

Review

COPD and Overweight, as a Problem in Present-Day Pulmonology

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Abstract

Increasing incidence of chronic obstructive pulmonary disease (4th place among all causes of death within the general population) and overweight, as one factor for progression of respiratory tract pathologies (more than 30% of world population suffers from overweight) suggest that further study of pathogenetic peculiarities of their combined course and search for new ways of differential pathogenetic therapy are important nowadays.

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Over the past decade, the understanding of the problem of chronic obstructive pulmonary disease (COPD) has significantly changed, however this pathology still remains an important medical, social and economic problem. As a matter of fact, it is a progressive disease which is accompanied not only by persistent airflow limitation but is also a complex and heterogeneous condition with marked extrapulmonary manifestations including disorders of cardiovascular system, dysfunction of skeletal muscles and diabetes [3, 6, 17]. According to the definition of GOLD-2017: "COPD is a common disease that may be prevented and treated, and is characterized by persistent respiratory symptoms and obstruction of airways due to pathologic changes of respiratory passages and/or alveoli...".

According to the latest statistics, about 4-22% of adults aged 40 years and older suffer from COPD [1, 26, 33]. The world's prevalence of the disease among men and women is 9.3 and 7.3%, and among smokers its rate is - 26.2 and 2.7% respectively [17]. A number of multicenter studies conducted in developed countries, show that the rates of morbidity, invalidity and mortality double every ten years. According to the data of World Health Organization (WHO) COPD affects 210 million people and, they estimate that this number will increase by 30 % in ten years (WHO, 2014).

Chronic obstructive pulmonary disease also results in significant social consequences in society. In Ukraine the rate of primary disablement among adult employable population due to diseases of respiratory organs became somewhat stable over the last 5 years and made up 1.1-0.9 per 10 thousand of working population. Yet annually, on average, 2000 people are initially recognized as disabled due to chronic obstructive pulmonary disease. It should be noted that the decrease of invalidity rate was facilitated by the practical application of modern approaches based on international recommendations and national protocols in accordance with the principles of evidence-based medicine that has significantly improved di-

agnostics, treatment and rehabilitation of patients suffering from this disease [12, 24, 35].

At the present stage of pulmonology development it has been established that the disease exacerbation is the most dangerous stage in COPD course [1, 6, 14, 27, 38]. Disease exacerbation may occur 1-4 and even more times a year and considerably expand patient's treatment costs. Destabilization of COPD course, particularly the one requiring in-patient treatment, is an evidenced factor for life quality impairment of such patients [7, 14, 39, 48]. Re-hospitalization requires special attention as it usually involves higher treatment costs than primary in-patient treatment [8-10, 12]. Great importance of disease exacerbation for the prognosis of COPD course was first reported in GOLD 2011 revised edition. This document provides the definition of COPD making a point that the disease exacerbations as well as comorbid pathologies have a great influence on the severity of its course in individual patients. Furthermore, GOLD 2011 document states that the number of exacerbation events over the past year was considered to be one of the principal criteria for possible future risks in COPD patients. The problem of establishing a definite diagnosis of COPD exacerbation on admission is also relevant [7, 9, 25, 26, 51]. Understanding the factors triggering and proceeding the exacerbation leading to in-patient treatment is vague, and information about this problem is limited and quite controversial [1, 2, 44, 46]. Consequently, it is essential to find other reliable markers of potential threat of COPD exacerbations, especially the severe ones.

Until recently, leading was the point of view that the severity of bronchial obstruction alone influences the frequency of exacerbations [30, 35, 40]. The correlation between the frequency of exacerbations and the severity of symptoms is exhibited in conclusions of advanced research works. However, these two factors are not completely independent and patients with moderate limitation of respiratory function may also suffer from frequent exacerbations [3-5, 7, 10].

Currently more and more attention is paid to the study of possible role of extra-pulmonary factors associated with the increase of COPD exacerbation risks [1, 2, 45, 53]. In recent years, extrapulmonary COPD effects have been widely discussed, as they exacerbate the disease course in individual patients and are essential part of "etiological pathogenetic circle". That is why they must be always taken into account in clinical management of patients [4, 14, 23, 29, 47]. Recognizing the presence of such manifestations is clinically important and may contribute to better understanding of the disease development. At the same time, the likelihood of systemic reactions is variable in different COPD stages and the frequency of their combined course increases with the disease progression. It has been shown that the development of extra-pulmonary COPD effects has an important clinical and prognostic value [5-7, 50].

One of these extra-pulmonary effects, having a negative influence on the course of chronic obstructive pulmonary disease, is overweight which is a risk factor for the development and rapid progression of a number of chronic diseases, including pathology of the respiratory tract (L.M.Niu, 2012; N.Hizawa, 2013; K.F. Rabe, 2014). A number of studies have revealed that the phenotype of COPD patient with marked overweight is associated with frequent exacerbations, accelerated decrease in pulmonary function, decreased strenuous activity and quality of patient's life, as well as increased economic costs [11, 19, 20, 29].

The fact that weight reduction leads to the decrease in the degree of clinical manifestations of COPD may prove the role of overweight in the development and rapid progression of respiratory pathology [43, 45, 49].

It has been established that the prevalence rate of chronic obstructive pulmonary disease and overweight is on the increase throughout the world. According to analysis and systematic reviews in 28 countries of the world the incidence of the pathology among adult population is approximately 10% (Y.I. Feshchenko et al., 2017). As reported by the WHO, more than 30% of world's population suffers from overweight, among them 16.8% - women, 14% - men. In Ukraine this index is 30% of adult population (in most European countries - 9-20%). At the same time, WHO predicts that nearly 700 million adults will have suffered from overweight by 2020; consequently, it is expected that these two states will combine with increasing frequency [2, 16]. The problem of excess body weight has lately moved beyond the limits of endocrinology and nowadays has turned into an acute general-medical and social problem. By the scale and incidence rate this problem has obtained the character of global epidemics [41, 42].

A number of epidemiologic investigations show that overweight generally occurs at early stages of COPD. It leads to a number of dysfunctions of various organs and systems, including the respiratory one. Alteration of respiratory muscle contractility is observed in such patients, resulting in the decrease of maximal inspiratory pressure, chest rise during breathing and decrease in lung volume. Chest rise reduction

leads to compensatory lengthening of inspiration and expiration resulting in the development of nonspecific bronchial hyperreactivity. It is proved that respiratory muscles in overweight people work two times harder to maintain adequate ventilation as compared to people with healthy body weight [29, 37, 41].

Scientists contend that overweight leads to the combination of both variants of pulmonary dysfunction, namely the restriction (decrease in lung volume) and obstruction (narrowing of distal airways) [43, 52]. Literature sources describe the influence of overweight on respiratory function, that involves: the decrease in diameter of peripheral airways causing bronchial hyperreactivity, limitation of the air flow from the lungs due to the reduction of lung volume (forced expiratory volume (FEV1) and forced lung capacity) [20, 35, 39]. Moreover, it was suggested that overweight is associated with systemic inflammation in chronic obstructive pulmonary disease having unfavourable influence on its course: alteration of respiratory function, increased activity of inflammatory processes due to immune changes associated with biological activity of fatty tissue as additional source of pro-inflammatory cytokines resulting in frequent exacerbations and rapid progression of the disease [1, 50].

Reduced physical activity due to shortness of breath and long-term use of systemic glucocorticosteroids to prevent exacerbation events at late stages of COPD progression are the possible mechanisms for increased risk of overweight development among patients suffering from chronic obstructive pulmonary disease (M. C. McCormack, 2015). Compulsory restriction of physical activity is the most common complaint among COPD patients, as it negatively influences their quality of life. Accumulation of fatty tissue is accompanied by the COPD-specific loss of muscle mass that has a negative influence on exercise tolerance completing the circle of sedentary lifestyle and excessive weight [3, 5, 8, 13].

In turn, body weight and sedentary lifestyle influence the usual COPD course (Sutherland E., 2004) causing exacerbations at early stages of the disease (Hurst J.R. et al., 2010), which have an important short- and long-term influence on patients with this pathology (Feshchenko Yu.I. et al., 2016). Long-term study conducted by Cotes J.E. (1996) showed that gaining only 1 kilo leads to the decrease of FEV1 level by approximately 17.6 ml, and forced lung capacity - by 21.4 ml in 8 patients and did not depend on their age.

COPD is a chronic inflammation of airways, and special importance in its pathogenesis belongs to cellular and molecular mechanisms. Pro-inflammatory cytokines are the key components of bronchial inflammation progression [15, 16, 21, 22]. A number of scientific investigations were conducted with the aim to study their role in the development and course of chronic obstructive pulmonary disease in Ukraine and other countries. A new phenomenon has been revealed: overweight is accompanied by pimelitis which proceeds with infiltration of fatty tissue by immunocompetent cells. Since inflammatory reaction occurs in well-vascularized and innervate tissue,

thus, due to this some systemic symptoms should be expected [34]. Currently it has been established that fatty tissue produces a lot of hormone-like substances, mediators, cytokines and chemokines which are commonly called adipokines or adipocytokines. They act both on local and system levels [5, 9, 11, 14]. In order to determine the role of inflammatory process as a specific COPD factor, it's necessary to differentiate between localized inflammation, which occurs directly within the tissues of bronchopulmonary complex, and systemic inflammation, which manifests itself by specific disorders and causes systemic reactions [19, 23, 27, 34]. Migration and activation of immunocompetent blood cells in tissues of bronchi and lungs, production and breakdown of matrix proteins, fibrosis and structural remodeling of bronchial and pulmonary walls are characteristic for localized inflammation. Activated cells in chronic inflammation are the source of a great number of inflammatory mediators. Localization and intensity of chronic inflammation, its nature and peculiarities of triggering mechanisms determine the specific nature of pathological process, character of clinical signs and symptoms, COPD progression rate, and are also the markers of adequate therapy and prognosis [16, 18, 28-32].

Of the adipokines described in recent years, particular attention is given to inflammatory markers, one of which is IL-6, which is produced by activated monocytes, macrophages, endothelial cells, fibroblasts, activated T-cells, as well as by a number of cells that are not immunocytes, and is one of the most active transmitters involved in the realization of immune reaction and inflammatory response [38, 50]. Equally important is the role of IL-6 in the regulation of synthesis of acute-phase proteins which promote inflammation. C-reactive protein (CRP) is one example of such acute-phase proteins. It instantly reacts to inflammation by elevating its level both in blood and other body fluids; moreover, this elevation is directly proportional to the intensity of inflammatory lesion (Casas JP et al., 2008). The levels of inflammatory proteins in systemic circulation are elevated even in stable COPD course, including the levels of CRP and IL-6, while inverse relationship is noticed between the levels of inflammatory mediators and FEV1, CRP, IL-6, and imbalance between pro-inflammatory and anti-inflammatory cytokines in favor of the former ones [13, 16, 34].

Imbalance between pro-inflammatory and anti-inflammatory cytokines in blood serum of patients becomes particularly notable in events of COPD exacerbations and is directly related to the peculiarity and severity of disease exacerbation course [34-36].

Recently reported studies show that high levels of inflammatory markers in patients with COPD may be associated with marked mortality rates among patients, their frequent hospitalization and quite rapid progression of this pathology, that's why this index may be used as prognostic marker particularly for patients with chronic obstructive pulmonary disease, chronic bronchitis and bronchial asthma (Savelikhina I.O., 2013; Melnyk O.P., 2014; Popadynets I.R., 2014), especially

in combination with other proinflammatory markers.

Consolidating the data from various scientific sources, COPD should be considered as a complex heterogeneous disease, in the course of which the most important and the most "tragic" event is its exacerbation that quite often may be fatal at terminal stages of the disease. Potential predictors of COPD exacerbations (especially those requiring in-patient treatment) include: clinical signs (for example, shortness of breath), anamnestic data (primarily the history of past exacerbations), changes in functional characteristics of respiratory tract, overweight (that significantly intensifies the course of disease), as well as a number of socioeconomic markers. Consequently, COPD is considered to be a complex pathology, and in order to prognosticate its course it is necessary to study not only the anamnesis and damage of bronchopulmonary apparatus, but also identify other system changes in the patient's body and define the levels of local inflammatory markers taking into account various phenotypes, particularly excessive body weight of patients.

Conclusions

The study of correlation between the frequency of COPD exacerbations and changes in IL-6 and C-reactive protein levels in patients with overweight will certainly make it possible to quickly, easy and accurately establish the process activity, make reasonable prognosis and choose adequate and individualized anticipatory treatment plan for every patient that is of great importance nowadays and still will be significant for improving the quality of life of such patients.

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