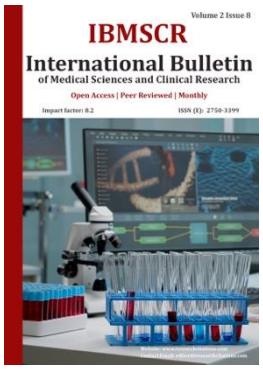

THE IMPORTANCE OF ENDOTHELIAL GLYCOCALYX AND ITS MARKERS IN EARLY DIAGNOSIS OF RENAL DYSFUNCTION IN CHRONIC HEART FAILURE

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Abstract

Chronic heart failure (CHF) is a multifactorial clinical syndrome characterized by high morbidity and mortality, frequently accompanied by renal impairment that progresses to cardiorenal syndrome. Recent studies have demonstrated that endothelial glycocalyx (EG) dysfunction plays a pivotal role in worsening renal function in CHF. Elevated serum concentrations of EG biomarkers — such as syndecan-1, heparan sulfate, and hyaluronic acid—are strongly associated with microalbuminuria, systolic dysfunction, and reduced glomerular filtration rate. Since conventional markers of renal dysfunction, including creatinine and cystatin-C, typically change only at advanced stages, the detection of EG-related factors alongside them may enable earlier identification of renal reserve decline and interstitial fibrosis. This, in turn, could support timely therapeutic interventions and improve outcomes in patients with CHF..

Key words: chronic heart failure, cardiorenal syndrome, endothelial glycocalyx, heparan sulfate, syndecan-1, cystatin-C, tumor necrosis factor-α.

Introduction. Chronic heart failure (CHF) is the most common cardiovascular disease, has a high mortality rate, and remains one of the most important socio-economic problems in the healthcare system [11]. Currently, according to the European Society of Cardiology (ESC) and the World Health Organization (WHO), the number of patients with CHF in the world exceeds 64 million, and this figure is expected to increase further in the next decade. It is considered the final stage of the cardiovascular disease continuum and is characterized by a sharp increase in the risk of high mortality. According to official epidemiological data, approximately 1.5-2.6% of the middle-aged population in the United States (USA) and European countries has heart failure, and its incidence increases with age, reaching 10% of people over 70 years of age and 70% of people 90 years of age and older. CHF is one of the most common serious complications in the population over 65 years of age, not only reducing quality of life but also causing hospital readmissions, increased demand for emergency care, and associated social problems [14]

In Europe, more than 5% of all hospitalized patients have an exacerbation of the disease. According to official data published in the 2021 issue of the European Journal of Preventive Cardiology, in 2017, 64.3 million people worldwide suffered from CHF, with an incidence of 831.0 men and 817.5 women per 100,000 population. Despite the positive results achieved in recent years in terms of treatment, one year mortality rate among hospitalized patients with CHF is 15.6% and the 5-year mortality rate is 45% [14].

In recent years, the pathophysiological relationship between the heart and kidneys, that is, the cardio-renal interaction, has been the focus of special scientific attention. In this

relationship, the endothelium and one of its main structures, the endothelial glycocalyx, are of great importance. The glycocalyx is a layer of specialized glycoproteins and glycosaminoglycans covering the surface of endothelial cells, which performs important functions such as blood vessel barrier function, inflammation, mechanical injury, and protection against oxidative stress [2].

Disruption of this structure leads to microcirculatory dysfunction, increased endothelial permeability, transduction of inflammatory mediators through the endothelium, and, at the same time, damage to the renal parenchyma. Therefore, biomarkers that assess the state of the endothelial glycocalyx, such as syndecan-1 and heparan sulfate, are of great importance in the early detection of renal dysfunction in CHF [16].

Aim: To study the importance of endothelial glycocalyx biomarkers in the early diagnosis of renal dysfunction in patients with CHF and their correlation with other factors based on the analysis of the literature published in recent years.

Main part. In the development of CHF, myocardial remodeling, hypertrophy, the development of fibrosis processes in it, and a decrease in the pumping function of the heart lead to hypoperfusion throughout the body. Over the past decade, much has been said about the problem of the "double epidemic", since the presence of symptoms of both diseases in most patients leads to the development of "cardiorenal syndrome". Cardiorenal syndrome reflects the both presence of cardiac and renal dysfunction or failure in a patient. There are five types of it, which are classified depending on which organ is the primary source of heart or kidney disease. In CHF, types I and II cardiorenal syndrome develop in most cases [16].

From a pathogenetic point of view, cardiovascular and renal diseases have common risk factors, such as arterial hypertension (AH) and diabetes mellitus, which are pathological structural and functional remodeling of the vessels. In this case, a complex process occurs, leading to the activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous systems. This condition leads to the retention of a large amount of sodium and, as a result, to excess fluid retention in the body, increased blood pressure and increased workload on the heart. Such pathogenetic changes primarily negatively affect the renal microcirculation, leading to the development of hypoxia and ischemia in the tissues and damage to the tubulo-interstitial tissue [7].

In the diagnosis of renal dysfunction, the presence of microalbuminuria-proteinuria, along with the serum creatinine indicator, is of great importance. However, a number of studies have shown that even a small amount of protein in the urine indicates the occurrence of irreversible morphological changes in the kidneys [19].

Therefore, special attention is paid to the development of new modern methods for early diagnosis of renal dysfunction and the search for markers with high specificity. Early detection of changes in renal function in patients with CHF allows them to prevent the development of chronic kidney disease (CKD).

It is known that endothelial dysfunction plays an important role in the pathogenesis of cardiovascular complications in this group of patients. According to data, endothelial dysfunction is, first of all, a violation of the balance between vasodilator, angioprotective and antiproliferative factors (nitric oxide - NO, prostacyclin, tissue plasminogen activators, C-type natriuretic peptide, endothelial hyperpolarizing factor) and vasoconstrictor, prothrombotic and proliferative factors (endothelin, superoxide anion, thromboxane A_2, tissue plasminogen activator inhibitor). Currently, special attention is paid to changes in endothelial function in

the mechanism of development of glomerular kidney damage. Glycocalyx is a thin but functionally complex structure located in the endothelial cell membrane, which is mainly composed of syndecan-1, heparan sulfate, hyaluronan, perlecan and chondroitin sulfate. The functions of this structure include:

• Acts as a selective barrier on the vascular surface;
• Supports anticoagulant activity;
• Limits leukocyte adhesion;
• Regulates endothelial response through specialized systems, accepting the load exerted by blood flow.

Ischemia, inflammation, hyperglycemia, oxidative stress, fluid overload, and inflammatory cytokines are factors that lead to damage to the endothelial glycocalyx, which directly affect this layer and cause its structural destruction [18]. Its fragmentation leads to increased permeability of the endothelial layer, impaired microcirculation, and impaired function of vital organs.

Inflammatory reactions that develop on the basis of CHF further damage the endothelial glycocalyx and the entire microvascular structure. Increased tumor necrosis factor-α (TNF-α) levels lead to impaired microcirculation and accelerate fibrosis processes, changing the nephron architectonics [17]. Also, the imbalance associated with oxidative stress and nitric oxide (NO) release increases endothelial dysfunction and causes an increase in inflammatory processes in the renal blood vessels [4]. Among the biomarkers indicating glycocalyx degradation, syndecan-1 (SDC-1), heparan sulfate (HS), hyaluronan (HA), and TNF-α occupy a key place. SDC-1 is a proteoglycan located on the surface of endothelial cells, and its increased concentration in the blood serum reflects the degree of glycocalyx degradation. In patients with CHF, SDC-1 levels have been found to increase before the decline in glomerular filtration, which allows for early detection of renal dysfunction [12]. Also, recent studies have shown that high levels of SDC-1 are associated with an increased risk of developing acute renal failure and death during hospitalization in patients [6].

Several biomarkers have been studied to elucidate the complex interplay between endothelial glycocalyx damage and fibrosis in patients with CHF. A 2014 study published in Circulation: Heart Failure assessed levels of the biomarker SDC-1 in 567 patients with CHF and compared it with another important fibrosis marker, galectin-3. The study found that SDC-1 levels were strongly correlated with galectin-3 and were associated with clinically relevant outcomes, particularly in CHF patients with preserved left ventricular ejection fraction (LVEF). That is, SDC-1 levels were found to be a marker of cardiac remodeling, fibrosis, and hypertrophy in patients with preserved CHF, and to be significantly predictive of clinical outcomes, including heart failure readmission or death (p=0.017) [15].

Heparan sulfate is a glycosaminoglycan, and its increased levels in the blood are considered a marker of microangiopathy. A study by Chen et al. (2022) found that heparan sulfate levels were significantly associated with the development of CKD in patients with CHF [10]. A study published in the American Journal of Cardiology in 2022 examined markers of endothelial glycocalyx degradation, including heparan sulfate, SDC-1, and hyaluronan, in 189 patients. The patients included in this study were divided into 3 groups: (1) decompensated systolic heart failure, (2) stable CHF (left ventricular ejection fraction (LVEF) < 40%), and (3) control group. The results showed that the level of heparan sulfate in the decompensated group was significantly higher and was significantly associated with glycocalyx damage and

overall mortality. A doubling of this marker increased the risk of death by 31.5% (p=0.040). This result provides the basis for evaluating heparan sulfate as an independent factor with significant significance in predicting the outcome of the disease. Other glycocalyx markers (SDC-1 and hyaluronic acid) did not have such prognostic significance. Therefore, plasma heparan sulfate levels can be used as an early marker of endothelial dysfunction and adverse clinical outcomes in patients with CHF [13].

Hyaluronic acid is a non-sulfated, anionic glycosaminoglycan that is a major component of the endothelial glycocalyx. It, together with proteoglycans on the surface of endothelial cells, plays an important role in maintaining the integrity of the endothelial barrier, regulating angiogenesis and microcirculation. In pathological conditions, namely in heart failure, hyaluronan molecules are released from the endothelial surface and enter the bloodstream, and their level in the fluid increases significantly. Therefore, this molecule is considered a marker of endothelial glycocalyx degradation [2]. Another study conducted in 2022 compared the levels of syndecan-1, heparan sulfate and hyaluronan in patients with acute decompensated heart failure (ADHF) and healthy controls. All of these markers were significantly elevated in the ADHF group compared to the control group [1].

Other studies have also shown that high levels of hyaluronan indicate endothelial glycocalyx dysfunction, but have not been shown to be statistically significant as a single biomarker for predicting outcome in CHF [2].

In addition, a study published in the Journal of Clinical Medicine (2024) that assessed endothelial glycocalyx status using in vitro sublingual microcirculation showed that increased level of hyaluronan was associated with increased risk of mortality in CHF. Although this study did not directly measure hyaluronan levels, it further supports the important role of glycocalyx dysfunction in the pathogenesis of CHF.

Another study found that patients with high levels of hyaluronan had decreased renal microvascular permeability and an inverse relationship with glomerular filtration rate [5].

Based on the above data, hyaluronan can be considered as one of the main factors reflecting the pathophysiological processes associated with endothelial glycocalyx disruption. However, it is not yet supported by sufficient evidence to be used as an independent prognostic biomarker in heart failure.

In recent years, the importance of glycocalyx biomarkers such as SDC-1, HS, and HA in predicting the outcome of CHF and renal dysfunction has been widely studied in clinical trials. A meta-analysis by Franchi et al. (2023) showed that high levels of these biomarkers were significantly associated with a higher risk of disease progression, readmission, and death in patients [9].

In etiological treatment, approaches aimed at protecting and restoring the endothelial glycocalyx are considered a priority. The results of scientific research conducted in recent years (2021) have confirmed the effectiveness of antioxidants (vitamin C, E) and NO donors in maintaining the integrity of the glycocalyx [8]. The literature also reports that angiotensin-converting-enzyme (ACE) inhibitors (enalapril, losartan) and mineralocorticoid receptor antagonists (spironolactone) can enhance renal microvascular protection [3]. Based on the above approaches, monitoring biomarkers in patients with CHF allows for the formation of individual approaches to treatment and timely implementation of therapeutic interventions, increasing the effectiveness of treatment. At the same time, it allows identifying pathogenetic

mechanisms in the development of CHF and renal dysfunction, improving treatment, and predicting the outcome of the disease.

Conclusion. Renal dysfunction in CHF is closely related to endothelial damage, and the breakdown of its main component, the glycocalyx, leads to microcirculation disruption, nephron damage, and the development CKD. In this case, biomarkers such as syndecan-1 and heparan sulfate, TNF-α, and cystatin-C are clinically important indicators for early diagnosis of endothelial dysfunction, selection of alternative therapies, and assessment of their effectiveness, as well as prediction of the degree of disease progression and outcome. Therefore, scientific research in this area is of practical importance

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