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

Ali Alavi Foumani1
Mojtaba Mehrdad1,2
Alireza Jafarinezhad1
Khadijeh Nokani3
Alireza Jafari1

1Inflammatory Lung Diseases Research Center, Department of Internal Medicine, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran; 2Razi Clinical Research Development Center, Guilan University of Medical Sciences, Rasht, Iran; 3Student Research Committee, Department of Internal Medicine, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Abstract: COPD is an irreversible chronic illness with airflow limitation. The aim of the current study was to assess the role of vitamin D3 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 D3 once a week for 4 weeks and then once a month for 4 months. There was no significant difference among FEV1, FEV1/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 D3, 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 D3, 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 D3 deficiency and COPD severity. Vitamin D3 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 enhanced differentiation. Vitamin D3 is also a potent regulator of such biological phenomena as angiogenesis, extracellular matrix production, and immunoresponse.10 Vitamin D3 supplementation decreases the risk of acute respiratory
infections and exacerbations of asthma.\textsuperscript{2} Jolliffe et al showed beneficial effects of vitamin D\textsubscript{3} in patients with COPD who had suffered vitamin D\textsubscript{3} deficiency (<10 ng/mL).\textsuperscript{2} They also confirmed that vitamin D\textsubscript{3} metabolites play a key role in inducing anti-infection effector mechanisms and decrease inflammatory responses.\textsuperscript{2} There have been fewer studies done on the role of vitamin D\textsubscript{3} in patients with COPD. Vitamin D\textsubscript{3} may affect quality of life, lung function, and number of exacerbations in patients with COPD.\textsuperscript{6,7,12} Han et al investigated the effects of vitamin D\textsubscript{3} in rat models of COPD.\textsuperscript{12} They showed that vitamin D\textsubscript{3} was able significantly to reduce inflammation and improve lung function. They believed that vitamin D\textsubscript{3} could be a novel clinical approach to treat patients with COPD.\textsuperscript{12}

There have not been any randomized, double blinded, placebo-controlled clinical trials done on the effectiveness of vitamin D\textsubscript{3} supplementation in patients with COPD. This study was designed to evaluate the effectiveness of vitamin D\textsubscript{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\textsubscript{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\textsubscript{3} as per GOLD guidelines.\textsuperscript{13} Cell counts, liver-function tests, ischemic electrocardiographic changes, calcium, phosphorus, and alkaline phosphatase of eligible patients were assessed for eligibility (n = 70). Randomized (n= 66)

- Assessed for eligibility (n = 70)
- Excluded (n=4)
  - Acute myocardial infarction in last 6 months (n=1)
  - Congestive heart failure (n=1)
  - Proven osteoporosis(n=2)

- Randomized (n = 66)
  - Allocated to intervention (Vitamin D\textsubscript{3}) (n=33)
    - Received allocated intervention (n = 33)
    - Did not receive allocated intervention (give reasons) (n = 0)
  - Allocated to placebo (n = 33)
    - Received allocated intervention (n = 33)
    - Did not receive allocated intervention (give reasons) (n = 0)

- Follow-up patients
  - Lost to follow-up (give reason) (n = 1)
    - Discontinued intervention (give reasons) (n = 0)
  - Lost to follow-up (give reason) (n = 2)
    - Discontinued intervention (give reasons) (n = 0)

- Analysis patients
  - Analyzed (n = 32)
    - Excluded from analysis (give reasons) (n = 0)
  - Analyzed (n = 31)
    - Excluded from analysis (give reasons) (n = 0)

*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$^2$, hypercalcinemia (≥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$_3$ metabolites, which is the accepted biomarker for vitamin D$_3$. In the next stage, radioimmunoassays were conducted to measure vitamin D$_3$ levels.

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 questionnaire was 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.

### Table 1 Studied variables before intervention in both control and vitamin D$_3$ groups

| Variables | Group | P-value |
|-----------|-------|---------|
| 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 | 24.53±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 | 0.528* |
| FEV$_1$/FVC (mean ± SD) | 56.75±12 | 58.76±9.82 | 0.949* |
| Exacerbations, n (%) | 10 (31.3%) | 11 (35.5%) | 0.472* |
| Exacerbations (mean ± SD) | 0.53±0.98 | 0.55±0.85 | 0.772*** |
| CAT score (mean ± SD) | 15.3±7.35 | 15.48±9.32 | 0.767**** |
| COPD severity, n (%) | 6 (18.8%) | 9 (29%) | 0.528* |
| 25-Hydroxyvitamin D$_3$ levels, ng/mL (mean ± SD) | 19.33±5.18 | 18.55±4.58 | 0.776**** |

Notes: *t-test; **Fisher’s exact test; ***Chi square; ****Mann–Whitney.

Abbreviations: BMI, body mass index; CAT score, COPD assessment test score; FEV$_1$. Forced expiratory volume at first second; FVC, Forced vital capacity.

Statistical analysis
The $\chi^2$ 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
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 al show that serum levels of vitamin D\(_3\) had significant correlations with the severity of COPD.

| 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.
They also observed that vitamin D₃ consumption improved pulmonary function and quality of life in COPD patients in six months. Patients were controlled with different doses of vitamin D₃. Serum vitamin D₃ 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 al reported that vitamin D₃ may reduce acute exacerbations of COPD symptoms in those with initially deficient levels. However, Jolliffe et al found no effect of vitamin D₃ supplementation on the rate of exacerbations among patients with COPD, but that vitamin D₃ supplementation has protective effects on patients with low vitamin D₃ levels (<25 nmol/L).²

Other studies found higher levels of vitamin D₃-binding protein in patients with COPD, which involved neutrophil chemotaxis and macrophage activation (which has an important role in COPD pathogenesis). Vitamin D₃-binding protein has a significant correlation with serum levels of vitamin D; therefore, increasing vitamin D₃ levels will increase those of vitamin D₃-binding protein.

However, Jolliffe et al found no effect of vitamin D₃ supplementation on the rate of exacerbations among patients with COPD, but that vitamin D₃ supplementation has protective effects on patients with low vitamin D₃ levels (<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 D₃. There has not been a study done on lung function, number of

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

| Variables   | Duration                                | Group        | Mean ± SD | P-value |
|-------------|-----------------------------------------|--------------|-----------|---------|
| FEV₁        | After 2 months from baseline            | Intervention | 0.7±1.1  | 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|         |
| FEV₁/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 2 months 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.
exacerbations, and quality of life in patients with COPD. Further studies seem to be required in this field.

As believed, consumption of vitamin D3 improves quality of life in patients with COPD patients.

According to the evidence, getting 10,000 IU/day in patients with deficient levels of vitamin D3 (1,500–2,000 IU/day) would not be toxic.

Undoubtedly, vitamin D3 therapy cheap, which and could be one of its important advantages.

Finally, vitamin D3 therapy could be a useful and safe option simultaneously with other procedures.

Conclusion
Vitamin D3 (50,000 IU) supplementation can improve quality of life in patients with COPD. In fact, COPD might be controlled by different levels of vitamin D3 in serum. We found that consuming 50,000 IU vitamin D3 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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