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Actual Issues of Pathogenesis, Clinical Picture and Treatment of Chronic Obstructive Pulmonary Disease in Combination with Diabetes Mellitus and Metabolic Syndrome.

AV Budnevsky, ES Ovsyannikov*, NV Polyakova, EY Malysh, and MS Mukhortova.

Voronezh State Medical University 394036, Voronezh, Russia

ABSTRACT

In the article we review the results of several large multicenter clinical trials on chronic obstructive pulmonary disease. It is shown that the presence of certain concomitant diseases contributes to the severity of the course of chronic obstructive pulmonary disease. Common comorbidities include diabetes mellitus, metabolic syndrome and cardiovascular diseases. There is a strong correlation between diabetes mellitus and metabolic syndrome with the degree and severity of the chronic obstructive pulmonary disease decompensation. The data show the connection between the formation of restrictive ventilatory defects and obesity. The results of a few studies have demonstrated the efficiency of roflumilast in patients with moderate to severe chronic obstructive pulmonary disease. It is concluded that comorbid conditions including diabetes mellitus have a great impact on the severity of the course and outcomes of chronic obstructive pulmonary disease.However, the peculiarities of treatment of chronic obstructive pulmonary diseasein the combination with diabetes mellitus have not been studied well enough, so further research may be necessary to better address the issue.

Keywords: chronic obstructive pulmonary disease, diabetes mellitus, metabolic syndrome, roflumilast.

Corresponding author

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INTRODUCTION

According to the World Health Organization, chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. In the past 20 years, the incidence of COPD moved from the 12th to the 4th place. The prevalence of the pathology is 10% in age group of 40 years and older. COPD mortality rate is projected to take the 3rd place by 2020 [1, 2].

One of the biggest problems that doctors treating COPD patients face is comorbidity. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017, a lot of attention should be paid to concomitant diseases as a factor that contributes to the severity of the course of COPD. Among the common comorbidities there are cardiovascular diseases, metabolic syndrome (MS) and diabetes mellitus, osteoporosis and depression [3-5].

According to the data collected in various trials, 2-16 % of COPD patients have diabetes mellitus [6-9]. 14 % of hospitalized patients with COPD suffer from diabetes mellitus. At present the incidence of this comorbidity is growing due to the increase of the prevalence of these diseases in the second half of life [1, 2, and 10].

Interesting data were presented by a group of Spanish researchers that analyzed the occurrence of extra pulmonary pathology in COPD patients. Out of 606 patients (average age 72.6 years) 63.4% had arterial hypertension, 35.8% had diabetes mellitus, 32.8% suffered from chronic heart failure, 20.8% - from ischemic heart disease, 19.3% were anemic, 34% had dyslipidemia; 4.5% of the patients examined died within 3 months [7, 8].

Diabetes mellitus is regarded as one of the main factors contributing to the severe course of COPD [10, 11]. Ya.N. Shoikhet found out that acute exacerbations occurred more often in COPD patients with diabetes mellitus: 53.8% had more than 3 exacerbations of COPD in a year while only 13.3% of COPD patients without diabetes mellitus had as many [11, 12]. Meanwhile, there is a definite lack of data on the mutual influence of COPD and diabetes mellitus [4, 13, and 14]. The main causes of death in COPD patients include cardiovascular diseases, lung cancer, and the progression of respiratory failure – in severe forms of COPD [1, 8]. The in-hospital mortality rate for patients with COPD exacerbations is about 10%. The risk factors for death are old age, a decrease in pulmonary function, the presence of diabetes mellitus, and a very severe condition prior to the admission to the intensive care unit [15-17]. So it is quite obvious that diabetes mellitus aggravates the course of COPD. The severity of the course and the frequency of complicated forms of COPD in patients with diabetes mellitus directly correlate with the degree and severity of its decompensation, the severity and prevalence of angiopathies. It was noted that changes of the pulmonary function in patients with COPD and diabetes mellitus were characterized by the rapid progression of restrictive ventilatory defects. On the other hand, in most cases diabetes mellitus stays decompensated even if the severity of inflammation in the lungs is reduced.

A number of studies were devoted to studying pulmonary hemodynamics with the help of doppler sonography of jugular veins in patients with COPD and diabetes mellitus. Pulmonary hypertension was shown to be more severe in patients with COPD and type 2 diabetes mellitus than in the ones with COPD but no concomitant diabetes [8, 18]. The presence of diabetes mellitus has proved to complicate the treatment of COPD exacerbation as pathogens often have antibiotic resistance. It is required to hospitalize the patients with COPD and diabetes mellitus, and often to an intensive care unit. A study demonstrated that lethality of hospitalized patients with COPD exacerbations and poor control of serum glucose levels was significantly higher [3, 5]. Patients with COPD exacerbations who received glucocorticosteroid therapy and had diabetes mellitus also had a significantly higher risk of developing gastrointestinal complications in the postoperative period in comparison with the patients who had no diabetes [10, 12]. On the other hand, a number of studies have shown that COPD is a risk factor for the development of diabetes mellitus. In 29.6% of cases symptoms of COPD preceded the diagnosis of diabetes mellitus for 5.4 years. In 8.4% of patients with COPD, the diagnosis of diabetes was established during the hospital stay [7, 15, and 19]. The Nurses Health Study demonstrated that patients with COPD had 1.8 times higher risk of developing diabetes mellitus than in general population [20].

In numerous animal experiments it has been established that hypoxia induces the development of insulin resistance [14, 16]. On the other hand, a decline in the spirometry values (in particular the forced

expiratory volume in the first second, or FEV1) is now considered as a risk factor for the development of diabetes mellitus [6, 7, and 21]. The unfavorable combination of COPD and diabetes mellitus can be explained by the increased production of inflammatory mediators (tumor necrosis factor (TNF), interleukin-6, C-reactive protein) in COPD patients which are considered the basis for the development of insulin resistance and type 2 diabetes [9, 17].

According to various data, MS, impaired glucose tolerance, and hyperinsulinemia are present in 57.5% of COPD patients [15, 22]. As for the results of another study, it is actually 44.6%. Assessing the individual components of MS it was revealed that abdominal obesity was observed in 52.2%, arterial hypertension - in 77.2%, and hyperglycemia - in 46.7 % of COPD patients [7, 19]. It has been demonstrated that the clinical course of COPD depends on the level of markers of systemic inflammation which plays a key role in the pathogenesis of COPD with MS. The C-reactive protein and fibrinogen levels are also higher in patients with COPD and MS which shows a greater intensity of systemic inflammatory response in patients with this comorbidity [16, 17]. In addition to the higher intensity of systemic inflammation, patients with the body mass index (BMI) of 30 and more kg/m2 have a high diaphragm position which contributes to the violation of the pulmonary ventilation, a decrease in the depth of breathing and mucociliary clearance. An inverse correlation was found between FEV1 and BMI ($r = -0.36$, $p = 0.02$) as well as between the Tiffeneau-Pinelli index and BMI ($r = -0.39$, $p = 0.01$) [18, 23].

It is known that adipose tissue produces leptin, a protein that enhances the esterification of fatty acids in adipocytes; apolipoprotein E, lipoprotein lipase as well as proinflammatory cytokines. It was noted that complaints of the cough with abundant discharge of mucocutaneous sputum, legs and feet edema, sleep disorders and headaches are more common in patients with COPD and MS than in the ones with isolated COPD. Besides, 36.4% of patients with COPD and MS have diffuse cyanosis, 75% have tachycardia, 90.3% - dry wheezes, 36.5% - hepatomegaly and peripheral edema, 24.5% - the involvement of the accessory breathing muscles. During spirometry it was noted that restrictive ventilatory defects were present in the patients with the combined pathology. A connection between the development of restrictive ventilatory defects and obesity was established ($p < 0.05$). 56% of patients with the comorbidity showed increased lung patterns because of the inflammatory infiltration of bronchial walls.

Electrocardiography signs of the right atrial and ventricular over load are seen in 29% of patients with COPD and MS and only in 11% of patients with isolated COPD. Levels of interleukin-6 and interleukin-8 correlate with the frequency of exacerbations and the duration of COPD ($r = 0.691$, $p < 0.05$, $r = 0.832$, $p < 0.05$ respectively). The duration of type 2 diabetes mellitus and impaired glucose tolerance correlates with the serum concentration of TNF ($r = 0.092$, $p < 0.01$), which is a mediator of insulin resistance [6, 15]. In the COPD and MS group of patients, there is a greater frequency and duration of exacerbations of COPD than in those with COPD only. It was demonstrated that levels of triglycerides, fasting glucose and C-reactive protein in the serum directly correlate with the frequency of COPD exacerbations [3,8,and 19]. While studying the parameters of systemic inflammation it was determined that in COPD and MS patients the TNF serum level is 38.3% higher, interleukin-6 - 28% higher, interleukin-8 - 38% higher than in patients with isolated pathology ($p < 0.05$). The increase in the concentrations of proinflammatory cytokines can be explained by their hyper production by the abdominal adipose tissue [15, 17, and 23]. It has been noted that the level of adiponectin in blood serum is lower in COPD and MS patients than in the ones with isolated COPD ($p < 0.05$) [18].

It is worth noting that ischemic heart disease tends to develop 9.8 years earlier in comorbid patients than those with isolated COPD. In MS and COPD patients, various cardiac rhythm and conduction disorders are more common: sinus arrhythmia at night - by 25.6%, transient atrioventricular and sinoatrial blockades - by 31.3%. Arrhythmias were often registered during prolonged periods (up to 76.5 ± 2.6 min/day) of myocardial ischemia, which coincided with the periods of impairment of BRONCHIAL PERMEABILITY and the biggest decrease in the blood saturation (according to pulse oximetry) [14 , 21].

In comorbid COPD and MS patients calcification of coronary arteries occurs at an earlier age than in patients without MS. The addition of MS to COPD increases the risk of developing cardiovascular complications by 1.5 times at the age of 50-59 years and by 3.5 times at the age of 40-49 years in comparison with the patients with isolated COPD. In patients with COPD and MS, acute cerebrovascular events were recorded 12.3% more often than in the ones without MS [16]. An imbalance of oxidant-antioxidant systems is also observed in COPD and MS individuals. While studying oxidative modification of proteins and lipid peroxidation

it was observed that in patients with the combination of COPD and MS the levels of aldehyde and ketone dinitrophenylhydrazones of neutral and basic type, diene conjugates, ketodienes and conjugated trienes, malonicdialdehyde in blood serum and erythrocytes were elevated in comparison with patients with COPD only. In addition, a decrease in the catalase activity and the level of reduced glutathione is noted [10, 12, 23, and 24].

The issue of treatment of COPD in the presence of MS and diabetes mellitus is of particular interest since glucocorticosteroids adversely affect the blood pressure level and lead to the increase of the glucose blood level [14]. There is evidence of a beneficial effect of the inhibitor phosphodiesterase-4-roflumilast on the glucose concentration. It was demonstrated that this medicine reduces the severity of impaired glucose tolerance. Among the patients treated with roflumilast, weight loss was noted in individuals with obesity and an improvement of the glycemic profile in the ones with type 2 diabetes mellitus. Clinical trials demonstrating the efficiency of roflumilast include multicenter randomized double-blind placebo-controlled studies of M2-107 [25, 26] and M2-112 [27].1411 patients with moderate and 1513 patients with severe COPD were included in these trials, which confirmed the increase in FEV1 and an overall improvement of the quality of life of the patients taking roflumilast compared with the group of patients receiving placebo. Since roflumilast is an anti-inflammatory medicine and not a bronchodilator, it should be used in addition to long-acting bronchodilators. The use of roflumilast by patients with a low frequency of exacerbations within 1 year reduces the risk of them switching to a group of patients with frequent exacerbations by 23% (risk factor 0.768, p = 0.0018). Roflumilast was well tolerated by the participants of the studies in question. The undesirable effects of phosphodiesterase type 4 inhibitors including roflumilast are related to the gastrointestinal tract and weight loss for the most part.

Thus, as a result of extensive clinical trials conducted on a broad population of patients a significant amount of data has been accumulated that show the high therapeutic potential of roflumilast aimed at treating COPD-specific inflammation. In the light of the association of COPD with insulin resistance and an increased risk of developing type 2 diabetes mellitus studies of the effect of roflumilast on the pathogenetic mechanisms of diabetes mellitus are very relevant [5]. In patients suffering from diabetes mellitus and taking roflumilast, there was no change in the serum glucose levels (both fasting and postprandial) or a slight decrease was observed [7, 8].

Treatment of diabetes mellitus in COPD patients should be performed according to standard recommendations. It should be noted that patients with the severe course of COPD are not recommended to reduce their weight to BMI being less than 21 kg/m2 [1, 2]. It has been proven that the anti-inflammatory properties of statins have a beneficial effect on the course of COPD and MS. Adding atorvastatin and metformin to standard therapy leads to a decline in the ultrasensitive C-reactive protein serum level, normalization of the lipid profile and glycemic parameters in patients with COPD and atherosclerosis on the background of MS and diabetes mellitus [28,29].

Thus, there is no doubt that comorbid conditions including diabetes mellitus have a great impact on the severity of the course and outcomes of COPD [18, 23]. However, the peculiarities of treatment of COPD in the combination with diabetes mellitus have not been studied well enough, so further research may be necessary to better address the issue.

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