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THE SIGNIFICANCE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF CHRONIC KIDNEY DISEASES

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Abstract: it is known that early manifestation of endothelial dysfunction has prognostic significance and is being studied by many foreign and local researchers, including that it occupies one of the leading positions in the structure of morbidity in patients with kidney pathology.
The article presents reasonable opinions about the importance of endothelial dysfunction in the development of chronic kidney diseases.
Key words: endothelial dysfunction, chronic kidney disease, renal nephrosclerosis, chronic pyelonephritis, dyslipoproteinemia, cytokine, proteinuria, atrophy, tubulo-interstitial kidney pathology.

Introduction

Recent studies have significantly changed the understanding of the role of the vascular endothelium in general homeostasis. Endothelial dysfunction (ED) is a central link in the pathogenesis of chronic diseases such as atherosclerosis, hypertension, diabetes mellitus, chronic kidney disease (CKD), and others. At the same time, endothelial dysfunction is systemic in nature and occurs not only in large vessels, but also in the microcirculation [1].
Nephrosclerosis [Greek nephros - kidney, sklerosis - compaction] - hardening and “curling” of the kidney as a result of its covering with connective tissue. It is observed in hypertension, pyelonephritis, renal tuberculosis, glomerulonephritis, kidney stones (nephrolithiasis), and others. In nephrosclerosis, mainly the small arteries (arterioles) of the kidney are damaged, they twist and break, as a result, the kidney epithelium dies.
It is now clear that the vascular endothelium is an active metabolic system that supports vascular homeostasis. It modulates vascular tone by performing a number of important functions, including the transport of solutes into the cells of the vascular wall, cell growth, formation of the extracellular matrix, protection of the vessels from adverse effects, regulation of chemotactic, inflammatory and reparative processes in the vessels, and response to local stimuli [2].
Endothelial dysfunction is one of the most important links in the development of interstitial inflammation and fibrosis in progressive forms of kidney damage [3].
Endothelial dysfunction is understood as an imbalance between the production of vasodilator, athrombophilic, and antiproliferative factors, on the one hand, and vasoconstrictor, prothrombotic, and proliferative substances produced by the endothelium, on the other.
There are four forms of endothelial dysfunction:

- vasomotor;
- thrombophilic;
- adhesive;
- angiogenic.

Endothelial dysfunction can be caused by various factors: tissue hypoxia, age-related changes, free radical damage, dyslipoproteinemia, cytokines, hyperhomocysteinemia, hyperglycemia, hypertension, exogenous and endogenous intoxications [4].

Endothelial dysfunction can lead to structural damage in the body: accelerated apoptosis, necrosis, desquamation of endothelial cells. However, functional changes in the endothelium usually precede morphological changes in the blood vessel wall [5].
Endothelial dysfunction may have prognostic significance due to its early manifestation. Currently, this pathology is being studied by many foreign and domestic authors, including in patients with kidney pathology, where it occupies one of the leading places in the pathogenesis of the disease.
In recent decades, there has been an increase in the number of patients with chronic kidney disease, even against the background of congenital pathology of the urinary system. The increase in the number of diseases is explained by the general deterioration of the environment, as well as by the improvement of disease diagnostics [6].
The urgency of the problem increases with the development of the final stage of kidney disease - kidney disease and its resulting disability, taking into account the high risk of developing progressive forms of chronic kidney disease.
In this regard, special attention is paid to the problem of early diagnosis of progressive kidney disease, detection of latent nephrological diseases.
Early detection of kidney disease can slow the development of nephropathy and, in some cases, even prevent the loss of kidney function. At the same time, late diagnosis of nephropathy is directly related to a high mortality rate [7].
Markers of ED include endothelin-1, von Willebrand factor, plasminogen activator inhibitor-1, decreased endothelial synthesis of nitric oxide, soluble fraction of blood vessel cell adhesion molecule-1, homocysteine, thrombomodulin, and the appearance of microalbuminuria. An integral sign of cardiorenal relationships is microalbuminuria (MAU). The main mechanism of albumin excretion into the urine is direct damage to the vascular endothelium.
As a result, the glomerular barrier becomes permeable to the dispersed (highly selective) fraction of albumin - a protein [8].
Given that the kidneys are the most arteriole-rich organ in the body, systemic endothelial damage manifests itself in the form of albuminuria. Therefore, the presence of microalbuminuria is usually associated with signs of endothelial dysfunction as a result of endothelium-dependent dilation of the arteries. There is also a direct relationship between the presence and development of arterial hypertension and microalbuminuria. A level of microalbuminuria of at least 4.8 μg/min is considered a cardiovascular risk [9].
Therefore, a gradation is currently proposed for optimal microalbuminuria (less than 10 mg per day), normomicroalbuminuria (10-20 mg per day) and usually elevated microalbuminuria (20-30 mg per day).
Thus, the main mechanisms of microalbuminuria in glomerular hyperfiltration and vascular endothelial damage (endothelial dysfunction) have now been identified.
Oxidative stress is one of the most studied mechanisms of endothelial dysfunction. Oxidative stress is characterized as a disturbance of the balance between excessive production of free radicals and a deficiency of antioxidant defense mechanisms. Oxidative stress is of great importance, as it is associated with the development of endothelium-dependent vasodilation. The involvement of free radicals in the inactivation of nitric oxide and the development of endothelial dysfunction has been proven [10].
According to foreign studies, a connection between oxidative stress and signs of endothelial dysfunction has been established. The second important link in the chain of mechanisms leading to nitric oxide deficiency and the development of endothelial dysfunction in renal pathology is arginine deficiency.
Studies of the role of endothelin-1 have shown that this is the only isoform found in endothelial cells of the aorta, endothelin-1 is also present in other organs, including the brain, heart, lungs, and kidneys. Previously, it was believed that endothelin-1 is synthesized only by endothelial cells.

It has been proven that renal epithelial cells, mesangial cells, leukocytes, macrophages, cardiomyocytes, and smooth muscle cells have this ability.

It is known that the level of proteinuria is more closely related to the rate of progression of the disease to renal failure than other clinical and laboratory parameters. Increased protein filtration through glomerular capillaries has a toxic effect due to the expression of a number of vasoactive and inflammatory molecules with an inflammatory phenotype, including endocytosis by proximal tubular cells that activate endothelin-1 transcription. Pharmacological reduction of proteinuria (by ACE inhibitors) led to normalization of renal endothelin-1 content.

However, endothelin receptor antagonists, which consistently reduce renal endothelin-1 damage, did not always reduce the development of proteinuria. The above supports the hypothesis that increased endothelin-1 levels are not the cause, but the result of a specific loss of protein. Also, ED is of great importance among the mechanisms of development of renal fibrosis and glomerulonephritis. It has been proven that renal arteries are distinguished by high sensitivity to endothelin-1. The effect of endothelin-1 on the development and progression of renal fibrosis has been established [11].

Hyperhomocysteinemia - homocysteine contributes to the formation and strengthening of nephrosclerosis. At the same time, three mechanisms of molecular dysregulation are distinguished: the first of them leads to a decrease in the content of compounds that cause endothelial dysfunction (NO, prostaglandin E_2, adenosine) and, at the same time, an increase in the production of thromboxane A_2, which causes vasoconstriction, contributes to a decrease in the lumen of the afferent and efferent arterioles, leads to a decrease in renal blood flow and provokes renal ischemia, which increases nephrosclerosis. There are studies that prove that homocysteine, even in low concentrations, clearly shows cytotoxic activity against the endothelium, is able to inhibit the activity of cyclooxygenase in its cells, as a result of which the production of prostacyclin decreases.

At the same time, with increased platelet aggregation, the formation of thromboxane A_2 increases, the activity of natural anticoagulants and tissue plasminogen activator decreases, which contributes to the formation of fibrosis.

Literature data indicate that currently cystatin C can be considered not only as a sufficient indicator of the state of renal function, but also as a possible biomarker of inflammation and endothelial dysfunction. According to research data, a significant increase in the level of cystatin C was found in patients with reduced renal filtration function.

The structure of the cystatin C gene and the high stability of the biosynthesis of the cysteine protease inhibitor determine the high stability of cystatin C. Due to these circumstances, the production of cystatin C does not depend on inflammation, tumor growth, age, sex, muscle mass and the level of hydration of the body. When the kidneys are involved in the pathological process, the filtration of cystatin C in the kidneys deteriorates, which leads to an increase in its content in the blood.

This protein has the following properties:

- is synthesized at a constant rate by all cells of the body that contain a nucleus;
- is freely filtered through the glomerular membrane;
- is completely metabolized in the kidneys;
- is not secreted by the proximal renal tubules.

All these properties suggest that cystatin may be a marker of CRF. Studies in hemodialysis patients have shown that their cystatin C levels are 13 times higher than in healthy patients [12].

Thus, cystatin C is a reliable indicator of renal function. It is more sensitive than creatinine to a decrease in CRF and serves as an effective marker for early detection of renal failure even with normal creatinine levels.

Lipocalin-2 is a secretory glycoprotein that is synthesized in small quantities in various tissues and organs, including the kidneys. In kidneys, lipocalin-2 gene is functionally activated only after harmful effects such as ischemia, nephrotoxins.

Although recent studies have shown that lipocalin-2 may be a sensitive biomarker of acute kidney injury, its role in chronic kidney disease is still poorly understood. Only recently have literature data emerged that suggest that it is a marker of the development and progression of kidney disease. In response to kidney injury, plasma and urinary NGAL levels increase dramatically.

Conclusion

Thus, in chronic diseases, when exposed to long-term damaging factors (hypoxia, toxins, immune complexes, inflammatory mediators, hemodynamics, etc.), endothelial cell activation and damage occur, resulting in pathological responses to the usual warning signs of vasoconstriction, thrombosis, and increased cell proliferation.

Adverse changes in the rheological properties of blood and vascular endothelium, capillary-trophic insufficiency, ischemia of renal tissue and ultimately nephron damage contribute to the development of glomerular and tubointerstitial fibrosis.

The longer the pathological response to irritating stimuli persists, the faster and more naturally the process becomes chronic and irreversible.

To date, there is a lack of scientific literature on the clinical and pathogenetic role of endothelial dysfunction in patients with tubulointerstitial kidney disease (TIRD). Optimization of diagnostics is a promising approach for predicting tubulointerstitial kidney disease. Endothelial dysfunction develops long before the appearance of structural changes in the kidney and is a leading pathogenetic factor in the formation of nephrosclerosis, which can be determined by assessing the clinical significance of endothelial dysfunction indicators.

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