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# The Study of Cytokine Levels in Chronic Viral Hepatitis and Liver Cirrhosis

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A B S T R A C T
*In recent years, there has been a steady increase in chronic diffuse liver diseases, which are characterized by severe, progressive and are one of the main causes of disability and mortality in developed countries. The course and prognosis of chronic hepatitis and liver cirrhosis are largely determined by the state of the immune status of the organism. At all stages of the immune response, cytokines take an active part in it, which regulate intercellular and intersystem interactions. The literature review presents current data on the role of cytokines in the development of CDLD and portal hypertension.*

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Cytokines are low–molecular-weight proteins that are produced and secreted mainly by activated cells of the immune system and are involved in the development of cellular or humoral immune reactions. Produced transiently, they have a short half-life and act in very low concentrations, binding to high-affinity receptors on the surface of target cells [4]. Cytokines do not have specificity for antigens and are mediators of intercellular communications, regulating the strength and duration of the immune response and the inflammatory process, participating in hematopoiesis, in transplantation and antitumor immunity, in the induction of tolerance and in many other vital processes [7]. Cytokines are an integral system, the main components of which are the producing cells, the cytokine protein itself, the receptor receiving it, and the target cell [4, 6]. Cytokines are characterized by the following general properties:

- synthesized in the process of implementing the mechanisms of natural or specific immunity;
- show their activity at very low concentrations (about 10-11 mmol/l);
- serve as mediators of immune and inflammatory reactions and have autocrine, paracrine and endocrine activity;
- act as growth factors and cell differentiation factors;
- form a regulatory network in which individual elements have a synergistic or antagonistic effect;
- possess pleiotropic (multifunctional)activity.

The course and prognosis of chronic hepatitis (HCG) and cirrhosis of the liver (CP) are largely determined by the state of the immune status of the body, and active participation in it at all stages of the immune response they take cytokines that regulate intercellular and intersystem interactions [44, 48, 15]. When the inflammatory process is chronicled with the participation of cytokines, liver tissue is damaged, fibrogenesis is activated, neoangiogenesis and scarring mechanisms are stimulated [6]. Prolonged cytokine synthesis can initiate the progression of the pathological process in the liver [6, 7]. In the formation of hepatocyte necrosis and the progression of CP is significant immunological disorders caused by dysfunction of Kupfer cells synthesizing proinflammatory cytokines play an important role [5, 4]. A large number of cytokines play a role in the regulation of fibrogenesis [1]. Determination of cytokine status in chronic liver diseases is important for determining the prognosis, since the level of cytokines

reflects the intensity of regenerative processes in the liver and the progression of the disease [15, 6 5].

It is described that in chronic viral hepatitis (CVH), due to the persistence of viruses, cytokine production and levels are disrupted [7]. It has been established that the mechanisms of the T-cell response are often unable to control the replication of the virus. In fact, it is precisely T-cell depletion, together with a decrease in proliferative abilities and impaired cytokine production, that can lead to the persistence of viral infection [5]. Cytokine production is normally absent or minimal. When cells are activated and physiological or pathological stimuli appear, the production of these autocrine, paracrine and endocrine molecules increases, thereby regulating the cellular response to external stimuli [4, 7]. Cytokines have a cascading nature of action, which is explained by the induction of production by one cytokine of another, as well as by synergism and antagonism in interaction. It is the imbalance of cytokine regulation and the imbalance of alternative pools of molecules in terms of biological activity that contributes to the development of pathology [5]. Activation of Th1-lymphocytes producing interferon-γ (IFN-γ), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α) and β leads to stimulation of the functions of T-lymphocytes, natural killers (NK) and macrophages, and the development of an immune response to T-the cellular type, which plays a crucial role in the antiviral protection of the body. Cytokines produced by cytotoxic T cells and macrophages (IFN-γ, IL-2, TNF-α) are capable of inhibiting virus replication in infected cells by non-cytolytic means, that is, without destroying hepatocytes [75]. Th2-lymphocytes secrete interleukins IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, stimulating mainly the humoral link of immunity. Some of them, in particular IL-4 and IL-10, have an anti-inflammatory effect mainly by suppressing the action of IFN-γ, which enhances the expression of HLA class II antigens on the surface of antigen-presenting cells. Th2-lymphocytes, releasing proinflammatory cytokines, block the proliferation and activation of Th1-lymphocytes, thus suppressing cytotoxic reactions and the destruction of the pathogen [8. 9].

Most researchers agree that the predominant participation of cytokines produced by Th2 lymphocytes is associated with the persistence of the virus, and those produced by Th1 lymphocytes with spontaneous recovery during elimination of the pathogen [5]. The conducted studies have shown the relative predominance of the amount of Th2 over the amount of Th1 in inflammatory cell infiltrates during the chronization of acute hepatitis C and the inverse ratio of the number of these types of helper lymphocytes and cytokines produced by them in case of recovery. Similar data were obtained in the study of cellular infiltrates in the liver of patients with chronic hepatitis associated with HBV infection.

Exacerbation of HCG associated with HBV, HCV infection is accompanied by a significant increase in the serum content of this cytokine. In HCV, an increased level of TNF-α is determined, followed by its decrease after effective antiviral treatment. These data are confirmed by the studies of D.M. Sobchak et al., V.V. Makashova et al., who obtained similar results and suggested using the study of the dynamics of cytokine, interferon statuses in combination with other criteria for the effectiveness of antiviral therapy.

Modern antiviral therapy is aimed at activating type 1 T-helpers, which presumably should be reflected in the generation of NO. Nitric oxide belongs to the factors of cellular immunity, its synthesis is stimulated by type 1 cytokines [. In CVH, it should be noted that cytokine levels directly depend on the severity and progression of the disease [2]. Significantly elevated levels of proinflammatory cytokines are more common in patients with severe course of the disease or in persons who have not responded to antiviral therapy, or in persons with developed relapse after completion of treatment. The highest cytokine levels are observed in patients with high inflammatory activity and a pronounced degree of fibrosis. There is a correlation of an increase in the concentration of pro-inflammatory cytokines with the detection of hepatitis C virus RNA, an increase in the level of alanine aminotransferase in blood serum. In patients with HCV, there is an increase in serum levels of proinflammatory IL-1ß, IL-6, and their high levels indicate a severe course of the disease, which contributes to prolonged circulation of the virus, its active replication and poor response to antiviral therapy.

Decrease in the activity of Th1 type and cytokines produced by them a significantly high level of anti-inflammatory cytokine IL-4 in the blood serum of patients with HCG may also contribute.

In CP, compared with stage II-III fibrosis, against the background of an increase in the level of proinflammatory cytokines TNF-α, IL-6 and IFN-γ, the secretion of IL-4 increases, which indicates that

the progression of fibrosis is associated with the activation of the humoral link of the immune system [43, 28, 35]. An increase in the concentration of proinflammatory cytokines in the blood serum of patients is associated with an increase in biochemical activity, the severity of cytolysis and cholestasis syndromes, the severity of cirrhosis and extrahepatic complications. The severity of non-inflammatory liver pathology directly correlates with the expression of monocytic chemoattractant protein-1, the highest concentration of which is determined in the blood of patients with acute liver failure [19, 12]. It has also been shown that the degree of fibrosis in chronic viral liver diseases is associated with the severity of its endothelial dysfunction and a significant increase in the production of vascular endothelial growth factor (vascular endothelial growth factor, VEGF) in patients [5]. There are data on the activation of cytokine cascade in cirrhosis of the liver. A number of studies have shown an increase in serum concentrations of IL-2, IL-6, IFN-γ and TNF-α in CP. Hyperproduction of proinflammatory cytokines TNF-α, IL-6 causes liver damage and correlates with the severity of the course of chronic liver diseases.

With decompensation of the CPU, an increase in the pro-inflammatory activity of blood cells is observed. The authors noted that patients with cirrhosis of non-viral etiology differed from patients with viral CP by a significantly smaller number of cytokines with an increased level of production. In the work of Bulatova I.A. et al. (2017) demonstrated that the development of CP, regardless of the etiological factor, is characterized by hyperproduction of the proinflammatory cytokine IL-6, reflecting the severity of hepatocyte damage, the severity of the inflammatory process and the progression of the disease. A more significant production of IL-6 was observed in the alcoholic genesis of the disease, which caused the rapid progression of cirrhosis.

Studies have shown the role of cytokines in chronic diffuse liver diseases with the development of portal hypertension,

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