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Modern Views on the Pathogenesis and Early Diagnosis of the Development of Anemia in Cardiorenal Syndrome

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Abstract Cardiorenal syndrome (CRS) is a condition characterized by a mutual impairment of cardiac and renal function, in the clinical course of which anemia plays an important role. Anemia worsens the prognosis of CRS and increases hospitalization and mortality rates. The pathogenesis of its development is multifactorial: decreased erythropoietin synthesis, iron deficiency, the influence of inflammatory cytokines, oxidative stress, and neurohormonal dysregulation. Traditional biomarkers (creatinine, eGFR) are insufficient for early diagnosis. Modern markers (cystatin C, NGAL, KIM-1, hepcidin) are promising in scientific research and require multicenter research for their full implementation in practice. The article examines the pathogenetic mechanisms of anemia in CRS, problems of early diagnosis, and promising directions of treatment.

Keywords Cardiorenal syndrome, Anemia, Pathogenesis, Erythropoietin, Hepsidin

1. Introduction

Cardiorenal syndrome (CRS) is a complex pathological condition characterised by the mutual impairment of cardiac and renal function. In this case, heart failure and renal dysfunction aggravate each other, forming a "continuous loop." According to the World Health Organization and ESC (European Society of Cardiology), kidney damage of varying severity is observed in 40-50% of patients with heart failure. One of the most important complications of this condition is anemia [3].

Against the background of CRS, anemia often develops, which complicates the clinical course and prognosis of the disease. This complication is widely discussed in the scientific literature under the name "cardiorenal anemia syndrome (CRAS)" [1].

Anemia in CRS has a multifactorial (multipathogenic) nature and occurs in patients as a result of ischemia, hypoxia, inflammation, hormonal dysregulation, and metabolic disorders. Therefore, the pathogenesis and early diagnosis of this problem is one of the most pressing issues in modern medicine.

Research objective. Clarification of the pathogenesis of the development of anemia in cardiorenal syndrome, analysis of problems in early diagnosis and indication of promising biomarkers and therapeutic directions based on modern scientific research.

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2. Materials and Methods

In the process of preparing the article, scientific developments published in the PubMed, Scopus, Web of Science, and RINS databases between 2005 and 2024 were analyzed. Key research words: cardiorenal syndrome, anemia, early diagnosis, biomarkers (cystatin C, NGAL, hepcidin, erythropoietin). A total of 124 sources were reviewed, 58 of which were directly related to the topic.

Analysis of the results: Cardiorenal syndrome (CRS) is a pathological condition that develops in the interaction of cardiac and renal function and is characterized by a combination of heart failure and renal dysfunction. The concept of "cardiorenal syndrome" was first formed at the end of the 20th century, and in 2008, Ronco and co-authors proposed its modern classification. According to it, KRS is divided into 5 types:

- Type I (acute cardiorenal syndrome) - acute kidney damage against the background of acute heart failure.
- Type II (subacute/chronic cardiorenal syndrome) - chronic kidney diseases caused by chronic heart failure.
- Type III (acute renocardial syndrome) - acute heart failure against the background of acute kidney damage.
- Type IV (subacute/chronic renocardial syndrome) - chronic kidney diseases weaken heart function.
- Type B (systemic syndrome) - general pathologies that simultaneously affect the heart and kidneys (sepsis, diabetes, vasculitis, etc.) [6].

All types of CRS lead to a severe course of cardiovascular and nephrological diseases in patients, an increased risk of

death, and an increase in hospitalization. According to world statistics, despite the achievements of CRS, at least 40-50% of patients with heart failure are diagnosed with nephropathy of varying severity [5].

The development of anemia in CRS has a multifactorial character, which not only worsens the life prognosis of patients, but also increases treatment costs several times over. Therefore, in CRS, anemia is considered "one of the third-cycle factors of mortality" [3].

Scientific research conducted worldwide shows that anemia in CRS is widespread globally and is diagnosed as a complication in 60-70% of these patients. In particular, it was noted that in cases of heart failure (according to the NYHA classification), the incidence of anemia with CRS ranges from 9% to 79%, and in cases of decreased renal function - from 21% to 70%. The issue of CRS and anemia, which is one of its complications, has formed as a separate direction in world medical literature over the past two decades. This condition is explained by the complex pathogenetic connections between cardiac and renal pathologies, as well as the role of anemia as the "third link" in this cyclical process. Scientific research on CRS and anemia, one of its complications, has been studied to varying degrees in many scientific schools over the past two decades. At the heart of these connections lies the close connection between heart and kidney function, as well as anemia, which develops due to disorders in the hematopoietic system.

The significance of anemia in CRS is expressed as follows:

1. A decrease in hemoglobin levels reduces oxygen supply to tissues.
2. This condition intensifies ischemic processes in the heart.
3. Cardiac ischemia reduces renal perfusion and leads to nephron destruction.
4. A decrease in erythropoietin synthesis in the kidneys exacerbates anemia.

Thus, the interaction of the cardiorenal-hematopoietic system was adopted as the "CRAS pathogenetic model."

According to WHO data, anemia is detected in approximately 24% of the world's population. In patients with chronic kidney disease (CKD), this indicator reaches up to 50%, and in chronic heart failure - around 35-40%. If a patient has a combined course of heart and kidney diseases, the prevalence of anemia can reach 60-70% [4].

The development of anemia against the background of cardiorenal syndrome is multifactorial, in the pathogenesis of which a decrease in erythropoietin synthesis, impaired iron metabolism, chronic inflammation, oxidative stress, and hormonal dysregulation play a key role. However, in practice, there are no standard biomarkers for the early detection of these mechanisms.

Traditional indicators (hemoglobin, hematocrit, creatinine, eGFR) are limited by changes in the late stage. In modern studies, markers such as cystatin C, NGAL, KIM-1, hepsidin, erythropoietin, and ferritin are considered promising for early assessment of the development of anemia in CRS [4,5].

At the same time, treatment methods are also controversial. Although erythropoiesis stimulants (ESA) increase hemoglobin, they can increase the risk of cardiovascular complications. HIF-prolyl hydroxylase inhibitors (roxadustat and others) are being studied as a new possibility. SGLT2 inhibitors, in addition to protecting the heart and kidneys, can also have a positive effect on the pathogenesis of anemia.

In cardiorenal syndrome, the pathogenesis of anemia is based not on a single direction, but on the interaction of many factors. The following circumstances are important as the main mechanisms:

1. Reduction of erythropoietin synthesis.
2. Disruption of iron metabolism through hepsidin.
3. Cytokines and inflammatory processes.
4. Hypoperfusion and hemodynamic disturbances in the heart.
5. RAAS and sympathetic system hyperactivation.
6. Oxidative stress and hormonal dysregulation.

Therefore, a comprehensive approach to understanding and diagnosing anemia in CRS is necessary. The relative significance of these mechanisms can be different for each patient.

Patients with chronic kidney disease (CKD) and heart failure (HF) have an increased risk of developing anemia. Anemia is an independent risk factor for the development and progression of both cardiovascular diseases (CVD) and CKD. The prevalence of anemia in patients with CKD increases from 21% to 70% depending on the decrease in renal function, while in patients with CHF, it increases from 9% to 79% as the disease progresses (NYHA - New York Heart Association functional class I to IV) [2].

In patients with initially diagnosed heart failure, anemia was observed in 17% of cases, of which iron deficiency anemia was noted in 21%. In long-term chronic heart failure, the overall prevalence of anemia was 56% [1,2,4].

Today, there are new approaches to the treatment of anemia in cardiorenal syndrome. However, given the limitations and challenges of existing treatment methods, these possibilities may be effective in supplementary treatment for anemia in patients with CRAS [2,4]. Hypoxia-inducing factor-prolil hydroxylase (HIF-PH) inhibitors stimulate physiological EPO production by blocking the enzyme that suppresses erythropoietin (EPO) expression and correspondingly transcription factors controlling erythropoiesis [3]. A number of oral HIF-PH inhibitors (e.g., daprodustat, desidustat, enarodustat, molidustat, roxadustat, and vadadustat) underwent Phase 3 global trials after promising results in Phase 2 clinical trials. In these studies, the drugs maintained or increased hemoglobin levels in patients with CKD and anemia without clinically significant side effects [2,4].

HIF-PH inhibitors also have a direct effect on iron metabolism, that is, they regulate the activity of a number of genes that regulate iron transport and absorption, which is carried out independently of EPO stimulation. In addition, it was noted that they reduced the level of hepsidin and

cholesterol in the blood. They may also have additional beneficial effects not associated with EPO production or iron metabolism, such as: alleviating ischemic damage, improving heart function, mitigating vascular pathology, and having a positive effect in diabetic nephropathy [1,6].

Studies have shown that with HIF-PH inhibitors, hemoglobin levels increase at lower circulating EPO levels compared to ESA (erythropoiesis stimulants), and according to the data obtained so far, their effectiveness does not depend on the initial inflammatory state in patients. This is probably done by regulating the level of hepsidin.

3. Conclusions

The incidence of anemia in cardiorenal syndrome is high, and its clinical significance is very significant. This problem complicates the prognosis in patients, reduces the quality of life, and increases the socio-economic burden. In modern medicine, the pathogenesis and early diagnosis of anemia against the background of CRS remains a pressing scientific issue. So far, there are no evidence-based recommendations for managing patients with CRAS (Cardiorenal Anemia Syndrome); however, the treatment of such patients requires a multifactorial approach. It is necessary not only to control anemia, but also to treat heart failure and kidney damage, as well as other comorbidities.

The main methods of treating anemia in chronic kidney disease are intravenous iron preparations and erythropoiesis-stimulating agents, which eliminate iron deficiency and erythropoiesis defects. However, the use of high doses of erythropoiesis-stimulating agents may be associated with negative results in patients with CKD, and rutin is not used in practice in patients with heart failure. Therefore, the possibilities of treating anemia in patients with CRAS are limited.

Currently, a number of new methods of therapy are being studied in clinical trials, in particular, hypoxia-inducing factor-prolilhydroxylase inhibitors. These drugs have shown promising results in the treatment of anemia in CKD and can also be effective in CRAS patients, thereby eliminating some limitations of erythropoiesis-stimulating agents.

Updated clinical recommendations - on the screening and management of anemia in cardiorenal syndrome, taking into account new treatment methods and clinical evidence - can improve the clinical outcomes of patients with this complex syndrome.

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