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DISORDER OF KIDNEY FUNCTION IN PATIENTS WITH COMORBIDITY AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract
The review describes the pathogenetic mechanisms of the two-way effect of the general systemic manifestations of chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) in comorbid situations. Most systemic manifestations of COPD, such as anemia, depression, mineral-bone disorders, cardiovascular complications, coincide with manifestations of CKD and can be mistakenly considered only as manifestations of COPD. Mechanisms underlying heart remodeling and the progression of CKD in COPD are distinguished, such as hypoxemia, systemic inflammation, endothelial dysfunction, activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, oxidative stress, and prolonged endogenous intoxication.

Keywords: Chronic obstructive pulmonary disease, chronic kidney disease, comorbidity, systemic manifestations.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation of the respiratory tract, and in the early stages of the disease, the inflammatory process developing after contact with aggressive substances (gases, aerosols, particles, most often tobacco smoke) can be reversible. However, over time, the inflammation of the respiratory tract becomes chronic, persistent, even regardless of the cessation of the etiological factor. COPD is a disease with irreversible or partially reversible, progressive obstruction of the respiratory tract and pathological reaction of the lung parenchyma with progressive chronic respiratory failure, proven by systemic effects, such as hypoxemia, chronic inflammation, oxidative stress and, as a consequence, endothelial dysfunction [1,2]. The exact mechanisms of systemic inflammation in COPD have not been sufficiently studied. It is assumed that local (bronchopulmonary) inflammation leads to the release of stress-induced cytokines and free radicals into the systemic blood circulation with the development of a generalized inflammatory reaction [3,5,7]. In 2019, more than 3 million people died from COPD, which amounted to almost 6% of all deaths in the world this year. More than 90% of deaths from COPD are detected in low- and middle-income countries. The frequency of COPD is steadily increasing. The World Health Organization predicts: for the period 1990-2020, COPD will move from the 6th place in mortality to the 2nd, and from the 12th to the 5th in morbidity. Large epidemiological studies have shown that COPD is characterized by systemic

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manifestations, increases the risk of developing cardiovascular diseases by 2-3 times, and ranks fourth among the main causes of chronic heart failure (CHF) [9]. According to various authors, signs of CHF occur in 20-23.6% of patients with COPD [9]. The relevance of studying COPD in comorbid conditions necessitates the adoption of standards for the diagnosis and treatment of internal diseases, provides for basic and alternative drugs.

Clinical manifestations of COPD change with comorbid pathology and require scientifically based and personalized therapy [10]. Patients with COPD have a higher risk of developing comorbidities, including lung cancer, pulmonary tuberculosis, dementia, and ischemic heart disease (IBD) [10,11,12]. The development of these concomitant diseases of COPD can be facilitated by the development of the above-mentioned diseases due to systemic inflammation. The incidence and prevalence of CKD continues to grow worldwide. CP has a progressive course and leads to the development of terminal cheche failure (TPN), associated with high mortality, deterioration of quality of life, high comorbidity, persistent loss of working capacity, and the need for expensive methods of replacement therapy (dialysis and transplantation) [13]. Age increase, SD, arterial hypertension (AH), and smoking are recognized as risk factors for the development of CKD [14,15,16]. According to the third national health and nutrition study (NHANES III), 6.2 million people (3% of the total US population) over 12 years old have serum creatinine levels above 1.5 mg/dl, and 8 million people (mainly over 65 years old) have glomerular filtration (GFR) rates below 60 ml/min [14]. The frequency of CKD increases with age in patients with COPD, regardless of gender and concomitant diseases.

In the study of Ringbaek T. et al., it was found that after stratification by sex and height, female patients with COPD had

a higher risk of developing CKD in the 60-69 age group (odds ratio 1.93) compared to other age groups. In a representative sample of adults, it was shown that the prevalence of CKD increases significantly with age [16]. Women with CKD with concomitant COPD have a higher mortality rate compared to men, indicating that the protective effect of estrogens in these cases is lost in women [17]. The high frequency of terminal stages of CKD development in both the general population of elderly people and elderly people with COPD can be explained by the high frequency of occurrence of AH, DM, cardiovascular diseases (CVD), and other comorbid conditions. Also, the increased risk of developing CKD in older age groups may be associated with involuntary decline in kidney function [15,16]. Patients with COPD and CKD have common risk factors for diseases, including DM and AH [16,17,18]. In patients with COPD, the risk of developing CBP is 1.6 times higher than in patients without lung pathology (OSH = 2.20; 95% confidence interval (CI) 1.83, 2.65) [15]. The presence of smoking in the medical history is one of the obvious reasons for the presence of COPD and CKD [16]. Former and active smokers had a higher risk of developing COPD. Nevertheless, some authors find a connection between CKD and COPD, regardless of smoking, suggesting the existence of other factors for their coexistence [17]. In the progression of CKD in COPD, an important place is occupied by hypoxemia, systemic inflammation, endothelial dysfunction, activation of the sympathoadrenal (SAS) and renin-angiotensin-aldosterone (RAAS) systems, oxidative stress, prolonged endogenous intoxication, and it should be noted that the inflammatory process has a negative impact on the renal vascular system. [18,19,20]. In addition to the presence of DM and hypertension, sleep apnea in COPD

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patients plays an important role in increasing the likelihood of developing CKD [12, 14, 17]. In most patients with COPD (25-60%), protein-energy deficiency develops, up to the development of "pulmonary cachexia" [18,19,20]. Damage to kidney vessels through the inflammatory process increases the risk of developing CKD [13,15,20]. In this condition, manifestations of systemic inflammation are observed with an increase in inflammatory cytokines, in particular, tumor necrosis factor alpha (TNF-alpha) (identified as a key intermediary in atherosclerosis) [10,13] and the protein transforming growth factor beta (TGF-β), which participates in the development of COPD and atherosclerosis [20]. Studies of inflammatory biomarkers in nephrological patients suggest that patients with chronic kidney disease undergoing chronic hemodialysis (CHD) have a high level of inflammation [20], which can also affect the respiratory system [18,19,20]. In patients with stage V CKD, the FVC1 (forced expiratory volume per second) and FVC (forced vital lung capacity) indicators are significantly lower with high levels of inflammatory markers such as C-reactive protein (CRP) and ferritin [16]. The pathophysiological basis for increased risk of kidney damage in COPD, especially in patients with hypoxia, is the involvement of renal endocrine mechanisms (including RAAS) and increased vascular wall rigidity [2,14,19]. Considering the other side of the two-way relationship between COPD and CKD, it should be noted that in the terminal stage of CKD, when there is a complex cascade of toxic, metabolic, and hemodynamic disorders affecting practically all organs and systems [18], including the respiratory system, lung dysfunction develops due to the direct action of circulating uremic toxins or secondarily in response to volumetric overload, anemia, weakening of the immune system, malnutrition, electrolyte and acid-base imbalance [9,17]. In COPD with protein-energy deficiency, along with a deterioration in nutritional status indicators [6], a decrease in body mass index, and a decrease in the amount of subcutaneous adipose tissue, a high concentration of prospons is also detected. Hypermetabolic-hypercatabolic syndrome, manifested by increased breakdown of tissue proteins and increased consumption of carbohydrate and lipid reserves and closely related to a systemic inflammatory reaction, metabolic acidosis, hormonal imbalance with anabolic effects, is diagnosed on average in half of CKD patients and is a result of a systemic inflammatory reaction [12,13,16]. Most systemic manifestations of COPD, such as cardiovascular complications, anemia, depression, and mineral-bone disorders, can also be observed in CKD, which is often mistakenly considered solely as manifestations of COPD [8,13,14]. Uremic toxins, some of which are anorexigens - products of protein metabolism, have a negative effect on the body, including the induction of oxidative stress mechanisms, endothelial dysfunction with impaired nitrogen oxide synthesis, the development of interstitial kidney fibrosis, muscle mass loss, as well as an increase in proteinuria and the rate of renal dysfunction progression [7,17,18]. COPD is associated with microalbuminuria in patients with hypoxic and hypercapnic conditions, which is a reflection of increased RAAS activity [1]. Systemic microvascular damage can also contribute to the development of CKD in COPD patients, which was confirmed in a study by Harris B. et al., where an inverse correlation was found between FVC1 and FVC with albuminuria [18]. In such a situation, there is a need to maintain the adequate nutritional status of patients with COPD in combination with CKD against a background of developing or already existing protein-energy insufficiency and to correctly limit protein intake in order to slow down the progression of renal failure. It has been established that a strict low-protein diet in combination with ketoanalogs of

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essential amino acids allows for a reduction in traditional and non-traditional risk factors, reducing the rate of progression of CKD, COPD, and CVD in comorbid patients without exacerbating protein-energy deficiency manifestations [5,6,18]. The detection of a negative correlation between the calculated CKD (CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration) and albumin levels ($r = -0.268$; $p < 0.05$), as well as alpha-1-globulin ($r = 0.334$; $p < 0.05$), confirms the well-known mechanisms of CKD development with a high-protein diet.

In conclusion, the article provides a detailed analysis of the phenomenon of renal dysfunction in patients with chronic obstructive pulmonary disease. The interaction of lung and kidney functions and the mechanisms of side effects are reflected in the processes of blood pressure, oxygen levels, and the elimination of toxins. This, in turn, is very important, since patient treatment strategies and care should take into account the state of both organ systems. The relationship between lung diseases and kidney function is of great importance in clinical practice, contributing to the development of standard and individual treatment approaches for patients. Continued research and analysis will allow us to offer more details and treatment methods, which will serve to improve the overall management and quality of patients.

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