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Effects of Vitamin D Supplementation on Exacerbation in Patients with Severe COPD

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Research Article

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Abstract

Introduction: Results from several studies indicated that vitamin D plays a role in a variety of immunologic processes such as modulation of inflammatory pathways and susceptibility to infections.

Aim of the study: To assess the effects of vitamin D supplementation on bacterial exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) with low vitamin D serum level.

Methods: We performed an observational, non-randomized, open-label study including 36 patients with severe COPD who besides the recommended chronic treatment for stable disease took oral vitamin D supplementation in dose of 2000 IU daily during a six month-period (Group 1). In addition, 35 patients with severe COPD, matched to the study subjects of the Group 1 by sex, age and serum vitamin D level, who did not receive vitamin D supplementation served as controls (Group 2). Analysis of exacerbations, including their incidence and duration, as well as incidence of relapses and duration of exacerbation-free interval, was done for each study subjects based on daily diary cards maintained by all of them during the mentioned period.

Results: Mean serum vitamin D levels at baseline did not differ significantly between examined groups (21.7 *vs.* 22.1; $P = 0.457$). At the end of the study its mean level was significantly higher in the Group 1 as compared to Group 2 (30.1 *vs.* 23.4; $P = 0.000$). Mean number of the first exacerbation over a six month-period was significantly lower in the Group 1 as compared to their mean number in the Group 2 (0.8 *vs.* 0.9; $P = 0.001$). Mean duration of the first exacerbation in the Group 1 (6.7 ± 1.2 days) was significantly lower as compared to its mean duration in the Group 2 (7.2 ± 1.3 days) ($P = 0.033$). Mean number of relapses registered in the Group 1 (0.2 ± 0.1) was significantly lower than its mean number registered in the Group 2 (0.4 ± 0.2) ($P = 0.000$). Mean exacerbation-free interval in the Group 1 (39.3 ± 10.1 days) was significantly longer than in the Group 2 (33.7 ± 11.8 days) ($P = 0.052$).

Conclusion: Our findings indicated that vitamin D supplementation may impact the incidence and duration of bacterial exacerbations in patients with COPD. There is a need of further studies to elucidate the role of vitamin D supplementation on the course of COPD.

Keywords: Chronic Obstructive Pulmonary Disease; Exacerbation; Exacerbation-Free Interval; Incidence Rate; Vitamin D Supplementation.

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Introduction

According to the actual update of Global Initiative for Chronic Obstructive Lung Disease (GOLD), exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy. COPD exacerbations are important events in the course of the disease due to their significant impact on the patients' quality of life, disease progression, hospitalization and readmission rates, mortality, and health care costs.

It is estimated that respiratory infections account for up to 80% of COPD exacerbations, of which bacterial infections are involved in around 50-70%. Viruses and non-infectious agents (e.g. environmental and workplace air pollution), but the cause is often not clear. Diagnosis of COPD exacerbations usually is empirical, based on their clinical presentation. More than 80% of COPD exacerbations are managed in outpatient setting with pharmacological treatment including short acting bronchodilators, antibiotics and/or corticosteroids. Current treatment guidelines recommend antibiotic therapy in patients with three cardinal symptoms (increased dyspnea, sputum volume and sputum purulence), as well as in patients with two cardinal symptoms if one of the two symptoms is increased purulence of sputum [1,2,3].

Vitamin D is a group of fat-soluble steroid hormone precursors the two major form of which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The major natural source of the vitamin D is synthesis of cholecalciferol in the lower layers of epidermis of the skin through a chemical reaction that is dependent on sun exposure. In addition, cholecalciferol and ergocalciferol can be ingested from the diet (fatty fish, egg yolk, mushrooms, fortified foods, etc.) and supplements. Vitamin D is present in only a few foods so it is commonly added as a fortification in manufactured foods (cow milk, soy milk, orange juice, etc.). Vitamin D from diet or from skin synthesis is biologically inactive and its activation includes two protein enzyme hydroxylation steps. 25-hydroxycholecalciferol and 25-hydroxyergocalciferol are two vitamin D metabolites (called 25-hydroxyvitamin D or 25-[OH] D) measured in serum to determine a person's vitamin D status [4,5,6].

Vitamin D is essential for normal bone development and mineralization through the regulation of calcium and phosphorus homeostasis. In addition, vitamin D also exhibits many non-sceletal effects [7,8,9,10]. Recent evidence suggests that vitamin D plays a role in a variety of immunologic processes such as modulation of inflammatory pathways and susceptibility to infections manifesting antibacterial, antiviral and anti-inflammatory effects [7,8,9]. Vitamin D deficiency has been linked to increased risk or severity of viral infections, including Covid-19 [10,11]. Results of several studies indicated that due to its immunomodulatory effects vitamin D supplementation may decrease the overall risk of acute respiratory tract infections. Furthermore, there is evidence that vitamin D supplementation may reduce the exacerbation rate in COPD patients with low baseline vitamin D levels [1,12].

Regarding the vitamin D serum levels, there is no consensus on its optimal levels for bone and overall health, i.e. recommendations on normal or optimal vitamin serum levels vary across authorities. The American Institute of Medicine (IOM) recommended a level between 20 and 40 ng/mL (50-100 nmol/L), while the American Geriatric Association recommended a level between 30 and 50 ng/mL (75–125 nmol/L). In contrast, the Vitamin D Council stated that even levels between 30 and 40 ng/mL are still not quite sufficient [13,14,15,16].

Causes of vitamin D deficiency include reduced sun exposure, skin pigmentation, genetic polymorphisms, and/ or inadequate intake. Vitamin D deficiency is prevalent worldwide concerning a considerable number of people. Using a definition of serum vitamin D level less than 20 ng/mL, it is estimated that up to a third of the world's population is deficient, while severe vitamin D deficiency, defined as serum level less than 12 ng/mL, is seen in approximately 7% of the population worldwide [10]. Despite the many potentially beneficial applications for vitamin D supplementation, there is currently no consensus on the recommended dosage for vitamin D intake, and dietary reference values in healthy individuals vary per country and per age group. Individual differences exist in the resulting increase in vitamin D levels depending on baseline serum level and sun exposure, treatment duration, and genetic background [12,17,18].

The aim of the present study was to assess the effects of vitamin D supplementation on incidence and duration of bacterial exacerbations in frequent exacerbators with severe COPD in whom its low serum levels were detected.

Methods

Study Design and Setting

An observational, non-randomized, open study was performed at the Institute for Occupational Health of RN Macedonia, Skopje, in the period September 2021-April 2022. Effects of vitamin D in patients with severe COPD were assessed by comparison of the incidence and duration of the first exacerbations, as well as the incidence and duration of relapses and duration of exacerbation-free interval between a group of patients with severe COPD with low vitamin D serum levels who received vitamin D supplementation over a six month-period and a group of COPD patients with similar characteristics who did not receive vitamin D supplementation in the mentioned period.

Study Subjects

Study population included 74 COPD patients (42 males and 32 females, aged 48 to 71 years), classified as GOLD grade 3, group D, according to the combined assessment of the disease. COPD in all subjects enrolled in the study was diagnosed and classified following actual recommendations at least three years before entering the study [1]. All study subjects were recruited in the stable phase of the disease, i.e. without any evidence of exacerbation for at least three weeks. The study subjects were divided in two equal groups (Group 1 and Group 2) matched by sex, age and serum level of vitamin D. The study subjects from the Group 1 took oral vitamin D supplementation in dose of 2000 IU daily during a six month-period besides the regular pharmacological treatment of stable disease, while the study subjects from the Group 2 did not receive vitamin D supplementation besides the recommended treatment of stable disease in the mentioned period.

Patients with a history of asthma, bronchiectasis, lung cancer, or other chronic respiratory disease, as well as those unable to complete diary cards and those with any contraindication for vitamin D supplementation were excluded from the study. None of the subjects enrolled in the study had history of Coronavirus disease. Furthermore, none of included subjects had positive epidemiological evidence for Coronavirus disease, nor positive

clinical findings or positive molecular test to SARS-CoV-2 before entering the study.

All study subjects were informed about the study and their written consent was obtained.

Study Protocol

Daily stable respiratory symptoms (baseline symptoms), medication use and history of exacerbations were noted in all subjects before entering the study. The Body Mass Index (BMI) as a measure of body fat based on height and weight that applies to adult population was determined in all study subjects by computed calculation using BMI calculator [19]. Classification of smoking status was done by the World Health Organization (WHO) recommendations. Passive smoking or exposure to environmental tobacco smoke was defined as an exposure to tobacco combustion products from smoking by others (at home, workplace, etc.), i.e. as a presence of at least one smoker in the household and/or in the workplace [20,21].

Spirometric measurements were not performed due to the risk of transmission of Coronavirus disease (SARS-CoV-2). According to the American Thoracic Society (ATS) recommendation, pulmonary functional testing in the period of pandemic should be limited to tests that are only essential for immediate treatment decisions [22].

Following the actual GOLD recommendations, COPD exacerbation was considered as acute worsening of respiratory symptoms that resulted in additional therapy [1]. Diagnosis of exacerbation was established empirically using the criteria described by Anthonisen et al. Bacterial etiology, i.e. exacerbation which was treated with antibiotic, was considered when the exacerbation met criteria of Anthonisen type I (presence of three cardinal symptoms: increased dyspnea, sputum volume and purulence) or type II (presence of two cardinal symptoms if increased purulence of sputum was one of the two symptoms). Exacerbations were treated on outpatient or inpatient basis following the actual GOLD recommendations. The course of exacerbation was evaluated as a function of resolution of symptoms and the treatment was considered to be successful if cure or clinical improvement was achieved. The cure, i.e. the clinical remission, was defined as complete resolution of the cardinal symptoms, whereas the clinical improvement was defined as return of the symptoms to their baseline severity [1,2]. Relapses, i.e. recurrent exacerbations, were defined as recurrence of worsened symptoms in the days and weeks after clinical remission of the former exacerbation [23].

All study subjects maintained daily diary cards on which they noted any appearance of increase in intensity of symptoms over their chronic (stable) symptoms. In addition, study subjects from the Group 1 also noted side effects of the vitamin D supplementation. A member of the study team saw study subjects within 48 hours of the detection of deterioration in symptoms and diagnosis was confirmed of each case. Exacerbation and its resolution were defined as it is mentioned above. Exacerbation number and their duration, as well as the time to the first and next exacerbations, were calculated for each study subjects based on data from diary cards for a six month-period of follow-up.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Distribution of the sample was checked by Shapiro-Wilk test. Analyses of the data included testing the differences in prevalence and comparison of the means by chi-square test (or Fisher's exact test where appropriate) and independent-samples *T*-test. A *P*-value less than 0.05 was considered as statistically significant.

Results

During the study period three subjects was infected by SARS-CoV-2 developing clinical manifestations of Coronavirus disease and they were excluded from the study. Results of the Shapiro-Wilk test indicated normal distribution in both examined groups ($P>0.05$). Demographic and other characteristics of the study subjects are shown on Table 1.

Table-1: Characteristics of the study subjects.

Variable	Group1 (n = 36)	Group 2 (n = 35)	P-value
M/F ratio	1.2	1.2	1
Mean age (years)	56.4 ± 5.9	57.1 ± 5.4	0.604
Mean BMI (kg/m2)	25.8 ± 2.7	26.1 ± 3.1	0.665
Mean duration of COPD (years)	6.7 ± 3.2	6.9 ± 3.7	0.808
Treatment of stable COPD			
LABA + LAMA + ICS	19 (52.8%)	18 (51.4%)	0.909
LABA + ICS	8 (22.2%)	7 (20.0%)	0.818
LABA + LAMA	5 (13.9%)	6 (17.1%)	0.705
LAMA	4 (11.1%)	4 (14.3%)	0.966
Oral theophyline	6 (16.6%)	4 (14.3%)	0.526
Vaccination			
Influenza vaccine	27 (75.0%)	27 (77.1%)	0.833
Pneumococcal vaccine	6 (16.7%)	8 (22.8%)	0.512
Covid-19 vaccine	30 (83.3%)	31 (88.5%)	0.526
Number of exacerbations in the previous year	2.7 ± 0.4	2.6 ± 0.3	0.238
Mean serum level of Vitamin D at baseline	21.7 ± 2.1	22.1 ± 2.4	0.457
Smoking status			
Active smokers	10 (27.8%)	8 (22.9%)	0.634
Ex-smokers	18 (50.0%)	21 (60.0%)	0.397
Never smokers	7 (19.4%)	6 (17.1%)	0.802
Exposed to ETS	14 (38.9%)	16 (45.7%)	0.561
Previous occupational exposure to noxious particles and gases	20 (55.6%)	22 (62.9%)	0.532
Comorbidities			
Arterial hypertension	10 (27.8%)	8 (22.9%)	0.634
Osteo-muscular disorders	6 (16.7%)	7 (20.0%)	0.717
Diabetes mellitus type 2	6 (16.7%)	5 (14.3%)	0.782
Ishaemic heart disease	5 (13.9%)	5 (14.3%)	0.962

Numerical data are expressed as mean value with standard deviation; frequencies as number and percentage of study subjects with certain variable.

COPD: Chronic Obstructive Pulmonary Disease; **M:** Male; **F:** Female; **BMI:** Body Mass Index; **kg:** Kilogram; **m:** Meter; **LABA:** Long-Acting Beta2-Agonist; **LAMA:** Long-Acting Muscarinic Antagonist; **ICS:** Inhaled Corticosteroid; **ETS:** Environmental Tobacco Smoke

The mean Vitamin D serum level at the end of the study in the Group 1 was significantly higher than in the Group 2 (30.1 *vs.* 23.4; $P = 0.000$) (Figure 1).

During the study period in all study subjects 62 first exacerbations were registered, 28 in the Group 1 (77.7%) and 34 in the Group 2 (97.1%). Exacerbation during the mentioned period did not occur in nine study subjects, i.e. in eight study subjects from the Group 1 (22.7%) and in one study subject from the Group 2 (2.9%). Mean number of the first exacerbation in study subjects from the Group 1 (0.8 ± 0.1) was significantly lower

as compared to its mean number in the Group 2 (0.9 ± 0.1) (P = 0.001) (Figure 2). Clinical remission of exacerbation in majority of the patient was obtained on outpatient basis. Hospitalization rate in all exacerbated study subjects was 22.6% (14/62), 17.8% (5/28) in the Group 1 and 26.4% (9/34) in the Group 2.

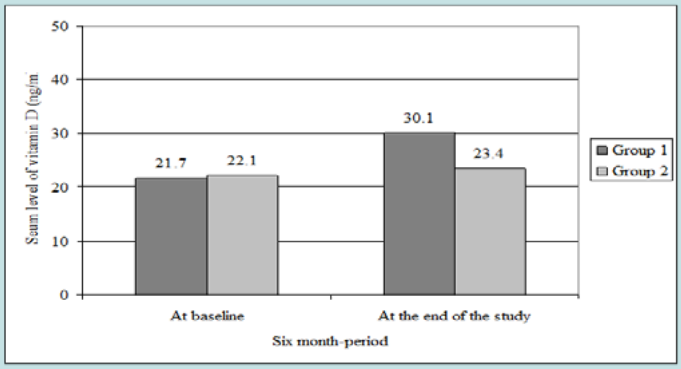

Figure 1: Mean serum level of Vitamin D at baseline and at the end of the study (ng/mL).

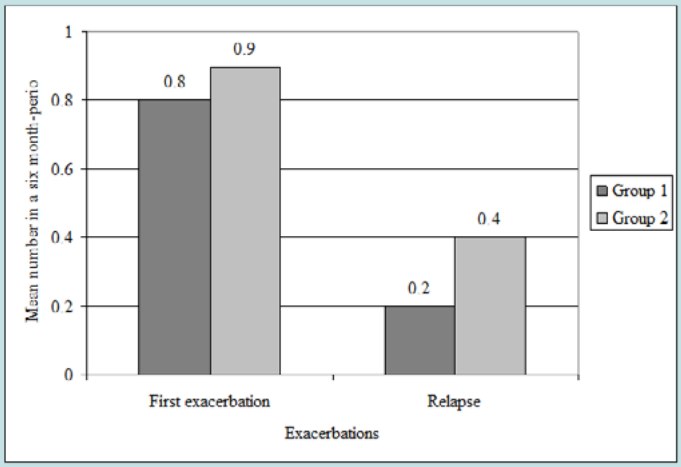

Figure 2: Mean number of the first exacerbation and relapse in the examined groups.

During the study period relapse was registered in 27.4% of the exacerbated subjects (17/62), i.e. in 17.8% (5/28) of the exacerbated subjects from the Group 1 and in 35.3% (12/34) of the exacerbated subjects from the Group 2. Mean number of relapses was significantly lower in study subjects from the Group 1 (0.2 ± 0.1) than its mean number in the Group 2 (0.4 ± 0.2) (P = 0.000) (Figure 2). Hospitalization rate in all study subjects with relapse was 29.4% (5/17), 20% (1/5) in the study subjects with relapse from the Group 1 and 33.3% (4/12) in the study subjects with relapse from the Group 2.

In both groups there was not any subject with two relapses during the study period.

Mean duration of exacerbation-free interval in the study subjects with recurrent exacerbation from the Group 1 (39.3 ± 10.1 days) was significantly longer than the exacerbation-free interval in the study subjects with two exacerbations in the Group 2 (33.7 ± 11.8 days) (P = 0.052) (Figure 3).

Mean duration of the first exacerbation was significantly lower among study subjects in the Group 1 who experienced exacerbation (6.7 ± 1.2 days) than in the Group 2 (7.2 ± 1.3 days) (P = 0.033). Mean duration of relapses among study subjects in the Group 1 (6.9 ± 1.2 days) as compared with their mean duration among study subjects in the Group 2 (7.6 ± 1.6 days) was at the border of statistical significance (P = 0.061) (Figure 4).

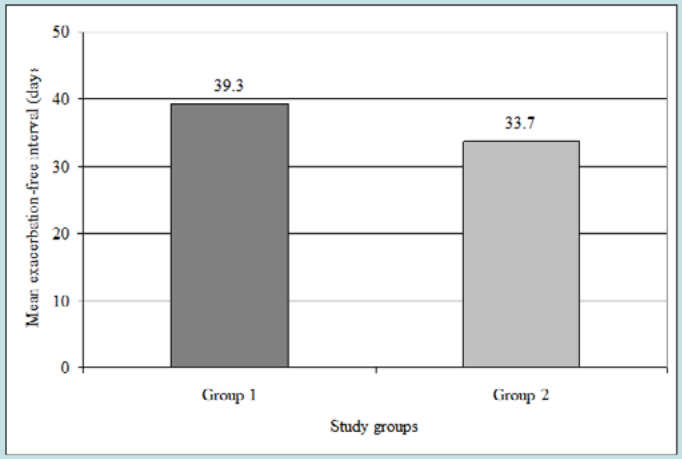

Figure 3: Mean exacerbation-free interval in the study subjects with relapse.

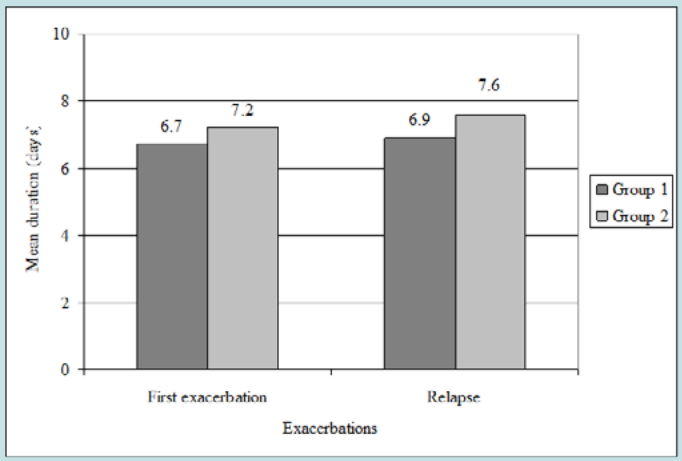

Figure 4: Mean duration of the first exacerbation and relapse in the examined groups (days).

Side effects of the supplementation with vitamin D was registered in five subjects in the Group 1 (13.8%). Registered side effects (metallic taste in the mouth, nausea, epigastric pain, and headache) were mild and self-limited and did not require premature discontinuation of the supplementation.

Discussion

Clinical relevance of vitamin D supplementation in patients with COPD is a matter of growing interest and many controversies in the last decades. There is no doubt regarding its immunomodulatory and anti-inflammatory effects but a number of studies in this field produced somewhat inconsistent results. Findings of these studies depend on their design, study sample size, characteristics of study population (age of study subjects, severity of disease, etc.), dosage of the supplemented vitamin D and duration of the supplementation, monitored parameters, etc.

Vitamin D deficiency is a general widespread issue in adults and may be a risk factor for respiratory impairment. Results

from several studies indicated that low serum levels of vitamin D are associated with more expressed respiratory symptoms, reduced levels of lung function parameters, i.e. forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow rate (PEFR), and increased daily dose of inhaled corticosteroid (ICS) but it is still unclear whether vitamin D deficiency affects COPD development and progression or whether patients with COPD develop a low vitamin D status as a consequence of the disease[24,25,26,27,28,29]. On the other side, in a multi-centre cross sectional study which included 278 COPD patients, Jolliffe et al. found significant association of vitamin D deficiency with reduced values of FEV_1 and FVC, but they did not find such association with the value of FEV_1/FVC ratio, quality of life in these patients, ICS dose, and the percentage of neutrophils and eosinophils in induced sputum [12].

In the present study we assessed the effects of vitamin D supplementation on exacerbations in patients with severe COPD by comparison of exacerbation incidence rate and duration, relapse rate, and exacerbation-free interval between a group of patients who received vitamin D supplementation during a six month-period and a group of patients who did not take vitamin D supplementation in the mentioned period. Study subjects from the examined groups had similar demographic characteristics. In both groups there still were a high proportion of active smokers that was similar to our findings from our previous studies with COPD patients [29,30]. In addition, in both groups more than a half of study subjects were exposed to noxious particles and gases at their previous workplace that confirmed a role of harmful occupational exposure on the COPD development and progression [31].

Baseline levels of serum vitamin D were similar in both examined groups, i.e. the mean serum values of vitamin D in both groups were at the lower limit of its normal values determined by some authorities. As it was mentioned in the text above, there still is not international consensus on the doses of supplemented vitamin D. In several studies which evaluated the effects of vitamin D supplementation in patients with COPD different doses were administered, e.g. bolus oral dose of 120 000 IU (3 mg) every two months for one year, monthly oral dose of 100 000 IU for one year, daily oral dose of 2000 IU for six months, daily oral dose of 1200 IU for six months, etc. [32,33,34,35,36].

We found significantly lower mean number of the first exacerbations and their significantly shorter duration following by significantly lower mean number of relapses and significantly longer exacerbation-free interval in the group supplemented with vitamin D as compared to the study subjects who did not receive vitamin D supplementation. As it is mentioned above, results of similar studies in this field are somewhat inconsistent. Based on the results of their study, Khan et al. indicated that vitamin D supplementation given for prolonged period, i.e. six months, had significant effects in reducing number of exacerbations in COPD patients[35]. On the other side, findings of the study performed by Lehouck et al. indicated that a high dose vitamin D supplementation may reduce exacerbations only in COPD patients with severe vitamin deficiency (serum levels less than 10 ng/mL) [33]. In addition, in their study including 1609 participants Burkes et al. found that vitamin D deficiency was associated with worse cross-sectional and longitudinal lung function and increased odds of prior COPD exacerbations suggesting that vitamin D levels may be a potentially useful marker of adverse COPD-related outcomes [37]. Meta-analysis of 25 randomized controlled trials in which efficacy of vitamin D supplementation in COPD patients were evaluated done by Li et al. showed that vitamin D used in patients with COPD could improve the lung function (FEV_1, FEV_1/FVC), 6-minute walk distance and reduce exacerbation, sputum volume and COPD Assessment Test (CAT) score[38]. Similar results were obtained in the systematic review and meta-analysis including 18 studies done by Zhu et al. [39]. On the other hand, Martineau et al. in their meta-analysis of 25 randomized controlled trials found protective effects of vitamin D regarding acute respiratory infections in individuals with its low baseline serum levels (less than 25 ng/mL) who received daily or weekly doses of vitamin D [40]. At the end, summarizing the recent knowledge about the effects of vitamin D supplementation on the course of COPD Milne & Sin conclude that there is conflicting evidence regarding the effects of vitamin D levels on the risk of COPD exacerbations, i.e. until further evidence should be generated, it seems reasonable to offer vitamin D supplementation to patients whose levels are less than 10 ng/mL, especially those with frequent exacerbations, as a meta-analysis of randomized controlled trial data suggests that supplementation in such individuals significantly reduces the risk of respiratory tract infections [41].

Findings of the present study should be interpreted in the context of its limitations. The study was neither blinded, nor randomized, and therefore can be a subject of possible selection bias. In addition, a small sample size and relatively short study period could have certain implications and its interpretation. On the other hand, the study design may be its strength, as it is documented by other real-life studies. Furthermore, the strength of the study could be the assessment of effects of vitamin D supplementation in a certain subgroup of COPD patients.

Conclusion

In conclusion, in an observational, non-randomized, open label study on effects of vitamin D supplementation on bacterial exacerbations in patients with severe COPD with low serum vitamin D kevels we found significantly lower mean number of exacerbations and their significantly shorter duration, significantly lower mean number of relapses and significantly longer duration of exacerbation-free interval in the group of patients with severe COPD and low serum levels of vitamin D supplemented by vitamin D than in the group of COPD patients with similar characteristics who did not receive vitamin D supplementation. Our findings confirmed a need of further investigations in this field in order to determine more precisely the role of vitamin D in the course of COPD.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. North Macedonia, Skopje gave approval for performing the study and publishing the results obtained (03-0302-610 - 11.09.2021).

Competing Interests: All authors hereby have declared that no competing interests exist.

Authors Participations

JM and SS participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. TP managed the literature searches and participated in the managing the analyses of the study. JM, SS, NKK, DBI, EJJ, DB and DM participated in data collection and managing the analyses of the study. All authors read and approved the final manuscript.

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