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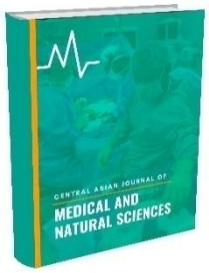

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# Monitoring of Kidney Fibrosis Changes in Patients with Chronic Heart Failure

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**Abstract:** Accession of chronic kidney disease in patients with chronic heart failure worsens the course and prognosis of the disease. And the main reason for the loss of kidney function is the changes in the proximal tubules and the associated tubulointerstitial fibrosis, which requires early diagnosis and adequate therapy.

**Key words:** cardio renal syndrome, chronic kidney disease, chronic heart failure, glomerular filtration rate.

The data of recent years indicates a steady increase in the number of patients suffering from chronic heart failure (CHF) in all countries of the world [28]. The prevalence of clinically pronounced CHF in the population remains significant, in different countries it affects from 0.4 to 2% of the population or more [29]. Among people older than 50 years, the incidence of CHF increases to 6-10% [31], and decompensation becomes the most common cause of hospitalization of elderly patients [33]. These figures convincingly indicate the obvious relevance of the issues of pathogenesis, treatment and prevention of heart failure [15]. Recently, much attention has been paid to the relationship between CHF and kidney damage within the cardiorenal continuum: the kidneys are not just a target organ for heart failure, but play a significant role in the development and progression of this syndrome [21]. It is believed that many factors associated with the development of chronic kidney disease (CKD) are also traditional cardiovascular risk factors (RF) [11]. On the other hand, non-traditional cardiovascular risk factors (anemia, chronic inflammation, oxidative stress, hyperuricemia, etc.) are associated with, and possibly caused by, progressive kidney dysfunction [5]. To date, the mechanism of CKD development in patients with CHF has not been fully studied [34]. It is believed that impaired renal function is mainly due to a decrease in cardiac output (CO) and chronic renal hypoperfusion [25]. However, there is no evidence of a relationship between a decrease in glomerular filtration rate (GFR) and left ventricular ejection fraction (LVEF). GFR in CHF patients with preserved LV systolic function has been reported to be comparable to GFR in patients with reduced LV EF [3]. The kidneys have been shown to have an amazing ability to maintain GFR: as long as the cardiac index (CI) remains above 1.5 L/min/m2, renal blood flow is maintained in patients with heart failure. Only when the SI decreases below the indicated values, does it decrease [10]. In the ESCAPE1 study, no relationship was found between most hemodynamic parameters (with the exception of right atrial pressure) measured during pulmonary artery catheterization and serum creatinine in 194 patients [17]. This

contributes to a decrease in renal blood flow, the development of ischemia and damage to the kidney tissue. Moreover, since the efferent arterioles under the influence of angiotensin II narrow more than the afferent arterioles, in the early stages of CHF, despite a decrease in renal blood flow, renal perfusion pressure and filtration fraction (FF) increase and normal GFR values \u200b\u200bare preserved (although the hyperfiltration associated with this contributes to damage to the renal filter and the development of microalbuminuria, which aggravates the violation of the functional state of the kidneys) [23,7]. With the progression of CHF, renal blood flow is significantly reduced, vasodilating nephroprotective systems are depleted, which contributes to a pronounced decrease in renal perfusion pressure, FF and, consequently, a decrease in GFR [16,1]. In addition to the vasoconstrictor action, norepinephrine, angiotensin II, endothelin and ADH, despite excess extracellular fluid, increase the retention of sodium and water by the kidneys [22]. At first, this contributes to the preservation of intravascular volume and the maintenance of renal excretory function [20], but then exacerbates cardiac dysfunction due to increased preload on the heart, as well as associated neurohumoral activation and, consequently, impairment of the functional state of the kidneys [2]. In addition to affecting renal hemodynamics and reabsorption of sodium and water, angiotensin II and aldosterone stimulate the production of transforming growth factor β by glomerular mesangial cells, which increases the synthesis of extracellular matrix components, such as biglycan, type I collagen, and fibronectin [12]. Accumulation of the glomerular matrix leads to the development of nephrosclerosis, the morphological substrate of CKD [14]. Along with a decrease in cardiac output and neurohumoral influences, the main links involved in the development of CKD in CHF are oxidative stress and activation of the inflammatory system [4]. In recent years, the presence of oxidative stress associated with an increase in the production of active oxygen radicals and a decrease in the level of antioxidants has been proven in patients with CKD [8]. It has been shown that oxidative stress promotes apoptosis and necrosis of cardiomyocytes, the development of arrhythmias, and endothelial dysfunction [19]. There is evidence that oxidative stress also develops in CHF [9]. Thus, in the myocardium of patients who had a heart attack, a decrease in antioxidant activity was found, which is closely associated with the progression of heart failure [6]. Prolonged hypoxia and a high concentration of uremic toxins have a pronounced cardiotoxic, vasotoxic and nephrotoxic effect. The nephrotoxic properties of uremic toxins are mainly due to their ability to be secreted in excess amounts in the proximal segments of the nephron and accelerate the processes of tubulointerstitial fibrosis, which is the main cause of loss of renal function. In the cells of the proximal tubules, they activate nicotinamide adenine dinucleotide phosphate (NADP(H)) oxidase and cause local oxidative stress, which, with the participation of the nuclear transcription factor NF-kappa B, induces the production of the profibrotic cytokine, TGF-β1. The latter is included in the processes of sclerotic damage to the renal tubules and their surrounding interstitial tissue. TGF-β1 is a key factor in the proliferative chain not only in the heart and blood vessels, but also in the development of nephrosclerosis, it belongs to the classical cytokines that, in the active state, stimulate the growth of cardiomyocytes and the proliferation of myofibroblasts, while simultaneously exerting an antiapoptotic effect on them. Ultimately, the development of myocardial hypertrophy, interstitial fibrosis, and a decrease in the elastic properties of the myocardium and blood vessels are associated with TGF-β1 [30]. The source of TGF-β1 in the kidneys are local macrophages, stimulation and overexpression of TGF-β1 lead to activation of the synthesis of collagen and other matrix components in the kidneys. An increase in the level of TGF-β1 in the blood of patients with CHF and an additional increase in this cytokine in the blood with the combination of CKD compared with CHF without CKD reflects the relationship of fibroplastic processes in the kidneys and regulates the process of collagenogenesis, as well as nephrosclerotic changes in the interstitial tissue of the kidneys [31]. Thus, as mentioned above, uremic toxins secreted in excess in the proximal segments of the nephron increase the concentration of TGF-β1 and accelerate the processes of tubulointerstitial fibrosis, which is the main cause of loss of renal function. T.Yamamoto et al. suggest [27] that TGF-β1 plays a role in the progression of glomerulosclerosis and interstitial fibrosis. Immunohistochemical

method showed a pronounced expression of TGF-β1 in the glomeruli of the interstitium in various forms of nephritis (IgA nephropathy, focal segmental glomerulosclerosis, nephritis with crescents and diffuse proliferative lupus nephritis), accompanied by the accumulation of fibronectin, as well as an inhibitor of plasminogen activator-1 (PAI-1 ). An increase in the amount of TGF-β1 mRNA was noted in the glomeruli, as well as in the periglomerular and tubulointerstitial areas, in places of macrophage infiltration and deposits of the endoplasmic reticulum. In the interstitium, TGF-β1 was expressed by macrophages, as well as tubular cells with peritubular mononuclear infiltration and arteries with thickened intima [35]. M.L. Nanchikeyeva, having examined a group of patients with arterial hypertension and kidney damage, determined that there is a direct correlation between the magnitude of microalbuminuria (MAU) and the level of urinary excretion of molecular mediators TGF-β11 and type IV collagen, reflecting endothelial dysfunction and associated mechanisms of fibroangiogenesis - pathophysiological Fundamentals of remodeling of the microvascular bed of the kidney in hypertensive nephropathy. Additionally, a close relationship between the level of urinary excretion of type IV collagen and the degree of increase in intrarenal vascular resistance (RI) in combination with a decrease in GFR indicates a later stage in the development of an early stage of hypertensive nephropathy [32]. In modern medicine, one of the early markers of impaired renal excretory function is cystatin C. Cystatin C is a 13 kDa protein that belongs to the family of cysteine proteinase inhibitors. It is synthesized by many cells of the body, constantly enters the bloodstream, is freely filtered in the glomeruli of the kidneys, is completely metabolized in the proximal tubules and is not secreted in them [24]. Numerous studies have confirmed the high diagnostic value of using cystatin C as a marker of renal excretory function in adult patients. [5]. The advantage of studying cystatin C as an earlier marker of kidney damage (even if insignificant) compared to creatinine is due to the small dependence of its plasma level on muscle mass, gender and age (except for children under 1 year old), as well as the virtual absence of tubular reabsorption and secretion. The clinical sensitivity of the determination of cystatin C in relation to kidney damage is 86%, the specificity is 82% [25]. Recent studies have highlighted the important role of the renal tubules in the development and progression of CKD. Regardless of the underlying disease and the presence of aggravating conditions, the pathogenic mechanisms that cause progressive kidney injury are reduced to tubulointerstitial diseases characterized by tubular atrophy and hypoxia, damage to peritubular capillaries, and interstitial fibrosis, ultimately explaining the irreversible development of chronic uremia. [fourteen]. In line with this view, it is now widely accepted that the degree of decline in kidney function in CKD is related to the degree of tubulointerstitial involvement rather than the severity of glomerular involvement. Indeed, some tubular proteins are used in a certain way in the study of the pathogenesis of tubular damage and the transition to chronic fibrosis, which leads to uremia [18]. An indicator of dysfunction of the proximal tubules is β2 microglobulin (β2-MG). It is a protein with a molecular weight of 12 kDa, considered part of the light chain of membrane-bound HLA antigens. The small size allows β2-MG to pass through the glomerular membrane, after which it is almost completely absorbed in the proximal tubules. With glomerular pathology, the filtration rate of β2-MG slows down, so its concentration increases in the blood and decreases in the urine. When the tubules are damaged, the amount of reabsorbed β2-MG decreases, so its level in the urine rises and in the blood falls. The sensitivity of the analysis of urinary β2-microglobulin is 83%, the specificity is 80% [13]. Thus, the above literature data show that the addition of CKD in patients with CHF worsens the course and prognosis of the disease. And the main reason for the loss of kidney function is changes in the proximal tubules and the associated tubulointerstitial fibrosis, which is poorly understood, requires early diagnosis and adequate therapy

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