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MECHANISM OF DEVELOPMENT AND DIAGNOSTIC MARKERS OF NEPHROPATHY IN ARTERIAL HYPERTENSION

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Abstract. Hypertension is an epidemic in our society and is the most common cardiovascular disease. So, many studies have shown a link between the severity and duration of hypertension and the frequency of development of CKD. At the same time, joining CKD leads to poor level control blood pressure (BP) and patient prognosis of arterial hypertension. Therefore, early detection of kidney damage is an urgent problem, the solution of which is complicated by the asymptomatic course of the initial stages of kidney damage, which essentially makes timely diagnosis difficult. Microalbuminuria (MAU) is a marker of kidney damage and the risk of cardiovascular complications. Increasing MAU has now acquired the value of an integral marker of poor prognosis since it reflects a generalized dysfunction of the endothelium, which causes damage to target organs (myocardium, vascular wall, kidney) and is observed even with a slight increase in urinary albumin excretion ("low-value albuminuria").

Keywords: arterial hypertension, chronic kidney disease, nephropathy, microalbuminuria

Inroduction. Arterial hypertension (AH) retains its leading position among the causes of terminal stages of chronic kidney disease (CKD). Microalbuminuria (MAU) is a marker of kidney damage and the risk of cardiovascular complications. Diagnostic significance established determining the indicator of functional renal reserve [39, 40]. During treatment difficult-to-control hypertension in patients with end-stage chronic renal failure acquire a diagnostic the value of magnetic resonance imaging and spiral computed tomography [41,46,54]. Dopplerographic study of intraparenchymal blood flow using an orthostatic test is successfully used for early diagnosis of structural and functional changes in renal vessels in arterial hypertension [42,47,53]. For the purpose of differential diagnosis of functional and organic changes in the renal arteries in arterial hypertension, myogenic stress testing is used, which gives an idea of speed indicators of blood flow and indicesperipheral resistance [43,48].

The level of creatinine (Cr) in the blood, followed by general assessment of glomerular filtration rate (GFR), as well as albuminuria - the most common markers used to assess kidney function. However, they mostly reflect damage glomerular

apparatus, which often occurs at later stages and indicates far advanced and mostly irreversible kidney damage [1–3,48,51].

Over the past few years there have been proposed a variety of early specific biomarkers of kidney damage, reflecting predominantly tubulointerstitial changes in renal tissue. These markers are recommended to improve diagnosis in the early stages of acute, including ischemic, kidney damage in numerous studies [4–6,48,50].

In addition, the determination of the above biomarkers in urine and blood is also used as additional diagnostic and prognostic criteria in patients with CKD of various etiology [7–10], including proportionally the severity of the lesion [11, 12]. Most Interest among the proposed biomarkers are cystatin C, NGAL (neutrophil gelatinase-associated lipocalin) - lipocalin associated with neutrophil gelatinase or Lipocalin-2, KIM-1(kidney injury molecule‑1) damage, L‑FABP (L‑type fatty acid binding protein) - the liver form of a protein that binds fatty acid.

Cystatin-S is an endogenous protein that has a lower molecular weight than creatinine, is produced by all nuclear cells in the body, is filtered through the glomeruli without obstruction, is completely excreted by the kidneys, and is not secreted in the proximal tubules. The listed properties were the basis for the use of cystatin-S in determining the filtration rate of the balls. In addition, its concentration is almost independent of the patient's age, sex, and muscle mass. For this reason, KDIGO experts have recommended the use of cystatin-S in the early stages of chronic kidney disease with a high risk of nephropathy [13, 14, 52].

The formula recommended by Houka (HocK) is widely used to determine the filtration rate of balls using the concentration of cystatin-S in the blood. Observations in 4,500 patients with diabetes mellitus confirmed that cystatin-C was more accurate in determining the rate of glomerular filtration rate than creatinine. Based on it, the authors noted a high reliability of creatinine with cycatin-C preclinical course, which sometimes lasts 10-20 years, and only then allows the detection of chronic kidney disease.

One important reason to estimate GFR in a patient is to decide whether the patient suffers from chronic kidney disease or not, and to classify the degree of the chronic kidney disease, if present. [15-18].

Based on a meta-analysis involving 90,000 patients, cystatin-S in the urine was shown to be a marker of impaired reabsorption in the renal proximal tubules, and in most cases was reported to be a sign of tubular dysfunction observed before microalbuminuria. However, when detecting cystatin-C in the blood and using it to calculate the rate of glomerular filtration, it is necessary to take into account obesity (fatty tissue increases it in the blood), thyroid dysfunction, patients receiving glucocorticoids or antibodies to this cellular protein. [19,44].

Nephrin, transmembrane protein of podocytes with m.m.160 kDA, a product of the NPHS1 gene, is the main structural protein of the slit filtration diaphragm and belongs to the adhesive proteins of the immunoglobulin superfamily [20,21]. The study of the structure of the nephrin and its location in the diaphragm of the podocyte legs led to the assumption that homophilic interactions result in the formation of a diaphragm hole as a result of the merging of two opposite podocyte legs. [22,23].

The observation of proteinuria in experiments in which monoclonal antinephrine antibodies were administered to rats also confirms the importance of nephrin in ball filtration. In Finnish-type congenital nephrotic syndrome, an NPHSI gene mutation was detected in response to proteinuria. This confirms that the nephrin glomeruli are part of the diaphragm hole involved in the filtration barrier. [24,25].
In addition, nephrin is involved in cell signal transmission. The nephrin in the diaphragm hole between the legs of the podocyte and the protein hole adjacent to them form an important functional complex by connecting the cytoskeleton with the actin part. [23-24].

Disruption of the architecture of the nephrin and the protein complex associated with it causes a similar change in podocytes. In this case, the podocyte legs are smoothed and proteinuria occurs [26-27].

Intensive expression of nephrin was detected in the early stages of diabetic nephropathy. However, in its later stages, nephrinuria decreases, but this is associated with impaired podocyte function. The level of nephrinuria can be reduced by blocking the renin-angiotensin system. Based on this, it is assumed that the effect of these drug groups occurs through nephrin [28,45].

The mechanisms of nephrin and its excretion in the urine, as well as the changes noted in podocytes, have been studied more extensively in diabetes mellitus. It is also important to detect these changes in hypertensive nephropathy. Because, as noted above, nephrinuria is a marker of nephropathy observed long before microalbuminuria. Thus, the detection of nephrinuria allows for early diagnosis of nephropathy, including its advanced form in hypertension. In addition, a comparative study of microalbuminuria and nephrinuria in hypertension will help determine the role of each of them in the development of nephropathy in this disease.

In recent years, the study of markers of endothelial dysfunction has included other parameters, including fibrinogenesis. It was It has been shown that in patients with essential hypertension I−III degrees according to the classification of the Russian medical society for hypertension when compared with normotensive representatives control group had a significant increased urinary excretion of transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), plasminogen activator inhibitor type 1 (PAI-1) and type IV collagen. Increase content

in urine TGF-β, VEGF and PAI-1 can be considered as an early sign of hypertensive kidney damage, an increase in urinary excretion of type IV collagen is associated with microalbuminemia and testifies in favor of activation processes of renal fibrogenesis. [30,31,32].

Hyperuricemia contributes to the progression of endothelial dysfunction [33, 34]. The formation of hypertensive nephropathy is based on endothelial dysfunction and remodeling of intrarenal vessels [35].

Increased pulse pressure is as a risk factor for target organ damage in patients with hypertension. Along with the development of the kidney dysfunction in the form of a decrease in glomerular filtration clearance, left ventricular hypertrophy, increased stiffness of the aorta and peripheral arteries develop in parallel [36].

Significant similarities are highlighted morphological changes in the heart and kidneys during the development of cardiovascular accidents and the renal continuum. A decrease in glomerular filtration in patients with essential hypertension is associated with a significant increase in the incidence of complications of coronary heart disease, atrial fibrillation, as well as diabetic and urate nephropathies , coronary kidney disease [37].

Hypertensive nephropathy is a consequence of a disruption in the functioning of the renal hemodynamic mechanisms that protect the glomeruli from the damaging effect of increased blood pressure (BP). As a result two fundamentally different pathological processes develop in the kidneys – ischemic and hypertrophic damage to the glomeruli, which lead to the formation of focal segmental glomerulosclerosis and increasing loss of kidney function. The reason for the first of which is an excess autoregulatory reaction complicated by obstructive hyalinosis of the afferent arterioles, ischemic damage to the glomeruli, and loss of part functioning nephrons. At the same time with ischemic damage to the kidneys in the remaining nephrons, a compensatory by its nature, the phenomenon of hyperfiltration, leading to loss of renal autoregulation and persistent glomerular hypertension. As a result of these hemodynamic disturbances, hypertrophic (proliferative) glomerulosclerosis develops in the kidneys. The key role is played by the hyperactivity of the cellular renin-angiotensin system of podocytes, which is accompanied by excessive production of TGF-β1, VEGF and PDGF, causing profibrotic structural and functional rearrangement of podocytes and mesangial glomerular cells [38].

For a long period of time, the only variant of kidney damage in arterial hypertension (AH) was considered hypertensive nephroangiosclerosis (damage mainly to the glomerular apparatus of the kidneys in AH). to the development of hypertension nephroangiosclerosis is also predisposed by concomitant hypertension, type 2 diabetes mellitus (DM), hyperuricemia, atherosclerotic stenosis of the renal

artery (ischemic kidney disease), embolization of the renal artery with cholesterol crystals, in which chronic renal failure increases. Thus, the concept of "kidney damage in hypertension", or hypertensive nephropathy, combines several nosological forms:

1. Classical hypertensive nephroangiosclerosis (often in combination with concomitant chronic urate tubulointerstitial nephritis and / or urate nephrolithiasis, diabetic nephropathy).

2. Atherosclerotic stenosis of the renal artery - ischemic kidney disease and / or cholesterol embolism of the intrarenal vessels.

Let us consider these nosological forms in more detail.

Hypertensive nephroangiosclerosis is a lesion mainly the glomerular apparatus of the kidneys in hypertension. Tubulointerstitial nephropathy is a primary lesion of the tubules and interstitial tissue of the kidneys due to immuno-inflammatory (autoimmune diseases), toxic (infections) and metabolic (impaired calcium, potassium, uric acid metabolism - urate nephrolithiasis) diseases. Diabetic nephropathy is kidney damage in diabetes mellitus, the morphological basis of which is nephroangiosclerosis of the renal glomeruli. Ischemic kidney disease is atherosclerotic stenosis of the renal arteries. Ischemic kidney disease occurs predominantly in patients with widespread and often complicated atherosclerosis. Cholesterol embolism of the intrarenal vessels is a special variant of ischemic kidney disease, characterized by embolism of the intrarenal arteries by cholesterol crystals, the source of which is an atherosclerotic plaque localized in the abdominal aorta or in the main renal arteries.

The pathogenesis of hypertensive nephroangiosclerosis and ischemic kidney disease. A key determinant of deterioration in kidney function is an increase in cystolic blood pressure. With hypertensive In nephroangiosclerosis, damage to glomerular endotheliocytes is considered the primary link, which occurs as follows. With an increase in systolic blood pressure, activation of the sympathoadrenal and renin-angiotensin-aldosterone systems, constriction of the afferent glomerular artery occurs with a decrease in effective renal blood flow and the formation of angiotensin - AII (leading factor), which causes spasm of the efferent glomerular artery and contributes to the development of intraglomerular hypertension, followed by hyperfiltration and increased protein permeability. In the future, hyperfiltration is aggravated, blood flow to the glomerular capillaries decreases, which is accompanied by the development of glomerular ischemia, long-term existence which leads to apoptosis of endotheliocytes and ultimately determines the development of nephroangiosclerosis.

Currently, hypertension is very often combined with other risk factors (RFs) for cardiovascular diseases: obesity, hyperuricemia, dyslipidemia, i.e. metabolic syndrome (MS), insulin resistance (IR) and type 2 diabetes mellitus (DM). Thus, an excess of insulin in the blood stimulates the proliferation of smooth muscle cells (SMC) of vessels, mesangial cells and renal tubulointerstitium, inducing the processes of local renal fibrogenesis. In addition, glycosylation end products cause the development the phenomenon of persistent hyperfiltration - a fundamental component of the pathogenesis of diabetic kidney damage.

The consequence of impaired uric acid metabolism is urate nephrolithiasis and chronic tubulointerstitial nephritis (uric acid and its salts lead to tubulointerstitial fibrosis), which are formed already at the stage of hyperuria.

Thus, urate dysmetabolism, almost always associated with high blood pressure (BP), leads to urate nephropathy. In obesity, the phenomenon of persistent hyperfiltration is well known. But the "nephrotoxic" hormone of adipose tissue, leptin, is still of decisive importance, as well as the transforming growth factor ß-factor (TGF-ß) and interleukin-6 produced by adipocytes.

As one of the likely mechanisms of kidney damage in AH, there may be a genetically determined insufficiency in the formation of endothelial vasodilators (primarily nitric oxide) in the renal microcirculatory system.

Major Progression Factors kidney damage:

• systemic hypertension;
• intraglomerular hypertension;
• proteinuria;
•increased intake of protein from food;
• tubulointerstitial fibrosis (nephrosclerosis);
• hyperlipidemia;
• hyperglycemia.

Ischemic kidney disease develops with atherosclerosis sclerotic stenosis of the renal artery and is determined by global hypoperfusion of the kidney tissue. In response to a decrease in the volume of blood entering the renal tissue, hyperactivation of the RAAS is observed, which makes it possible to keep the glomerular filtration rate (GFR) relatively constant. Most the renal tubulointerstitium is ischemic. As hypoperfusion increases, atrophy of the tubulointerstitium and its fibrosis increase. Complete obliteration of the renal artery accompanied by atrophy of the corresponding kidney. Intrarenal artery embolism is considered a special variant of ischemic kidney disease. cholesterol crystals, the source of which is an atherosclerotic plaque. Simultaneous massive embolism with cholesterol crystals of intrarenal vessels leads to a sharp ischemia of the renal tissue and acute renal failure,

accompanied by an intractable rise in blood pressure. If the embolism grows slowly (chronic variant), then cholesterol crystals injure the vessel wall, enter the renal tubulointerstitium, activate complement components and cause eosinophilic tubulointerstitial nephritis [29].

Conclusion. From the above literature, one can conclusion that cardiovascular and renal continuums develop in parallel and in close interconnection. Early markers of engagement hearts correlate with the initial manifestations of kidney involvement. The onset and progression of changes in the heart and kidneys during largely due to similar hemodynamic, neurohumoral and genetic mechanisms. In addition, there is a certain selectivity of target organ damage, the causes of which require further study. However, practitioners should take into account the fact of early development of nephropathy in cardiovascular disease, especially AH. It is necessary to remember the existence of an early marker of this process in the form of microalbuminuria, which is currently performed by all laboratories in polyclinics. In the initial stages, nephropathy is reversible, if appropriate drug treatment is carried out in time as a secondary prevention of hypertensive nephroangiosclerosis with the subsequent development of chronic renal failure; the drug of choice will be an angiotensin-converting enzyme inhibitor, and mandatory control of MAU is necessary. To assess the effectiveness of the treatment of hypertension with target organ damage, the restoration of endothelial dysfunction at the level of the microcirculatory bed should be monitored, for which it is necessary to use the vascular adaptation index, which acts as an integral indicator of both neurohormonal and metabolic responses to various stressful effects. In the absence of normalization of microcirculatory parameters, the risk of complications remains high and requires active work in a group of such patients.

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