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Original Article

COPD as metabolic pathology: problem of common oxidative stress, endotoxicities and neurotoxicity

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Abstract

Chronic obstructive pulmonary disease (COPD) is an often severely disabling chronic lung disease with a high prevalence of over 250 million cases worldwide. Metabolic syndrome is a comorbidity of COPD and increases medical costs. Interrelationships between metabolic syndrome and early COPD remain unclear. The aim of the presented work was to study the relationship between the development of oxidative stress, endotoxicities and neurotoxicity as a manifestation of a violation of the general metabolic state in patients with COPD. Biochemical, immunohistochemical methods, an electrophysiological examination (encephalography, computer electroencephalogram (EEG) with the analysis of visual evoked potentials) and statistical analysis were used. Thus, a comparison of the obtained data indicates that the development of bronchopulmonary disease's neurotoxic effect exceeds the general toxic. Certain disorders of the nervous system lead to disorders of integrative signaling systems, which affect the functioning of the lungs and the development of general systemic metabolic pathology. Systemic inflammation promotes the manifestation of metabolic abnormalities and other extra-pulmonary comorbidities that are interconnected in nature. Future progress needs to focus on molecular mechanisms that drive the heterogeneity of COPD disease progression.

Keywords: COPD, metabolic syndrome, oxidative stress, endotoxicosis, neurotoxic effects.

Introduction

Chronic obstructive pulmonary disease (COPD) is an often severely disabling chronic lung disease with a high prevalence of over 250 million cases worldwide. Currently, according to a global study by the World Health Organization, chronic obstructive pulmonary disease is the third leading cause of death and deteriorating health in the world [1–3]. The major pathological features of COPD are obstructive bronchiolitis, emphysema, and mucus hypersecretion [4]. Chronic airway inflammation in COPD has been traditionally characterized by neutrophilic inflammation with emphysematous destruction. Type 2 eosinophilic inflammation is normally associated with asthma [2].

Most of the current treatment algorithms are based on the severity of symptoms and exacerbation history and recommend the use of drugs other than inhalation medications when symptoms remain or exacerbations occur. The definition and staging by GOLD is rather uniform, as defined by lung function, symptoms and exacerbation history, despite COPD being a heterogeneous disease in its pathological manifestations in patients [5, 6]. However, it has also become apparent that there are remaining issues that are difficult to resolve with the current treatment algorithm. COPD patients face a number of unmet needs, such as symptoms, exacerbations, physical inactivity, and loss of social activities [7–10].

Hypoxia is an important physiological stimulus for organisms. During adaptation to the low oxygen content in cells and tissues, genes that participate in the metabolism of glucose and iron, angiogenesis and cell proliferation are activated. Inflammation in various tissues develops local hypoxia due to microcirculatory

disturbances, as well as an increase in oxygen demand of the immune cells during their infiltration into the inflammatory focus [11].

Several promising approaches can be identified for comorbid conditions in COPD patients, such as bronchiectasis, asthma, heart failure, sleep apnea, malnutrition, cardiovascular disease and frailty. Importantly, the published evidence shows that these interventions bring significant improvements in patient-centered outcomes, including symptoms, dyspnea, exacerbations, and quality of life. By contrast, there remain unanswered questions about adequate treatment strategies for comorbid pulmonary hypertension, gastroesophageal reflux, anxiety, and depression. These comorbidities, which are also associated with the diversity of COPD, can cause patients' unmet needs to resist usual care [3, 7–9]. COPD and cardiovascular disease (CVD) frequently coexist, and the relationship can be explained by shared risk factors, lung hyperinflation, loss of vascular capacity, oxidative stress, and systemic inflammation [12]. An association between gastroesophageal reflux (GER) and COPD has been recognized. The underlying mechanism of GER in COPD patients has been considered to be micro-aspiration and bronchoconstriction due to vagal nerve reflex induced by esophageal acid reflux, while GER also causes inflammation and edema in the airways, increases bronchial hyperresponsiveness [13, 14]. Sarcopenia is one of the representative extra-pulmonary manifestations in COPD patients [15].

Depression is more prevalent in COPD patients than in a comparable general cohort. Anxiety tended to be similar, and the prevalence was higher in patients with more severe COPD [16]. Depression may be primarily driven by a patient's perception of a serious chronic disease comprising symptoms and limitations to daily activities rather than by the underlying inflammatory pathology in COPD [17]. Frailty is defined as a clinical state of vulnerability to stressors following age-associated deterioration in multiple organs and molecular systems. The physical characteristics include muscle weakness, weight loss, low energy production, and reduced exercise tolerance. Frailty often leads to the onset of a negative spiral called the "cycle of frailty", and it is significantly associated with adverse health outcomes such as a sedentary lifestyle, hospitalization, and mortality [18, 19].

Polypharmacy is a major issue commonly encountered in COPD patients, as all the comorbidities and syndromes are treated in isolation. This means that the risk of adverse events due to combining drugs is increased, and compliance may become difficult, particularly in the elderly/frail group of patients. Metabolic syndrome is a comorbidity of COPD and increases medical costs. Interrelationships between metabolic syndrome and early COPD remain unclear [20]. Therefore, identifying convergent mechanisms that can treat lung/systemic inflammation and comorbidities such as metabolic syndrome (MetS) concurrently should be a key focus for future therapeutic interventions [21]. However, treatable conditions that are not recognized as therapeutic targets may be latent in patients with COPD. Determining the main links in COPD pathogenesis in the patients can change the general strategy for the disease treatment, which will be based on targeted pathogenic influence rather than treating symptoms.

Oxidative stress is now recognized as a major predisposing factor in the pathogenesis of both COPD and MetS. It is an excellent target for COPD and MetS therapies. Currently, several endogenous non-enzymaticnonenzymatic and enzymatic antioxidants antioxidants are widely used to combat oxidative stress in the lungs. The commonly used non-enzymaticnonenzymatic antioxidants include glutathione, ascorbic acid, uric acid, α-tocopherol and proteins used to prevent the Fenton and Haber–Weiss reactions. The enzymatic antioxidants mainly include catalase, SOD isomers, and GSH-associated enzymes. Although oxidative stress is an excellent target, these agents are not very effective [22–24]. Disruption of metabolic pathways leads to the development of endotoxicosis. The nervous system plays a leading role in the development of adaptive and compensatory reactions as an integral functional mechanism.

Therefore, *the aim* of the presented work was to study the relationship between the development of oxidative stress, endotoxicities and neurotoxicity as a manifestation of a violation of the general metabolic state in patients with COPD.

Material and methods

This work is based on the results of examination and treatment of 269 patients due to bronchopulmonary diseases hospitalized in the Dnipro' Municipal Hospital during the period 2018–2019. The COPD cohort included patients (men and women) older than 40 years who had been diagnosed with COPD (ICD-10 codes J42, J43, J44) (n=126), asthma (J45, J46) (n=96) and COPD-related disease as pneumonia (J12–J17) (n=47). The control group consisted of 50 healthy volunteers.

In all blood serum samples, the content of indicators for lipid peroxidation processes[malondialdehyde (MDA), total antioxidant activity (AOA)] [25], endotoxicities (middle mass molecules (MMM)) were determined [26]. Additionally, the level was evaluated by the neutral cell adhesion molecule (N-CAM) as a convenient neurospecific marker for the study of neurotoxic effects. N-CAM level in serum was determined by competitive enzyme-linked immunosorbent assay ELISA using monospecific rabbit antisera against all three N-CAM polypeptides to study the possible neurotoxic effects in bronchopulmonary pathology development [27].

An electrophysiological examination of patients with COPD and asthma was performed to assess CNS functional state. Computer encephalography (REG) with the use of software and hardware "Regina", computer electroencephalogram (EEG) with the analysis of visual evoked potentials (VEP) with "Neurolab-2000" using.

The statistical analysis was performed by the Statistica 10.0 program. Differences between groups were analyzed using Student's t-test, and P-values <0.05 were considered statistically significant. The results are presented as the median and interquartile range in the form of the 25th and 75th percentiles.

Results

The pathogenesis of COPD involves several pathogenetic processes, including oxidative stress, inflammation, protease/antiprotease imbalance, apoptosis, cellular senescence, endogenous intoxication, and neurotoxic affects; however, the relative contribution of each of these pathologies to COPD varies among patients.

To confirm the hypothesis that the revealed changes were due to the presence of COPD, the biochemical parameters were evaluated in patients with different obstructive bronchial-lung diseases in comparison indexes healthy persons. It was shown that MDA level was increased on 44% (in case of chronic non-obstructive bronchitis), 51% (chronic obstructive bronchitis), 36% (bronchial asthma) and 48% (pneumonia) (Table 1). There was also a decrease in total antioxidant activity of 29%, 34%, 18% and 11%, respectively. Manifestation of lipid peroxidation on background antioxidant system depression exacerbates oxidative stress.

Complex metabolic disorders and nonspecific clinical manifestations are characterized as endogenous intoxication. An increased MMM level is indirect evidence of oxidative stress manifestation due to the excessive generation of reactive radicals, which is capable of damaging the phospholipid cell membrane structures in different organs. MMM level in patients with bronchial asthma exceeds the control by 31%, chronic non-obstructive bronchitis – by 31%, chronic obstructive bronchitis – by 46% and pneumonia – by 69%. This might be used to control endotoxemia phenomena in the treatment of COPD patients and to describe disorders of cell membrane structures.

Studies of neuro-specific marker proteins of cellular and subcellular elements of nervous tissue in pathologies associated with disorders of the central nervous system (CNS) are quite relevant because, in many cases, they are due to changes in the permeability of the blood-brain barrier (HEB) and yield neurospecific proteins in the bloodstream. N-CAM is an integral membrane glycoprotein

Table 1: Blood serum indexes of patients with different bronchial-lung diseases.

Index	Groups				
	Control, n=50	Chronic nonobstructive bronchitis n=28	Chronic obstructive bronchitis n=98	Bronchial asthma n=96	Pneumonia n=47
MDA, mol/mL	6.53 [5.72; 7.34]	9.41 [7.32; 11.05]	9.90 [7.74; 12.06]	8.86 [5.72; 12.00]	9.52 [7.66; 11.38]
AOA, mol/L	3.83 [3.27; 4.39]	2.72 [1.63; 3.81]	2.51 [1.28; 3.74]	3.14 [2.45; 3.83]	3.42 [2.26; 4.58]
MMM, 254 nm c.u.	0.26 [0.19; 0.33]	0.34 [0.25; 0.43]	0.38 [0.29; 0.47]	0.34 [0.27; 0.43]	0.44 [0.23; 0.65]
N-CAM, mcg/g total protein	3.22 [2.50; 3.94]	8.03 [5.11; 10.95]	8.96 [6.23; 11.69]	5.68 [2.71; 8.65]	7.37 [2.73; 12.0]

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localized on the outer side of the neuronal membrane. Bronchopulmonary pathology development leads to the accumulation of N-CAM in the serum, which depends on the disease's nosology. Thus, the maximum concentration of N-CAM was detected in the serum of patients with COPD (mean level was 8.96 μg/g of total protein to 3.22 μg/g of total protein in the control group), then patients with non-obstructive bronchitis (8.03 μg/g of total protein), in patients with acute pneumonia, the average level of N-CAM was 6.40 μg/g of total protein, bronchial asthma, 5.675 μg/g of total protein, respectively.

An electrophysiological examination has shown that in the presence of COPD, EEG changes were detected in 98% and asthma – 83% of the patients. In the power spectrum of the EEG disappears, the dominant peak in the alpha rhythm and the spectrum is flattened at all fundamental frequencies, which confirms the desynchronization of neuronal activity due to hypoxia of the brain, which occurs in disorders of pulmonary hyperventilation.

In addition, comparison of background REG allowed allocating at the given contingent three types of characteristic changes: at 57% of inspected persons, dystonia was diagnosed, 23% – a hypertonia, 20% of persons – a hypotonus. At inflammatory process intensification in 75% of patients determines the vagotonic reactivity of the autonomic nervous system, while in remission, vagotonus was observed in 50% of cases.

Discussion

Oxidative stress, caused by an imbalance between increased oxidative burden and the defective antioxidant system, is involved in cellular and tissue damage related to the pathogenesis and progression of many acute and chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD) [28]. The oxidant generates airway inflammation that leads to the production of proinflammatory cytokines, neutrophils, eosinophils, lymphocytes, and macrophages by potentiating the action of histamine, which injures lung tissues and causes inflammation, modulates the function of all classes of biomolecular, targeting almost all substrates in the cell, impair membrane function, inactivate membrane-bound receptors, and increase tissue permeability. Oxidative stress also causes small-airway fibrosis. These airway-epithelium injuries decrease the protective capacity of the epithelium against inhaled oxidants and further enhance inflammation. Therefore, oxidative stress causes airway inflammation, which gives rise to a further oxidative burden, thereby forming a vicious cycle. Also, lipid-peroxidation products are reactive molecules that can cause smooth-muscle contraction and subsequently contribute to bronchial hyperresponsiveness (BHR). Oxidative stress can impair the function of antiproteases, such as α1-antitrypsin and secretory leukoprotease inhibitors, thereby accelerating the breakdown of elastin in the lung parenchyma [29, 30].

In healthy lungs, antioxidants, such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx), provide an endogenous biological defense against cellular or organ injury caused by ROS. Reduced antioxidant and antiprotease enzyme activity (SOD, CAT, GPx, α1 antitrypsin); altered expression of ROS-related enzymes (decreased in CAT, GPx, SOD, and increase in iNOS) activation of metalloproteinases lead to an imbalance of biological molecules, damage intracellular signaling and activation of signaling pathways, resulting in the development of systemic inflammation [31, 32].

Oxidative stress is also apparent in metabolic syndrome (MetS). Unlike COPD, oxidative stress in this context mainly arises from the activation of specific biochemical pathways (*e.g.*, oxidative metabolism in mitochondria), increased cellular production as a result of inflammation, exhaustion of cellular antioxidant mechanisms, as well as lipid peroxidation, which is typically seen during metabolic syndrome (MetS) and in particular obesity. In addition to systemic inflammation, *in vivo*, studies have demonstrated that chronic hyperglycemia can trigger endothelial dysfunction in the blood vessels of diabetic patients via the excessive generation of ROS. The oxidative stress and inflammation inflicted by hyperglycemia can result in sarcomeric injury via activation of proteolytic machinery. This leads to contractile protein wasting and, consequently, a loss of force-generating capacity of diaphragm fibers in patients with COPD [21].

The lack of convincing evidence of monovalence in the development of endotoxicosis has led to the idea of it as a complex multifactorial pathological process, which has, however, a universal mechanism of formation. At the early stage of development, the leading universal mechanisms of tissue hypoxemia are the activation of lipid peroxidation and anaerobic transformation of glycolysis. The source of endogenous toxic factors can be organo- and cytolocalized substances (trypsin, lipases, transaminases, lysosomal enzymes and cationic proteins, breakdown products of myoglobin and hemoglobin, free radicals) and effector substances of regulatory systems of the body (antigenic amines, intermediate

and final products of lipid peroxidation, tumor necrosis factors, interleukins, prostaglandins, leukotrienes, thyroid and steroid hormones). At the same time, normal transport systems, in particular serum albumin, are blocked by toxic metabolites, which cannot be released in places of natural detoxification. Under these conditions, erythrocytes do not fully perform their transport function but only sorb toxic substances [33]. MMM affects the functioning of all body systems and organs. Their structure is similar to that of regulatory peptides. They can connect and block cell receptors, thereby changing intracellular metabolism and functions [33, 34].

One of the most important aspects of the organism's integral functioning is the presence of molecular mechanisms of signaling systems connection, which ensure the realization of physiological and biochemical effects of hormones and neurotransmitters. The leading role in the development of adaptive and compensatory reactions belongs to the nervous system. Neurotoxicity is one of the most serious toxicological problems, as damage to even a small number of neurons can have unpredictable consequences for the whole body. Due to the uniqueness of the characteristic features of the nervous system (spatial division of the main part of the cell and axons, nerve and glia independence, myelination, synaptogenesis, neurotransmission), neurons are specifically damaged by neurotoxins.

In blood serum, neurospecific proteins in norm are practically not found [27]. The increase in their content may be the result of brain tissue destruction, the central neurotransmitter systems disruption and changes in the functioning of the hematoencephalic barrier (HEB). Inflammation of the respiratory tract and deterioration of functional and respiratory barriers may play a role in the emergence of neuropathology. This phenomenon is a promoter of the intensification of free radical processes and damage to the subendothelial matrix, not only of lung tissue but also of brain barriers [35].

N-CAM is expressed by neurons and is involved in controlling the processes of neurite outgrowth and synaptogenesis, the nervous system's plasticity, and the formation of a neural network during development [36]. The presence of N-CAM in the serum of COPD patients indicates a violation of the resistance of the blood-brain barrier and the release of neurospecific proteins into the bloodstream, which under certain conditions can cause autoimmune aggression, changes in the signaling system and distortion of the cellular response to certain extreme stimuli.

It is noteworthy that in some patients with acute pneumonia, the concentration of N-CAM reached 12 μg/g of total protein, probably due to the effects of toxins of microorganisms that cause paralytic dilation of small vessel walls and increase their permeability with subsequent blood clotting and decreased volume circulating fluid. This can be the main pathogenetic link of infectious-toxic shock and lead to significant disorders of perfusion of organs, primarily the lungs, brain and kidneys. It is possible that the significant accumulation of N-CAM may be a negative prognostic sign of the manifestation of cerebral disorders in such patients due to blood stasis in the capillaries of the brain and edema of its tissues.

The EEG showed a pattern of unregulated disorganized alpha rhythm, single flashes of sharp waves and increased response to hyperventilation. Features of EEG are confirmed by some increase of average and long-latent components of VEP and a decrease in amplitude of cortical response in a cognitive phase that testifies to deterioration of information processing arriving, first of all, to nonspecific cortical structures. Dysregulatory ergotrophic and trophotrophic functions of the ANS were characteristic for most of the examined patients (almost 83% of cases). Patients with COPD developed spastic-atonic syndrome.

Thus, a comparison of the obtained data indicates that the development of bronchopulmonary diseases' neurotoxic effect exceeds the general toxic. Certain disorders of the nervous system lead to disorders of integrative signaling systems, which affect the functioning of the lungs and the development of general systemic pathology.

Hypoxia, which develops in pulmonary pathology, can lead to cerebral ischemia. The consequence of neuronal dysregulation is extensive communication between neurons and immune cells, which is involved in the inflammation of the airways and the development of their hyperreactivity, which, in our opinion, leads to an inadequate response of the body's systems, including the lungs, to exogenous influences, aggravates certain disorders and leads to the development of general systemic pathology [37, 38].

In fact, the majority of patients with COPD die of non-respiratory disorders, making them comorbidities to COPD. The best-recognized systemic manifestations of COPD include systemic inflammation, cardiovascular diseases (CVD), muscle wasting and dysfunction, osteoporosis, anemia, and clinical depression and anxiety. Importantly, much of the disease burden and health care utilization in COPD is associated with the

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management of its comorbidities (*e.g.*, skeletal muscle wasting, ischemic heart disease, cognitive dysfunction) and infectious viral and bacterial acute exacerbations. Many patients with COPD also present with metabolic syndrome (MetS), a cluster of conditions including diabetes and prediabetes (insulin resistance), abdominal obesity, high cholesterol and high blood pressure. Each metabolic risk factor is associated with one another, and together these risk factors promote atherosclerosis. When both COPD and MetS coexist, the occurrence of these comorbidities and complications is amplified [39].

Oxidative damage activates resident cells in the lung (*e.g.*, epithelial cells and alveolar macrophages) to generate chemotactic molecules that recruit additional inflammatory cells and perpetuate oxidative stress in the lung. Collectively, these events lead to a vicious cycle of persistent inflammation, accompanied by chronic oxidative stress, which leads to disturbances in the protease-anti-protease balance, defects in tissue repair mechanisms, endotoxicities and neurotoxicities development, accelerated apoptosis and tissue destruction resulting in the spillover of proinflammatory mediators into the systemic circulation. Systemic inflammation promotes the manifestation of cardiovascular disease, metabolic abnormalities and other extra-pulmonary comorbidities which are interconnected in nature. Impaired pulmonary function decreases oxygen-exchange efficiency, which in turn would trigger hypoxemia and limit physical activity. Both hypoxemia and physical inactivity *per se* are capable of directly and indirectly promoting the development of metabolic syndrome and other comorbidities [20, 37–41].

Comorbidities can have a significant influence on the course of COPD, affecting disease-related symptoms and increasing morbidity and mortality in patients. To halt the worrying increase in the burden of COPD improved and personalized treatment strategies are needed. Future progress needs to focus on molecular mechanisms that drive the heterogeneity of COPD disease progression, as it is known that some patients can progress rapidly while others can remain relatively stable for years. Therefore, new approaches are urgently needed to slow or even stop the progression of this disease and reduce mortality. Studies indicate that the management of comorbid COPD can be improved by engaging in a multidisciplinary team-based approach. A collaborative effort from different disease specialists and health care professionals, together with disease self-management and management programs, could improve the outcomes of patients with comorbid COPD [28, 42, 43].

Conclusion

In 2017, a new two-step algorithm for the treatment of COPD was proposed. This algorithm was based on the severity of symptoms and phenotypes or treatable traits, and patient-specialized assessment targeting eosinophilic inflammation, chronic bronchitis, and frequent infections is recommended after exacerbation occurs despite maximal bronchodilation therapy. However, recent studies have revealed the clinical characteristics of patients who should have second controllers added. We again realized that treatable traits should be assessed and intervened for as early as possible. Moreover, the treatment algorithm is necessary to be adapted to the situation of clinical practice, taking into account the characteristics of the patients.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Bioethics Committee of the Dnipro State Medical University in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical principles of medical research with the participation of people" and "General declaration on bioethics and rights of man (UNESCO)".

Consent to participate

Written informed consent was obtained from the participants.

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