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Innate and Adaptive Immunity in Patients with Chronic Kidney Disease

Jumaniyazov J. S. [1], **Nuraliev N. A.** [2]

[1, 2] Bukhara State Medical Institute

Abstract: Chronic kidney disease (CKD) is defined as a supranosological concept characterized by structural damage to the kidneys and/or a decrease in their function for 3 months or more, regardless of the nosological diagnosis of chronic renal disease [18, 30]

Numerous studies have established that acute kidney injury (AKI) is associated with bacterial infection, sepsis or ischemic reperfusion injury, and CKD occurs as a result of various diabetic complications, hypertension, obesity and autoimmunity [1, 18, 30]. It is important to note that inflammation and activation of the immune system are common main characteristics for both AKI and CKD.

In this review, we found it expedient to briefly dwell on the components of innate and adaptive immunity, relying on the published scientific sources of recent years of foreign and domestic researchers on this topic.

Inflammation and activation of the immune system are important factors in the development of both acute and CKD. The innate immune response is nonspecific and is the first barrier to the penetration of pathogens. According to John D. [27] adaptive immune response allows the body to effectively recognize certain pathogens and respond to them with primary and secondary immune responses. Although they are often referred to as separate systems, innate and adaptive immunity function together, regulating the overall function of the immune system.

Several key components of innate immunity are involved in the progression of renal disease, including the complement system, toll-like receptors (TLR), dendritic cells, macrophages, natural killer cells (NK cells), as well as pro- and anti-inflammatory cytokines [7, 8].

Numerous studies have established that complement is an important component of the innate immune response. It consists of blood serum proteins, inert in a normal state, which work in a cascade, they destroy and remove pathogens. There are three main ways of complement activation - classical, alternative and lectin. Altered complement regulation is involved in the development of CKD, although complement also performs a protective function. Early complement components are important for accelerating the elimination of immune complexes and, therefore, indirectly protect the kidneys from diseases mediated by immune complexes. These facts emphasize the place of the complement system in the pathogenesis of CKD [14, 20].

Another representative of innate immunity - TLRs are a group of cell surface proteins that serve as antigen recognition receptors. They bind to pathogenic and/or opportunistic microorganisms (UPM) and initiate an inflammatory reaction. TLRs are involved in both the development of AKI and CKD. The TLR content directly, closely correlates with the severity of renal failure, as well as

inflammatory markers, which indicates the place of TLR in the pathogenesis of CKD in humans [19, 24].

Antigen-presenting dendritic cells are crucial for the activation of T-lymphocytes and the establishment of T-cell-mediated inflammation of the glomeruli of the kidneys. Dendritic cells are of hemoloietic origin, are located in the kidneys and have receptors that contact and capture antigens. Upon contact with the antigen and activation, dendritic cells transmit signals to T-cell receptors, which leads to their activation [20].

Macrophages act as mediators of inflammation and immune modulation. They are common in the kidneys of patients with CKD. Macrophages are activated by immune complexes associated with complement or T-lymphocytes. In kidney disease, macrophage activation often occurs secondary to complement activation or effector T cells activated by antigens not specific to the kidneys, which suggests that macrophages may not be noticeable initiators of kidney disease. Nevertheless, both AKI and CKD are associated with an increase in the number of macrophages in the kidneys [7, 14].

NK cells can cause macrophage activation by releasing IFN-γ and are themselves activated by cells that do not have a major histocompatibility complex of Class 1 (MHC1) present on the cell surface. The presentation of the antigen by dendritic cells induces the production of cytokines by NK cells and contributes to the progression of kidney disease, it has been established that NK cells protect the body from CKD [7, 16].

According to John D. Imig and Michael J. [27], the function of the adaptive immune system is controlled by T- and B-lymphocytes. B-lymphocytes produce autoantibodies, which leads to the development of renal diseases, Goodpasture syndrome and IgA nephropathy. Two main types of T cells are involved in the adaptive immune system - CD8+ and CD4+ cells. Activation of CD8+ cells leads to kidney damage. Th17 cells belonging to CD4+ lymphocytes are CD4+ROR γ + cells and produce cytokines IL-17, IL-21, IL-22. Cytokine Th17 promotes kidney inflammation by increasing TNF-α expression and activation of chemokines, which leads to the invasion of immune cells into the kidneys. In addition, there are many regulatory T cells (Treg), which is CD4+CD25+FoxP3+. Treg inhibit the function of the adaptive immune system and promote self-tolerance, thereby protecting the body from autoimmune diseases. It is assumed that the immunomodulatory effect of Treg occurs due to the release of cytokines TGF-β and IL-10, which can inhibit the release of cytokines Th1. Suppression of Treg cells and/or dysfunction contributes to the development of autoimmune diseases and inflammation. An increase in the Treg population may delay the onset of kidney damage and inflammation. The same results were published by A.A. Yarilin [22].

The causal role of cytokine IL-17A has been shown in hypertension, glomerulonephritis and other kidney lesions. Adaptive immune response and IL-17A contribute to kidney damage, which have been proven in experimental models of kidney damage. Unlike other experimental models of renal injury, deficiency of the adaptive immune system or IL-17A did not weaken the induction or progression of CKD after nephrectomy in mice [23, 31].

Regardless of whether innate or adaptive immunity, AKI or CKD is involved, it is obvious that inflammatory cytokines play a central role as mediators of immune function and initiators of kidney damage. However, cytokines play an immunomodulatory role, which can prevent the development of kidney failure. The studies studied chronic changes in renal hemodynamics and tubular transport, which occur as a result of the action of certain cytokines. The contribution of cytokines to renal hemodynamics and tubular dysfunction depends on the pathological state, inflammatory mediators and localization of inflammation [16, 20].

Cytokines and inflammatory mediators, such as TNF-α, TGF-β and IL, affect sodium excretion, renal blood flow and GFR. The introduction of TNF-α sharply reduces renal blood flow and GFR, and also causes natriuresis in mice in the experiment. The Th1 cytokine IFN-γ plays a dual role in the pathogenesis of renal insufficiency, contributing to and limiting the progression of the disease, the presence of IFN-γ receptors is necessary to slow the development of renal damage caused by macrophage-secreted growth factors in the kidneys MRL-Fas (lpr) [7, 35].

According to the authors [16, 38], TGF-β did not affect the afferent vasoconstrictor reactions of arterioles, adenosine or angiotensin. Insulin-like growth factor-1 (IGF-1) is another factor that restores autoregulation of afferent arterioles in experimental CRF. It is proved that IL-1 and IL-6 dilate the arterioles of skeletal muscles, basilar and coronary arteries. IL-1 dilates peripheral arteries, but not renal arterioles, and increases sodium excretion by directly affecting renal epithelial cells. These studies demonstrated that cytokines and inflammatory mediators directly altered renal blood flow and GFR.

It is believed that VEGF plays a key role in the formation and maintenance of the filtration barrier, is expressed in podocytes and can act through Flt-1 receptors on endothelial cells. On the other hand, elevated VEGF levels were associated with glomerular damage, including hyperfiltration, hypertrophy, and proteinuria [7, 16].

Mesangial cells are another specialized type of glomerular cells that are affected by cytokines, mediating damage to the glomeruli. During immune damage, resting mesangial cells are activated by the fibroblast phenotype, which releases cytokines and oxidants. Activated mesangial cells generate cytokines such as IL-1, RANTES, MCP-1, TGF-β and heparin-binding epidermal growth factor (HB-EGF). Increased levels of cytokines and growth factor lead to proliferation of mesangial cells. Then the phenotype of mesangial cell fibroblasts secretes extracellular matrix components and promotes the development of glomerular sclerosis [10, 38].

Glomerular proteinuria, which leads to damage to the underlying tubule cells, is a generally accepted theory that links these two renal structures in relation to progressive kidney disease. Proteinuria has a direct effect on tubule damage by damaging intracellular lysosomal pathways. In addition, albumin increases chemotaxis and growth factors. TGF-β and IGF-1 bind to proteins and stimulate proximal tubule cells to release MCP-1, which causes tubulointerstitial fibrosis, activating macrophages to release TGF-β [23].

According to Sokurenko S.I. et al. [17], one of the main points in the pathogenesis of CKD is assigned to violations of the regulation of the T-link of immunity. CD8+ lymphocytes play a leading role in the pathogenesis of CKD, but it is possible that changes in the function and number of T-suppressors are secondary and caused by changes in T-helpers. The authors revealed an increase in the concentration of IL-8 in the blood serum and in the supernatant of peripheral blood mononuclear cells of patients with CKD/CRF in the acute stage. The theory of the leading role of violations of the activation of the T-link of immunity in the pathogenesis of this pathology explains the positive effect of immunosuppressive therapy. Glucocorticoids, alkylating agents and cyclosporine A suppress T-cell activation and have an anti-lymphokine effect.

The purpose of the study is Ermishina V.I. et al. [3] there was a study of clinical, biochemical and immunological parameters in the dynamics of treatment of complicated chronic pyelonephritis against the background of intercurrent diseases. The authors found that metabolic changes in these patients are characterized by structural and functional instability of cytomembranes and a decrease in immunological resistance of the body. The assessment of the immune status allowed us to state functionally significant deviations from the norm at the systemic and pathologically significant at the local level of antibacterial protection of these patients, which is one of the reasons for the recurrence and chronization of microbial-inflammatory kidney damage.

IgA nephropathy (IgAN) is the most common form of primary chronic glomerulopathy in both adults and children. The authors' study included 53 patients with IgAN aged 6-17 years who were under observation at the Republican Center of Pediatric Nephrology and Renal Replacement Therapy in Minsk. In patients with IgAN, the concentration of aberrant deGal-IgA1 was significantly higher in comparison with patients with Schenlein-Genoch nephritis and healthy individuals. The authors concluded that in childhood, in most cases, IgAN has a low rate of progression and does not lead to complete loss of kidney function [6]. The features of the activity of the immune system in this pathology were also revealed in the work of Kawasaki Y. et al. [29].

Sustained activation of innate immunity involves the induction of immune system regulation mediators that suppress innate and adaptive immunity, similar to the concept of "tolerance to

endotoxins" in chronic infections. The authors concluded that metabolic and hemodynamic changes in CKD also alter the composition and function of the normal microflora of the large intestine [9, 26].

Vanholder R., Glorieux G. [36] believe that the problem of the relationship between the normal microflora of the large intestine and the host with impaired renal function is bidirectional. On the one hand, substances with toxic properties are formed in the large intestine; on the other, with a decrease in GFR, functional and then organic changes occur in the intestinal mucosa first. The end result of both pathophysiological pathways is microinflammation against the background of incompetence of the pre-activated immune system.

In CKD, there is an increase in the quantitative composition of facultative microflora (Escherichia spp., Enterobacter spp., Klebsiella spp., Proteus spp., Lachnospiraceae, Ruminococcaceae) and a decrease in the indigenous intestinal microflora (Bifidobacterium spp., Lactobacillus spp., Bacteroidaceae, Prevotellaceae), which leads to dysbiosis. [34]. Proteolytic bacteria possess urease, uricase, p-cresol and indole-forming enzymes. As a result, the concentration of a number of toxic substances in the colon increases significantly - CMPF, hippuric acid, indole-3-acetic acid, indoxyl sulfate, kynurenic acid, P-cresol sulfate [33].

Studies by some authors have established that uremia is a condition of acquired immunodeficiency, which is the cause of infections in CKD. Uremia suppresses not only innate host defense against pathogens, but also inflammation caused by crystals, uremia also violates antigen-specific adaptive immunity [10, 26].

Studies show that patients with ESRD demonstrate a lower seroconversion rate, a lower peak antibody titer, and a faster decrease in protective antibody titers than healthy ones. In this study, the authors assessed IgG levels against two vaccine antigens (tetanus toxin (TT) and diphtheria toxin (DT)), the bacterium Salmonella enterica serovar Enteritidis (SEn) and the viral pathogen cytomegalovirus (CMV) in two independent cohorts. In patients with CKD, antibody responses to various antigens were equivalent compared to healthy ones. This indicates that humoral responses are maintained to certain antigens in patients with CKD, and thus the disease does not necessarily cause global immunodeficiency. Indeed, humoral immunity to antigens is well maintained and the cellular immune response to these antigens is also preserved [37].

Deeper knowledge of the immune homeostasis of the kidneys has revealed features that make this organ sensitive to various types of immune-mediated damage; for example, molecular structures associated with kidney damage (DAMP) and a predisposition to crystal formation. The kidney plays a central role in the homeostasis of electrolytes and the removal of toxins, and therefore, when its function is disrupted, the normal function of immune effector cells and microbial intestinal homeostasis are disrupted. CRF increases susceptibility to infection and contributes to increased inflammatory reactions [32].

Yushchuk N.D. et al. [21] conducted studies to assess the location of the parameters of the cellular and cytokine links of the immune response in kidney damage in patients with HIV infection. The study included 40 patients with HIV infection. In patients with HIV infection, taking into account the presence or absence of proteinuria, kidney damage developed against the background of a more pronounced drop in the blood content of the T-helper subpopulation of lymphocytes with a predominance of pro-inflammatory and immunosuppressive reactions. With a decrease in CD4+ lymphocyte levels of 100,000 cells/ml in patients with kidney damage, there was an increase of more than 50 times of the profibrotic cytokine TGF-β, which plays an important role in the progression of renal damage, and a statistically significant increase in TNF-α. The leading role of TNF-α in combination with high viral load and depression of the immune system has been established in the development of kidney damage in HIV infection.

The authors [11] studied patients with CKD stages 3-5 at the stages of conservative treatment, dialysis therapy and kidney transplantation (n=72). The main cause of the development of CRF in children - CAKUT syndrome has been determined. Children with CRF have immunocomplex pathology, the hypoimmune state of both cellular and humoral immunity links is more pronounced at

the predialysis stage of the disease. In patients with kidney transplantation, changes in the immune system are caused by the use of immunosuppressive therapy. The correlation of high and moderate strength between CD3+-, CD4+-lymphocytes and hemoglobin levels, as well as GFR levels, is shown.

In their studies, Buryak V.N., Babich V.L. [2] studied the features of the immune status of chronic non-obstructive pyelonephritis in 118 children aged 7-14 years. A significant increase in IL-4, IL-10 and IL-17 was revealed in the absence of an increase in the average concentrations of proinflammatory representatives of the cytokine status of IL-1ß and TNF-α. In children with this pathology, the presence of a tendency to decrease the functional activity of the mechanisms for limiting and eliminating the inflammatory reaction in the kidneys was found.

In another work, a comparative study of the levels of pro- and anti-inflammatory cytokines (IL-1ß, TNF-a, IL-6, IL-8, IL-10, RAIL) in the blood serum and saliva of patients with CKD was carried out. It was found that the concentration of IL-6 and IL-8 in saliva significantly correlated with the development of diseases of the oral mucosa in patients with CKD. The results of the study allowed us to confirm the important role of cytokine interactions in the pathogenesis of inflammation in CKD, as well as to state differences in the cytokine profile in different variants of this pathology. These changes lead to an imbalance in the local immune response of the mucous membranes and the development of both autoimmune and inflammatory diseases of the oral cavity. The levels of IL-6 and IL-8 in saliva significantly correlated with the development of diseases of the oral mucosa in patients [12].

Zakharova N.B. et al. [5] in their work presented the results of a study of patients with coralloid nephrolithiasis complicated by latent pyelonephritis and exacerbation of chronic pyelonephritis. It was found that the increase in inflammatory changes of the urinary tract is accompanied by a significant increase in proinflammatory cytokines in the urine. Among these cytokines, IL-8 had the greatest sensitivity and specificity, as well as diagnostic value.

Zhiznevskaya I.I. et al. [4] provide the results of observation of 139 children with glomerulonephritis. Based on a multifactorial analysis of the results of the assessment of humoral, cellular immunity, as well as cytokine status, statistically significant immune predictors were determined that allow predicting the nature of the course of this pathology in school-age children, starting from the moment of its manifestation. This allowed the authors to start pathogenetic therapy in a timely manner in accordance with the severity of the immunopathological process and improve the prognosis, in addition, the diagnostic and prognostic significance of determining the cytokine status of blood serum in children with various nosological forms of kidney disease has been proven.

In another study, 255 children with stage 1 and 2 CKD had an increase in serum TNF-α, which the authors recommend as a highly specific marker of chronic acute pyelonephritis, while a decrease in TNF-RII concentration was attributed to clinical and laboratory remission of pyelonephritis. An increase in TNF-α and TNF-RI is recommended as a marker of autoimmune inflammation. The authors believe that the deficiency of IL-2, IL-10 and TGF-β3 with an increase in IL-2R in the blood should be used as a marker of inflammatory and autoimmune kidney diseases, and an increase in TGF-β1 as an early marker of the development of nephrosclerosis. An increase of TNF-α/IL-10 by more than 4 times makes it possible to position it as an additional diagnostic criterion for the inflammatory and autoimmune process in the kidneys. An increase in urinary excretion of TNF-α against the background of a decrease in IL-10 while maintaining consistently high concentrations of TGF-β1 is a marker of inflammation and fibrosis in inflammatory kidney diseases and glomerulonephritis [15].

It was found that the involvement of IL-6 and TNF-α in the processes of tubulointerstitial damage in patients with renal dysfunction is confirmed by their negative correlation with GFR. A number of studies have determined the relationship between elevated levels of IL-6 and an inflammatory reaction in the renal tubules and glomeruli. The authors point to a close relationship between proinflammatory cytokinemia and the progression of renal dysfunction. These data allowed us to conclude that in patients with a therapeutic profile with a high risk of renal dysfunction, there is a

close relationship between the calculated GFR, IL-6 and TNF-α concentrations in the blood serum, which contributes to the progression of CKD [13].

Kamei N. et al. [28] showed that with the slowing of GFR in patients with CKD, the concentration of TNF-α in the blood serum increases with a simultaneous increase in the number of soluble receptors of types 1 and 2. Obviously, an increase in the concentration of TNF-α can serve as a marker of deterioration of renal filtration function.

As a result of their research, Gerald Cohen and Walter H. Hörl [25] proved that kidney dysfunction leads to impaired metabolic activity of the kidneys and impaired glomerular filtration, which leads to a delay in toxic solutes affecting all organs of the patient. CVD and infections are the main causes of increased morbidity and mortality among patients with CKD. The authors believe that complications are directly or indirectly related to a violation of immune protection.

Thus, an analysis of the literature of recent years by domestic and foreign researchers has shown that there are enough studies on the immunological aspects of CKD in patients, an assessment of the immune and cytokine status in these patients is given, the results of studies on the mechanism of damage and/or protection of kidney tissue by immune cells are presented. However, the issues of assessing the immune and cytokine status in patients in the dynamics of the course and outcome of this pathology have not been fully resolved.

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