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Characteristics of Congenate and Adaptive Immunity in Patients with Chronic Kidney Disease: Literature Review

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Abstract The article provides a review of literature sources on the study of immunological aspects of chronic kidney disease in patients, an assessment of the immune and cytokine status in these patients, and the results of studies on the mechanism of damage and/or protection of kidney tissue by immune cells.

Keywords Chronic kidney disease, Innate immunity, Adaptive immunity, Cytokines, Inflammation

1. Introduction

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

Numerous studies have established that acute kidney injury (AKI) is associated with bacterial infection, sepsis or ischemia-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 immune system activation are common core characteristics of both AKI and CKD.

In this review, we considered it appropriate to briefly dwell on the components of innate and adaptive immunity, based on published scientific sources in recent years by foreign and domestic researchers on this topic.

2. The Main Results and Findings

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 pathogen penetration. According to John D. [27] and the adaptive immune response allows the body to effectively recognize certain pathogens and respond to them with a primary and secondary immune response. Although they are often referred to as separate systems, innate and adaptive immunity function together to regulate the overall function of the immune system.

Several key components of the innate immune system are involved in the progression of kidney disease, including the complement system, toll -like receptors (TLRs), dendritic cells, macrophages, natural killer (NK) cells, and 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 serum proteins, normally inert, that work in a cascade to destroy and remove pathogens. There are three main pathways of complement activation - classical, alternative and lectin. Altered complement regulation has been implicated in the development of CKD, although complement also has a protective function. Early complement components are important for accelerating the clearance of immune complexes and therefore indirectly protect the kidneys from immune complex-mediated diseases. These facts emphasize the place of the complement system in the pathogenesis of CKD [14,20].

Another member of the innate immune system, TLRs are a group of cell surface proteins that serve as antigen recognition receptors. They bind to pathogenic and/or opportunistic microorganisms (OPM) and initiate an inflammatory response. TLRs are involved in both the development of AKI and CKD. TLR content directly and 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 critical for T cell activation and the establishment of T cell-mediated glomerular inflammation. Dendritic cells are of hemoloethic origin, located in the kidneys and have receptors that contact and capture antigens. Upon contact with an 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

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secondary to complement activation or effector T cells activated by non-kidney-specific antigens, suggesting that macrophages may not be prominent initiators of kidney disease. However, both AKI and CKD are associated with increased numbers of macrophages in the kidney [7,14].

NK cells can induce macrophage activation through the release of IFN- γ and are themselves activated by cells that do not have major histocompatibility complex class 1 (MHC1) present on the cell surface. Antigen presentation by dendritic cells induces the production of cytokines by NK cells and promotes the progression of kidney disease; NK cells have been found to provide protection against CKD [7,16].

According to John D. Imigand Michael J. [27] The function of the adaptive immune system is controlled by T and B lymphocytes. B lymphocytes produce autoantibodies that lead to the development of kidney diseases, Goodpasture syndrome and IgA nephropathy. Two main types of T cells are involved in the adaptive immune system - CD8+ and CD4+ cells. And activation of CD8+ cells leads to kidney damage. Th17 cells related to CD4+ lymphocytes are CD4+ROR γ+ cells and produce the cytokines IL-17, IL-21, IL-22. The Th17 cytokine promotes kidney inflammation by increasing the expression of TNF- α and activating chemokines, which leads to invasion of immune cells into the kidneys. In addition, there is a variety of regulatory T cells (Treg), which is CD4+CD25+FoxP3+. Tregs suppress the function of the adaptive immune system and promote self-tolerance, thereby protecting the body from autoimmune diseases. The immunomodulatory effects of Tregs are hypothesized to occur through the release of the cytokines TGF-β and IL-10, which may inhibit the release of Th1 cytokines. Treg cell suppression and/or dysfunction contributes to the development of autoimmune diseases and inflammation. Increasing the Treg population may delay the onset of renal injury and inflammation. The same results were published by Yarilin A.A. [22].

The causative role of the cytokine IL-17A has been shown in hypertension, glomerulonephritis and other kidney lesions. The adaptive immune response and IL-17A contribute to kidney injury, which has been demonstrated in experimental models of kidney injury. In contrast to other experimental models of renal injury, deficiency of the adaptive immune system or IL-17A did not attenuate the induction or progression of CKD after nephrectomy in mice [23,31].

Whether innate or adaptive immunity, AKI or CKD are involved, it is clear that inflammatory cytokines play a central role, both as mediators of immune function and as initiators of kidney injury. However, cytokines play an immunomodulatory role, which can prevent the development of renal failure. Studies have examined chronic changes in renal hemodynamics and tubular transport that result from the action of certain cytokines. The contribution of cytokines to renal hemodynamics and tubular dysfunction depends on the pathological condition, inflammatory mediators and location of inflammation [16,20].

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

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

VEGF is thought to play 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 have been associated with glomerular damage, including hyperfiltration, hypertrophy, and proteinuria [7,16].

Mesangial cells are another specialized cell type in the glomerulus that are targeted by cytokines to mediate glomerular damage. During immune injury, quiescent mesangial cells are activated to a fibroblast phenotype that 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 factors lead to proliferation of mesangial cells. The mesangial cell fibroblast phenotype then secretes extracellular matrix components and promotes the development of glomerular sclerosis [10,38].

Glomerular proteinuria leading to damage to underlying tubular cells is the generally accepted theory that links these two renal structures in relation to progressive kidney disease. Proteinuria has a direct effect on tubular 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 by 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 considered to be dysregulation of the T-link of immunity. The leading role in the pathogenesis of CKD belongs to CD8+ lymphocytes, but it is possible that changes in the function and number of T-suppressors are secondary and caused by changes in T-helper cells. The authors detected an increase in the concentration of IL-8 in the blood serum and in the

supernatant mononuclear cells of the peripheral blood of patients with CKD/ESRD in the acute stage. The theory of the leading role of impaired 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 antilymphokine effect.

The purpose of the study by Ermishina V.I. et al. [3] 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 the immunological resistance of the body. Assessment of the immune status made it possible to state functionally significant deviations from the norm at the systemic level and pathologically significant deviations at the local level in the antibacterial protection of these patients, which is one of the reasons for the recurrence and chronicity 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 for 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 Henoch-Schönlein 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 renal function [6]. THE characteristics of the immune system in this pathology were also disclosed in the work of Kawasaki Y. etal. [29].

Sustained activation of innate immunity involves the induction of immune regulatory mediators that suppress innate and adaptive immunity, similar to the concept of "endotoxin tolerance" in chronic infections. The authors concluded that metabolic and hemodynamic changes in CKD also alter the composition and function of the normal colonic microflora [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 hand, when GFR decreases, first functional and then organic changes occur in the intestinal mucosa. The end result of both pathophysiological pathways is microinflammation due to the incompetence of the pre-activated immune system.

In CKD, there is an increase in the quantitative composition of facultative microflora (Escherichiaspp., Enterobacter spp., Klebsiellaspp., Proteusspp., Lachnospiraceae, Ruminococcaceae) and a decrease in indigenous intestinal microflora (Bifidobacterium spp., Lactobacillus spp., Bacteroidaceae, Prevotellaceae), which leads to dysbiosis. [34]. Proteolytic bacteria possess urease, uricase, p-cresol-indole-forming enzymes. As a result, the concentration of a number of toxic substances in the colon significantly increases - 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 congenital host defense against pathogens, but also crystal-induced inflammation, uremia also impairs antigen-specific adaptive immunity [10,26].

Studies show that patients with ESRD exhibit lower rates of seroconversion, lower peak antibody titers, and more rapid declines in protective antibody titers than healthy controls. In this study, the authors assessed IgG levels against two vaccine antigens (tetanus toxin (TT) and diphtheria toxin (DT)), the bacterium *Salmonellaenterica* 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 to some antigens are maintained 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].

Greater knowledge of renal immune homeostasis has revealed features that make this organ susceptible to various types of immune-mediated injury; for example, kidney damage-associated molecular patterns (DAMPs) and susceptibility to crystal formation. The kidney plays a central role in electrolyte homeostasis and toxin removal, and therefore when its function is compromised, normal immune effector cell function and gut microbial homeostasis are disrupted. CRF increases susceptibility to infection and promotes increased inflammatory responses [32].

Yushchuk N.D. et al. [21] conducted studies to evaluate the parameters of the cellular and cytokine components 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 content of the T-helper subpopulation of lymphocytes in the blood with a predominance of pro-inflammatory and immunosuppressive reactions. When the level of CD4+ lymphocytes decreased to 100,000 cells/ml in patients with kidney damage, there was a more than 50-fold increase in the profibrotic cytokine TGF-β, which plays an important role in the progression of renal damage, and a statistically significant increase in TNF -α. In the development of kidney damage in HIV infection, the leading role of TNF -α in combination with a high viral load and depression of the immune system has been established.

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 chronic renal failure in children has been

identified - CAKUT syndrome. Children with chronic renal failure have an immune complex pathology, a hypoimmune state of both cellular and humoral immunity, which is more pronounced at the pre-dialysis stage of the disease. In kidney transplant patients, changes in the immune system are caused by the use of immunosuppressive therapy. A correlation of high and moderate strength was shown between the indicators of CD3 +, CD4 + lymphocytes and the level of hemoglobin, as well as the level of GFR.

In their research, Buryak V.N., Babich V.L. [2] studied the characteristics 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 pro-inflammatory representatives of the cytokine status IL -1β and TNF -α. In children with this pathology, there was a tendency to reduce the functional activity of the mechanisms for limiting and eliminating the inflammatory reaction in the kidneys.

Another study conducted a comparative study of the levels of pro- and anti-inflammatory cytokines (IL-1β, TNF-a, IL-6, IL-8, IL-10, RAIL) in the blood serum and saliva of patients with CKD. It was found that the concentration of IL-6 and IL-8 in saliva significantly correlates with the development of diseases of the oral mucosa in patients with CKD. The results of the study made it possible to confirm the important role of cytokine interactions in the pathogenesis of inflammation in CKD, as well as to establish 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] presented the results of a study of patients with coral nephrolithiasis complicated by latent pyelonephritis and exacerbation of chronic pyelonephritis. It has been established that the increase in inflammatory changes in 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] present the results of observation of 139 children with glomerulonephritis. Based on a multifactorial analysis of the results of assessing indicators of humoral, cellular immunity, as well as cytokine status, statistically significant immune predictors were identified that make it possible to predict 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 indicators of the cytokine status of blood serum in children with various nosological forms of kidney diseases was proven.

In another study, in 255 children with stages 1 and 2 CKD, an increase in serum TNF-α levels was noted, which the authors recommend as a highly specific marker of chronicity of 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 a 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 in 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 with persistently high concentrations of TGF-β1 is a marker of inflammation and fibrosis in inflammatory kidney diseases and glomerulonephritis [15].

It has been established 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 increased levels of IL-6 and the inflammatory response in the renal tubules and glomeruli. The authors point out 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 at high risk of developing renal dysfunction, there is a close relationship between the value of the estimated GFR, the concentration of IL-6 and TNF-α in the blood serum, which contributes to the progression of CKD [13].

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

3. Conclusions

As a result of his research, Gerald Cohenand Walter H. Hörl [25] proved that kidney dysfunction leads to impaired metabolic activity of the kidneys and impaired glomerular filtration, which leads to the retention of toxic solutes that affect 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 impaired immune defense.

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, and 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 of patients in the dynamics of the course and outcome of this pathology have not been fully resolved.

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