Original Article

Evaluation of micronutrients in stable COPD patients

Turan Onur MD[1], Sarıoglu Nurhan MD[2], Turan Pakize Ayse MD[3], Özdemir Özer MD[4], Fazlıoglu Nevin MD[5], Köseoglu Mehmet MD[6], Özkanay Hayat MD[6], Mirici Arzu MD[7]

[1]*Department of Chest Diseases, Izmir Katip Celebi University, Atatürk Research and Training Hospital, Izmir, Turkey*
[2]*Department of Chest Diseases, Balıkesir University, Balıkesir, Turkey*
[3]*Department of Chest Diseases, Menemen State Hospital, Izmir, Turkey*
[4]*Department of Chest Diseases, Kemalpasa State Hospital, Izmir, Turkey*
[5]*Department of Chest Diseases, Tekirdağ Namık kemal University, Tekirdağ, Turkey*
[6]*Department of Biochemistry, Izmir Katip Celebi University, Atatürk Research and Training Hospital, Izmir, Turkey*
[7]*Department of Chest Diseases, Çanakkale University, Çanakkale, Turkey*

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% (mild: 59.6%, intermediate: 25.7%, severe: 14.7%), 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). 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 the basic functions in COPD patients, including decreased respiratory muscle strength and an impaired immune system. On the other hand, the energy requirement of patients 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 characterized by chronic inflammation and oxidative stress, which drive disease progression and lead to worsening 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 plays a significant role in maintaining genome stability. Similarly, the antioxidant activity of folate may help reduce airway and systemic inflammation in COPD patients.

Corresponding Author: Prof. Dr. Onur Turan, Department of Chest Diseases, Izmir Katip Celebi University Atatürk Research and Training Hospital, Basın sitesi 35360 Karabağlar/İzmir
Tel: +905323523461
Email: onurtura@yahoo.com
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The intake of vitamins and micronutrients, which have protective effects against lung function decline, may help maintain average lung function levels and slow the deterioration of lung function indicators. In this way, micronutrients could 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] Vitamin B-12 and folate deficiencies can occur secondary to severe malnutrition in COPD patients due to basal distance execution, reduced caloric intake, and decreased body mass index (BMI).[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 vitamin B-12, D, and folic acid levels in stable COPD patients, compare them with healthy controls, and examine the relationship between these vitamin levels and pulmonary function parameters.

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 was defined as the absence of any episodes of acute respiratory symptom worsening during the period when blood samples were collected from the 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 were stored at -80°C until analysis, and all samples were analyzed simultaneously at the end of recruitment.

Serum vitamin B-12 and folate levels were measured using chemiluminescence immunoassay (CLIA) (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 COPD exacerbation is defined 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 presented 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 vitamin B-12 (21.7% vs. 16.7%, $p = 0.344$) deficiencies. Vitamin D deficiency was found in 68.9% of COPD patients (Figure 1), with 59.6% classified as mild, 25.7% as moderate, and 14.7% as severe. Vitamin status and relationships with parameters of COPD patients are shown in Table 2.

There was no significant relationship between the presence of vitamin 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 micronutrient levels in COPD patients, comparing them with healthy controls. To our knowledge, this 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

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, %	*p* 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 asit, ng/mL	6.5	6.05	0.424
Vitamin B-12, pg/mL	359.7	312.1	0.385

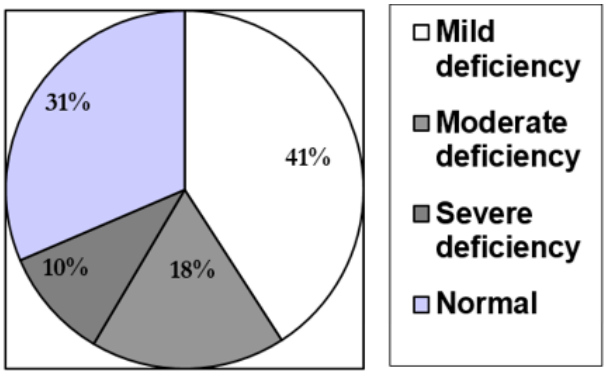

Figure 1. Vitamin D deficiency in COPD patients.

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		B-12 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

exacerbations in COPD patients. Additionally, COPD patients with low vitamin D and folate may experience a decrease in quality of life (QoL).

Our results revealed that more than two-thirds of COPD patients have vitamin D deficiency. Vitamin D deficiency is a common issue 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 approximately 60% of patients and severe in up to 36%.[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] Fernández-Lahera et al. demonstrated that older individuals with COPD had lower vitamin D levels.[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 QoL4 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 QoL,[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 vitamin B-12 deficiency. There are only a few studies on vitamin 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 vitamin 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 serum and plasma samples were stored at -80°C, the delay in analyzing vitamin levels after blood collection is a limitation.

The low number of female COPD patients in this study may limit the statistical comparison between genders. Additionally, larger randomized controlled trials are needed to more objectively assess vitamin deficiencies in COPD patients.

Conclusion

As a result, the findings of this study show that vitamin D, vitamin 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 DISCLOSURES

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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REFERENCES

1. Braun SR, Keim NL, Dixon RM, Clagnaz P, Anderegg A, Shrago ES. The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease. Chest. 1984;86:558-63. doi: 10.1378/chest.86.4.558.
2. Hunter AM, Carey MA, Larsh HW. The nutritional status of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1981;124:376-81. doi: 10.1164/arrd.1981.124.4.376.
3. Schols AM. Nutritional advances in patients with respiratory diseases. Eur Respir Rev. 2015;24:17-22. doi: 10.1183/09059180.00010914.
4. Heffner JE, Repine JE. Pulmonary strategies of antioxidant defense. Am Rev Respir Dis. 1989;140:531-54. doi: 10.1164/ajrccm/140.2.531.
5. Donastin A, Amin M, Yulistiani. Mechanism of High Dosage Vitamin D Supplementation on The Lung Function and Quality of Life of Stable COPD Patients. Pharmacogn J. 2023;15: 274-8. doi:10.5530/pj.2023.15.74
6. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-81. doi: 10.1056/NEJMra070553.
7. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010; 65:215–20. doi: 10.1136/thx.2009.120659.
8. Paulin FV, Zagatto AM, Chiappa GR, Müller PT. Addition of vitamin B12 to exercise training improves cycle ergometer endurance in advanced COPD patients: A randomized and controlled study. Respir Med. 2017;122:23-9. doi: 10.1016/j.rmed.2016.11.015
9. Beletić A, Mirković D, Dudvarski-Ilić A, Milenković B, Nagorni-Obradović L, Đorđević. Questionable Reliability of Homocysteine as the Metabolic Marker for Folate and Vitamin B12 Deficiency in Patients with Chronic

Obstructive Pulmonary Disease. J Med Biochem. 2015;34:467-72.
10. Zasloff M. Fighting infections with vitamin D. Nat Med 2006; 12:388–90.n doi: 10.1038/nm0406-388.
11. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023. Available from: http://goldcopd.org
12. Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: A review focusing on exacerbations. Am J Health Syst Pharm. 2020;77:259-68. doi: 10.1038/nm0406-388.
13. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999; 54:581–6. doi: 10.1136/thx.54.7.581.
14. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. Am Rev Respir Dis. 1992;145:1321-7. doi: 10.1164/ajrccm/145.6.1321.
15. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;933:580-6. doi: 10.1378/chest.93.3.580.
16. Polatlı M, Yorgancıoğlu A, Aydemir Ö, Demirci NY, Kırkıl G, Naycı SA, et al. Validity and reliability of Turkish version of St. George's respiratory questionnaire. Tuberk Toraks. 2013; 61: 81-7. doi: 10.5578/tt.5404.
17. Planas M, Alvarez J, García-Peris PA, de la Cuerda C, de Lucas P, Castellà M, et al. Nutritional support and quality of life in stable chronic obstructive pulmonary disease (COPD) patients. Clin Nutr. 2005;24:433-41. doi: 10.1016/j.clnu.2005.01.005.
18. Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE. Vitamin D status and longitudinal lung function decline in the Lung Health Study. Eur Respir J. 2011;37:238-43. doi: 10.1183/09031936.00146509.
19. Lokesh KS, Chaya SK, Jayaraj BS, Praveena AS, Krishna M, Madhivanan P, et al. Vitamin D deficiency is associated with chronic obstructive pulmonary disease and exacerbation of COPD. Clin Respir J. 2021;15:389-99. doi: 10.1111/crj.13310.
20. Malinovschi A, Masoero M, Bellocchia M, Ciuffreda A, Solidoro P, Mattei A. Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients. Respir Res. 2014;15:131. doi: 10.1186/s12931-014-0131-0
21. Heulens N, Decramer M, Janssens W. Severe vitamin D deficiency: a biomarker of exacerbation risk? Am J Respir Crit Care Med. 2013;187:214-5. doi: 10.1164/ajrccm.187.2.214a.
22. Sakem B, Nock C, Stanga Z, Medina P, Nydegger UE, Risch M, et al. Serum concentrations of 25-hydroxyvitamin D and immunoglobulins in an older Swiss cohort: results of the Senior Labor Study. BMC Med. 2013;11:176. doi: 10.1186/1741-7015-11-176.
23. Fernández-Lahera J, Romera D, Gómez Mendieta A, Martínez Verdasco A, Fernández-Bujarrabal J, Santiago A. Prevalence of vitamin D deficiency in patients with chronic obstructive pulmonary disease. Eur Respir J. 2015, 46: PA3977
24. Carson EL, Pourshahidi LK, Madigan SM, Baldrick FR, Kelly MG, Laird E, et al. Vitamin D status is associated with muscle strength and quality of life in patients with COPD: a seasonal prospective observation study. Int J Chron Obstruct Pulmon Dis. 2018;13:2613-22. doi: 10.2147/COPD.S166919.
25. Jolliffe DA, James WY, Hooper RL, Barnes NC, Greiller CL, Islam K, et al. Prevalence, determinants and clinical correlates of vitamin D deficiency in patients with Chronic Obstructive Pulmonary Disease in London, UK. J Steroid Biochem Mol Biol. 2018;175:138-45. doi: 10.1016/j.jsbmb.2017.01.019.
26. Khan NA, Saini H, Mawari G, Kumar S, Hira HS, Daga MK. The Effect of Folic Acid Supplementation on Hyperhomocysteinemia and Pulmonary Function Parameters in Chronic Obstructive Pulmonary Disease: A Pilot Study. J Clin Diagn Res. 2016;10:17-21
27. Lee E, Park S. Serum folate concentration and health-related quality of life among the elderly in South Korea. Health Qual Life Outcomes. 2021;19:267. doi: 10.1186/s12955-021-01899-2.