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PATHOPHYSIOLOGY OF RENAL DYSFUNCTION IN CHRONIC OBSTRUCTIVE LUNG DISEASE: MODERN VIEWS

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Abstract. *Chronic obstructive pulmonary disease (COPD) is an irreversible chronic disease characterized by persistent and progressive narrowing of the airways, predominantly chronic bronchitis and pulmonary emphysema. Its development is caused by smoking (the main risk factor), air pollution, industrial dust, respiratory infections in childhood, and some genetic factors, in particular, α1-antitrypsin deficiency. Chronic inflammation in the small bronchi and alveoli, bronchial obstruction, destruction of alveolar structures, and gas exchange disorders play an important role in the pathogenesis of the disease.*

Chronic obstructive pulmonary disease (COPD) causes profound disorders not only of the respiratory system, but also of other vital organs, including the function of the kidneys. This article analyzes the main pathophysiological mechanisms of renal dysfunction developing against the background of COPD, including hypoxia, inflammatory mediators, neuroendocrine disorders, and hemodynamic disturbances. Decreased renal perfusion and activation of the renin-angiotensin-aldosterone system lead to structural changes in the renal tissue. Modern studies show that systemic inflammation and oxidative stress also play an important role in these processes. The article also provides a clinical assessment of the relationship between renal failure and COPD.

Keywords. *Chronic obstructive pulmonary disease, renal dysfunction, pathophysiology, hypoxia, inflammation, RAAS, oxidative stress, nephroprotection, systemic inflammation, comorbidity.*

ПАТОФИЗИОЛОГИЯ ДИСФУНКЦИИ ПОЧЕК ПРИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ: СОВРЕМЕННЫЕ ВЗГЛЯДЫ

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Аннотация. *Хроническая обструктивная болезнь лёгких (ХОБЛ) — это необратимое хроническое заболевание с постоянным и прогрессирующим сужением дыхательных путей, характеризующееся преимущественно хроническим бронхитом и эмфиземой лёгких. Его развитию способствуют курение табака (основной фактор риска), загрязнение атмосферы, промышленная пыль, респираторные инфекции в детстве и некоторые генетические факторы, в частности, дефицит α1-антитрипсина. Хроническое воспаление в мелких бронхах и альвеолах, бронхиальная обструкция, разрушение альвеолярных структур и нарушения газообмена играют важную роль в патогенезе заболевания.*

Хроническая обструктивная болезнь легких (ХОБЛ) в глубокой степени нарушает не только дыхательную систему, но и деятельность других жизненно важных органов, в том числе почек. В данной статье анализируются основные патофизиологические механизмы почечной дисфункции, развивающейся на фоне ХОБЛ, включая гипоксию, медиаторы воспаления, нейроэндокринные изменения и нарушения гемодинамики. Снижение почечной перфузии и активация ренин-ангиотензин-альдостероновой системы приводит к структурным изменениям в ткани почек. Современные исследования показывают, что состояния системного воспаления и окислительного стресса также играют важную роль в этих процессах. Также в статье дается клиническая оценка взаимосвязи между почечной недостаточностью и ХОБЛ.

Ключевые слова. *Хроническая обструктивная болезнь легких, дисфункция почек, патофизиология, гипоксия, воспаление, РААС, окислительный стресс, нефропротекция, системное воспаление, коморбидность.*

SURUNKALI OBSTRUKTIV O‘PKA KASALLIGIDA BUYRAK DISFUNKSIYASINING PATOFIZIOLOGIYASI: ZAMONAVIY QARASHLAR

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Annotatsiya. *Surunkali obstruktiv o'pka kasalligi (SO'OK) — bu nafas yo'llarining doimiy va progressiv torayishi bilan kechadigan, qaytmas xususiyatga ega surunkali kasallik bo'lib, asosan surunkali bronxit va o'pka emfizemasi bilan tavsiflanadi. Uning rivojlanishiga tamaki chekish (asosiy xavf omili), atmosferaning ifloslanishi, sanoat changlari, bolalikdagi respirator infeksiyalar va ayrim genetik omillar, xususan, α1-antitripsin yetishmovchiligi sabab bo'ladi. Kasallik patogenezida kichik bronxlar va alveolalardagi surunkali yallig'lanish, bronxial obstruksiya, alveolyar tuzilmalar yemirilishi va gaz almashinuvining buzilishi muhim o'rin tutadi.*

Surunkali obstruktiv o'pka kasalligi (SOO'K) nafaqat nafas tizimini, balki boshqa hayotiy organlarni, jumladan buyrak faoliyatini ham chuqur darajada buzadi. Ushbu maqolada SOO'K fonida rivojlanadigan buyrak disfunksiyasining asosiy patofiziologik mexanizmlari, jumladan gipoksiya, yallig'lanish mediatorlari, neyroendokrin o'zgarishlar va gemodinamik buzilishlar tahlil qilinadi. Buyrak perfuziyasining pasayishi va renin-angiotenzin-aldosteron tizimining faollashuvi buyrak to'qimalarida strukturaviy o'zgarishlarga olib keladi. Zamonaviy tadqiqotlar ko'rsatishicha, sistemali yallig'lanish va oksidlovchi stress holatlari ham ushbu jarayonlarda muhim rol o'ynaydi. Shuningdek, maqolada buyrak yetishmovchiligi va SOO'K orasidagi o'zaro bog'liqlik klinik jihatdan baholanadi.

Kalit so'zlar. *Surunkali obstruktiv o'pka kasalligi, buyrak disfunktsiyasi, patofiziologiya, gipoksiya, yallig'lanish, RAAS, oksidlovchi stress, nefroprotektsiya, sistemali yallig'lanish, komorbidlik.*

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive respiratory disease characterized by persistent airflow restriction. The disease is mainly formed as a result of a persistent inflammatory process in the respiratory tract caused by cigarette smoke, biofuel smoke, industrial dust, and harmful gases. The pathogenesis is based on structural changes in the small bronchi and alveoli, the release of inflammatory mediators, hypersecretion of mucous membranes, and degradation of elastic tissues.

The morphological basis of COLD is such pathological conditions as chronic bronchitis and emphysema. In chronic bronchitis, inflammation and increased mucus secretion in the bronchial mucosa are observed, while in emphysema, ventilation-perfusion imbalance occurs, accompanied by the destruction of the alveolar wall and a shortening of the air exchange surface. These changes lead to systemic disorders such as hypoxemia, hypercapnia, and metabolic imbalance.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2023), COLD is a disease characterized by incomplete airflow restriction, arising in response to prolonged exposure of the respiratory tract to harmful particles or gases. The criterion for diagnosis is the ratio of FEV1/FVC, which is one of the spirometric indicators, below 0.70.

According to epidemiological data, COPD is one of the leading causes of death and disability worldwide, negatively affecting the quality of life and life expectancy of millions of people annually. According to the World Health Organization (WHO), COLD has been listed as the third most common cause of death since 2024. The disease is usually diagnosed in people over 40 years old who have smoked for many years or lived in harmful environmental conditions.

Clinical and experimental studies conducted in recent years have shown that COPD has a systemic effect not only on the pulmonary system, but also on the cardiovascular, musculoskeletal, metabolic, and even renal systems. In particular, renal dysfunction developing against the background of chronic hypoxemia and inflammation is one of the least studied, but clinically significant aspects of the disease. Therefore, it is important to assess COPD not only as a respiratory disease, but also as a multisystem chronic pathology.

The results of the latest systematic analysis of the relationship between COPD (Chronic Obstructive Pulmonary Disease, COPD) and chronic kidney disease (Chronic Kidney Disease, CKD) showed that the probability of developing CKD in patients with COPD is significantly higher, and as a result of the meta-analysis, it was approximately OR = 1.54 (95% CI: 1.28 1.84).

In patients with COPD with CKD, not only does CKD develop, but the clinical prognosis of COPD also worsens: short-term mortality increases during the exacerbation of the disease (acute exacerbation), as well as a negative impact on long-term survival with COPD.

Chronic Systemic Inflammation: In many studies, it has been established that in patients with COPD, the levels of pro-inflammatory mediators such as interleukin 6 (IL 6), TNF α, C-reactive protein (CRP) are elevated in the blood/plasma. These mediators exert a nephrotoxic effect on renal glomerular capillaries, interstitial tissues, and tubular cells. Against the background of inflammation, the risk of fibrosis, cell apoptosis, and glomerulosclerosis increases. For example, in meta-analysis and cohort studies, in patients with COPD with a high level of inflammation, the stage of CKD increases rapidly.

Oxidative Stress and Mitochondrial Dysfunction Oxidative stress plays a central role in the pathogenesis of COPD; fum fumes and other irritants are accompanied by an increase in reactive oxygen forms (ROS) in the respiratory tract and a weakening of antioxidant defense. ROS activity damages endothelial cells, podocytes, and tubular epithelial cells in the kidneys, stimulating cell apoptosis through toxic changes. Also, oxidative stress can activate the RAAS system, which leads to impaired glomerular hyperfil-

tration or percussion. Mitochondrial dysfunction, energy deficiency in cells, disruptions in the electron transport chain intensify oxidative reactions and increase intracellular oxidative damage. Mitochondrial dysfunction associated with COPD has been actively studied in recent years.

Hypoxia, Hypercapnia and Perfusion Disorders In COPD, decreased alveolar ventilation, air exchange disorders lead to hypoxemia and sometimes hypercapnia. These conditions cause disorders in the systems that ensure oxygen delivery to the blood, including renal perfusion. Hypoxic conditions alter intracellular gene expressions such as Hypoxia-inducible factors (HIF), which stimulate reactions such as metabolic adaptations, angiogenesis, and increased erythrocyte solution via HIF 1α and HIF 2α. However, in the long term, these adaptations may be unsuitable, leading to the loss of renal structure due to interstitial fibrosis and cell death.

Damaged Metabolism and Toxic Substances In COPD patients, oxidation and hypoxia can lead to metabolic loss (acidosis) and electrolyte changes, resulting in damage and impaired ion transport in tubular cells. Accumulation of toxic substances: heavy metals (for example, cadmium) from cigarettes and other environmental toxins enter the body and accumulate in bone, lung, and kidney tissues. These substances can disrupt glomerular filtration and lead to tubular damage. The authors of the meta-analysis noted evidence for this trend. Clinical Evidence: Risk Factors and Biomarkers.

In cohort studies, among patients with stages of CKD, factors contributing to the rapid development of renal dysfunction were such signs as mild/moderate COPD combined with COPD (GOLD 1 2), systolic blood pressure (SBP), hemoglobin (Hb) and albumin (Alb) levels, as well as a significant clinical symptom - edema.

In the meta-analysis, it was found that in the case of COPD and CKD combined, the probability of developing CKD is high even after taking into account such irreplaceable factors as chronic diseases - diabetes, hypertension, advanced age, smoking.

COPD and kidney interactions: Chronic obstructive pulmonary disease (COPD) is a multisystem disease that is not limited to the respiratory system, but in many cases affects many systems, including kidney function. Studies conducted in recent years indicate the need for a more in-depth study of the pathophysiological relationship between COPD and renal failure. The complex interaction between these two systems is expressed through a condition called pulmonary-renal syndrome. This syndrome arises as a result of physiological and pathological relationships between the cardiovascular, respiratory, renal, and immune systems.

Understanding pulmonary-renal syndrome: Pulmonary-renal syndrome is a complex of mutual dysfunctions arising between the pulmonary and renal systems, in which a pathological process in one system causes functional insufficiency in the other. Hypoxemia, hypercapnia, chronic inflammation, and oxidative stress developing against the background of COPD reduce the glomerular filtration rate in the kidneys. Conversely, impaired renal function, especially in cases of chronic renal failure (CHF), leads to the accumulation of toxins in the body, disruption of acid-base balance, and deterioration of lung gas exchange.

Co-inflammation (inflammation cross-talk) theory: One of the explanatory mechanisms for the connection between COPD and kidneys is the theory of co-inflammation (inflammation cross-talk). According to this theory, a chronic inflammatory process in one system has a systemic effect on other organs through cytokines, chemokines, and other mediators. For example, in COPD, inflammation in the lung tissue causes the release of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β. These mediators, reaching the kidneys through the bloodstream, intensify inflammation in the nephrons and glomerular structures. Also, chronic inflammation in the kidneys, in turn, increases the activation of inflammasomes in the lung tissue. This condition is called "inflammatory cross-talk."

Cytokine and immune system binding: Cytokines are one of the main molecular mediators of the interaction between the lungs and kidneys. Pro-inflammatory cytokines (IL-6, IL-8, TNF-α) cause an exacerbation of not only local, but also systemic inflammation. Immunological imbalance, especially in patients with COPD, exacerbates autoimmune and inflammatory processes in the kidneys. A decrease in the activity of T-regulatory cells and an increase in the activity of neutrophils lead to tissue damage in the kidney. Inflammation in the kidneys, in turn, negatively affects the lungs through a decrease in antioxidant protection, an increase in the production of endothelin-1 and angiotensin II. Thus, the mutual cytokine signaling between the lungs and kidneys creates a double-sided harmful cycle.

The role of acid-base balance and carbonic anhydrase inhibitors: In COPD, respiratory acidosis often develops as a result of hypercapnia and metabolic compensation. In response to this, the kidneys maintain the body's pH balance by reabsorbing bicarbonate. However, in the case of renal failure, this compensatory mechanism is disrupted, and metabolic acidosis intensifies. The enzyme carbonic anhydrase plays an important role in regulating the exchange of H+ and HCO3− ions in the respiratory and renal systems. Carbonic anhydrase inhibitors (such as acetazolamide) increase bicarbonate excretion through the kidneys by reducing the activity of this enzyme and preventing the aggravation of metabolic acidosis. However, their long-term use should be carried out with caution in patients with COPD, as this can lead to weakening of the respiratory center.

In recent years, a number of modern clinical studies have been conducted aimed at studying the

complex interaction between chronic obstructive pulmonary disease (COPD) and renal failure. In particular, cohort studies and meta-analyses revealed an increased risk of developing chronic renal failure (CHF) in patients with COPD. Meta-analyses published between 2022 and 2024 show that the likelihood of decreased renal function (eFR) increases as FEV1 levels decrease. This once again confirms the connection between systemic inflammation and oxidative stress.

Among the biomarkers involved in these processes, KIM-1 (Kidney Injury Molecule-1), NGAL (Neutrophil Gelatinase-Associated Lipocalin), and Cystatin C are of particular importance. In particular, Cystatin C is a sensitive indicator of glomerular filtration, which is significantly more reliable than creatinine in the early detection of kidney damage. NGAL and KIM-1 are early signs of tubular damage and allow determining the preclinical stages of renal dysfunction in patients with COPD.

In modern diagnostic approaches, eGFR (estimated Glomerular Filtration Rate) serves as the main indicator in assessing kidney function. eGFR, determined using the CKD-EPI formula, is especially important in detecting a gradual decrease in renal function in patients with COPD. In addition, the detection of microalbuminuria is widely used in clinical practice as an early marker of endothelial kidney damage.

From a pharmacological point of view, some drugs used in the treatment of COPD, in particular, corticosteroids, beta-2 agonists, and anticholinergics, can have various effects on kidney function. Long-term use of inhalation corticosteroids can negatively affect glomerular pressure through mineralcorticoid retention and hypertension. Also, systemic steroids reduce renal perfusion and increase the risk of nephropathy. Beta-2 agonists disrupt the electrical balance between the heart and kidney system through hypokalemia. Therefore, in the modern approach to treatment, it is necessary to take into account the functional relationship between the lungs and the kidney system, and to monitor the nephrotoxic effect of drugs.

Early identification of the relationship between COPD and renal failure has important diagnostic and therapeutic significance in clinical practice. Especially in patients with COPD, early detection of nephropathy through regular monitoring of kidney function (eGFR, microalbuminuria, Cystatin C) and timely implementation of treatment strategies improve the patient's prognosis. In the prevention of nephropathy, it is important to optimize anti-inflammatory therapy, carefully use nephrotoxic drugs, monitor blood pressure, and maintain hydration status. Modern clinical guidelines (GOLD, KDIGO) support a multi-system approach and require the integrated work of a pulmonologist, nephrologist, and general practitioner. This approach increases the possibility of preventing systemic complications, including kidney damage, and maintaining a quality of life in COPD patients.

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