Volume 4, Issue 5, May 2026 ISSN (E): 2938-3765

CLINICAL AND LABORATORY FEATURES OF CARDIORENAL SYNDROME IN PATIENTS WITH DIABETES

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Abstract

Violation of the kidney filtration function is common enough among patients with cardiovascular disease (CVD), especially against disorders of carbohydrate metabolism (IGM). Renal dysfunction (PD) is associated with more frequent development of cardiovascular complications. In turn, the probability of the development of renal disease in patients with cardiovascular disease is significantly higher than in the general population. These bidirectional pathogenetic mechanisms existing between cardiovascular and kidney diseases were the basis for the formation of the cardiorenal syndrome concept. The review discusses the general parts of pathogenesis within the cardiovascular continuum. In addition, it shows the effect on metabolic disorders during CVD combined with renal dysfunction. The review reveals a recent view on the main mechanisms of cardiorenal syndrome.

Keywords: Cardiorenal syndrome, systemic inflammation, endothelial dysfunction, insulin resistance.

Introduction

Cardiorenal Metabolic interactions are one of the most current and discussed problems of modern medicine. It is related to steadfast increase in the prevalence of cardiovascular pathology, high morbidity with diabetes mellitus (DM) (388 million people) [4,12] and also to raise in the frequency of detecting renal dysfunction (RD). So, chronic kidney disease (CKD) is detected in 45-60% of cases among patients with chronic heart failure (CHF) [9]. The epidemiologic research has revealed a high prevalence of RD among patients with acute forms of ischemic heart disease as well (30.5-43.9%) [13].

The basis for the formation of the concept of the cardiorenal continuum was high risk of complications in patients with comorbid pathology, two-way connections that exist between cardiovascular disease (CVD) and RD [2]. Over the last few decades, results of scientific research have confirmed the correctness of the proposed concept; however, the mechanisms underlying the relationship between CVD, renal pathology, and diabetes mellitus have not been fully understood. Researchers are currently considering pathophysiologic mechanisms, including endothelial dysfunction, systemic inflammation, insulin resistance (IR), dyslipidemia, hypercoagulability, and increased platelet aggregation. Systemic inflammation takes a significant role in the basis of cardiovascular complications in patients with diabetes mellitus and RD. As research of past years shows, a high level of C-reactive protein(CRP) is a powerful predictor of cardiovascular events [11, 12], the prognostic value of which significantly exceeds the level of low-density lipoproteins (LDLP).

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During the investigation of indicators of oxidative stress in patients with myocardial infarction (MI), it was revealed that patients with complicated postinfarction period are characterized by a significant increase in the activity of lipid peroxidation (LPO) and a decrease in antioxidant protection[2] . The predictive role of systemic inflammation in hyperglycemic conditions is confirmed by a number of studies. So it was found that patients after an episode of unstable angina pectoris in combination with diabetes had higher values of indicators of inflammation markers, which were associated with a complicated course of the hospital period, in contrast to patients without carbohydrate metabolism disorders (CMD) [1]. Moreover, the role of complex immune reactions in the processes of atherogenesis is beyond doubt. Systemic inflammation is a potential mechanism for the development of endothelial dysfunction, which in turn plays a leading role in the formation of cardiorenal syndrome [7].

Analyzing the possible mechanisms of the effect of CVD on the development of renal dysfunction (cardiorenal syndromes of the 1st and 2nd types), it is important to note the mechanism of renal perfusion disturbance, which is characterized by pronounced neurohumoral changes and is accompanied by endothelial dysfunction and oxidative stress.

Confirmation of the close relationship between diseases of the cardiovascular system (CVS) and kidneys is also the fact that with a pronounced impairment of the contractility of the left ventricular (LV) myocardium, a decrease in the glomerular filtration rate (GFR), as a rule, coincides with the appearance of another unfavorable predictor - an increase in natriuretic peptides[15].

Decreased cardiac output in MI is accompanied by impaired renal perfusion and increased venous pressure[12]. We have previously shown that in patients with ST-segment elevation myocardial infarction, acute heart failure (AHF) class II-IV according to Killip is an independent predictor of RD development [3].

The study by C. Jeon (2016) also found that class III-IV AHF, according to Killip, was a significant factor in the deterioration of renal function along with such diseases as arterial hypertension (AH), obesity[14]. Hypertensive disease is one of the most common causes of RD, while the development of hypertensive nephrosclerosis is significantly accelerated in the presence of metabolic disorders. The PIUMA study has found that even with an uncomplicated course of essential hypertension, a moderate decrease in GFR leads to a doubling of the risk of cardiac death.

In conditions of reduced filtration function of the kidneys, the rate of progression of atherosclerosis increases[11]. The researchers noted that endothelial dysfunction develops even with a slight decrease in renal function and is associated with an increased cardiovascular risk[12].

It is known that dyslipidemia is present already in the early stages of CKD, while significant changes in the lipid profile are preceded by a decrease in apolipoproteins (A-I, A-II), which leads to a decrease in the level of high-density lipoproteins (HDL). Another factor that promotes the decline of HDLP in conditions of GFR (<60 ml/min / 1.73 m2) is that LDLP is significantly susceptible to peroxidation, which makes it even more atherogenic. Probably, it is this mechanism that explains that patients with RD are characterized by a higher prevalence and severity of coronary atherosclerosis compared with patients without renal dysfunction.

It is known that CVS remodeling occurs already in the early stages of PD, increasing the risk of CHF and life-threatening heart rhythm disturbances[15]. Studies have revealed a significant role of neurohormonal activation against the background of a decrease in GFR, leading to the progression of

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interstitial fibrosis and left ventricular hypertrophy (LVH) [14]. The fact of an increase in the concentration of aldosterone in the blood was established already in the early stages of a decrease in renal function[15]. A number of studies have established an association of a decrease in coronary reserve in patients with CKD, despite an insignificant lesion of the coronary bed[6,13]. Thus, in the study of M. Ragosta, a decrease in coronary reserve in patients with diabetic nephropathy compared with patients with diabetes mellitus and preserved renal function was found [14].

Equally important is the study of the mechanisms underlying the effect of (CMD) on renal function and CVD risk [12,13]. Diabetic dyslipidemia includes decreased HDL cholesterol, hypertriglyceridemia, and increased "small, dense" LDL cholesterol. A number of studies have revealed the damaging effect of dyslipidemia on the endothelium of nephron capillaries [13]. It was found that oxidized LDL increases the synthesis of components of the mesangial matrix, which contributes to accelerated sclerosis of the glomeruli [8]. In the study by A. Tozawa, hypertriglyceridemia was a significant predictor in the development of proteinuria. However, a number of studies have not revealed an association between lipid profile and the incidence of RD [15].

In addition, the effect of CMD on renal function is realized through IR and hyperinsulinemia, which is also interrelated with systemic inflammation, which is of significant importance in the pathogenesis of cardiovascular complications. Under physiological conditions, insulin has a selective effect on protein synthesis by hepatocytes, stimulating the production of albumin and reducing the synthesis of acute phase proteins. The opposite situation is observed during the acute phase of the inflammatory response. In conditions of chronic hyperinsulinemia and IR, an increase in the synthesis of proinflammatory factors (fibrinogen, CRP, plasminogen activator inhibitor) is characteristic, which undoubtedly has a significant role in enhancing thrombus formation and contributes to atherosclerotic lesions of the vascular bed. Studies have shown that the activity of subclinical inflammation correlated with biochemical markers of IR [10].

The universality of the mechanism of IR formation in CKD is currently being discussed. In addition, a genetic predisposition in the formation of peripheral IR in patients with impaired renal function is being investigated. It is believed that peripheral insulin resistance is a phenotypic manifestation characteristic of certain nosologies and has no relationship with the degree of decline in renal function, since it is the result of a combination of gene polymorphisms. In addition, there are many factors affecting the severity of IR. Thus, when studying the prevalence of metabolic syndrome components, in particular IR, lower values of immunoreactive insulin were found among residents of regions with extreme living conditions [5].

Metabolic disorders in diabetes form a whole complex of risk factors for CVS. A synergistic effect of diabetes mellitus on inflammation processes in the formation and progression of atherosclerosis has been established [12]. Diabetes mellitus can serve as a trigger mechanism in the development of vascular inflammation; however, it is possible that the opposite is also possible - sluggish chronic inflammation may be an important pathogenetic mechanism in the development of diabetes.CMD have an adverse effect on the prognosis of patients with CVD through the mechanism of excessive accumulation of end products of glycation with the formation of free radicals, leading to an increase in the consumption of nitric oxide, the deficiency of which leads to a weakening of vasodilation, causing endothelial dysfunction. It is known that the formation of effective collateral blood flow

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occurs as a result of angiogenesis, which is significantly reduced in conditions of hyperglycemia, which significantly worsens the prognosis of patients, especially in conditions of acute myocardial ischemia [8, 10].

Metabolic disorders, leading not only to cardiovascular complications but also to progressive loss of renal function, significantly worsen the prognosis of patients. In the earlier population-based study WESDR (Wisconsin epidemiological study of diabetic retinopathy), which included patients with type 2 diabetes, an increase in cardiovascular mortality was shown by 2.7 times with albuminuria, and with proteinuria, 3.7 times compared with patients without kidney's damage. The state of chronic hyperglycemia triggers a cascade of biochemical changes in the glomeruli, tubules, and interstitium of the kidneys, which leads to the activation of collagen synthesis and a decrease in collagenolytic enzymes. As a result, there is an excessive accumulation of collagen, which becomes a key link in the formation of diabetic nephrosclerosis and further loss of kidney function[6, 7].

Nevertheless, patients with diabetes represent a prognostically heterogeneous group, which is determined by the presence of damage to target organs and is associated with the duration of CMD; on the other hand, it provides an opportunity to improve the prognosis, improving the early diagnosis and treatment of patients with metabolic disorders. Secondary cardiorenal syndrome (type 5 cardiorenal syndrome) is characterized by the presence of combined cardiac and renal pathology due to acute and chronic systemic disorders (sepsis, sarcoidosis, amyloidosis, systemic vasculitis, systemic lupus erythematosus) [4, 5].

However, data on the prevalence of secondary cardiorenal syndrome are very limited due to the large number of acute and chronic predisposing conditions. Despite the modern advances in fundamental and clinical cardiology, the problem of studying the pathophysiological mechanisms of PD and assessing its impact on the prognosis of patients with CVD, SMD, as well as the development of and the introduction of new effective methods for predicting cardiovascular complications are far from a final decision and requires comprehensive research. Identification of the exact mechanisms of cardiorenometabolic relationships in the future will allow improving approaches to treatment and thereby improve the prognosis of patients with comorbid pathology [8, 10].

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