadeh A, Pezeshgi A. Administration of vitamin D to ameliorate dyspnea of chronic obstructive pulmonary disease patients: a randomized controlled trial. Immunopathol Persa. 2019;5(2):e22. DOI:10.15171/ipp.2019.22.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the common causes of human mortality affecting millions around the world. The global lung foundation estimates that COPD rate, as the third leading cause of death will increase by 2020 (1). The obstruction of airways during COPD is not completely reversible and sometimes is progressive and is associated with abnormal lung inflammatory response (2). Several risk factors such as exposure to occupational dust and smoking are associated with COPD. In addition, avoiding the risk factors can slow down or stop COPD progress (3). Recently, the association between serum levels of vitamin D and incidence of COPD related disabilities was considered seriously (4). Studies have shown that vitamin D deficiency is common in patients with COPD due to less food intake, lower vitamin D synthesis in the elderly, less outdoor activity, a reduced amount of exposure to sunlight and corticosteroids consumption. It was approved that serum levels of vitamin D in COPD patients without glucocorticoid therapy are lower than healthy volunteers at the same age (5,6). Vitamin D plays an important role in the regulating of immune system via interacting between 1,25-dihydroxyvitamin D and the vitamin D

Key point

In a randomized controlled trial on forty chronic obstructive pulmonary disease patients with vitamin D deficiency, we found vitamin D supplementation had a positive effect on the improvement of dyspnea severity.

receptor (7). The increased prevalence of osteoporosis in patients with COPD persuaded scientists to concentrate about the relationship between the prevalence of this disease and the serum level of vitamin D. Subsequently, further research about serum level of vitamin D in COPD patients showed that vitamin D deficiency is clearly more common in COPD patients in comparison with the general population (8).

Objectives

The vitamin D role in the pathogenesis of COPD is unknown. Recent investigations have focused on the ability of vitamin D to modulate immune responses in COPD patients. This study was designed to determine the effect of vitamin D supplementation therapy on the clinical symptoms and spirometric indices of a group of COPD patients.

Patients and Methods

Study population

The study designated as a randomized controlled trial. The study was performed on patients who admitted as COPD cases (based on history and pulmonary function tests) in the Vali-e-Asr university hospital of the Zanjan (2016). According to global obstructive lung disease (GOLD) criteria, patients were categorized in stages of II, III and IV (11). Forty COPD patients with vitamin D deficiency were enrolled into two groups; cases group who used vitamin D and control group who received placebo. A total number of 20 patients for each group were calculated using the sample size estimation formula. Confidence level of 95% and the test power of 80% were considered statistically. Blood samples were obtained to evaluate 25-hydroxyvitamin D serum levels using enzyme-linked immunosorbent assay (ELISA) as well as serum albumin and calcium levels using spectrophotometry. A pulmonary test (spirometry) was conducted for all of them. In the next step, patients with vitamin D deficiency (less than 30 ng/mL) were randomly distributed into two groups as previously mentioned. The cases group received one vitamin D3 pearl (50 000 IU) weekly plus one calcium-vitamin D tablet daily for three months in addition to the standard treatment for COPD (according to the stage of the disease). Control group received placebo daily and weekly (similar to cases group) for three months in addition to the standard treatment for COPD (according to the stage of the disease). One month after the last dose of vitamin D and placebo, spirometry was performed again for all patients. Finally, the findings of spirometry, serum vitamin D level and degree of dyspnea based on the modified Medical Research Council (mMRC) dyspnea scale were recorded in both groups (10). Age, gender, height, weight, occupation, duration of disease, smoking per pack/year and possible history of corticosteroid consumption of patients was collected using questionnaire (11). Inclusion criteria were; COPD patients without exacerbations during the past two weeks. The vitamin D serum level lower than 30 ng/ml was another inclusion criterion. The cases with COPD treatment and routine approach for vitamin D deficiency were included. Other inclusion criteria were COPD who have not consumed vitamin D, calcium and anticonvulsants during the last 6 months. Exclusion criteria were; patients with COPD exacerbation in the last two weeks. The cases with no COPD treatment or had not vitamin D deficiency were excluded too. Accordingly, patients with COPD, who administered vitamin D, calcium or anticonvulsants during the last 6 months were excluded. Lack of cooperation as well as changing in COPD drugs were another cases for excluding. Presence of kidney disease (GFR<60 mL/min), liver disease (liver enzymes level two times more than normal levels), bone disease, granulomatous disorders, parathyroid disease, malnutrition, malabsorption (inflammatory bowel disease and celiac disease, and also any type of malignancy) were the items for excluding.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Before the study, written informed consent was obtained from all patients who participated in the study. Permission for conducting present study obtained from deputy of research in Zanjan University of Medical Sciences (#A-11-203-3). All information about individuals was coded and kept confidential. The medical ethics committee of Zanjan University of Medical Sciences approved the project (ethical code# ZUMS.REC.1395.202). This randomized controlled trial was registered in Iranian Registry of Clinical Trials (identifier: IRCT2017042919554N12; http://www.irct.ir/trial/17481).

Statistical analysis

The normality of variables distribution was evaluated using Shapiro-Wilk test. The results of quantitative variables were expressed as mean ± standard deviation (SD) and qualitative variables were expressed based on absolute and relative frequency. Parametric two samples *t* test and non-parametric chi-square test were also applied. For data analysis we used SPSS software version 22 (SPSS Inc, Chicago, IL). All statistical differences were considered significant at the level of *P* value lower than 0.05.

Results

A total number of 40 patients with vitamin D deficiency out of 130 admitted COPD cases were identified (27 female cases and 13 male cases in the range of 31-82 years-old). The demographic characteristics of patients including age, height, weight, duration of disease and smoking, are presented in Table 1.

There was no significant difference between demographic variables of cases and control groups. The average age of women and men was 56.92 ± 13.81 years and 60.69 ± 15.6 years old, respectively since, there was no significant difference between the two groups (P =

Table 1. Comparison of COPD associated variables in both groups

	Cases group	Control group	*P* value*
Age (y)	62.05±13.58	54.25±14.34	0.89
Height (cm)	160.35±8.51	157.95±9.23	0.39
Weight (kg)	69.35±13.15	68.91±8.47	0.08
BMI (kg/m^2)	27.02±5.1	27.94±5.01	0.5
Disease duration (y)	10.22±2.01	6.55±1.53	0.15
Smoking (pack/year)	3.55±1.38	6.41±2.13	0.14

0.4). In this study, 11 patients (27.5%) were smokers and nine cases cease smoking before the start of the study. Regarding severity of dyspnea, cases in the stage II (50% of cases group) and stage III (25% of cases group) treated with vitamin D at the beginning of the study. Regarding severity of dyspnea, patients in stage II (60% of control group) and stage III (25% of the control group) were enrolled in the control group. Both groups did not show significant differences about severity of dyspnea at the beginning of the study ($P=0.4$). In the term of smoking (20% of cases group and 35% of the control group) did not show significant differences as well ($P=0.5$). They did not show any significant difference ($P=0.5$) about corticosteroid therapy in each group. The frequency of dyspnea severity (based on mMRC criteria) was compared before and after treatment in both groups. According to the results, 20% of mMRC1 patients and 65% of mMRC2 patients in the cases group showed the clinical improvement of dyspnea. In the control group who treated with placebo, 25% of mMRC2 patients and 55% of mMRC3 patients showed exacerbation of dyspnea at the end of the study. The severity of dyspnea was significantly reduced ($P=0.03$) in cases group after receiving vitamin D pearl compared to the control group (Table 2).

As shown in Table 3, the FEV1 levels were 68.95±11.02 percent and 63.75±9.34 percent in the control group before and after treatment respectively that showed a significant decrease in lung functionality ($P=0.01$). The FEV1 levels were 67.13±17.30 percent and 68.79±14.19 percent in the control group before and after treatment with vitamin D respectively that showed no significant changes in lung functionality ($P=0.5$). In other words, the administration of vitamin D did not improve the spirometric indices.

Discussion

As it was already mentioned, all participants were matched about variables that interact with COPD. About 20%, 65% and 10% of patients in the cases group were in mMRC classes of I, II and III respectively after three-month treatment with vitamin D. In the control group, 25%, 55% and 20% of patients were in mMRC classes of II, III and IV respectively since the differences between two groups were statistically significant ($P=0.03$). In other words, treatment with vitamin D improves the degree of dyspnea (based on mMRC criteria) in patients with COPD, while the amount of dyspnea in patients was slightly exacerbated by placebo. Studies showed that, when the serum level of vitamin D exceeds 20 (ng/mL), it plays a protective role against moderate to severe attacks of COPD (13). Studies have shown, a significant correlation between serum levels of vitamin D and pulmonary functionality in COPD patients (6). A direct linear relationship between serum vitamin D levels and FEV1 volume was also confirmed (9,14). Several studies have been conducted on the relationship between serum vitamin D levels with COPD severity. There were meta-analytic studies to compare serum levels of vitamin D in patients with mild to moderate COPD (GOLD 1-2) and moderate to severe COPD (GOLD 3-4) that

Table 2. Comparison of dyspnea severity (based on MMRC criteria) before and after treatment in each group

Dyspnea severity	Before		*P* value	After		*P* value*
	Cases group No. (%)	Control group No. (%)		Cases group No. (%)	Control group No. (%)	
MMRC 1	1 (5)	0 (0)		4 (20)	0 (0)	
MMRC 2	10 (50)	12 (60)		12 (60)	5 (25)	
MMRC 3	5 (25)	5 (25)	0.4	2 (10)	11 (55)	0.03
MMRC 4	2 (10)	3 (15)		1 (5)	2 (10)	
MMRC 5	2 (10)	0 (0)		1 (5)	2 (10)	
Total	20 (100)	20 (100)	-	20 (100)	20 (100)	-

*$P<0.05$ was considered as statistically significant.

Table 3. Comparison of spirometric indices before and after treatment in each group

Time	FEV1 (%)		*P* value	FEV(L)		*P* value*
	Cases group (mean ± SD)	Control group (mean ± SD)		Cases group (mean ± SD)	Control group (mean ± SD)	
Before	67.13 ± 17.30	68.95 ± 11.02	0.60	1.56 ± 0.69	1.66 ± 0.40	0.50
After	68.79 ± 14.19	63.75 ± 9.34	0.10	1.66 0.61±	1.55 0.39±	0.50
P value	0.50	0.01	-	0.07	0.01	-

*$P<0.05$ was considered as statistically significant.

indicated, low serum levels of vitamin D in severe cases in comparison with mild disease (15-17). In a systematic review survey on about 21 studies, after comparing of 4818 COPD cases with 7175 controls, it was shown that the serum levels of vitamin D in OPCD patients was significantly lower than those in the control group. It stated that low serum levels of vitamin D were associated with COPD exacerbation and the severity of the disease as well, but no association was found between COPD attacks and vitamin D levels (18). It was revealed in another study that the frequency of decrease in serum levels of vitamin D in COPD patients was very common and associated with the vitamin D binding gene varieties. In this study, after 3months administration of vitamin D supplementation therapy, a limited effect on the reduction of the severity of clinical symptoms and spirometric indices in COPD patients compared to placebo was detected (19). In a recent study, the relationship between serum levels of vitamin D and lung function in patients with COPD was evaluated. Standard COPD treatments were provided for all 100 participants and 50 cases who received an extra 100 000 IU vitamin D every month up to 3 months. At the end of the study, people who received extra vitamin D had more respiratory muscle strength and more walking ability in comparison with those who did not receive vitamin D (19). The study conducted by Sanjari et al on 120 patients with vitamin D deficiency, showed that one-week short-term treatment with vitamin D (50 000 units) or daily Rocaltrol (0.25 μg) showed no significant effect on the improvement of spirometric indices in comparison with placebo. However, the quality of life and severity of dyspnea were significantly improved in patients receiving vitamin D and Rocaltrol compared to placebo receiving group, which was consistent with our study (20). To find the effects of vitamin D on asthma patients, Ginde et al found that vitamin D reduces respiratory infections, prevents asthma attacks, reduced steroid resistance, and also reduced the chronic asthma control (21). Recently, several studies have shown that replacement therapy with vitamin D reduces COPD exacerbations and improves FEV1 in patients with COPD (22). Jung et al evaluated the association between vitamin D and lung function in patients with chronic lung obstruction. In this study, serum levels of vitamin D in 193 patients with COPD were measured. Then, lung function in each patient was evaluated after a 6-minute walk. The study showed, 6.2% of patients had normal serum levels of vitamin D, 14.5% of them had low serum levels of vitamin D and 79.3% of patients showed vitamin D deficiency. Lung function in these patients showed people with vitamin D deficiency caused the lowest lung functionality. The found, the prevalence of vitamin D deficiency was high among the Korean COPD patients. Experiences have shown that adjuvant therapy with vitamin D supplements in addition to the standard COPD treatment should be used for these patients (23). The lack of significant vitamin D modulation effects in patients with COPD can be due to small and large airway obstruction, which appears to be irreversible due to the regenerative process (24).

Vitamin D applies a variety of actions, such as immune system modification, anti-inflammatory role, natural resistance to certain diseases, induction of immune responses to macrophages, induction of Th1 cell immune responses and T Cell differentiation to produce specific immune responses against infections. Vitamin D also plays a role in the regulation of innate and acquired immune responses due to specific cytokines. Vitamin D, depending on the micro-environment, dosage, and route of entry, can play a role in regulating T-reg, CD38 positive B cells, and CD4 positive Th17. Vitamin D also plays an important role in signaling and macrophage stimulation to increase response to mycobacterial infections (25,26). An important role of vitamin D in interacting with innate immunity and maintaining the normal functioning of the immune system has been demonstrated. Therefore, more studies are necessary to detect exact role of vitamin D COPD patients.

Conclusion

In this study, vitamin D supplementation showed a positive effect on the improvement of the dyspnea severity (based on mMRC criteria) in COPD patients while placebo exacerbated dyspnea. Vitamin D did not have a significant effect on the spirometric indices in comparison with placebo in patients with COPD. Regarding the results of the presented study, in addition to the standard treatment for COPD, simultaneous standard treatment of COPD with vitamin D possess a positive outcome to rehabilitate and prevent exacerbation of dyspnea in patients with COPD. It recommends that large number of COPD cases should consume vitamin D therapy for a prolonged time to obtain accurate results.

Study limitations

Our study was conducted on a limited proportion of patients in a short time. We suggest investigating a large group in the future similar studies.

Authors' contribution

SD and AE conceived the study, design idea and data analysis. AEs contributed to immunological advising. MAK contributed to clinical advising. SAS contributed to editing of the paper. AP contributed to the final edition. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

This study was approved and granted by Zanjan University of Medical Sciences (#A-11-203-3).

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