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MONOCYTIC CHEMOTACTIC PROTEIN-1 AND TRANSFORMING GROWTH IN PATIENTS WITH NEPHROSCLEROSIS ON THE BACKGROUND OF CHRONIC PYELONEPHRITIS

RESULTS OF TESTING FACTOR-β1 URINARY EXCRETION

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Abstract: Studies have confirmed the importance of renal nephrosclerosis as a pathomorphological basis of renal failure, in which proteinuria plays an important role in chronic pyelonephritis. In this case, the nephrotoxic effect of proteinuria is carried out through interstitial inflammation, which ends with the development of nephrosclerosis of the kidneys.

In addition, the processes of accumulation of extracellular matrix components, as well as apoptosis of cells of kidney tubules develop, which lead to atrophy of tubules, expansion of interstitial volume, loss of peritubular capillaries.

Key words: monocyte chemotactic protein-1, transforming growth factor-β1, chemokine, matrix components, informative non-invasive method, profibrogenic cytokines, proteinuria, creatinine, interstitial fibrosis, nephrosclerosis, nephroprotective strategy.

Relevance. The central link of the mechanism of interstitial inflammation is the activation of the epithelial cells of the kidney tubules under the influence of the harmful components of the proteinuria process with the production of molecular mediators of inflammation, as well as monocytic chemotactic protein-1 (MCP-1), as well as the transformation of the transforming growth factor - β1 (TGF-β1), the formation of renal nephrosclerosis and provides paracrine-autocrine regulation of developmental processes [1].

The effect of the above markers is related to changes in intercellular matrix exchange. By activating the synthesis of collagen and other matrix components (fibronectin, laminin), TGF-β1 contributes to the development of glomerular hypertrophy, thickening of basement membranes, and increased nephrosclerosis of the kidneys in patients with chronic pyelonephritis.

In addition, TGF-β1 accelerates the development of interstitial fibrosis by stimulating matrix synthesis by ductal epithelial cells and interstitial fibroblasts.

The profibrogenic properties of TGF-β1 are enhanced by its stimulating effect on the synthesis of connective tissue growth factor, which has similar effects to TGF-β1. Another mechanism of profibrogenic effect of TGF-β1 is inhibition of synthesis of matrix metalloproteinases - enzymes that break down the intercellular matrix [2].

TGF-β1 is a multifunctional cytokine that was first isolated from platelets in 2009 and

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studied in vitro to stimulate cell growth and induce cell transformation. TGF-β1 is an important regulator of proliferation, cell differentiation, apoptosis, inflammation, immune response, and extracellular matrix remodeling.

Materials and methods. A number of researchers believe that TGF-β1 plays a role in the development of glomerulosclerosis and interstitial fibrosis. Using the immunohistochemical method, clear expression of TGF-β1 in glomeruli and interstitium is observed in various forms of nephritis, fibronectin inhibitor-1, as well as accumulation of fibronectin-1. Also, an increase in the amount of TGF-β1 mRNK is noted in the periglomerular and tubulointerstitial areas, in the areas of macrophage infiltration and in the endoplasmic reticulum [3].

A number of studies indicate the informative value of urinary excretion of MCP-1 and TGF-β1 for monitoring renal fibrogenesis in patients with renal nephrosclerosis based on chronic pyelonephritis. From the level of MCP-1 of 4.0 pg/ml, it can be evaluated as a sign of the initial stage of fibrosis formation (more than 10% of the total area of the cortical layer). The level of this factor in urine at a concentration of more than 20 pg/ml is evaluated as informative signs of tubulointerstitial fibrosis formed in chronic pyelonephritis [4].

Thus, urinary excretion of monocytic chemotactic protein-1 and transforming growth factor is a noninvasive method for evaluating tubulointerstitial fibrosis in patients with chronic pyelonephritis in the presence of renal nephrosclerosis.

In their study, the effect of early induction of angiotensin-converting enzyme inhibitors on renal recovery was investigated by assessing levels of TGF-β1 and other cytokines, as well as microalbuminuria. As a result, it is concluded that TGF-β1 in microalbuminuria can be used as a biomarker for early detection of kidney damage in patients with chronic pyelonephritis [5].

Thus, the introduction of urine tests into clinical practice significantly expands the diagnostic possibilities, allows for non-invasive monitoring of the development of the disease and the effectiveness of nephroprotective therapy.

Research results and discussion. According to the results of the study (Table 6), a direct and reliable correlation between the level of MCP-1 in urine and creatinine was revealed. In patients with renal nephrosclerosis due to chronic pyelonephritis, high excretion of MCP-1 in urine was noted. The profibrogenic effect of this chemokine is also confirmed by the results of examining the MCP-1 index in urine in group 2 [6].

Table 6

The amount of MCP-1 and TGF-β1 in urine according to the presence/absence of nephrosclerosis in patients with chronic pyelonephritis (M±m)

Indicators	Control group n = 24	group 1 n = 40	group 2 n = 38

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Monocyte chemotactic protein - 1 (MCP-1), pg/ml	0,45±0,03	4,92±0,63	39,56±2,98
Transforming growth factor - β1 (TGF-β1), pg/ml	1,76± 0,13	2,03±0,17	3,62±0,29*

Note: *- significant compared to the comparison group, R < 0.05.

It was found that there were significant differences in the quantitative indicators of MCP-1 in patients of group 1 and 2: 4.92±0.63 pg/ml and 39.56±2.98 pg/ml, respectively. The obtained data indicated that an increase in the number of indicators compared to patients without nephrosclerosis is associated with the development of renal nephrosclerosis on the basis of chronic pyelonephritis [6].

Based on the results of the study, determination of the levels of MCP-1 and TGF-β1 in urine is an informative non-invasive method for evaluating kidney nephrosclerosis in chronic pyelonephritis.

In order to standardize the results of the study, an additional study of the level of creatinine in the urine is carried out, since the concentration of creatinine in the urine is related to the level of reabsorption of water in the tubules of the urinary system.

All patients with renal nephrosclerosis secondary to chronic pyelonephritis had higher urinary MCP-1 excretion than controls.

The role of MCP-1 as the main chemokine acting mainly in the interstitial region is also confirmed by the fact that its level is maximal with the predominance of glomerular fibrosis. In contrast to MCP-1, the level of urinary excretion of TGF-β1 fibrogenic growth factor in patients was significantly higher not only compared to healthy people, but also compared to group 1 patients. At the same time, an inverse relationship between TGF-β1 indicators and creatinine level, as well as glomerular filtration rate was determined.

It can be seen that patients with renal nephrosclerosis developed on the basis of chronic pyelonephritis have a 2.6 - fold increase in tumor necrosis factor - TNF-α compared to healthy individuals. It should be noted that the increase in TNF-α concentration in urine reflects the intensity of autoimmune lesions and inflammation in the kidney tissues.

Thus, according to the results of the study, an increase in the level of MCP-1 was noted in the urine of patients who developed kidney nephrosclerosis due to chronic pyelonephritis.

The level of MCP-1 in the urine is directly related to the value of daily proteinuria, which is consistent with modern ideas about renal nephrosclerosis. MCP-1, secreted from the apical membrane by renal tubular cells, is thought to be the main source of urine in most forms of chronic kidney disease, with only a small amount of MCP-1 entering the tubular space and urine and being filtered from the blood through the glomerular capillary wall. This pathway is of great importance in rapidly developing forms of glomerulonephritis, and inflammatory changes in the glomeruli significantly change their permeability, including

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inflammatory cytokines.

MCP-1, secreted from the basolateral sections of tubular cells, enters the interstitium and contributes to the formation of an inflammatory infiltrate in it. The identified connection confirms the existence of a pathogenetic chain "proteinuria- MCP-1 tubular secretion - interstitial inflammation - fibrosis" in renal nephrosclerosis in patients with chronic pyelonephritis [105; 256-268-б.].

The profibrogenic effect of MCP-1 is explained by the activation of the synthesis of TGF-β1 by macrophages. In conditions of increased production of TGF-β1, resident fibroblasts turn into myofibroblasts - the main profibrogenic cells with the ability to produce large amounts of extracellular matrix components. We found a correlation between MCP-1 and TGF-β1 and urine indices in patients with interstitial fibrosis [7].

Conclusion. Overall, the results of our study confirm that interstitial fibrosis is a dynamic process, and considering urine as a substrate closely related to the kidney may provide valuable information about inflammatory and fibrotic processes in the kidney.

In particular, determining the level of profibrogenic cytokines MCP-1 and TGF-β1 in urine is an informative non-invasive method for evaluating renal nephrosclerosis in chronic pyelonephritis. In the experiment, there was a reason to believe that urine tests can be used to monitor the activity of the disease, evaluate its prognosis, and justify therapy.

Thus, detection of an early, potentially relapsing stage of fibrosis is an indication for active immunosuppressive therapy, while an accelerated stage of fibrosis mainly justifies the transition to a nephroprotective strategy.

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