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Pathogenetic Mechanisms of the Influence of Chronic Obstructive Pulmonary Disease on the Development of Renal Pathology

Artem Aleksandrovich Rubtsov[1], Malik Fazilovich Aliskerov[2], Alexandr Sergeevich Baidukov[1], Violetta Viktorovna Zhuravleva[3], Milana Lemaevna Djabrailova[3], Ekaterina Dmitrievna Sukhanova[4]

[1]Tula State University, Tula, RUSSIA.
[2]Dagestan State Medical University, Makhachkala, Republic of Dagestan, RUSSIA.
[3]Rostov State Medical University, Rostov-on-Don, RUSSIA.
[4]North Caucasus Federal University, Stavropol, RUSSIA.
**Corresponding Author (Tel: +79183500889, Email: ruslankalmykov777@yandex.ru).*

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Abstract

This research paper examines in detail the effect of COPD disease with a focus on the defeat of the urinary system. The relevance of this work is confirmed in the steadily increasing frequency of secondary kidney damage. The study of this phenomenon is necessary since timely detection of complications from the urinary tract against the background of chronic obstructive pulmonary disease will reduce the transition from acute kidney diseases to chronic.

Disciplinary: Medicine.

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is an independent nosological unit, the characteristic feature of which is a relatively irreversible restriction of the passage of airflow in the respiratory system. As a rule, this disease has an exponential character of development, the trigger

for which is an excessive inflammatory reaction of the pulmonary parenchyma to irritation by pathogenic particles and gases of various kinds, especially in the lower parts of the lungs. To date, COPD is a common cause of morbidity and mortality in urbanistically developed countries and cities due to etiological triggers and factors, and this trend has long been a social problem [1]. According to modern statistics (2021-2022), this disease is observed in every twentieth person among the contingent older than 40-45 years. In the Russian Federation and Eastern European countries, there are officially more than 3.5 million patients with COPD, and according to calculations based on epidemiological studies, the number may exceed 15 million. In addition to the fact that COPD affects the respiratory and cardiovascular systems (as a burdened consequence with the development of respiratory insufficiency and chronic cor pulmonale with early disability), today COPD is considered from the perspective of multimorbidity [2].

2 Pathogenetic Mechanisms of the Influence of Chronic Obstructive Pulmonary Disease on the Development of Renal Pathology

Chronic obstructive pulmonary disease is a multicomorbid disease, that is, a disease that coexists with two or more systemic pathologies associated with common pathogenetic mechanisms. Therefore, the issue of studying the functional state of the renal system is of close interest to medical professionals, because it is known that the state of kidney health has a complex effect on the entire body as a whole through hormonal and cardiovascular effects. Based on modern foreign data, glomerular filtration rate (GFR) less than 60 ml/min/1.73 m2 is a predictor of cardiovascular disease [3]. Although, as experience shows in clinical practice, patients with COPD, even with very small decreases in the GFR parameter from the norm, are even more susceptible to cardiovascular risk, which for this cohort of patients is combined into a cardiorenopulmonary continuum model.

According to the results of laboratory and imaging diagnostic methods, the supranosological concept of chronic kidney disease in COPD implies a violation of the integrity of the renal parenchyma at the molecular level or a violation of their functional component for 3-4 months from the onset of the disease, regardless of etiology [4,5].

In the early stages of the development of chronic kidney disease, an asymptomatic clinical picture is observed, which makes the diagnostic search difficult and ineffective. At the same time, timely pharmacological nephroprotective and immunomodulatory therapy and prevention can reduce the likelihood of developing end-stage chronic kidney disease in more than half of all cases [6].

For the purpose of an effective diagnostic search, it is proposed to divide all known risk factors for the development of chronic kidney disease into two groups: modifiable (smoking, obesity, dyslipidemia, taking nephrotoxic drugs, autoimmune and inflammatory processes, hyperhomocysteinemia, anemia, disorders of phosphorus-calcium metabolism, etc.) and unmodified (elderly, male, belonging to separate ethnic groups, a history of kidney disease, etc.). Currently, it is well known that a high degree of comorbidity in COPD and the presence of risk factors not only lead to the development of chronic kidney disease but also are an etiological trigger for the indicator of high mortality in the early stages of dialysis. And despite the variety of

morphological forms of chronic kidney disease, the outcome of each of them is nephrosclerosis, the rate of development of which is determined by both the nature of the disease and the quantitative and qualitative presence of risk factors for chronic kidney disease [7-10].

It has been precisely proved that the progression of chronic kidney disease is associated with tubulointerstitial fibrosis in both tubulopathies and glomerulopathies, and the decrease in GFR is highly correlated with the degree of interstitial, not glomerular lesions. This depends primarily on the degree of damage to the epithelial layer lining the tubular apparatus, which is more sensitive and, in pathological conditions, more susceptible to hypoxia than glomeruli. Most of the intrarenal blood flow is provided by the cortical substance of the kidney, in which almost all the glomeruli are located, which determines the filtration function. As a consequence, even with severe renal ischemia, the glomeruli can remain intact for a long time, unlike the cellular remnant of the tubulointerstitial, which undergoes atrophy and fibrosis [11].

Thus, chronic renal ischemia occurs due to a decrease in glomerular blood flow, activating at the beginning local vasoconstrictor mechanisms – renin-angiotensin-aldosterone system (RAAS), which causes an increase in intracellular pressure, and with the development of hyperfiltration – an adaptive mechanism to maintain kidney function for some time. Further, already in conditions of hypoxia, the effectiveness of this adaptive mechanism decreases, which leads to full and pronounced hypoperfusion of the glomeruli of the kidney, as a result of which GFR decreases and the level of serum creatinine in blood plasma naturally increases.

It is known that glomerular hyperfiltration is the basis of the triggering mechanism of microalbuminuria [9,10]. The previous activation of RAAS also contributes to the progression of chronic renal disease: the substance angiotensin II (the main effector peptide of RAAS, which causes vasoconstriction and is the main regulator of the synthesis of the hormone aldosterone formed in the glomerular zone of the adrenal cortex) is a kidney growth factor, causing proliferation and phenotypic changes of fibroblastic elements that turn into myofibroblasts and enhance matrix deposition in the interstitial. Thus, the following stages are distinguished in the formation of nephrosclerosis: glomerular hypertension, tubulointerstitial inflammation, and fibrosis [11].

COPD is associated with the development of impaired renal function and structure, this is a proven fact [12-15]. One of the pioneers in this direction was Y. van Gestel et al., who conducted a cohort scientific study that demonstrated that COPD is associated with chronic kidney disease, and the severity of COPD is associated with increased mortality in patients with such kidney problems [16]. Another retrospective study conducted by specialists from National Health Insurance Research in China, which included 7739 patients with COPD who were monitored for more than 10 years at the dispensary, confirms the correlation between COPD and kidney disease, regardless of gender. The results of the C.Y. Chen team [17] demonstrated the effect of systemic inflammatory reaction and hypoxia in patients with COPD on kidney function with the development of chronic kidney disease and an increase in the risk of its occurrence by more than 1.5 times compared with general population indicators. The possible pathogenetic relationship between COPD and this pathology is also evidenced by the confirmed results that the intensity of the course of emphysema in tobacco smokers, assessed by CT, is a trigger springboard for the development of renal failure [18].

Thus, it can be concluded that the survival of patients with COPD depends on the presence of concomitant pathologies, in particular from chronic kidney disease. It follows from this that CKD can be considered from the perspective of a prognostic factor of mortality in patients with COPD. The results of scientific papers by I. Elmahallawy and M. Qora demonstrate a high prevalence of renal pathology in COPD patients, reaching almost 50% in all cases, which undoubtedly causes a focus on a direct link [19].

Thus, tobacco smoking, high incidence of dyslipidemia in COPD, along with chronic systemic inflammation, oxidative stress, imbalance of the proteolysis–antiproteolysis system, ventilation-perfusion disorders with the development of permanent hypoxia have an adverse effect on kidney function, contributing to the development and progression of CKD in patients of this category.

3 The Role of Inflammatory Markers in COPD in the Formation of Kidney Dysfunction

Known markers of systemic inflammatory response in COPD are found not only in the respiratory system, but also in the general blood flow, which manifests itself in the form of an increase in the number of leukocytes and C-reactive protein, TNF. The biological markers of chronic inflammation are neutrophils, macrophages and T-lymphocytes. Under the influence of triggering mechanisms, neutrophils circulate in the blood plasma and are concentrated in large quantities in the pulmonary parenchyma. It is a source of free radicals. Neutrophils secrete lysosomal enzymes, neutrophil elastases, metalloproteinases, which, along with the main inflammatory cytokines, are the main mediators of inflammation in COPD [20]. Due to the excessive concentration of neutrophils in the respiratory tract, the imbalance of the proteolysis–antiproteolysis system and oxidants–antioxidants increases, oxidative stress and cytokine storm develop, contributing to the release of free radicals in the respiratory system even more intensively [21,22]. As a result, local protease inhibitors are depleted, which, along with the release of a large number of neutrophil proteases, mainly neutrophil elastase, leads to a violation of the integrity of the alveolar wall, involvement of lung tissue in the pathological process and the development of emphysema [23-24]. Oxidative stress in patients with COPD can also be promoted by further infection [25,26]. So, systemic inflammatory response causes endothelial damage due to a number of mechanisms contributing to this effect. In particular, inflammatory cytokines - in response to their effects, the permeability of the endothelial lining increases.

Studies in the pathophysiology of the urinary system have proved that about a third of their entire endothelium is localized in the microcirculatory bed of the kidneys and large renal vessels, so the kidneys are one of the first targets for aggressive factors in the pathological cascade [27]. Systemic inflammation in COPD is accompanied by membrane–destructive processes with the release of prostaglandins and leukotrienes, chemical mediators of inflammation, which leads to a violation of lipid metabolism [28-30]. More than 40% of patients with COPD develop dyslipidemia. Oxidative stress and cytokine storm cause narrowing of vascular tracts and increased absorption of oxidized low-density lipoprotein cholesterol, as well as inhibition of nitric oxide, which leads to

even greater vasoconstriction [31,32]. Thus, the contribution of the adverse effects of LDL to the systemic manifestations of COPD is obvious.

4 Conclusion

Tobacco smoking, which is the main cause of COPD, causes the progression of CKD, inducing endothelial dysfunction of the glomeruli, provoking the occurrence and progression of albuminuria. The results of numerous studies indicate smoking as a risk factor for reducing GFR. Thus, pathogenetic disorders formed in COPD in the form of chronic systemic inflammation, oxidative stress, imbalance of the proteolysis–antiproteolysis system, ventilation-perfusion disorders, endothelial dysfunction, and dyslipidemia form the basis for the development of kidney dysfunction. A characteristic feature of COPD is the presence of exacerbations, which are usually associated with increased inflammatory response. Systemic inflammation, especially in the presence of frequent exacerbations, forms a wide range of comorbid pathology, including can cause kidney dysfunction. In a study by M. Barakat et al. in COPD patients, the effect of COPD exacerbation on the development of acute renal failure and higher mortality in COPD patients with the development of acute renal failure was revealed. It has been shown that CKD affects mortality during the first 6 months after COPD exacerbation. It is also noteworthy that there is a positive correlation between albuminuria on the one hand, and the indicators of forced expiratory volume for the 1st second (FEV1) and the frequency of COPD exacerbations on the other, as well as a significant positive correlation between FEV1 and the renal vascular resistance index. The established correlations probably serve as evidence of the systemic effects of COPD mediated by endothelial dysfunction. The association of albuminuria with the severity of COPD and the severity of obstructive disorders obviously indicates the presence of a pathogenetic relationship of renal dysfunction with COPD, most likely realized through hypoxemia. COPD patients with frequent exacerbations showed significantly higher urinary excretion of β2-microglobulin, which reflects the adverse effect of COPD on the renal tubular apparatus.

5 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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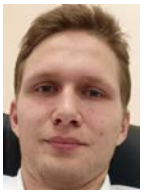
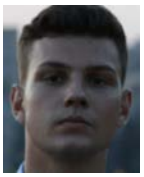
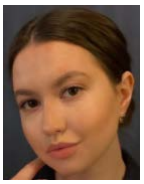
Artem Aleksandrovich Rubtsov is a student of Tula State University, Tula, Russia



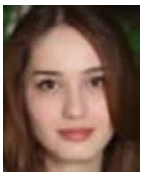
Malik Fazilovich Aliskerov is a student of Dagestan State Medical University, Makhachkala, Republic of Dagestan, Russia



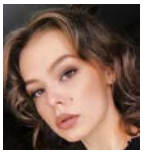
Alexandr Sergeevich Baidukov is a student of Tula State University, Tula, Russia



Violetta Viktorovna Zhuravleva is a student of Rostov State Medical University, Rostov-on-Don, Russia



Milana Lemaevna Djabrailova is a student of Rostov State Medical University, Rostov-on-Don, Russia



Ekaterina Dmitrievna Sukhanova is a student, Department of Food Technology and Engineering, North Caucasus Federal University, Stavropol, Russia