VIA MEDICA

ORIGINAL RESEARCH

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Vitamin D status of severe COPD patients with chronic respiratory failure

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Abstract

Introduction: The aim of the study was to measure the concentrations of vitamin D in serum of COPD patients with chronic respiratory failure in comparison to healthy control group. The correlation between the levels of vitamin D in serum and the selected clinical, spirometric and blood gas parameters was the additional aim of the study.

Material and methods: The study included 61 patients with diagnosed COPD in stadium of chronic respiratory failure (45 men and 16 women) and 37 healthy controls (19 men and 18 women). The following procedure were performed in all studied subjects: detailed history (especially: daily activity, diet, tobacco and alcohol use), post-bronchodilator spirometry, assessment of 25(OH)D in serum and for COPD group only blood gas analysis. Recruitment for the study was conducted from November to April. Statistical analysis was performed using the following statistical methods: t-Student test, Mann-Whitney U test, Spearman correlation test and Chi-kwadrat test.

Results: There was no significant differences between COPD and control group for the levels of 25(OH)D in serum. Median and lower; upper quartile were respectively following: 24,75 nmol/l (16,9; 36,4) vs. 24,06 nmol/l (16,3; 37,2), p=0,69. Vitamin D deficiency was present in 60 COPD patients (98,3% of all patients) and in 36 control group subject (97,3% of all healthy volunteers). The difference was not statistically significant. The levels of vitamin D in serum did not significantly correlated with any of studied parameters (spirometry, blood gas, age, the level of activity, BMI, tobacco smoke exposure and others). However, the level of activity in COPD group correlated positively with spirometry values and negatively with age and number of exacerbations.

Conclusion: The results of the study showed that in autumn-winter time in Poland there are very frequent deficiency of vitamin D in serum not only in COPD patients in respiratory failure stage but also in elderly healthy persons. However, in contrary to expectations the deficiency of vitamin D in COPD patients with respiratory failure were similar to that seen in healthy persons.

Key words: COPD, vitamin D, chronic respiratory failure, long-term oxygen therapy

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Introduction

Chronic obstructive pulmonary disease (COPD) of appropriate intensity and duration may lead to the development of respiratory failure, initially latent, and then at rest together with right ventricular failure. The lower reference limit for partial pressure for oxygen (PaO_2) of 60 mmHg corresponds to oxygen saturation of arterial blood haemoglobin of approximately 90%. Improving the prognosis for COPD patients with chronic respiratory failure is possible thanks to long-term oxygen therapy, which reduces the involuntary spasm of pulmonary vessels in response to hypoxia, decreases pressure in the pulmonary circulation and significantly prolongs life. Recently, COPD has no longer been regarded as a disease limited to the respiratory

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system only. Extrapulmonary disorders induced or exacerbated by COPD include atherosclerosis, thrombophilia, cachexia, gastrooesophageal reflux, anxiety-depressive disorder, myopathy, increased carcinogenesis even after quitting tobacco smoking, osteoporosis with pathological fractures, diabetes type 2, metabolic syndrome, and circulatory insufficiency. Osteoporosis and muscle weakness can simultaneously result from concomitant vitamin D insufficiency [1].

Vitamin D is a hormone synthesised in the skin due to solar ultraviolet radiation with a wavelength of 290–315 nm (UV-B). The substrate is ergosterol or 7-dehydrocholesterol, precursor in endogenous synthesis of cholesterol. Longer exposure does not lead to overproduction due to photolysis. Vitamin D is entirely 25-hydroxylated in the liver, thus the serum level of the formed 25-hydroxyvitamin D (25(OH)D) reflects vitamin D concentration in the body reliably. Active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is formed in the cells of proximal tubules and hormonally acts via the vitamin D receptor present in most cells [2, 3]. Synthesis of $1,25(OH)_2D$ is strictly regulated, and the catabolism of 25(OH)D and $1,25(OH)_2D$ is very efficient. The active form of vitamin D increases absorption of calcium and phosphorus from bowel contents, stimulates production of bone matrix proteins, facilitates bone mineralisation, acts antiproliferatively on parathyroid glands, conditions proper strength of muscle contractions, reduces risk of falls, affects cellular angiogenesis, division, differentiation and apoptosis as well as functioning of the immune system [2, 3]. A correlation of vitamin D insufficiency with a number of disorders has been found, and lower vitamin D concentration is associated prognostically with the increased risk of death by 35% [4]. The occurrence and exacerbation of disorders depend considerably on lifestyle, which also affects vitamin D concentration. Limited physical activity decreases exposure to UV-B, and in obesity, the excess fatty tissue captures vitamin D. Presently, the lower reference value for 25(OH)D is 30 ng/ml (75 nmol/l). The levels of 25(OH)D serum concentration are as follows: deficiency < 25 nmol/l; insufficiency 25–50 nmol/l; suboptimal level 50–75 nmol/l; recommended level 75–250 nmol/l, toxicity > 250 nmol/l [2, 3]. Vitamin D insufficiency is common in countries of the temperate zone; in the Polish population studies similar results are presented, and it is regular vitamin D supplementation that significantly affects its reserves. Some researches were conducted using proper methodology, but in small groups of patients; and the only major Polish study is based on populations of big cities, without exclusion criteria or information about concomitant disorders and supplementation [5–8]. Biological relevance of vitamin D is still being reassessed: as a result, the minimum recommended concentration was changed, which had previously been 5 ng/ml.

COPD sufferers are more likely to have vitamin D insufficiency due to limited physical activity, frequent indoor stay, premature skin ageing, temporary or long-term use of glucocorticoids, unbalanced diet. Glucocorticoid therapy exacerbates osteoporosis by acting on calcium metabolism, sex hormones and directly affecting bone tissue and myopathy [9, 10], starting from daily doses of prednisone of 7–7.5 mg. Systemic inflammation and sedentary lifestyle exacerbate calciuria and osteopenia in mechanisms independent of vitamin D [1]. In the COPD Assessment Test (CAT) [11], 2 out of 8 items: "I am very limited doing activities at home" and "I have no energy at all" share the characteristics of a variety of other conditions as well vitamin D insufficiency. Vitamin D concentrations in COPD sufferers have been evaluated more and more often in the world literature [12–15], whereas there is a shortage of Polish studies of this type. Attempts have been made to find a correlation between vitamin D concentrations and spirometric parameters in huge populations, without specifying the participant's disease. Mean FEV_1 (forced expiratory volume in one second) and mean FVC (forced vital capacity) were lower in the quintile of the lowest vitamin D concentration in comparison to the quintile of the highest concentration; these differences were still valid even after taking into account active pastime forms [16]. Another study has revealed a significant correlation only in overweight and obese men [17]. In the Norwegian population, a chance increased 2.4 times for the abnormal FEV_1/FVC% at the level of 25(OH)D <50 nmol/l, but this concerned active smokers only [18]. In patients diagnosed with COPD, emphysema or chronic bronchitis, a significantly lower 25(OH)D level was observed [19]. Janssens et al. noticed all year long 25(OH)D concentrations lower by 33% in COPD patients of GOLD stage 4 in comparison to controls [14]. In the NHANES study 3rd Edition, no significant differences were observed of 25(OH)D level in those diagnosed with emphysema and chronic bronchitis as compared to others, but the correlation of mean FEV_1 and 25(OH)D was stronger than in controls [16]. Low vitamin D concentrations in autumn and winter

may facilitate the production of inflammatory cytokines and more frequent COPD exacerbations.

The primary objective of the study was to compare 25(OH)D levels in COPD patients in respiratory failure stage with the control group and to analyse the correlation of 25(OH)D concentration with selected clinical, gasometric and spirometric parameters.

Materials and methods

The recruitment of the study group took place in the Domiciliary Oxygen Therapy Team of the Pulmonary Medicine District Hospital in Wodzisław Śląski, Poland, and in the Pulmonology Clinic of the Central Clinical Hospital of the Medical University of Silesia (CSK ŚUM) in Katowice, Poland. The controls were inhabitants of the same area as the patients, of similar age, if possible, flatmates (usually the patients' spouses). 61 COPD patients and 37 controls were recruited, who fulfilled the inclusion and exclusion criteria. The study was financed by the Medical University of Silesia within the scope of statutory research of the Chair and Clinic of Pulmonology. The approval of the Bioethical Committee of the Medical University of Silesia in Katowice was obtained.

Inclusion criteria to the study group were the following:

— giving a written informed consent for participation,
— diagnosis of COPD, in spirometry persistent obstruction in post-bronchodilator spirometry (FEV1%VC measured 15 minutes after inhaling 400 μg salbutamol < 70%),
— chronic respiratory failure with indications for LTOT (at least 3-month history of hypoxaemia, not associated with disease exacerbation of PaO2 ≤ 55 mmHg or PaO2 56–60 mm Hg together with at least one of the following: radiological or ultrasonographic features of pulmonary hypertension, polycythemia with the peripheral blood haematocrit of ≥ 55%, features of right ventricular hypertrophy in ECG),
— above 18 years of age,
— stable disease in the last 4 weeks.

Inclusion criteria to the control group were as follows:

— giving a written informed consent for participation,
— lack of respiratory disorders or symptoms,
— normal spirometry values,
— above 18 years of age
— lack of acute infections in the last 4 weeks.

Exclusion criteria (both groups) included the following:

- pregnancy,
- severe renal failure or severe liver impairment, or other diseases affecting vitamin D concentration,
- using medicinal preparations and dietary supplements with vitamin D or cod-liver oil within the last 3 months,
- contraindications to spirometry (recent ophthalmic surgery, coronary or cerebrovascular incident within the last month, pneumothorax, haemoptysis, aortic aneurysm, severe dyspnoea excluding the participant's cooperation).

In the study group, information was collected about COPD exacerbations, diet, stimulants and physical activity; post-bronchodilator spirometry and gasometry of arterialised blood from the earlobe were performed; venous blood was collected to determine 25(OH)D serum level. In the control group, information was collected about diet, stimulants and physical activity; post-bronchodilator spirometry was performed; venous blood was collected to determine 25(OH)D concentration. Patients were recruited from November to April — to avoid the impact of more intense summer sunlight on the measurement results, without repeating in summer and early autumn. Spirometry with the flow-volume loop was performed with Master Screen Pneumo (Carefusion, Yorba Linda, USA) (Wodzisław Śląski) and Master Lab (Jaeger® Carefusion, Yorba Linda, USA) (Katowice) spirometers. Domiciliary Oxygen Therapy in Poland is financed by the Polish National Health Fund which requires two spirometry tests during the year. As spirometry parameters in COPD without exacerbations decrease steadily with age, and routine spirometry is not recommended more often than every 3 years [11], spirometry done within the last 6 months during a recruitment visit was accepted in the study group, unless exacerbations were noted. Gasometry of arterial blood at rest was replaced with less invasive earlobe arterialised capillary blood gas analysis [20, 21]. Gasometry was performed directly on blood collection in the same room using the blood gas analysers: AVL Compact (Roche Diagnostic, Rotkreuz, Switzerland) (Wodzisław Śląski) and Gem® Premier 3000 (Wefren Group IVD, Barcelona, Spain) (Katowice). To arterialise the blood, Neo-Capsiderm ointment (Herbapol Poznań) was used while rubbing the earlobe. Gasometry was performed in the sitting position, following an at least two-hour break in oxygen supplementation. 25(OH)D serum concentration was determined in

Table 1. Demographic data for study and control group

	Study group	Control group
Age (years)	71.8 (± 6.9)	69.7 (± 8.2)
Men/women	45/16	19/18
FEV_1 % predicted*	36.9 (27.4; 51.7)	109.0 (95.7; 119.0)
FVC % predicted*	61.0 (52.6; 73.5)	108.6 (93.0; 115.0)
FEV_1%FVC*	46.2 (39.2; 58.1)	80.6 (76.7; 83.0)
BMI (kg/m^2)	29.7 (25.2; 33.2)	27.5 (25.5; 36.2)
PaO_2 (mm Hg)	51.0 (48.0; 54.0)	–
$PaCO_2$ (mm Hg)	46.0 (42.0; 50.0)	–
Ph	7.42 (7.40; 7.44)	–
Pack years of smoking	47 (± 20)	–
Serum vitamin D level (nmol/l)	24.75 (16.9; 36.4)	24.06 (16.3; 37.2)

$PaCO_2$ — partial pressure of carbon dioxide in arterial blood, FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; BMI — body mass index
*Data are presented as arithmetic mean and standard deviation for normalized parameter (age); or median and lower/upper quartile for parameters with abnormal distribution (other parameters)
Statistical differences between the test and control groups when $p < 0.05$ were marked

the Function Tests Laboratory of the Pulmonology Department of CSK ŚUM in Katowice-Ligota with the use of 25OH Vitamin D direct day ELISA kit (Immundiagnostic AG, Bernsheim, Germany). The blood was centrifuged to obtain the serum, and frozen at the temperature of –72 °C, which was caused by the necessity of simultaneous analysis of 80 specimens. Freezing specimens does not affect the measurement results.

To evaluate physical activity, 5 items in a questionnaire were used. Other questionnaire points concerned the following: present or past tobacco smoking including the number of pack-years of smoking, severity of coughing up sputum, osteoporosis, pathological fractures. COPD patients were also asked about exacerbations within the last 3 years requiring treatment in a hospital ward, at home, in ICU. Statistical analysis was done with the Statistica 10 programme (Statsoft Polska). For investigating normality of distribution, the Shapiro-Wilk test was used. Differences between the groups were assessed with the t-Student test (normal distribution in both groups) or the U-Mann-Whitney test (nonparametric distribution). The analysis of correlation was done with Spearman's rank correlation coefficient, as at least one of the analysed parameters always had abnormal distribution. The statistical significance level was $p < 0.05$. A comparison of prevalence of vitamin D insufficiency in the groups was done with the chi-squared test. The results were graphically depicted using box and bar charts.

Results

98 individuals were recruited: 61 patients aged 54–88 into the study group, and 37 people aged 57–93 as controls. The mean age in the study group was 71.8 years (± 6.9 years), in the control group 69.7 years (± 8.2 years). They did not differ significantly as for age. The mean number of pack-years of smoking in the study group was 47 (± 20); only 1 control reported smoking tobacco. The control group comprised 19 men and 18 women. A smaller number of controls and gender differences were caused by not recruiting some of the spouses or flatmates due to: the patient living alone, considerable airway obstruction in 12 individuals, vitamin D supplementation, contraindications to spirometry. The study group included 45 men and 16 women. Initially, 85 COPD patients with chronic respiratory failure had given their consent. From these, 24 individuals were excluded due to: falsely elevated FEV_1%VC > 70% caused by severe dyspnoea and short time of forced expiration, vitamin D supplementation, contraindications to spirometry. The demographic data for both groups are presented in Table 1.Vitamin D serum concentrations did not differ significantly between the study and control groups, being respectively [median and (lower and upper quartile)]: 24.75 nmol/l (16.9; 36.4) vs. 24.06 nmol/l (16.3; 37.2), $p = 0.69$. The result is presented in Figure 1. Basing on the clinical interpretation of 25(OH) D concentration, COPD patients were divided

into subgroups of: deficiency, insufficiency, suboptimal, and recommended levels of vitamin D. None of the patients had toxic vitamin D concentration. The study and control groups did not differ significantly in the subgroups. Vitamin D insufficiency below the current norm was observed in 60 COPD patients (98.3%) and in 36 controls (97.3%) without statistically significant difference. The results are presented in Table 2 and Figure 2. Vitamin D levels did not differ significantly between individual months. Type II hypercapnic respiratory failure occurred in 39 of 61 patients in the study group.

Only 4 patients in the study group declared using oral glucocorticoids; statistical analysis could not be performed due to the lower number of patients. 37 COPD patients declared applying inhaled glucocorticoids. Excluding those using oral glucocorticoids, 25(OH)D serum levels did not differ significantly between COPD patients applying inhaled glucocorticoids and other COPD patients, and they respectively were [median and (lower and upper quartile)]: 28.2 nmol/l (17.6; 43.2) vs. 24.5 nmol/l (13.5; 36.4), p = 0.60. The result is presented in Figure 3.

No statistically significant correlation was found of vitamin D concentration with the following parameters: clinical (age, BMI, activity assessment, nutrition, number of exacerbations, severity of coughing up sputum, number pack-

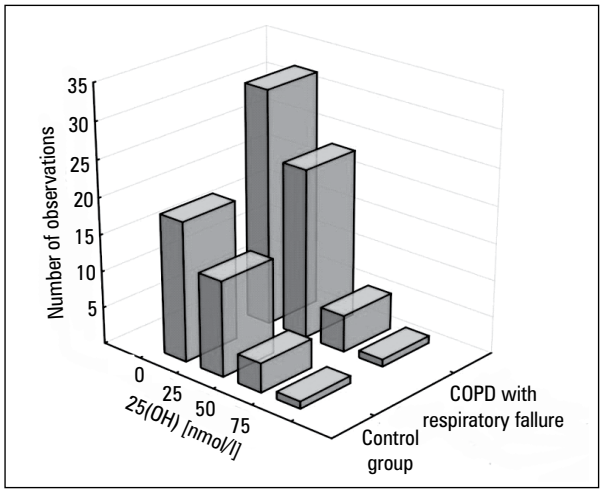

Figure 2. Clinical interpretation of 25(OH)D concentration into subgroups of: deficiency, insufficiency, suboptimal, and recommended levels of vitamin D for study and control group

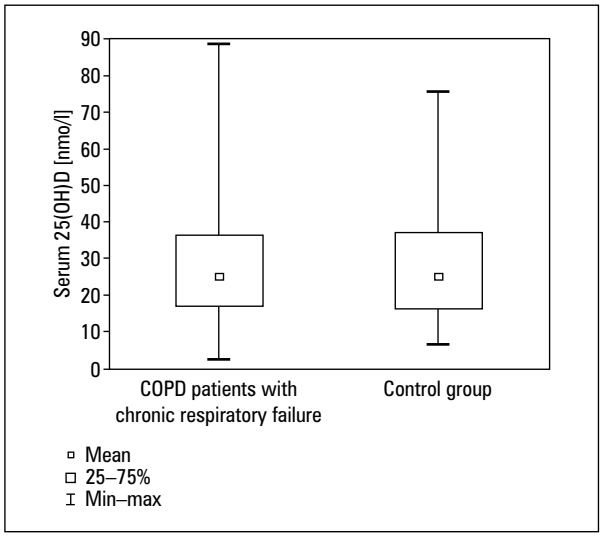

Figure 1. Serum 25(OH)D level of severe chronic obstructive pulmonary disease patients with chronic respiratory failure vs control group

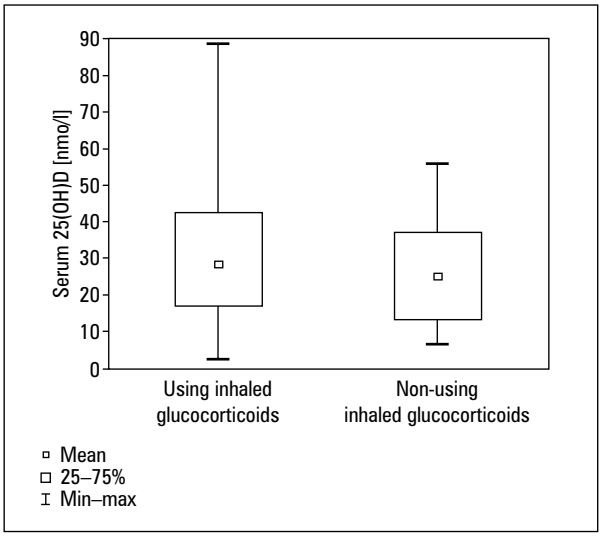

Figure 3. Serum 25(OH)D levels between chronic obstructive pulmonary disease (COPD patients using inhaled glucocorticoids and other COPD patients

Table 2. Clinical interpretation of serum 25(OH)D level for study and control group

	Serum 25(OH)D level [nmol/l]			
	Deficiency 0–25	**Insufficiency 25–50**	**Suboptimal 50–75**	**Recommended 75–250**
Study group	32	23	5	1
Control group	19	13	3	1

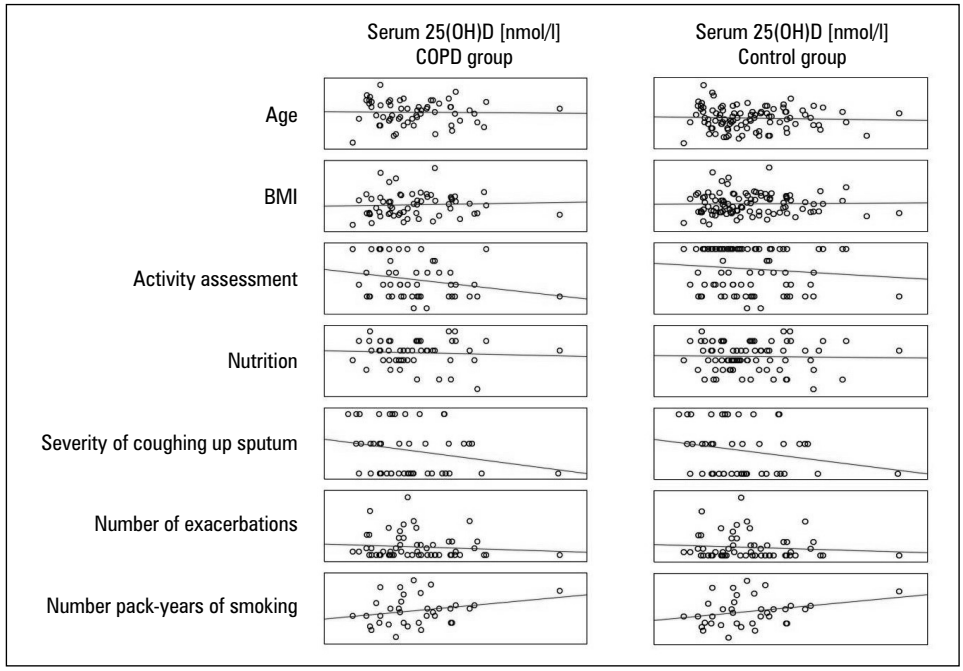

Figure 4. Correlation for vitamin D concentration with the age, body mass index (BMI), activity assessment, nutrition, number of exacerbations, severity of coughing up sputum, number pack-years of smoking

years of smoking), spirometric (FEV_1%, FVC%, FEV_1%VC), gasometric (pO_2, pCO_2, pH). As for other parameters, the following statistically significant correlation coefficients were obtained: positive between FEV_1%, FVC%, FEV_1%VC and activity, negative between pCO_2 and FEV_1%, FVC% and pH, pCO_2 and pO_2, negative between the number of exacerbations and activity and between activity and age (Fig. 4).

Discussion

Despite strong presumptions, no statistically significant difference was observed comparing vitamin D serum concentration in COPD patients with chronic respiratory failure and controls. Vitamin D insufficiency occurs commonly in countries with moderate latitude, especially in seasons with less sunlight. Less physical activity in the study group did not affect the median of vitamin D concentration, showing no statistically significant correlation of 25(OH)D concentration with activity. Paradoxically, this might be caused by the recruitment from late autumn to early spring in order to avoid the impact of sunlight on the results. The choice of the seasons might have smooth and blur possible differences below the statistical significance due to lack of vitamin D synthesis in the skin. Among hypotheses, two presumptions are dependent on sun exposure: less physical activity and premature skin ageing. This poses a question: Would a statistically significant difference be recognised while determining vitamin D concentration at the end of summer? Due to the fact that 25(OH)D concentrations will differ after several cloudy or rainy days or following intense summer sunlight exposure, collecting material to determine 25(OH)D concentration should take place within a few days. Less physical activity does not have to equal less exposure of the skin to the sun: a patient sitting during many hours in the garden may have a higher 25(OH)D serum concentration than a patient of the same degree of fitness, living in the northern side of a building without a lift. The opposite situation may be observed in a healthy individual who leads an indoor sedentary lifestyle and rarely goes for a walk.

The more severe COPD stage and more frequent exacerbations, the greater the frequency of using systemic glucocorticoids- hence their catabolic influence on vitamin D might have led to false positive results. Low socioeconomic status associated with COPD sufferers, and thus a possibly monotonous, unhealthy diet might not have been valid for the studied population of Upper Silesia, where the majority were former employees of a coal mine, with pension 2-3 times higher than the average one in Poland.

A comparison of obtained results with those by other researchers has revealed both the com-

patible and divergent results. Jackson et al. have presented significantly lower concentration of 25(OH)D = 41.5 nmol/l in the COPD subgroup vs controls 54.8 nmol/l, (p = 0.03); however, their COPD patients did not have respiratory failure and relatively high 25(OH)D concentrations have resulted from participants recruited both in summer and winter [19]. The authors have also presented a graph of the group of COPD patients with 25(OH)D concentration statistically significantly lower by 14.6 nmol/l in winter in comparison to summer, but without differentiating between subjects who take supplements and those who do not. Janssens *et al.* [14] have described mean 25(OH)D concentration of 40 nmol/l in 30 COPD patients of GOLD Stage 4 in comparison to 61.5 nmol/l in the control group [14], but they have not presented differences in the COPD group vs controls in individual seasons, which could make it possible to compare with own results [14].

No correlation was found of ventilatory parameters with 25(OH)D concentration in the study and control groups. Some researchers have reported statistically significant correlation in various subgroups of both controls and COPD patients [16–18]. The publications have lacked critical cause-and-effect analysis: decreased spirometric parameters have meant decreased physical fitness, less exposure to UV-B, and thus lower 25(OH)D concentrations. The reason for not finding a correlation of ventilatory parameters with 25(OH)D concentration may be a relatively small number of participants in the study group in comparison to the quoted articles (NHANES: more than 10,000 participants). An alternative reason for lack of correlation between activity parameters and 25(OH)D concentrations might be accurate characteristics, homogenousness and narrowing of the study group (patients with very severe COPD in the stage of respiratory failure), while in other studies [16–18], the population was not limited to COPD and patients were in various stages of disease, which might have facilitated the observation of a connection.

Statistically significant positive correlation coefficients of activity with ventilatory parameters and the negative correlation coefficient with age prove the relevance and simplicity of questionnaire items and genuineness of the responses given. The correlations found between spirometric and gasometric parameters result from COPD pathophysiology. An interesting issue discussed in the literature is the attempt to assess the correlation between 25(OH)D concentration and risk of COPD exacerbations. However, such data were not to be collected owing to the short observation time.

Study limitation

The authors constantly use gasometry with arterialised blood of the earlobe due to less invasiveness compared to arterial blood. The awareness of the possibility of a slight understatement of the pO_2 value using this method, which was discussed by some authors, did not influence the obtained results [22]. GOLD classification is not useful in grading treatment and therapeutic interventions in patients in terminal stage of COPD. Therefore, the division of patients into GOLD in COPD with respiratory failure in our publication is pointless, with predictable dominance of patients in stages III and IV and in groups C and D. A large part of the study group, as many as 16 people from 61 presented pCO_2 values in the range of 44–46 mmHg. With the mandatory upper limit of pCO_2 = 45 mm Hg, repeating daily or hourly gas measurements in this group may result in completely different rates of patients with type I and II respiratory failure due to tolerable pCO_2 measurement bias and circadian fluctuations. Therefore, in the article, the percentage of patients with type I and II respiratory failure should only be considered as approximate in such a group. Accordingly, further analyses of possible association of vitamin D levels with type of respiratory failure in our opinion have no scientific basis.

Conclusion

Vitamin D insufficiency is very common in autumn and winter in Poland in elderly COPD sufferers and healthy individuals. 25(OH)D serum concentration in patients with severe COPD and chronic respiratory failure is not significantly lower as compared to the control group.

No correlation was observed of ventilatory, gasometric, or activity parameters with 25(OH)D concentration in COPD patients.

The questionnaire responses revealed that the activity of patients with advanced COPD and respiratory failure decreased.

Statistically significant positive correlation coefficients were found between patients' activity and FEV_1%, FVC%, FEV_1%FVC and pO_2, and a negative correlation coefficient between activity and age.

Conflict of interest

The authors declare no conflict of interest.

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