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Evaluation of micronutrients in stable COPD patients

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ABSTRACT

Background and Objectives: Chronic obstructive pulmonary disease (COPD) is a disease characterized by malnutrition, a catabolic process, and chronic inflammation; thus, vitamin deficiency may occur frequently. We aimed to evaluate the levels of micronutrients in stable COPD patients. **Methods and Study Design:** There were 168 COPD patients from six pulmonology departments, with 36 healthy controls. The patients also performed pulmonary function tests and filled out the St. George's Respiratory Questionnaire (SGRQ). Serum vitamin B-12 and folate levels were measured using the chemiluminescence immunoassay (CLIA) method. Plasma 25-OH D3 levels were measured by high-performance liquid chromatography (HPLC). **Results:** Our results revealed vitamin D deficiency in 68.9% (59.6%: mild, 25.7%: intermediate, 14.7%: severe), vitamin B-12 deficiency in 21.7%, and folic acid deficiency in 50% of COPD patients. There was a significant difference between the COPD and healthy control groups regarding vitamin D deficiency (68.9% vs. 16.6%; $p < 0.001$). The mean plasma 25-OH-D level was significantly lower in COPD patients ($p < 0.01$). There was a positive correlation of plasma 25-OH-D level with the SGRQ impact score ($r = 0.174$, $p = 0.028$) and a negative correlation with age and number of exacerbations (respectively; $r = -0.248$, $p = 0.002$, and $r = -0.160$, $p = 0.044$). **Conclusions:** Vitamin D, B-12, and folate deficiencies frequently occur in COPD patients. Low plasma levels of 25-OH-D may be associated with advanced age and a higher number of exacerbations in patients with COPD. COPD patients with low vitamin D and folate may experience a decrease in quality of life.

Key Words: COPD, micronutrients, vitamins, vitamin D, vitamin deficiency

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease characterized by progressive airflow limitation. Comorbidities and extrapulmonary complications are also frequently observed in COPD.

Nutritional problems are among the several factors contributing to COPD. Malnutrition develops in approximately 25-50% of COPD patients.^{1,2} Malnutrition has negative effects on basic functions in COPD patients, such as decreased respiratory muscle strength and an impaired immune system. On the other hand, the energy requirement of the patient increases due to the excess energy needed for respiration, increased inflammatory processes, and changing levels of hormones and cytokines.³

Micronutrients play a vital role in the management of COPD, particularly regarding their effects on inflammation, oxidative stress, and immune functions.⁴ COPD is associated with chronic inflammation and oxidative stress, which contribute to disease progression, with worsening clinical symptoms and acute exacerbations. Antioxidants, including micronutrients, can suppress oxidative stress by neutralizing free radicals. Vitamin D is an important antioxidant that facilitates the balance of mitochondrial activity, preventing protein oxidation associated with oxidative stress, lipid peroxidation, and DNA damage.⁵ Vitamin B-12 has a proven antioxidant effect and significantly affects the stability of the genome. The antioxidant activity of folate may have mitigated the airway and systemic inflammatory reactions of COPD patients.

The intake of vitamins and micronutrients, which all have protective effects on the loss of lung function, may improve the average level of lung function and protect the rate of lung function indicators. In this way, micronutrients may reduce disease progression and improve outcomes for COPD patients.⁵

Vitamin D deficiency is common in COPD patients due to factors such as malnutrition, decreased skin vitamin D synthesis, decreased exposure to sunlight, and the predominance of glucocorticoid-induced catabolic processes.⁶ It may occur in over 60% of patients with severe COPD and is quantitatively related to disease severity.⁷

COPD patients are known to have lower micronutrient and vitamin B-12 levels than the healthy population.⁸ B-12 and folate deficiencies can occur secondary to severe malnutrition in COPD patients due to basal distance execution, decreased caloric intake, and decreased body mass index.⁹

In COPD, especially during exacerbations, various cytokines associated with systemic inflammation and acute-phase proteins increase, and abnormal changes occur in circulating cells.¹⁰ Frequent exacerbations may also cause changes in vitamin and mineral content in COPD patients.

We aimed to evaluate the levels of vitamin B-12, D, and folic acid in stable COPD patients, compare the results with healthy controls, and determine the relationship between vitamin levels and pulmonary parameters.

MATERIALS AND METHODS

There were 168 COPD patients from six pulmonology departments who met the inclusion criteria. Thirty-six healthy controls with a similar distribution of age and gender were also included in this cross-sectional study. Demographics and patient characteristics were recorded.

Diagnosis of COPD was confirmed with a previous post-bronchodilator forced expiratory volume in 1 s (FEV1) / forced vital capacity (FVC) ratio of less than 70%. The inclusion criteria were:

- Diagnosis of COPD according to the GOLD Guidelines.¹¹
- No active COPD exacerbation at the time of the visit.

COPD patients with the presence of diseases (malignancy, malabsorption, chronic liver disease, chronic kidney failure, endocrinological disease) that may affect serum vitamin levels, or those who have received vitamin replacement for any reason in the past six months, were excluded.

COPD is defined as being “stable” when symptoms are well managed and pulmonary decline is minimized. This means there is no episode of acute respiratory symptom worsening during the period in which blood samples are taken from included COPD patients.¹²

Healthy controls were selected from patients who were admitted to outpatient clinics of six pulmonology departments, with a similar distribution of age and gender, but without any known chronic disease or comorbidity in the hospital registry system, including COPD or a history of vitamin replacement.

Venous blood samples taken from the participants were centrifuged by placing 2 cc in EDTA tubes, and the separated serum and plasma samples were stored in the medical biochemistry laboratory of the centers. The prepared sera had been stored in deep freezers at -80°C until the day of analysis, and all patient samples were analyzed simultaneously after the end of patient recruitment.

Serum vitamin B-12 and folate levels were measured using the chemiluminescence immunoassay (CLIA) method (Advia Centaur XP, Siemens Healthcare Diagnostics Inc., USA). Plasma 25-OH D3 levels were measured by high-performance liquid chromatography (HPLC) (Thermo Scientific UltiMate 3000, Austria).

The reference range for 25-OH D3 is 20-70 µg/L (Vitamin D deficiency: 10-20 µg/L: mild, 5-10 µg/L: moderate, <5 µg/L: severe). The reference range for vitamin B12 is 211-911 ng/L (B-12 deficiency: <210 pg/mL). A folate level >5.38 µg/L is the normal value (Folate deficiency: <5.38 ng/mL).

Participants were evaluated for spirometric parameters, modified Medical Research Council (mMRC)¹³ dyspnea scale, and St. George Respiratory Questionnaire (SGRQ) at the admission visit by pulmonologists in the relevant clinics. The spirometry testing method was standardized at the centers participating in the study. All patients underwent standard post-bronchodilator spirometry (Spirolab III S/N A23-053, Rome, Italy); FEV1, FVC, and

FEV1/FVC were recorded. Participants performed a minimum of three forced blows, and the best values were taken for interpretation.

Patients were classified into groups (A, B, or E) based on their spirometric values, exacerbation, hospitalization history in the last year, and symptomatic assessment according to the combined classification of GOLD 2023.¹¹ The definition of a COPD exacerbation is accepted as an acute event characterized by dyspnea and/or cough and sputum worsening over <14 days.¹¹ The rate of hospitalizations and acute exacerbations in the previous year for each patient was obtained from the hospital database.

The SGRQ is a disease-specific quality of life assessment tool used in COPD.¹⁴ This questionnaire includes sections measuring symptoms, activity limitation, and the social and emotional impact of the disease. Overall scores range from 0 to 100; a score of zero represents no health impairment, and a score of 100 indicates maximal health impairment. The minimum clinically important difference (MCID) value has been accepted as 4 units for significant improvement in SGRQ score.¹⁵ The validated Turkish version of the questionnaire was used in the study.¹⁶

In the sample size calculation, using the “Open Epi” program and data from a similar study done previously,¹⁷ the power was set at 90%, the level of type I error was set at 5%, and the required number of patients was calculated as 125. The minimum number of patients to be included, taking a 10% reserve, was determined to be 138.

The study was approved by the Institutional Ethics Committee of Izmir Katip Çelebi University (Approval date and number: 27.09.2018/IRB #0107). Written informed consent was obtained from all patients. The study adhered to the guidelines of the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 software (SPSS, Chicago, IL, USA). Baseline characteristics, including demographic data, clinical, and physiological parameters, were summarized using descriptive statistics. Continuous variables such as age, FEV1, FVC, FEV1/FVC, mMRC, and SGRQ were represented by mean and standard deviation if normally distributed or median and interquartile range if not normally distributed. Categorical data, such as sex and the presence of improvement in clinical and physiological parameters, were represented by numbers and percentage values. The chi-square test was used to compare categorical data; paired t-tests were used for continuous data between COPD patients and

healthy controls. All tests were two-tailed, and a p -value less than 0.05 was accepted as statistically significant.

RESULTS

There were 152 men (90.5%) and 16 women (9.5%) with a mean age of 65.9 ± 8.6 in our patient group, and 32 men (88.9%) and 4 women (10.1%) with a mean age of 64.9 ± 8.3 in the control group. The mean plasma 25-OH-D levels were significantly lower in COPD patients than in healthy controls ($p \leq 0.001$). There were no meaningful differences in the other vitamin levels between the COPD group and healthy controls. Demographics and vitamin levels of the patient and healthy control groups are in Table 1.

There was a significant difference between COPD patients and the healthy control group in terms of vitamin D deficiency (68.9% vs. 16.6%, $p < 0.001$). Our results revealed no significant differences between COPD and control groups in terms of folic acid (50% vs. 47.2%, $p = 0.427$) and B-12 (21.7% vs. 16.7%, $p = 0.344$) deficiencies. Vitamin D deficiency was present in 68.9% of COPD patients: 59.6% mild, 25.7% intermediate, and 14.7% severe. Vitamin status and relationships with parameters of COPD patients are shown in Table 2.

There was no significant relationship between the presence of B-12, folic acid, and vitamin D deficiency and having severe COPD (group E) ($p = 0.476$, 0.556, and 0.808, respectively).

There was a positive correlation between plasma 25-OH D levels and SGRQ (impact) score ($r = 0.174$, $p = 0.028$), while plasma levels of 25-OH D showed a negative correlation with age and the number of exacerbations in the last year (respectively, $r = -0.248$, $p = 0.002$, and $r = -0.160$, $p = 0.044$). There was no correlation between vitamin levels and parameters such as FEV1 level and mMRC (Table 3).

DISCUSSION

In the present study, we assessed the levels of micronutrients in COPD patients, comparing them with healthy controls. To our knowledge, our cross-sectional study demonstrates that most COPD patients have vitamin deficiencies. There was a significant difference between COPD patients and the healthy control group in terms of vitamin D deficiency. The mean plasma 25-OH-D level was found to be significantly lower in COPD patients than in healthy controls. Low plasma levels of 25-OH D may be associated with advanced age and a higher number of exacerbations in COPD patients. Additionally, COPD patients with low vitamin D and folate may experience a decrease in quality of life.

Our results revealed that more than two-thirds of COPD patients have vitamin D deficiency. Vitamin D deficiency is a common problem in COPD patients, with a high prevalence previously reported, varying between 30-70% in COPD patients.¹⁸ It has also been demonstrated to be more common in patients with COPD than in healthy controls,¹⁹ as shown in our study.

Vitamin D deficiency has been reported as mild to moderate in about 60% and severe in as high as 36% of patients.²⁰ Severe vitamin D deficiency was determined in approximately 15% of COPD patients according to our results. Since severe vitamin D deficiency is related to more frequent disease exacerbations and hospitalizations, it needs to be identified in COPD patients.

Some studies have reported that low vitamin D levels are associated with increased frequency of respiratory infections in both COPD patients and healthy adults, and the role of vitamin D deficiency in acute exacerbations of COPD (AECOPD) is still debated.^{5, 20} However, our results indicate that decreased levels of vitamin D are associated with increased frequency of acute exacerbations of COPD. Heulens et al. demonstrated that patients with vitamin D levels below 10 ng/mL experienced the highest number of AECOPD.²¹ Conflicting findings in the literature might depend on the fact that COPD patients with worse clinical conditions were already taking vitamin D supplements.

It is known that older individuals have lower 25-hydroxyvitamin D (25(OH)D) plasma levels than younger adults.²² Lahera et al. demonstrated that COPD individuals with higher age had lower levels of vitamin D.²³ The decrease in vitamin D intake, especially in elderly COPD patients, may explain this result.

There was a positive correlation between plasma 25-OH D levels and SGRQ (impact) score according to our results. Vitamin D deficiency is found to be associated with respiratory quality of life (QoL)⁴ in a study. The 25(OH)D concentration was found to positively predict muscle strength and QoL at both the end of winter and the end of summer in COPD patients.²⁴ Although some studies do not find a relationship between vitamin D deficiency and quality of life,²⁵ the general opinion in the literature is that optimal vitamin D status may have potential benefits for QoL in COPD patients.^{4,24}

Our results revealed that 21.7% of COPD patients had B-12 deficiency. There are only a few studies on B-12 deficiency in COPD patients. The prevalence of vitamin B-12 deficiency was reported as 34.4% in a previous report.⁶ Belitic et al. reported a prevalence of B-12 deficiency between 4% and 58% depending on the cut-off level in patients with COPD.⁷

Folic acid deficiency was reported in half of the COPD patients in our study. Additionally, a positive correlation was detected between folic acid level and the impact score in SGRQ. COPD patients seem to have a poor folic acid status, which varies between 32-90% in the literature.^{7,26} Folic acid is a water-soluble micronutrient playing a major role in general metabolism and energy homeostasis, which can affect quality of life in the case of deficiency. Lee et al. revealed higher QoL in the elderly with higher serum folate concentrations.²⁷ However, there are no other studies in the literature on folic acid levels and quality of life in COPD patients.

Our study has some limitations. Although the prepared serum and plasma samples are stored in a deep freezer at -80°C, the lack of immediate analysis of vitamin levels in the blood taken is a limitation of our study.

The low number of females in the COPD patients included in the study may constitute a deficiency in statistical comparison between genders. Furthermore, larger randomized controlled studies are required to evaluate vitamin deficiencies in COPD patients objectively.

Conclusion

As a result, the findings of this study show that vitamin D, B-12, and folic acid deficiencies can frequently occur in COPD patients. Careful attention must be paid to COPD patients with advanced age and a high number of exacerbations regarding vitamin D deficiency. COPD patients with low vitamin D and folate may experience a decrease in quality of life.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

All authors (OT, NS, FB, PAT, ÖÖ, NF, MK, HÖ and AM) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Comparison of patient and control groups in terms of parameters including vitamin levels

	Patient group (n=168) n, %	Control group (n=36) n, %	<i>p</i> value
Parameters			
Gender (male / female)	152 / 16 (90.5% / 9.5%)	32 / 4 (88.9% / 11.1%)	0.434
Age (mean)	65.9±8.6	64.9±8.3	0.724
Active smoking (yes / no)	45 / 123 (26.8% / 73.2%)	6 / 30 (16.7% / 83.3%)	0.182
Comorbidities (present / not)	100 / 68 (59.5% / 41.5%)	29 / 7 (80.6% / 19.4%)	0.653
Vitamins, serum levels			
Vitamin D, µg/L	16.6	28.9	<0.001
Folic acid, ng/mL	6.5	6.05	0.424
Vitamin B-12, pg/mL	359.7	312.1	0.385

Table 2. Vitamin status and relationship with parameters of COPD patients

Parameters	Gender (male /female) <152 / 16>	p value	Comorbidities (present / not) <100 / 68>	p value	COPD (severe / not severe) <63 / 105>	p value	Active smoking (yes/no) <45 /123>	p value
Vitamin D								
Normal (n=52)	45/7	0.248	26/12	0.304	17/35	0.549	10/38	0.820
Low (n=116)	107/9		74/56		46/70		35/85	
Folic acid								
Normal (n=84)	73/11	0.080	44/28	0.692	24/60	0.418	25/59	0.605
Low (n=84)	79/5		56/40		39/45		20/64	
Vitamin B-12								
Normal (n=132)	122/10	0.302	84/71	0.190	50/82	0.419	35/97	0.520
Low (n=36)	30/6		16/17		13/23		10/26	

COPD: chronic obstructive pulmonary disease.

Table 3. Correlation of vitamin levels among parameters

Parameters	Vitamin D level		Folic acid level		B12 level	
	R	p	R	p	R	p
Age	-2.224	0.004	0.019	0.818	-0.018	0.821
FEV1, lt	0.080	0.320	0.141	0.129	-0.124	0.190
Smoking (package.year)	-0.110	0.180	0.221	0.056	-0.131	0.159
mMRC	-0.122	0.127	-0.010	0.916	-0.175	0.425
COPD, spirometric stage (1-4)	-0.087	0.275	-0.024	0.797	-0.083	0.375
Number of exacerbation (last 1 year)	-0.160	0.044	0.014	0.880	-0.063	0.502
SGRQ, symptom score	0.081	0.311	0.052	0.652	-0.081	0.483
SGRQ, impacts score	0.174	0.028	0.310	0.009	-0.124	0.298
SGRQ, activity score	0.119	0.133	0.169	0.158	-0.074	0.535

FEV1; Forced expiratory volume in 1 s, mMRC: modified Medical Research Council, COPD: chronic obstructive pulmonary disease; SGRQ: St. George Respiratory Questionnaire

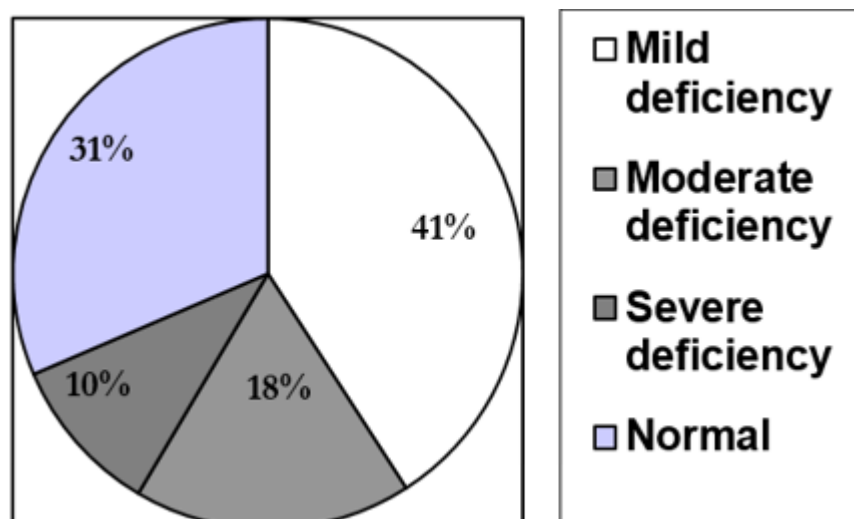


Figure 1. Vitamin D deficiency in COPD patients.