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METABOLIC PHENOTYPES OF COPD: PECULIARITIES OF PATIENT MANAGEMENT (review of literature, own research results)

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Abstract. CImportance of the determination and correction of metabolic changes in patients with chronic obstructive pulmonary disease (COPD) increases with each passing year. Nutritional disorders, sarcopenia, obesity or development of cachexia significantly affect the clinical manifestations of COPD, impair the quality of life of the patient and increase the risk of exacerbations, cardiovascular events and death. Thorough study of the relationship between COPD and the constitutional characteristics of the patient has allowed to describe four metabolic phenotypes, to develop a stratification scale for determining the risk of cardiovascular events and death. Etiological factors and pathogenesis of skeletal muscle dysfunction (SMD), as the most significant comorbid state in COPD, have been established. For diagnosis of SMD are proposed such methods as bio-impedancemetry with determining the amount of muscle tissue, hand grip dynamometer test and a 6-minute walk test to evaluate its functional capacity. According to our own studies, the incidence of SMD in patients with COPD was 34 %. It was associated with more severe symptoms, frequent exacerbations, the worst parameters of quality of life due to limiting motor activity. Correction of metabolic disturbances in COPD patients requires an integrated approach, which includes not only basic treatment, but also smoking cessation, protein-, amino acid- and vitamin D-enriched nutrition, increased physical activity, the use of anabolic steroids, personalized interval training. Based on European guidelines for the rehabilitation of patients with COPD and SMD, we have developed and offered a personalized set of physical exercises. The regular execution of this complex contributed to improving the quality of life and physical activity of a patient with severe COPD.
Key words: chronic obstructive pulmonary disease, sarcopenia, skeletal muscle dysfunction, rehabilitation.

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The peculiarities of the clinical course of chronic obstructive pulmonary disease (COPD) in patients with different constitutional characteristics have attracted the attention of researchers for a long time.

In 1968, Filley et al. proposed to divide COPD patients, depending on constitutional changes and clinical course of the disease, in 2 phenotypes: bronchial (*Blue Bloater*) and emphysematous (*Pink Puffer*) [7].

Patients with a bronchial type were characterized by overweight or obesity, had frequent exacerbations with worsening cough and sputum production. They usually had cardiovascular comorbidity, which in combination with bronchial and pulmonary involvement led to the formation of chronic cor pulmonale and development of heart failure. Patient had typical appearance — "*Blue Bloater*" [7].

In the case of emphysematous type, the course of COPD was stable with rare exacerbations. Progressive shortness of breath and domination of emphysematous changes in the lungs accompanied by muscle atrophy and weight loss were prevalent in clinical manifestations. The patient looked exhausted with enlarged thorax and severe dyspnea — "*Pink Puffer*" [7].

Further studies of the relationship between constitutional characteristics, specific features of metabolism and clinical course of COPD allowed the working group of experts of the European Respiratory Society (ERS) to

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identify and describe four metabolic COPD phenotypes [23].

According to the current ERS Statement, COPD in patients without severe metabolic disturbances is characterized by a stable course without significant structural changes in the lung parenchyma revealed by computed tomography, normal structure and size of skeletal muscles with the prevalence of type I myocytes, absence or early signs of the atherosclerotic process of the large arteries, the normal amount of hypodermic and visceral fat [23].

The presence of cachexia in patients with COPD is accompanied by a progressive structural changes in the pulmonary tissue with the formation of emphysema, loss of bone tissue with the development of osteoporosis, skeletal muscle atrophy with the replacement of myocytes type I by myocytes type II, resulting in loss of strength and endurance, significant reduction in the amount of subcutaneous and visceral fat. These changes lead to rapid progression of respiratory failure, even in the absence of frequent exacerbations [23].

COPD patients with obesity are more likely to have atherosclerosis of the aorta, cerebral and coronary arteries than patients with other phenotypes, leading to the development of concomitant diseases of the circulatory system and increased risk of cardiovascular events and death. The clinical course of COPD is characterized by symptoms of bronchitis and frequent exacerbations. Chest computed tomography reveals bronchiectases formed due to prolonged progressive inflammation. This category of patients has increase amount of subcutaneous and visceral fat, normal characteristics of skeletal muscles [23].

Patients with COPD who do not have external signs of cachexia or obesity, but with decrease in the size, strength and endurance of skeletal muscle revealed during careful examination of the body composition are classified as sarcopenia group. They don't have any domination in the structural changes of the bronchi and lungs — the same signs of emphysema and bronchitis. They don't have significant atherosclerosis, osteoporosis. The amount of visceral and subcutaneous adipose tissue is within the normal range or slightly increased. The course of the disease in such patients is accompanied with frequent exacerbations, decreased physical activity and increased risk of death [23].

On the basis of the obtained data, a stratification scale was proposed for determining the risk of death and cardiovascular events in patients with COPD taking into account the features of the body structure.

Constitutional changes and nutritional disorders in patients with COPD develop due to the influence of a significant number of etiological factors, which can include genetic features, frequent exacerbations, metabolic disorders, inappropriate nutrition, aging, the presence of chronic concomitant diseases, drug use, smoking, hypercapnia, acidosis, hypoxia, chronic systemic inflammation. But the most significant is low physical activity. The interaction of these factors contributes to the development and progression of oxidative stress, stimulates the processes of autophagy, proteolysis, apoptosis, catabolism, increases the production of myostatin. The processes of protein anabolism are suppressed, which in the complex leads to a disorder of regeneration, an increase in the destruction of muscles [3].

There are changes in myocytes of skeletal muscles: decreased density of mitochondria and the oxidant capacity of enzymes. The cell loses contact with capillaries. These processes lead to an increase in rapidly expanding fibers, development of myofiber atrophy and formation of type II myocytes which are not capable of fully performing the function [3]. The skeletal muscle dysfunction (SMD), which is characterized by a decrease in their size, reduced strength, endurance, and increased fatigue develops in patient [20].

The key principles and methods for diagnosing SMD are presented in the recommendations of the European Working Group on Sarcopenia in Older People. Magnetic resonance imaging, spiral computed tomography, dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance are used to assess structural changes in muscle tissue. The first three methods are expensive and are not readily available for use in screening studies. However, the bioelectrical impedance analysis, which determines the content of fat, muscle tissue, body mass index — general and fat-free, and others, allows to objectively and accurately assess the basic structural characteristics of the patient's body. The method is non-invasive, cost-effective and informative [5].

Hand grip dynamometer test of the dominant hand, measuring knee extensors muscle strength, cardio-respiratory testing, dosed walk tests (6-minute walk test) are recommended for estimation of the functional ability of skeletal musculature. Among these methods, the hand grip dynamometer test and the 6-minute walk test are most commonly used, in contrast to measuring knee extensors muscle strength and cardio-respiratory testing, which require additional, bulky equipment, specially trained personnel, and additional conditions for conducting estimation [5].

According to a number of international studies, the prevalence of SMD in patients with COPD is observed in one-third of cases in the European continent. Disorders are even found in patients with mild bronchial obstruction, according to GOLD 1-2. The SMD frequency is increased in case of worsening airways conductivity and reaches almost 40 % in patients with very severe obstruction (GOLD 4). The negative effect of skeletal muscle loss on COPD symptoms, quality of life of patients and increasing mortality rates was also proved [18, 22, 24].

With purpose to study of SMD influence on the clinical presentation, course of COPD and quality of life we investigated 143 patients with COPD, whose average age was (65.2 ± 11.3) years. COPD symptoms were assessed according to Order number 555 MOH of Ukraine (27.06.2013) [1] and GOLD 2019 recommen-

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dations [25] with calculation of score of the COPD Assessment Test (CAT) and the Modified British Medical Research Council (mMRC) Questionnaire. Spirometry test after inhalation 400 mcg salbutamol was used for assessment of severity of bronchial obstruction according to GOLD classification. Frequency of COPD exacerbation in a year was estimated with data of medical records and patient's notes.

Evaluation of the metabolic disorders was performed with investigation of patients using monitor of body composition «OmronBF511». It defined body mass index (BMI), fat tissue, visceral fat. Presence of obesity was evaluated according to World Heath Care Organization recommendations on the base of BMI (body mass divided to square of height in meters): < 18.5 kg/m^2 — insufficient weight, 18.5–24.9 kg/m^2 — normal weight, 25-29.9 kg/m^2 — overweight, 30-34.9 kg/m^2 — obesity I degree, 35-39.9 kg/m^2 — obesity II degree, ≥ 40 kg/m^2 — obesity III degree.

Revealing sarcopenia was grounded on the estimation of skeletal muscle content, index of skeletal muscle (ISM), calculated as skeletal muscle mass divided to square of height in meters. The strength of skeletal muscles was estimated using a dynamometer of hand DK-100. The criterion of sarcopenia was a decreased ISM ≤ 8.5 kg/m^2 for male and ≤ 5.75 kg/m^2 for female when combined with the reduction of the results of the hand grip dynamometer test < 27 kg for and < 16 kg for female [5].

Patient's Quality of life was assessed with adopted for Ukraine version of Sent George Hospital Questionnaire (SGRQ).

We revealed a decrease in the size and strength of skeletal muscle in 50 (34.0 %) people. The assessment of the patient's body composition in accordance with the recommendations of the European Working Group on Sarcopenia in Older People among 38 obese subjects (BMI ≥ 30) allowed to detect 6 (15.8 %) with signs of sarcopenia, among 27 patients with cachexia (BMI < 18.5) this pathology was observed in 10 (37.0 %), among 78 patients with normal or overweight (BMI = 18,0-29.9 %) it was in 34 (43.6 %) cases. That is, according to our data, SMD is most commonly diagnosed in patients without significant malnutrition.

Analysis of main parameters of COPD course showed that exacerbations were more common in the groups of patients with cachexia and obesity, whereas in patients without metabolic disorders, the exacerbations during the year were almost twice lower (Table 1).

The evaluation of COPD symptoms by the CAT and mMRC scales was significantly worse in patients with cachexia, sarcopenia and obesity compared with patients without metabolic disorders.

The degree of bronchial obstruction according to the lung function test was the most severe in patients with cachexia and sarcopenia. FEV1 in obese patients and in patients without metabolic disorders did not differ statistically and corresponded to the moderate obstruction.

The analysis of quality of life parameters showed the worst condition in patients with cachexia. Somewhat better quality of life was in COPD patients with obesity and sarcopenia. At the same time, a more significant effect on the quality of life in patients with cachexia was limitation of physical activity, while in other groups of patients the symptoms of COPD had the greatest impact on the deterioration in quality of life.

Thus, our data show a significant modifying effect of metabolic disorders accompanied by SMD on the course of COPD.

On the basis of the data obtained from the study of COPD course in patients with changed body composition and SMD, a comprehensive approach to their management during the rehabilitation was developed. Patients are advised to stop smoking [15, 25]. Highly intensive interval training is developed individually [25, 28, 29]. The nutrition correction includes increasing intake of foods enriched in protein, easily absorbed amino acids, and vitamin D [3, 10, 11,14]. Considering the proven positive effects of anabolic steroids on the function and structure of muscle tissue, in particular testosterone, oxandrolone, megestrol, growth hormone, they are recommended for personalized use [2, 13, 17, 26, 27, 30]. On the other hand, the systemic corticosteroids use should be avoided.

Priority in management of COPD patient with SMD is to increase the level of daily physical activity [4, 6, 16, 19].

Table 1. Influence of SMD on the COPD course and quality of life

Indicators	Cachexia (n = 27)	Without metabolic dysorders (n = 30)	Obesity (n = 37)	Sarcopenia (n = 49)	p-value
Number of exacerbations during last 12 months	2.8 ± 1.7	1.5 ± 1.4	2.3 ± 1.5	1.7 ± 1.3	0.002
CAT, score	23.3 ± 8.1	14.9 ± 6.1	15.9 ± 8.1	17.7 ± 6.4	< 0.001
mMRC, score	2.9 ± 0.8	2.0 ± 0.9	2.6 ± 1.0	2.3 ± 1.1	0.004
FEV_1, % predicted	32.7 ± 15.5	52.7 ± 17.7	54.6 ± 13.5	47.8 ± 15.3	< 0.001
Quality of life by Sent George Hospital Questionare					
Sypmtoms, score	76.0 ± 15.5	66.6 ± 13.4	72.0 ± 13.9	71.5 ± 11.4	0.065
Activity, score	83.1 ±15.9	54.9 ± 17.1	64.9 ± 19.5	64.3 ± 21.5	< 0.001
Impact, score	61.7 ± 19.9	39.9 ± 17.0	46.9 ± 15.1	49.3 ± 13.7	< 0.001
Total,score	70.2 ± 15.9	48.8 ± 14.3	56.5 ± 14.3	57.3 ± 14.3	< 0.001

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Table 2. Complex for training of patients with COPD and skeletal muscle dysfunction according to severity of bronchial obstruction

Parameters	ОФВ$_1$ відповідно до GOLD1	ОФВ$_1$ відповідно до GOLD2	ОФВ$_1$ відповідно до GOLD3	ОФВ$_1$ відповідно до GOLD4
Diaphragm breathing	RR = 10/min, duration 4 min	RR = 10/min, duration 3 min	RR = 10/min, duration 2 min	RR = 10/min, duration 1 min
Shoulder up	3 attempts 10 times	3 attempts 8 times	3 attempts 6 times	3 attempts 5times
Twisting on the spine mobility	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times
Bringing hands behind	3 attempts 10 times	3 attempts 8 times	3 attempts 6 times	3 attempts 5 times
Twisting on the press	3 attempts 10 times	3 attempts 10 times	3 attempts 5 times	3 attempts 5 times
Squatting	3 attempts 10 times	¾ amplitude, 3 attempts 10 times	½ amplitude, 3 attempts 10 times	1/4 amplitude, 3 attempts 5 times
Taking legs standing	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times
Bowing legs standing	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times	3 attempts 10 times
Lifting on toes	3 attempts 20 times	3 attempts 15 times	3 attempts 10 times	3 attempts 5 times
Diaphragm breathing	RR = 10/min, duration 4 min	RR = 10/min, duration 3 min	RR = 10/min, duration 2 min	RR = 10/min, duration 1 min

Individual program of physical activity is performed to reduce the sensitivity of the central nervous system to dyspnea, to reduce anxiety and depression, to reduce dynamic hyperinflation and to correct the SMD [4].

In accordance with the official recommendations of the American Thoracic Society and the European Respiratory Society for pulmonary rehabilitation of patients with COPD, physical activity is distributed:

- endurance muscle training, which can be high-intensity, low-intensity and interval,
- strength training, which includes training the extremities, respiratory muscles and the development of flexibility,
- transcutaneous neuromuscular electrical stimulation, which allows adjusting the duration and intensity of working certain skeletal muscle groups, especially in patients who are significantly restricted in physical activity.

The interval endurance training in combination with individualized exercises that increase spinal flexibility and muscle strength of the limbs and the chest is the most effective and convenient for COPD patient.

When developing an individual program of physical activity for a patient with cardio-respiratory diseases, one should keep in mind a number of limitations for performing them. Usually, patients have disorder of gas exchange and conductivity of airways, respiratory muscle dysfunction, which reduces oxygen supply to working skeletal muscles. The presence of coronary insufficiency and heart failure, SMD significantly limit the motor activity of the patient due to the direct relationship between the physical exertion and the deterioration of symptoms [8, 9, 12, 20, 21]. Therefore, the patient has a low level of motivation for physical activity. He needs a continued explanatory work, consulting and motivating support, developing the safe, easy and enjoyable exercise complex that would create a positive and optimistic mood for him. Only in such conditions, the rehabilitation of the patient will be successful and will contribute to improving the course of COPD, the correction of SMD.

Table 3. Dynamics of the main symptoms and signs of COPD, quality of life and signs of DSM in the patient K., on the background of a regular implementation of the personalized complex of physical exercises

Parameters	Before physical exercise	After 6 weeks of training
CAT, score	23	21
mMRC, score	3	3
Quality of life (SGRQ),score	80.1	71.6
Skeletal Muscle index, kg/m2	6.7	7.5
6-minutes' walking test, m	60	75
Hand grip dynamometry, %	72,6	83
Spirometry, FEV$_1$, % predicted	42	42

A systematic review of publications aimed at determining the effect of increasing physical activity on the condition of COPD patients, performed by Gimeno-Santos E et al, revealed decreasing the risk of exacerbations and mortality in case of increased physical activity [8].

Based on the recommendations of the American Thoracic Society and the European Respiratory Society for the rehabilitation of patients with COPD and SMD [21], we have developed a personalized set of 10 simple exercises (Table 2). Duration and intensity of training depends on the physical condition of the patient, the severity of his obstruction and the limitation of motor activity. Exercises are recommended to be performed at least twice a day, before eating.

The complex of these exercises was offered to 28 patients who completed inpatient treatment for COPD exacerbation. Everyone was given a motivational conversation. Instructions were given for explaining how to perform exercises. The first 3-4 trainings under the supervision of the instructor were conducted. There were 23 patients who agreed to perform a set of exercises in the hospital. However, only 15 patients continued the training after the discharge.

In Table 3 we present the data of the patient K., 70 years, with more than 10 years' history of COPD, who performed exercises for 6 weeks.

The main symptoms of COPD have not changed. However, we found an improvement in the patient's

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quality of life, an increase in the skeletal muscle index, the length of the distance during a 6-minute test, and data of hand grip dynamometry.

Thus, metabolic disturbances and development of SMD in patients with COPD have a significant negative effect on the course of the disease, increasing the risk of exacerbations, cardiovascular events and death, and significantly decreases the quality of life of the patient.

For their correction, a set of measures should be used that include smoking cessation, rationalization of nutrition, use of anabolic hormones, personalized interval training and increased physical activity.

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