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CLINICAL TRIAL REPORT

Impact of vitamin D on spirometry findings and quality of life in patients with chronic obstructive pulmonary disease: a randomized, double-blinded, placebo-controlled clinical trial

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Abstract: COPD is an irreversible chronic illness with airflow limitation. The aim of the current study was to assess the role of vitamin D_3 on quality of life and pulmonary function in patients with COPD. A randomized, double-blinded clinical trial was conducted in 63 patients with COPD. Patients were placed into intervention and placebo groups. Each individual in the intervention group took 50,000 IU vitamin D_3once a week for 8 weeks and then once a month for 4 months. There was no significant difference among FEV_1, FEV_1 /FVC, and number of exacerbations in patients with COPD ($P>0.05$). In the intervention group, a significant difference was observed in quality of life at 2 months ($P<0.001$) and 6 months ($P<0.001$). In addition, qualitative analysis showed that the status of exacerbation had not got worse six months after initiation in the intervention group. The current study shows that consumption of 50,000 IU vitamin D_3, as a convenient supplementation in a daily diet, is able to increase quality of life in patients with COPD.

Keywords: airflow obstruction, chronic, 25-hydroxyvitamin D_3, life quality

Introduction

COPD is a chronic inflammatory disorder with irreversible and progressive limitation of expiratory airflow, mainly affecting the small airways, that is associated with systemic inflammation and multiorgan involvement.[1] It was estimated that COPD had caused 3.2 million deaths worldwide in 2015.[2] In Europe, 40 million people have different stages of COPD, of which 60% suffer from significantly impaired lung function.[3]

Different risk factors have been suggested for COPD development, including genetic and environmental factors; however, cigarette smoking is known to be the most damaging factor.[4] Other risk factors include passive smoking, hyperreactivity of airways, occupational exposure, air pollution, male sex, advanced age, respiratory infection, and low socioeconomic status.[2,5–7]

There is a significant correlation between vitamin D_3 deficiency and COPD severity. Vitamin D_3 plays an important role in COPD pathogenesis.[8] It has a variety of effects on human bodyfunction, including reduced cell proliferation,[9] increased apoptosis, and[10] enhanced differentiation. Vitamin D_3 is also a potent regulator of such biological phenomena as angiogenesis, extracellular matrix production, and immunoresponse.[11] Vitamin D_3 supplementation decreases the risk of acute respiratory

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infections and exacerbations of asthma.[2] Jolliffe et al showed beneficial effects of vitamin D_3 in patients with COPD who had suffered vitamin D_3 deficiency (<10 ng/mL).[2] They also confirmed that vitamin D_3 metabolites play a key role in inducing anti-infection effector mechanisms and decrease inflammatory responses.[2] There have been fewer studies done on the role of vitamin D_3 in patients with COPD. Vitamin D_3 may affect quality of life, lung function, and number of exacerbations in patients with COPD.[6,7,12] Han et al investigated the effects of vitamin D_3 in rat models of COPD.[12] They showed that vitamin D_3 was able significantly to reduce inflammation and improve lung function. They believed that vitamin D_3 could be a novel clinical approach to treat patients with COPD.[12]

There have not been any randomized, double blinded, placebo-controlled clinical trials done on the effectiveness of vitamin D_3 supplementation in patients with COPD. This study was designed to evaluate the effectiveness of vitamin D_3 on quality of life، lung function, and number of exacerbations in patients with COPD.

Methods

A randomized, double-blinded, placebo-controlled clinical trial was conducted on patients who had been referred to the respiratory clinic of Razi Hospital between August and December 2015 (Figure 1). This was a pilot study, and the sample size was set at 30 patients in both the control and intervention groups. Levels of vitamin D_3 were measured in eligible patients before intervention. Sampling was performed in the same season, with the same daily activity and the same sunlight exposure.

Patients who were included had 10–30 ng/mL vitamin D_3 as per GOLD guidelines.[13] Cell counts, liver-function tests, ischemic electrocardiographic changes, calcium, phosphorus, andalkaline phosphatase of eligible patients

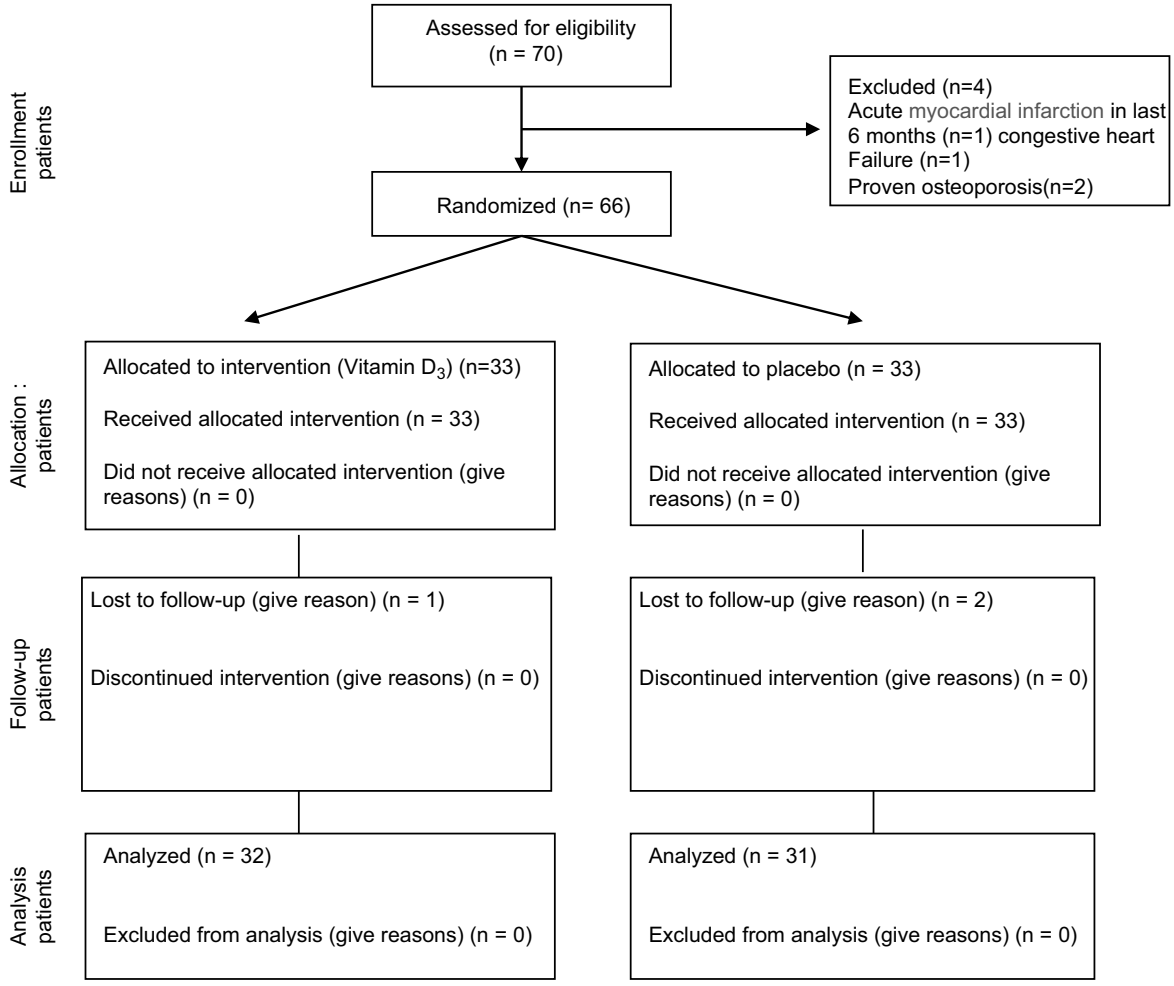

Figure 1 Study flowchart (CONSORT format).

were normal. Patients with COPD were stable in terms of physical and clinical health.

Patients not included had congestive heart failure, osteoporosis, acute myocardial infarction, glomerular filtration rate ≤45 mL/min/1.73 m^2,[14] hypercalcemia (~>10.3), malignancy, and sarcoidosis. In addition, patients who had used long-term azithromycin, with very low levels of vitamin D_3 (<10 ng/mL), and who took antiepileptic drugs were excluded.

Clinical symptoms of eligible patients included shortness of breath, especially during physical activities, wheezing, chest tightness, clearing the throat first thing in the morning, and a chronic cough with mucus (sputum).

Primary outcomes of the study were quality of life measured by COPD Assessment Test (CAT) score and lung function evaluated by spirometry of patients with COPD. It is important to say that chest X-rays were not used for patients with COPD.

Study valuables comprised age, sex, body-mass index, cigarette smoking, FEV_1, FEV_1/FVC, number of exacerbations, CAT score, COPD severity, and vitamin D_3 in blood.

Patients with COPD received 0.5–1 mg steroid per kilogram of body weight when exacerbating for 7–14 days. Both patients and questioners did not have any information from the study groups. Subsequently, placebo (gelatin) and vitamin D_3 were placed in two separate envelopes, then classified according to random blocks. We used stored plasma samples to measure circulating vitamin D_3metabolites, which is the accepted biomarker for vitamin D_3.[15] In the next stage, radioimmunoassays wereconducted to measure vitamin D_3 levels.[16]

Finally, 63 patients remained: 32 for intervention and 31 as controls. The study received ethics approval from the Committee on Publication Ethics of Guilan University of Medical Sciences, and patients filed written informed consent. General health questionnaires were used to enroll patients with symptoms of COPD. The CAT questionnairewas first translated into Persian and then back into English.

Patients placed in the intervention group took 50,000 IU vitamin D_3, and those in the control group received placebo once a week for 8 weeks, then once a month for 4 months. After 6 months, the same questionnaire was used. Double-blinding was applied on both patients and care providers during the study.

Statistical analysis

The χ^2 test was performed to compare qualitative variables between two groups. Normal parameter distribution was checked by Kolmogorov–Smirnov test. Student's *t*-test and paired *t*-test were used for variables distributed normally. Mann–Whitney *U* and Wilcoxon tests were performed on

Table 1 Studied variables before intervention in both control and vitamin D groups

	Variables	Group		*P*-value
		Intervention (vitamin D_3)	Control (placebo)	
The beginning of the study	Age (years)	67.9±7.9	68.4±7.8	0.748*
	Sex (male)	30 (93.8%)	30 (96.8%)	0.573**
	BMI (kg/m^2)	24.33±2.13	24.55±1.94	0.665*
	Cigarette smoking (per year) (mean ± SD)	32±14	31±13	0.866*
	FEV_1 (mean ± SD)	57.98±17.67	57.7±17.99	0.949*
	FEV_1/FVC (mean ± SD)	56.75±12	58.76±9.82	0.472*
	Exacerbations, n (%)	10 (31.3%)	11 (35.5%)	0.722***
	Exacerbations (mean ± SD)	0.53±0.98	0.55±0.85	0.658****
	CAT score (mean ± SD)	15.3±7.35	15.48±9.32	0.767****
	COPD severity, n (%)	6 (18.8%)	9 (29%)	0.294**
		16 (50%)	9 (29%)	
		5 (15.6%)	9 (29%)	
		5 (15.6%)	4 (12.9%)	
	25-Hydroxyvitamin D_3 levels, ng/mL, (mean ± SD)	19.33±5.18	18.55±4.58	0.528*

Notes: *t-test; **Fisher's exact test, ***Chi squre; ****Mann–whitney.
Abbreviations: BMI, body mass index; CAT score, COPD assessment test score; FEV1, Forced expiratory volume at first second; FVC, Forced vital capacity.

variables that did not have normal distribution. Two-tailed $P<0.05$ was considered significant.

Results

In this study, 30 men (93.8%) and two women (6.3%) were in the intervention group and 30 men (96.8%) and a woman (3.2%) in the placebo group. The mean age of those in the intervention group was 67.9±7.9 years and in the placebo 68.4±7.8 years.

At the beginning of the study, FEV_1, FEV_1/FVC, and CAT scores, number of exacerbations, and percentage of severity did not show significant differences between the intervention and control groups ($P>0.05$, Table 1). Neither FEV1 nor FEV1/FVC showed significant differences between the intervention and control groups (Table 2). There were significant differences in serum levels of vitamin D_3 between the intervention and control groups (51.83 vs 19.43 ng/mL) within 2–6 months from baseline ($P<0.001$, Table 2). There were no statistical differences in exacerbations between the groups after 2 months, within 2–6 months, or after 6 months from baseline. In addition, the qualitative analysis showed that exacerbations had not worsened after 6 months in the intervention group (Table 3). CAT scores showed statistical differences between the groups at 2 months from baseline in quality of life at every stage in the intervention group (Table 3).

Discussion

The current study reported a randomized, double-blinded, placebo-controlled clinical trial on the effect of vitamin D_3 supplementation on lung function and quality of life in patients with COPD. Janssens et alshow that serum levels of vitamin D_3 had significant correlations with the severity

Table 2 Studied variables at 2 and 6 months after intervention in both control and vitamin D groups

			Intervention (vitamin D_3)	Control (placebo)	*P*-value
After 2 months	FEV_1 (mean ± SD)		58.69±17.68	57.87±18.06	0.857*
	FEV_1/FVC (mean ± SD)		57.43±12.09	58.9±9.56	0.593*
	Exacerbations, n (%)		3 (9.4%)	3 (9.7%)	>0.999**
	Exacerbations (mean ± SD)		0.09±0.3	0.1±0.3	0.968****
	CAT score		14.25±7.43	15.29±9.53	0.842****
	COPD severity, n (%)	A	6 (18.8%)	6 (19.4%)	0.665**
		B	15 (46.9%)	14 (45.2%)	
		C	3 (9.4%)	6 (19.4%)	
		D	8 (25%)	5 (16.1%)	
After 6 months	FEV_1 (mean ± SD)		58.93±17.73	58.18±17.91	0.868*
	FEV_1/FVC (mean ± SD)		57.74±11.86	59.2±9.99	0.6*
	Exacerbations, n (%)		4 (12.5%)	8 (25.8%)	0.179***
	Exacerbations (mean ± SD)		0.16±0.45	0.32±0.6	0.184****
	CAT score (mean ± SD)		13±7.47	15.65±9.46	0.250****
	COPD severity	A	6 (18.8%)	6 (19.4%)	0.979***
		B	14 (43.8%)	13 (41.9%)	
		C	5 (15.6%)	6 (19.4%)	
		D	7 (21.9%)	6 (19.4%)	
	25-hydroxyvitaminD_3 levels (mean ± SD), ng/mL		51.83±7.93	19.43±5.22	<0.001*

Notes: *Student's t-test; **Fisher's exact test; ***$\chi 2$; ****Mann–Whitney U test.
Abbreviation: CAT, COPD Assessment Test.

Table 3 Mean differences in studied variables in both control and vitamin D groups

Variables	Duration	Group	Mean ± SD	*P*-value
FEV_1	After 2 months from baseline	Intervention	0.7±1.11	0.073*
		Control	0.18±1.19	
	Between 2 and 6 months from baseline	Intervention	0.25±0.74	0.820*
		Control	0.31±1.44	
	After 6 months from baseline	Intervention	0.95±1.88	0.089*
		Control	0.49±1.22	
FEV_1/FVC	After 2 months from baseline	Intervention	0.67±1.27	0.116*
		Control	0.15±1.35	
	Between 2 and 6 months from baseline	Intervention	0.32±1.03	0.944*
		Control	0.3±1.17	
	After 6 months from baseline	Intervention	0.99±1.28	0.640**
		Control	0.45±1.51	
Exacerbations	After 2months from baseline	Intervention	−0.44±1.01	0.431**
		Control	−0.45±0.77	
	Between 2 and 6 months from baseline	Intervention	0.06±0.5	0.129**
		Control	0.23±0.5	
	After 6 months from baseline	Intervention	−0.38±0.83	0.613**
		Control	−0.23±0.72	
CAT score	After 2 months from baseline	Intervention	−1.09±1.03	0.001**
		Control	0.19±1.01	
	Between 2 and 6 months from baseline	Intervention	−1.25±1.63	<0.001**
		Control	0.35±1.02	
	After 6 months from baseline	Intervention	−2.34±1.41	<0.001**
		Control	0.16±1.04	

Notes: *Student's *t*-test; **Mann–Whitney *U* test.
Abbreviation: CAT, COPD Assessment Test.

of COPDand exacerbations.[17] They also observed that vitamin D_3 consumption improved pulmonary function and quality of life in COPD patients in six months. Patients were controlled with different doses of vitamin D_3. Serum vitamin D_3 in the intervention group increased from 19.33 to 51.83 ng/mL. Subsequently, quality of life and pulmonary function began to recover and exacerbations in patients with COPD were reduced. Furthermore, Lehouck et alreported that vitamin D_3 may reduce acute exacerbations of COPD symptoms in those with initially deficient levels.[18] On the other hand, Hornikx et al showed prescribing 3 mg vitamin D_3 every 2 months over 1 year also maintain moderate or acute exacerbations, but not for upper respiratory tract infections (<50 nmol/L or 20 ngr/mL).[19] They demonstrated that consuming 100.000 IU vitamin D_3 3 months significantly improved inspiratory muscle strength and maximal oxygen uptake.[19] In other words, deficient vitamin D_3 can also reduce actin and troponin, impair calcium uptake in the sarcoplasmic reticulum, adjust protein synthesis, and increase apoptosis.[20] Banerjee et al demonstrated that vitamin D_3 stimulated the airway smooth-muscle cells to express vitamin D_3 receptors and regulated inflammation, contraction, and remodeling in other cell types.[21]

Other studies found higher levels of vitamin D_3–binding protein in patients with COPD, which involved neutrophil chemotaxis and macrophage activation (which has an important role in COPD pathogenesis). Vitamin D_3-binding protein has a significant correlation with serum levels of vitamin D; therefore, increasing vitamin D_3 levels will increase those of vitamin D_3–binding protein.[22,23]

However, Jolliffe et al found no effect of vitamin D_3 supplementation on the rate of exacerbations among patients with COPD, but that vitamin D_3 supplementation has protective effects on patients with low vitamin D_3 (<25 nmol/L).[2]

The findings of this study have some limitations. Firstly, this study was single-centered; therefore, the results require further investigation. Secondly, liver function, electrocardiography, calcium, and albumin of COPD patients were not measured. Thirdly, the sample was small and there was low power to detect an effect from vitamin D_3. There has not been a study done on lung function, number of

exacerbations, and quality of life in patients with COPD. Further studies seem to be required in this field.

As believed, consumption of vitamin D_3 improves quality of life in COPD patients.

According to the evidence, getting 10,000 IU/day in patients with deficienct levels of vitamin D_3 (1,500–2,000 IU/day) would not be toxic.[22] Undoubtedly, vitamin D_3 therapy cheap, which and could be one of its important advantages.[23] Finally, vitamin D_3 therapy could be a useful and safe optionsi-multaneously with other procedures.

Conclusion

Vitamin D_3 (50,000 IU) supplementation can improve quality of life in patients with COPD. In fact, COPD might be controlled by different levels of vitamin D_3 in serum. We found that consuming 50,000 IU vitamin D_3 increased quality of life in COPD. In addition, we found that exacerbations had not worsened after 6 months.

Availability of data and material

Data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The approval ID of the research-ethics certificate is 1910354603 at Guilan University of Medical Sciences. This was approved on January 1, 2013.

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Disclosure

The authors report no conflicts of interest in this work.

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