Exacerbation of chronic obstructive pulmonary diseases as a risk factor of the skeletal muscle dysfunction

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ABSTRACT

Background: Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) contributes to increased systemic inflammation, oxidative stress, hypoxia, hypercapnia and other risk factors of the skeletal muscle dysfunction.

Aims and Objectives: This study aimed to determine whether the frequency of the COPD exacerbations promotes deterioration of the skeletal muscle dysfunction in patients with COPD and to figure out which characteristics of the muscles will reflect this changes. Materials and Methods: We examined 98 male COPD patients, mean age 60.4±11.2 years, GOLD groups B, C, D. To assess the degree of skeletal muscle dysfunction we used hand-grip strength, 6-minute walk test, bioelectrical impedance analysis. Quality of life was evaluated using St. George’s respiratory questionnaire (SGRQ). Results: Increase in the frequency of COPD exacerbations was associated with the decrease in the 6-minute walk test distance (r = -0.214, P = 0.034) and with the rise of sarcopenia according to the results of bioelectrical impedance analysis – lower fat-free mass index (r = -0.201, P = 0.047). Frequency of COPD exacerbations had a weak correlation with the degree of the activity limitation component of SGRQ (r = 0.436, P < 0.001). Conclusions: COPD exacerbation plays an important role in progression of the skeletal muscle dysfunction. It decreases endurance of the skeletal muscles, diminishing their size, which manifests itself in reduced exercise tolerance. Increase in the frequency of the COPD exacerbations also worsens all components of the life quality.

KEY WORDS: Chronic obstructive pulmonary disease exacerbation, comorbidity, skeletal muscle dysfunction

INTRODUCTION

Skeletal muscles dysfunction is chronic obstructive pulmonary disease (COPD) comorbidity, which significantly affects the quality of life, functional state of the organism, and surviving of the patients.[1] Development of the skeletal muscle dysfunction in COPD patients contributes to the presence of numerous risk factors, which include reduced physical activity during the day,[2] smoking,[3] hypoxia,[4] hypercapnia,[5] oxidative stress,[6] usage of the systemic glucocorticosteroids,[7] malnutrition,[8] systemic inflammation,[9] imbalance of anabolic and catabolic hormones,[10] and Vitamin D insufficiency.[11]

COPD exacerbation is an acute condition, which is extremely important for patients, increasing frequency of hospitalization, worsening life quality, and ventilatory function.[12] In addition to this negative effect on the progression of COPD, exacerbation indirectly through the action of various catabolic stimuli promotes the progression of skeletal muscle dysfunction. Patient’s organism during exacerbation is intensively affected by the
following risk factors of the skeletal muscle dysfunction: hypoxia,\textsuperscript{[13]} hypercapnia,\textsuperscript{[14]} malnutrition,\textsuperscript{[15]} decreased physical activity,\textsuperscript{[16]} increased systemic inflammation,\textsuperscript{[17]} administration of the systemic glucocorticosteroids,\textsuperscript{[7]} oxidative stress,\textsuperscript{[18]} and decrease in the level of anabolic hormones.\textsuperscript{[10]}

In this study, we used the handgrip dynamometry, bioelectrical impedance analysis, and 6-min walking test (6MWT) in stable COPD patients and compared it with COPD exacerbation frequency to assess the influence on skeletal muscles.

**MATERIALS AND METHODS**

This was a prospective cross-sectional study carried out in the Propedeutic Department to Internal Medicine, National Pirogov Memorial Medical University, Vinnytsia, and Pulmonological Department of the Vinitsia City Clinical Hospital No 1, Vinnytsia, Ukraine.

We examined the patients discharged from the pulmonology department after treatment of COPD exacerbation. The study was conducted after being approved by the Ethical Committee of the University and obtaining informed consent from the patients.

We examined 98 male patients with stable COPD, mean age – 60.4 ± 11.2 years. Demographic and clinical characteristics of patients are presented in Table 1.

COPD was diagnosed on the basis of past history, physical examination, and spirometric data according to the Global Initiative for Obstructive Lung Disease guidelines.\textsuperscript{[19]}

Patients belonged to the COPD groups B, C, and D. The distribution of these groups was as follows: Group B – 31 patients (31.6%), Group C – 42 patients (42.9%), and Group D – 25 patients (25.5%). All patients received a standard therapy according to the COPD group to which they belong.

We use a specific program for patient history monitoring in Vinnytsia region – «Doctor Eleks» assessed the history of previous COPD exacerbations. We assessed the frequency of exacerbation, obtained treatment, and evidence of hospitalization.

Assessment of the skeletal muscle dysfunction (SMD) was done by studying the functional state of skeletal muscles (strength, endurance) and its mass. Skeletal muscles strength was estimated using handgrip dynamometry of the dominant hand with a certified handgrip dynamometer «DK-100» with further comparison of the obtained data with the age normal values for this gender.\textsuperscript{[20]} The method provided a three-time measurement by maximal isometric handgrip muscle contraction with the registration of the best attempt.

Endurance, needed for evaluation of exercise tolerance, was determined by the 6MWT.\textsuperscript{[21]} During this test, we assessed distance walked for 6 min, number of stops, use of the short-acting bronchodilator, and degree of shortness of breath at the beginning and at the end of the test by Borg Scale.

Bioelectrical impedance analysis was used to investigate skeletal muscle mass. This method is recommended for assessing the skeletal muscle mass in patients with COPD by the European Working Group on Sarcopenia in Older People\textsuperscript{[22]} and was chosen by us because of its mobility, speed in usage, and low cost. Using bioelectrical impedance, we obtained skeletal muscle percentage in the body and fat-free mass (FFM). Other more sensitive indicators for assessment skeletal muscle mass were calculated based on it: FFM Index (FFMI) and Skeletal Muscle Index (SMI). FFM is calculated as a FFM adjusted for the squared height, SMI – as a skeletal muscle mass adjusted for the squared height. These indices are the most informative for the diagnosis of skeletal muscle dysfunction, because it excludes the effect of fat tissue on results.

All patients filled out the St. George’s Respiratory Questionnaire (SGRQ) by themselves with the official Ukrainian translations.\textsuperscript{[23]} According to this questionnaire, the following components of the quality of life were calculated: total – the impact of the disease on overall health status; symptoms – the effect of respiratory symptoms, their frequency and severity; activity – the activities that cause or are limited by breathlessness; and impact – the aspects concerned with social functioning and the impact of psychological problems.

Descriptive statistics were used to characterize the population.

Obtained anamnestic data, patient survey results, and questionnaire data were formed in the order and

Table 1: Demographic and clinical characteristics of the patients

| Patient characteristics                        | n (%) or mean±SD |
|------------------------------------------------|------------------|
| Age (years)                                    | 60.4±11.2        |
| Group B (number of patients)                    | 31 (31.6)        |
| Group C (number of patients)                    | 42 (42.9)        |
| Group D (number of patients)                    | 25 (25.5)        |
| Exacerbation frequency (per year)               | 2.33±11.3        |
| Handgrip strength (percentage from age normal value) | 77.6±18.6 |
| 6MWT distance (m)                              | 319.1±111.2      |
| Bioelectrical impedance analysis                |                  |
| FFMI (kg/m²)                                   | 19.4±2.6         |
| SMI (kg/m²)                                    | 8.5±1.5          |
| SGRQ                                           |                  |
| Total                                          | 58.9±15.9        |
| Activity                                       | 65.4±20.5        |
| Symptoms                                       | 71.2±14.4        |
| Impact                                         | 51.5±17.0        |

SD: Standard deviation, 6MWT: 6-min walking test, SGRQ: St. George’s Respiratory Questionnaire, FFMI: Fat-Free Mass Index, SMI: Skeletal Muscle Index
interval scales of statistical data. According to the Kolmogorov–Smirnov test, they were not subject to normal data distribution. Therefore, the rank correlation was calculated according to the Spearman criterion. Stepwise multiple regression analysis was performed.

**RESULTS**

The mean frequency of the COPD exacerbations was quite high (2.3 ± 1.4/year), which corresponds to the prevalence of Groups C and D among the patients.

According to the results of the examination of the skeletal muscles, functional status and muscle mass were reduced [Table 1]. Handgrip strength of the muscles was only 77.6% ± 18.6% of the age norm, and the distance of 6MWT was 319.1 ± 111.2 m, that was significantly different from the proper indicators, which according to Bohannon must exceed 600 m.\[24]\] FFMI and SMI were accordingly 19.4 ± 2.6 kg/m\(^2\) and 8.5 ± 1.5 kg/m\(^2\), which corresponds to previously published by Ischaki et al. research on the determination of these indicators in the population of COPD patients.\[25]\]

Results of the statistical analysis of the obtained data are shown in Table 2. By calculating the rank correlation using Spearman criterion, we identified the number of correlations with different strength. Thus, we found a weak negative correlation between the growing of the COPD exacerbation frequency and 6MWT distance (\(r = -0.214; P = 0.034\)) [Figure 1].

It was found that frequency of the COPD exacerbations had a weak negative correlation with the FFMI (\(r = -0.201; P = 0.047\)) [Figure 2].

After assessment of the life quality components, according to the SGRQ, a weak-positive correlation between the frequency of the COPD exacerbations and the impact of the disease on overall health status (\(r = 0.478; P < 0.001\)) and all its components were found: the activities that cause or are limited by breathlessness (\(r = 0.436; P < 0.001\)), the effect of respiratory symptoms, their frequency and severity (\(r = 0.395; P < 0.001\)), and the aspects concerned with social functioning and the impact of psychological problems (\(r = 0.41; P < 0.001\)) [Table 2]. In a step-wise multiple regression analysis, total score (partial \(R^2 = 0.048, P < 0.0001\)) was positively related to frequency of COPD exacerbations.

**DISCUSSION**

Our study aimed to determine whether the frequency of the COPD exacerbations affects the degree of the skeletal muscle dysfunction in patients with COPD and to determine which characteristics of the muscles will reflect this effect.

According to these tasks, we found that in COPD patients with frequent exacerbations, the degree of SMD was significantly greater than in those who had exacerbations less frequently [Table 2]. Hence, the increase in the

| Characteristics     | Correlation coefficient | \(P\)  |
|---------------------|-------------------------|-------|
| Handgrip strength   | -0.158                  | 0.121 |
| 6MWT distance       | -0.214                  | 0.034 |
| FFMI                | -0.201                  | 0.047 |
| SMI                 | -0.172                  | 0.092 |
| SGRQ Total          | 0.478                   | <0.001|
| Activity            | 0.436                   | <0.001|
| Symptoms            | 0.395                   | <0.001|
| Impact              | 0.41                    | <0.001|

The results are presented as a Spearman correlation coefficient. 6MWT: 6-min walking test, SGRQ: St. George’s Respiratory Questionnaire, FFMI: Fat-Free Mass Index, SMI: Skeletal Muscle Index

Figure 1: Correlation between the frequency of the chronic obstructive pulmonary disease exacerbations and the 6-min walking test distance

Figure 2: Correlation between the frequency of the chronic obstructive pulmonary disease exacerbations and the Fat-Free Mass Index
frequency of COPD exacerbations negatively affects the functional state of skeletal muscles by reducing exercise tolerance on the basis of the 6MWT results. Pitta et al. in their study also point out that according to the daily monitoring of physical activity in patients who suffered the COPD exacerbation, even in a month after the completion of treatment in the hospital, there was a decrease in walking time compared with stable patients. Alahmari et al. had shown a decrease in the 6MWT distance of patients during exacerbation and for 3–7 days after the exacerbation.16

Regarding the effect of exacerbation on the skeletal muscle mass, it should be noted that this issue is much less studied. Hopkinson et al. proved the presence of a negative correlation between the frequency of the COPD exacerbations and FFM,17 and also found out that the decrease of the FFM in COPD patients was associated with the deterioration of the airflow limitation and poor quality of life. Martinez-Llorens et al., using bioelectric impedance analysis, found a significant difference in the size of the skeletal muscle of persons hospitalized for COPD exacerbation and stable patients. Vilaró et al. established on the basis of the FFM, that the degree of the skeletal muscle dysfunction strongly correlated with the presence of previous or present exacerbation of COPD. The results of our study coincide with these data and indicate that the rise in the frequency of exacerbations is negatively reflected in the skeletal muscles mass. Thus, the decrease of the FFM by the results of bioelectric impedance analysis is associated with frequent exacerbations [Table 2].

The results of our study did not reveal a significant difference in the skeletal muscle strength in patients with frequent and rare COPD exacerbations [Table 1], which differs from a number of previously published works. Kazuya et al. had shown that there is a correlation between the frequency of COPD exacerbations and strength of the erector spinae muscles. Vilaró et al. proved that in patients who were often hospitalized in case of the COPD exacerbations, the handgrip dynamometry results were significantly lower than those with stable COPD. Of course, there are data, and our own observations confirm them, regarding the effect of the COPD exacerbation on muscle strength during exacerbation and in the short period after discharge from the hospital. Alahmari et al. found the reduction of the quadriceps femoris muscle strength during COPD exacerbation and within 7 days after that. However, according to the Spruit et al. data, this negative effect on the skeletal muscle was maintained for about 90 days, after which the strength of skeletal muscle restores to previous values. That is, in the study of our group of COPD patients, the decrease in muscle strength due to the COPD exacerbation could only be observed in patients who suffered from it in the last 3 months, as result of which correlation have not been confirmed.

Decrease of the life quality during the COPD exacerbations well studied by many scientists such as Roche et al. Nevertheless, our study found out that the life quality of patients in the period between exacerbations depends on the overall frequency of the COPD exacerbations over the past year [Table 1]. That is, the deterioration in the quality of life, which occurs during exacerbation, remains extremely long. This negative impact on the overall quality of life is due to negative effects on all life quality components, but most severe due to the activities that cause or are limited by breathlessness. Quite a few scientific researches have been studying this issue. Among them, we should highlight Steer et al. who found that the reduced components of life quality were restored to the baseline level in 3 months after exacerbation, except for the activities that cause or are limited by breathlessness – for a complete recovery of which it takes 6 months. Andøenes et al. had shown that exacerbation was such a severe physiological stress for the body that improving the quality of life above the level before exacerbation was possible in patients only in 9 months after the COPD exacerbation.

CONCLUSIONS

We found that COPD exacerbation has an important role in the progression of skeletal muscle dysfunction. As a result of the frequent exacerbations, there is a decrease in endurance of skeletal muscles diminishing their size, which manifests itself in reduced exercise tolerance. In addition, due to the increase in the restriction of the physical activity in patients with more frequent COPD exacerbations, there is a decline in all components of the life quality.

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Conflicts of interest
There are no conflicts of interest.

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