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THE IMPORTANCE OF DETERMINING THE STATUS OF VASCULAR ENDOTHELIUM IN THE DEVELOPMENT OF GLOMERULARY AND TUBULOINTERSTITIAL FIBROSIS

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Abstract: The article presents the results of a study to determine the prognostic significance of markers for predicting the degree of damage to renal structures at the stages of treatment of patients with nephrosclerosis on the background of chronic pyelonephritis.

Keywords: Endothelial dysfunction, apoptosis, endothelin-1, plasminogen activator inhibitor - PAI-1, von Willebrand factor, fibrinolysis, endothelial cell desquamation, hypercoagulation.

Introduction

Recent studies have significantly changed the understanding of the role of the vascular endothelium in overall homeostasis. Endothelial dysfunction is a central link in the pathogenesis of chronic diseases such as atherosclerosis, hypertension, diabetes mellitus, chronic kidney disease, etc.

At the same time, endothelial dysfunction is systemic in nature and occurs not only in large vessels, but also in the microcirculatory system. Endothelial dysfunction is one of the most important links in the development of interstitial inflammation and fibrosis in progressive forms of kidney damage.

Endothelial dysfunction can lead to structural damage in the body: accelerated apoptosis, necrosis, desquamation of endotheliocytes. Endothelial dysfunction is considered to have prognostic value due to its early manifestation. Early detection of the disease allows to slow down the progression of nephrosclerosis and in some cases even prevent the loss of kidney function [1].

Endothelin-1 is a 21-amino acid peptide that is the most potent vasoconstrictor known, more potent and long-lasting than angiotensin-2. Studies of the role of endothelin-1 have shown that it is the only isoform found in aortic endothelial cells, and it is also present in other organs, including the brain, heart, lungs, and kidneys. [2].

Previously, it was believed that endothelial-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. Its synthesis is regulated in an

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autocrine manner. The synthesis of endothelin-1 is controlled by physicochemical factors such as vascular pulsatility, blood pressure, pH, and hypoxia.

There are several types of cells in the kidneys that produce endothelin, including endothelial cells, mesangiocytes, and epithelial cells that support its cumulative production.

Endothelial activation and injury are important in the development of a wide range of pathological conditions. It is clear that assessing the state of endothelial cells will be of great clinical importance for expanding the possibilities of diagnosing the activity of the immune-inflammatory process and predicting the development of complications [2].

Recent studies have shown the importance of changes in the functional activity of leukocyte cells, the structure and function of their membranes in the pathogenesis of nephrosclerosis, their changes can affect endothelial function, the rheological properties of blood, the hemostasis system, perfusion processes, and hematopoietic metabolism, which is important in determining the severity of the disease [3].

At the same time, although there are many studies that reveal various aspects of this problem in chronic kidney disease, in our opinion, the role of local and endothelial mechanisms of inflammation in renal nephrosclerosis in patients with chronic pyelonephritis has not been comprehensively and multistagely studied. It is known that the level of proteinuria is more closely related to the dynamics of the level of endothelin-1 than to other clinical and laboratory parameters.

The observation of an increased concentration of endothelin-1 in the blood of patients with renal nephrosclerosis, especially when this pathology is accompanied by chronic pyelonephritis, is a consequence of the loss of protein from the body. Therefore, the obtained materials on the dynamics of endothelin-1 in the blood indicate one of the mechanisms of the development of renal fibrosis in chronic pyelonephritis [4].

Activated endothelium leads to a violation of antithrombotic potential and, as a result, participates in the coagulation and fibrinolysis processes. When the integrity of the vascular endothelium is impaired, platelet adhesion and aggregation at the site of injury are impaired, leading to the development of thrombosis. The long-term effect of endothelial activation on the procoagulant system is mediated by the activation of plasminogen and its endogenous inhibitor in the blood (plasminogen activator inhibitor - PAI-1), as well as von Willebrand factor.

The results show that the level of PAI-1 in patients with nephrosclerosis due to chronic pyelonephritis was significantly increased compared to the control group (Table 2).

Table 2

Description of endothelial dysfunction indicators in patients with nephrosclerosis due to chronic pyelonephritis

		Patients with chronic pyelonephritis without	**Patients with nephrosclerosis**

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Indicators	Healthy individuals, n=24	nephrosclerosis, n = 40	due to chronic pyelonephritis, n = 38
Endotelin - 1, pg/ml	33,72±2,78	54,89±5,21*	132,64±9,73*
t-PA, ng/ml	5,51±0,47	4,02±0,34*	3,38±0,27*
PAI-1, ng/ml	4,78±0,37	5,67±0,43*	8,89±0,74*
Willebrand factor, %	108,34±19,38	136,23±11,03*	188,51±16,24*
Antitrombin III, %	90,12±7,67	81,43±7,89*	61,54±5,37*

Note: * - P<0.05 is significant compared to healthy individuals.

Similar results were observed for t-PA (tissue plasminogen inhibitor) and were found to be 52% higher than in healthy subjects. At the same time, the level of antithrombin III was significantly reduced compared to healthy subjects.

Since the vascular endothelium is a source of synthesis of not only anticoagulant factors, but also fibrinolysis factors (plasmin system), a decrease in the concentration of tissue plasminogen activator and activation of its activator inhibitor in patients with renal nephrosclerosis due to chronic pyelonephritis indicates not only endothelial dysfunction, but also disorders in the fibrinolytic pathway.

The results show that the mechanisms resulting from the synthesis and degradation of the main elements of the extracellular matrix and the insufficiency of fibrinolysis play an important role in the development of renal fibrosis, which, among other factors, is regulated by the plasminogen activator inhibitor [5].

Activation of PAI-1 indicates increased fibrin clot formation in response to glomerular endothelial cell injury.

Increased plasma PAI-1 levels have been shown in many studies in patients with hemolytic uremic syndrome, and the degree of this increase is associated with the outcome of the disease.

Endothelial dysfunction is known to be one of the most important links in the development of interstitial inflammation and fibrosis in progressive forms of kidney damage. Endothelial dysfunction leads to structural damage in the body, namely, accelerated apoptosis, necrosis, and desquamation of endothelial cells.

The increased concentration of endothelin-1 in the blood of patients with renal nephrosclerosis is a consequence of the loss of the protein. Therefore, the results obtained on the dynamics of endothelin-1 in the blood indicate one of the mechanisms of the development of renal fibrosis on the background of chronic pyelonephritis. It is known that plasminogen activator inhibitor regulates cell adhesion and migration and plays an important role in inflammation, wound healing, angiogenesis and metastasis of tumor cells.

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When damaged or activated, the endothelium can change its antithrombotic potential to prothrombotic, its ability to adequately participate in coagulation and fibrinolysis is impaired [6].

In endothelial cell damage, the prothrombotic potential is provided by the secretion of von Willebrand factor, tissue factor, and tissue plasminogen activator inhibitor. The procoagulant effect of endothelial activation can be measured by changing the balance of tissue plasminogen activator and its endogenous inhibitor in the blood, as well as von Willebrand factor.

As can be seen from the results of the study, we can see that PAI-1 levels are significantly increased in patients with renal nephrosclerosis on the background of chronic pyelonephritis compared to those in the comparison group.

Conclusion

In our studies, a significant decrease in the level of antithrombin III was noted. Since the vascular endothelium is the site of synthesis of not only anticoagulant factors, but also fibrinolysis factors (plasmin system), a decrease in the concentration of tissue plasminogen activator and activation of its activator inhibitor in patients with renal nephrosclerosis on the background of chronic pyelonephritis indicates not only endothelial dysfunction, but also fibrinolytic disorders.

In turn, activation of PAI-1 indicates increased fibrin thrombus formation in response to damage to glomerular endothelial cells.

Based on the results obtained, it can be said that in nephrosclerosis, which develops on the basis of chronic pyelonephritis, activation and damage of endothelial cells occur, as a result of which pathological responses occur in the form of vasoconstriction, thrombosis, hypercoagulation with intravascular fibrinogen deposition, and impaired microrheology.

Changes in the rheological properties of blood contribute to a decrease in adaptation in nephrons with damage and detachment of the vascular endothelium, and then the development of glomerular and tubulointerstitial fibrosis.

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