

# Disorders Of The Immune System And Their Immunological Rehabilitation In Patients With Chronic Pancreatitis

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## **RESUME:**

*The immune system studied in 36 patients with chronic pancreatitis (CP) and 32 healthy individuals. In patients with CP showed a deficit of T-lymphocytes and subset tension humoral immunity and cytokine profile: TNF- $\alpha$ , IL-4, IL-6. Using thymoptinum (dose of 0.8-1.0 mg per course) in conjunction with conventional treatment in patients with CP led to an increase in cellular immunity and stabilization of cytokine levels.*

*Keywords: chronic pancreatitis,immunity,infringement, Thymoptinum, immunocorrection, interleykines.*

## **1. RELEVANCE:**

Serious changes in the human habitat, the increasing role of innovative technologies in the food industry, the transformation of lifestyle and the spread of the “Western type of nutrition” have led to an increase in pancreatic (pancreas) pathology [2, 8, 9, 26].

Chronic pancreatitis (CP) is a progressive pancreatic disease characterized by the appearance of acute inflammatory process during exacerbation, the gradual replacement of the organ parenchyma with connective tissue and the development of insufficiency of exo- and endocrine gland function. Over the past 30 years, a global trend has been revealed in increasing the incidence of CP by more than 2 times [5, 6, 9, 24, 37].

CP in terms of prevalence, increase in incidence, temporary disability and the cause of disability is an important socio-economic problem of modern medicine. Structurally, among diseases of the gastrointestinal tract, CP is from 5.1 to 9%, and in general clinical practice, from 0.2 to 0.6%. For 100,000 people, 7–10 new cases of CP are recorded per year. In recent years, the incidence of CP has been increasing, which is associated with increasing alcohol abuse [2, 9, 24, 26, 28, 30, 37].

So, the prevalence of pancreatic diseases among adults over the past 10 years has increased 3 times, and among adolescents - more than 4 times. It is believed that this trend is associated with an increase in alcohol consumption, including low quality, a decrease in food quality and general living standards. Typically, CP develops between the ages of 35-50; among

women, the proportion of women has increased by 30%. The values of the parameters of the incidence of CP are constantly growing due to improved diagnostic methods, the recent emergence of new methods of visualization of the pancreas with high resolution, allowing the detection of CP in the earlier stages of the disease [26, 29, 30].

In the scientific periodicals, we can meet a number of studies indicating a significant depression in the parameters of the cellular and humoral components of the immune system in patients with CP. In the vast majority of studies, when assessing the cellular status in CP, a decrease in the level of T(CD3+) lymphocytes was shown [7, 34].

When pathology is transformed into a stage of remission, the content of the total pool of T (CD3+) cells, as a rule, tends to increase, but it still stays at a significantly more “reduced” level. With CP, the number of lymphocytes that form “full” rosettes (full T-RAC) decreases and the absolute number of lymphocytes that do not form rosette cells of rosettes (the so-called zero-cells – 0-cells) increases. The highest level of 0-lymphocytes is shown in severe forms of CP, since this subpopulation is represented by antibody-dependent and natural killers that have a cytolytic and cytotoxic effect. Despite the constant growth of interest on the part of researchers in studying the issue and the role of various cytokines in the etiology and pathogenesis of pancreatic diseases, we have not found a lot of works on their participation in the development of CP. It is likely that this can be partially attributed to the fact that induced acute pancreatitis (OP) in an animal experiment or, for example, reactive pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) in clinical practice is, as it were, “ideal models” for studying pathological processes in the pancreas. However, in contrast to the aforementioned one, the high mortality rate in cases of OP and pancreatic necrosis necessitates a priority search for unexplored pathogenesis mechanisms with the prospect of developing new treatment methods. In this situation, the process of studying interleukins (IL) in CP has gone “as if into the shadow” [15].

Due to the tendency of most diseases to pathomorphosis, which has been demonstrated in recent years, the researchers faced the problem of complicating the clinical diagnosis of CP, and in some cases, to establish a diagnosis of CP, it is necessary to use the whole complex and arsenal of modern diagnostic methods (ERCP, computed tomography, endoscopic endosonography, biochemical tests and the study of exocrine pancreatic function), which, however, is not always available, especially during outpatient examination [15, 32].

Inflammatory processes in the pancreas can develop due to impaired functioning of the immune system, which are based on an allergic reaction, as well as a response to a bacterial factor [12, 17].

Many studies of recent years have shown that the vast majority of the immune regulatory effects of the immune system are mediated by cytokines. Immune cytokines / IL are the focus of modern clinical immunology [3, 22].

Due to the advent of methods for the quantitative determination of cytokines, cardinal changes have been achieved in understanding their role in normal and pathological conditions. Many researchers indicate that IL are key factors in the immune genesis of a wide range of diseases, largely determining the direction of the pathological process, its severity and outcome [3, 22].

In gastroenterology, to date, material has been accumulated regarding the content of individual cytokines in chronic diseases of the digestive system, including CP [22, 23].

Until recently, the participation of activated pancreatic enzymes was key in the emergence and progression of CP, but according to modern concepts of the pathogenesis of the disease, the main role belongs to IL/cytokines. The participation of cytokines such as IL-1 $\beta$ , IL-6, IL-8, IL-10, TNF- $\alpha$ , and others in the development of CP, its progression, and the formation of complications has been shown [15, 23].

Destruction of pancreatic tissue leads to a change in its antigenic properties, while being only a trigger mechanism for triggering nonspecific immune responses that ensure the formation and progression of the process, regardless of the etiological factor [11, 20].

Based on the modern concept of assessing the level of health from the point of view of the theory of adaptation, the basis of this process is the inhibition of the adaptive reactions of the body, up to the failure of adaptation [21].

It should be noted that to date, immune disorders and their immunological correction in patients with CP remain insufficiently studied. Moreover, there is also a shortage of studies on the problem of immune correction in pancreatitis [13, 15]. Meanwhile, the need for such studies for doctors and immunologists is important and relevant, since the solution of these issues is important for clinical and practical immunology [11, 15, 21].

*The aim of this work* was to study the parameters of the immune system and conduct immune corrective treatment in patients with CP.

## 2. MATERIAL AND METHODS

36 patients (33-65 years old) with a diagnosis of CP were examined. The diagnosis was made on the basis of complaints, medical history, objective and laboratory examination, instrumental data: ultrasound, FGDS, panoramic radiography of the abdominal organs. The control group of donors consisted of 32 healthy individuals (25–55 years old). The concentration of serum immunoglobulins (SI) of classes A, M, and G was determined by Mancini radial immunodiffusion [22].

The parameters of cellular immunity (T-lymphocytes and its subpopulations, B-lymphocytes) were identified using monoclonal antibodies (Sorbert-Service LLC, Russia) [19]. Quantitative assessment of serum TNF- $\alpha$ , IL-6, IL-4 levels was carried out using a ProCon reagent kit (Protein circuit LLC, St. Petersburg) by enzyme-linked immunosorbent assay.

Immune corrective therapy was carried out in 15 patients. Thymoptinum (Uzbekistan) 0.8–1.0 mg per treatment course (dose of 100  $\mu$ g / day for 8–10 days) was used as an immunologic preparation. It should be noted that the drug Thymoptinum contains a complex of polypeptides from the thymus gland of mammalian animals. Lyophilized powder, white or yellow with a yellowish tint.

Thymoptinum is produced in the form of lyophilized powder of 100  $\mu$ g (0.0001g) in hermetically sealed glass vials. Immunity indicators were studied twice: before and after 1 month after treatment).

## 3. RESULTS AND DISCUSSION

The results of the studies indicated that in patients with CP there was a significant suppression of the cellular component of the immune system, expressed in a 0.7-fold decrease in the total pool of lymphocytes - T (CD3+) –  $35.3 \pm 2.6\%$  compared with the control group where this indicator amounted to  $52.4 \pm 1.8\%$  ( $p < 0.001$ ).

The differences revealed in this case were highly significant. In addition, a 0.8-fold decrease in the absolute number of T (CD3+) cells ( $p < 0.05$ ) was found. We also revealed a significant suppression of subpopulations of T-lymphocytes with helper suppressor function, T<sub>H</sub> (CD4+) –  $29.5 \pm 1.1\%$  ( $p < 0.001$ ) and  $341.8 \pm 32.1$  cells / 1  $\mu$ l of blood ( $p < 0.001$ ) (in the control  $36.5 \pm 0.7\%$  and  $616.4 \pm 44.3$  cells / 1  $\mu$ l of blood, respectively), the content of T<sub>C</sub> (CD8+) is  $13.8 \pm 1.4\%$  ( $p < 0.05$ ) and  $127.3 \pm 9.8$  cells / 1  $\mu$ l of blood ( $p < 0.01$ ). Moreover, the immune regulatory index was 2.1.

On the other hand, from the B (CD19+) cell unit side, the opposite nature of changes was observed, namely, the tendency to increase as a relative parameter was  $20.6 \pm 2.3\%$  ( $p < 0.05$ ), which was 1.4 times higher such values of the control group and absolute – 1.7-fold increase –  $385.8 \pm 33.4$  cells / 1  $\mu$ l of blood (in the control –  $230.1 \pm 26.7$  cells / 1  $\mu$ l of blood).

A significant increase in the B-cell component of immunity against the background of suppression of T-cells in CP was also reflected in the SI spectrum. For example, we found a marked increase in IgA production to  $3.97 \pm 0.41$  g / l ( $p < 0.05$ ).

This process could probably be explained by the fact that in the body of patients with CP there is a transformation of the immunological defense in response to enzymatic intoxication of the body.

A high IgG content was demonstrated –  $22.42 \pm 0.75$  g / l ( $p < 0.001$ ) (in the control  $15.9 \pm 0.94$  g / l), which was 1.4 times significantly higher compared to the control. The concentration of heavy and primary “pentameric” IgM was within the normal range of  $1.7 \pm 0.2$  g / l ( $p > 0.05$ ).

Under the influence of conservative treatment, there was no restoration of T (CD3+) cells and its subpopulation profile. At the same time, there was a tendency towards a decrease in the SI of IgA and IgG classes.

An analysis of the spectrum of cytokines showed that in patients with CP during the period of exacerbation, the values of pro-inflammatory cytokines significantly increased: TNF- $\alpha$  to  $202.6 \pm 22.3$  pg / ml (normal –  $24.5 \pm 5.1$  pg / ml;  $p < 0.001$ ), and IL-6 was increased 6 times ( $317.4 \pm 53.5$  pg / ml and  $47.8 \pm 11.2$  pg / ml, respectively, at  $p < 0.001$ ).

The level of anti-inflammatory IL-4 increased by 4.3 times compared with the norm, which was statistically confirmed ( $157.5 \pm 36.7$  pg / ml and  $32.6 \pm 14.3$  pg/ml, respectively;  $p < 0.001$ ).

So, in patients with CP, secondary immunodeficiency was found, for the elimination of which we used Thymoptinum, used in combination with basic therapy (antienzymes, antispasmodics, antibacterial drugs, etc.).

Immune corrective therapy led to an increase in both relative –  $54.7 \pm 3.2\%$ , and in absolute values of T (CD3+)–lymphocytes -  $992.3 \pm 64.8$  cells / 1  $\mu$ l.

In parallel, an increase and stabilization of Tx (CD4+) and Tc (CD8+) was observed. Moreover, the immune regulatory index was 2.2.

IgA concentration was moderately reduced during treatment. There was a tendency to increase IgM to  $2.23 \pm 0.2$  g / l and IgG to  $23.7 \pm 1.62$  g / l 1 month after treatment, however, it should be noted that IgG was also high during remission, which was probably due to the severity and duration of the pathological process, as well as a decrease in reparative processes in the pancreas [16, 18].

During traditional treatment in patients with CP, there was a moderate decrease in the levels of TNF- $\alpha$ , IL-6 ( $p > 0.05$ ; compared with the data before treatment) and a slight increase in IL-4 to  $172.3 \pm 41.1$  pg/ml.

Under the influence of immune corrective therapy conducted against the background of traditional treatment, a marked decrease in proinflammatory cytokines was revealed in patients with CP: TNF- $\alpha$  to  $118.4 \pm 29.1$  pg / ml, IL-6 to  $133.6 \pm 51.8$  pg / ml.

In addition, a decrease in the production of anti-inflammatory cytokine IL-4 to a level of  $95.2 \pm 27.4$  pg / ml was observed.

In recent years, the development of severe forms of pancreatitis and their complications has been associated with the overproduction of inflammatory cytokines.

Along with changes in the complement system in inflammatory pancreatic diseases, a significant increase in the content of pro-inflammatory cytokine of leukocyte origin, TNF- $\alpha$ , was established in terms of TNF- $\alpha$  functional activity, similar to cytokines such as IL-1 $\beta$  and

IL-6, which together reflect the active participation of immune system products humoral and cellular genesis in the development of acute inflammatory process and exacerbation of chronic in the pancreas [38].

With CP, a significant increase in the level of TNF- $\alpha$  was observed in patients with antibodies to the antigen from pancreatic tissues, trypsin, and insulin. With CP, a positive reliable correlation of TNF- $\alpha$  with the level of trypsin in the blood serum was observed ( $p < 0.05$ ).

Thus, the obtained data indicate the undoubted participation of the complement system and tumor necrosis factor (TNF- $\alpha$ ) in the inflammatory process during exacerbation of CP associated with an increase in antibodies in the blood to the structural and secretory components of the pancreas [31].

The sequence of events with the participation of immunologically mediated mechanisms may look as follows: the action of a probable etiological factor leads to an exacerbation of the chronic inflammatory process and to damage to pancreatic tissue, which has high "immunogenicity" [15].

Pancreatic antigens that enter the circulation in some patients cause the formation of antibodies in significant quantities. These antibodies can react not only with antigens circulating in the blood, but also with pancreas fixed in the tissues.

The antigen+antibody reaction is accompanied by an increase in complement consumption and a decrease in the levels of its inflammatory components C1 – C5 with the formation of fragments C3a, C4a, C5a, which are powerful mediators of inflammation and chemo attractants, causing leukocyte migration directed to the focus of inflammation, their activation with increased secretion of various cytokines inflammatory action, including TNF- $\alpha$  [31, 39]. Another option is possible, in which the organism responds to pancreatic alteration factors associated with a probable etiological factor by non-specific activation of C1 – C5 due to proteolytic conversion of complement proteins with the subsequent involvement of the alternative, and through the feedback loop, classical complement activation pathway with further activation of leukocytes and secretion of TNF- $\alpha$ , the level of participation of which affects the depth of damage, the release of antigens into the circulation, and the production of antibodies to them [10, 18].

ILs are activators of inflammation. IL-2, IL-6 are associated with immune inflammation and pancreatic fibrosis. Taking into account all these mechanisms of pancreatic fibro genesis activation in CP, it is necessary to indicate drugs that directly inhibit fibro genesis processes, except for the indirect inhibitor of intestinal endotoxin-lactulose. The leader among all lactulose preparations is dufalac [1, 3, 4].

Endotoxin is a specific lipopolysaccharide that is synthesized by the bacterial membrane of the gram-negative proteolytic flora of the colon. In 95% of cases it is of intestinal origin. Increased synthesis of endotoxin causes a general toxic effect on the body, activates immune inflammation in the tissues (pancreas, liver, etc.) through the TNF- $\alpha$  system, cytokines, IL-2, 6, which leads to stimulation of inflammation and fibrotization of parenchymal organs in chronic, chronic hepatitis and cirrhosis. In addition, endotoxin is a prooxidant, increasing the intensity of the processes of peroxidation of membrane cell formations (reduces their resistance), including pancreas.

A number of diseases: burn disease, sepsis, multiple organ injuries, OP and reactive CP (acute attack of CP), acute and chronic hepatitis, cirrhosis of the liver, obstructive jaundice, ulcerative colitis, Crohn's disease, are associated with a risk of developing endotoxemia. The translation of intestinal endotoxins into the blood is prevented by protective factors: the normal ratio between the anaerobic flora and gram-negative flora prevents the excessive growth of gram-negative bacteria, intact mucus-forming epithelial cells that produce a

protective layer of mucus, and an adequate amount of cholic acids that neutralize endotoxin. Metabolites formed as a result of enhanced membrane peroxidation –malondialdehyde (MDA) and endotoxin itself initiate increased activity of immunocompetent Kupffer cells and lipocytes, resulting in increased collagen synthesis by these labels and, as a result, liver fibrotization [4, 10, 11, 15, 18].

The data of a number of authors indicate that different concentrations of TNF $\alpha$  are recorded in CP. Szuster–Ciesielska A. et al. observed an increase in the levels of TNA– $\alpha$  and IL–6 in patients with alcoholic liver cirrhosis and chronic pancreatitis [35].

When studying the content of the TNF– $\alpha$  cytokine in acute pancreatitis (OP) and CP, it was shown that its level was significantly higher in OP than in patients with CP [15, 17, 25].

It should be noted nevertheless that in the majority of studies conducted in patients with CP, higher levels of TNF– $\alpha$  were noted and it is believed that its level correlates with the severity and exacerbations of CP [31, 33, 36].

In our opinion, and according to other authors, the pancreas is a particularly “immunogenic” organ; it is difficult to transplant attempts. Currently, more and more scientific works are appearing, showing significant violations in the cellular and humoral links of immunity in CP. In most studies of the state of cellular immunity in CP, a decrease in the content of T-lymphocytes was noted [4, 7, 14, 33].

Upon transition to remission, the number of T–lymphocytes increases, but remains significantly reduced. With CP, the number of lymphocytes forming “full” rosettes (full T–RFC) decreases, and the content of lymphocytes that do not form rosettes (0 cells) increases. A particularly high level of 0–lymphocytes was noted in severe forms of CP, since this subpopulation is represented by antibody-dependent and natural killers that have a cytolytic and cytotoxic effect [4, 7, 14, 15, 23].

With exacerbation of CP, the number of T–helpers and T–suppressors decreases, and the ratio between T–helpers and T–suppressors also changes. According to the ratio of helpers / suppressors, some researchers identify groups of patients with CP with an autoimmune component (helpers / suppressors <1.5) and immunodeficiency (helpers / suppressors > 5.0) [7, 11, 14, 17, 34].

In general, the majority of authors assessed the functional state of T-lymphocytes in CP as reduced. Cellular immunological reactions to pancreatic tissue have been the most studied with CP.

More than half of patients with CP have a positive reaction of blast transformation of lymphocytes to pancreatic tissue. At the same time, there is no consensus on the severity of cellular immunological reactions to pancreatic tissue in the stage of exacerbation and remission.

A number of researchers note their increase in the acute stage, while there is evidence of an increase in cellularimmunological reactions and in the stage of remission of CP, detected with the same frequency. In patients with CP, a positive reaction of inhibition of migration of leukocytes with antigen from pancreatic tissue was noted; cell sensitization to trypsin and insulin was detected with the greatest changes during the exacerbation period [7, 11, 14, 17, 21–23, 39].

Summarizing the aforesaid, it can be concluded that the opinion about the leading role of the cellular component of immunity in the chronicity and progression of CP seems to be quite reasonable, while in the case of OP, shifts in factors of humoral immunity are predominantly noted.

In recent years, the attention of many researchers has been attracted by the study of the pathogenetic role of cytokines in the development of diseases (pancreas), which, in particular, is associated with details of the function of T–helpers (Tx1 and Tx2) producing different

spectra of cytokines (Tx1 secrete interleukin-2 (IL), tumor necrosis factor- $\beta$  (TNF), interferon- $\gamma$  (TFN); Tx2 secrete IL-4, IL-5, IL-10; T-cells of both subpopulations secrete IL-3, TNF- $\alpha$ , granulocyte-macrophage colony-stimulating factor) [3, 4, 34].

IL-6 is produced by monocytes, fibroblasts, endotheliocytes, as well as macrophages, lymphocytes, mast cells, eosinophils after stimulation. In addition to stimulating the synthesis of acute phase proteins by liver cells, IL-6 acts as a growth factor for mature B-lymphocytes and induces their conversion into plasmocytes [4, 22, 38].

The participation of IL-6, as well as other pro-inflammatory cytokines, in the pathogenesis of CP has been determined by many authors, and one of the main roles is given to the initiation of IL-6 local inflammatory process in the pancreas into a systemic inflammatory reaction with the development of intoxication, and, in severe cases, multiple organ failure syndrome [3, 18, 22].

In other studies on a model of reactive pancreatitis after ERCP, an increase in plasma concentrations of IL-6 in the first day to  $16.6 \pm 2.06$  was noted;  $73.0 \pm 15.6$  and  $235.5 \pm 26.31$  pg / ml for various degrees of severity (from mild to severe, respectively). On the second day, the authors noted a progressive increase in IL-6 levels to  $18.92 \pm 3.28$ ;  $100.17 \pm 11.56$  and  $438.2 \pm 71.5$  pg / ml for mild, moderate to severe and severe pancreatitis, moreover, these concentrations correlated with an increase in plasma concentrations of C-reactive protein, while significant changes in pancreatic lipase not noted. Based on the data obtained, the authors concluded that IL-6 is a marker of the severity of reactive pancreatitis [15, 22, 23, 38, 39].

According to other data, on the first day of development of ERCP-induced pancreatitis, an increase in the content of IL-6 in peripheral blood was noted to 81.6 pg / ml.

An increase in plasma concentrations of IL-6 in the acute phase of pancreatic damage was observed in an experiment in rats, in clinical trials with pancreatic necrosis, and recent data indicate that the sensitivity of IL-6 determination in pancreatic necrosis is 100%, specificity is 20%, and the prognostic value is 55% [3, 4, 22].

At the same time, in patients with chronic alcoholic pancreatitis (AP), there were no significant changes in IL-10 in blood plasma. The increase in blood IL-10 in patients undergoing ERCP correlates with the severity of abdominal pain syndrome and the duration of ERPH, which can be explained as a protective immune response as opposed to the induction of pro-inflammatory cytokines - IL-1, IL-6, TNF- $\alpha$ , etc.[3, 18, 22, 23].

We found single data on the involvement of IL-4, IL-11, IL-18, IL-22 in pancreatic lesions, which requires further study and analysis. Tumor necrosis factor alpha (TNF- $\alpha$ ) - 17 kDa protein, active as a trimer. Also known by the name cachectin, macrophage cytotoxin; produced by activated monocytes / macrophages, neutrophils, T-cells, NK cells, fibroblasts [3, 4, 22].

By contacting the receptor (TNF- $\alpha$ ), the tumor necrosis factor is capable of triggering a cell death program. TNF- $\alpha$  causes endothelial damage with a decrease in anticoagulant activity and an increase in thrombogenic potential; enhances the synthesis of acute phase proteins and inhibits the activity of cytochrome P-450 in the liver, enhances the activity of macrophages and their synthesis of IL-1 and IL-6. TNF- $\alpha$  is also able to induce fever both directly (by stimulating the synthesis of prostaglandin E<sub>2</sub> by endotheliocytes of the hypothalamic vessels) and indirectly (via induction of IL-1 release).

A significant increase in TNF- $\alpha$  in the blood of patients with recurrent course of CP was noted, with higher values observed in patients with the alcoholic origin of the disease [1, 4, 22].

There is evidence of a significant difference in plasma levels of TNF- $\alpha$  in patients with CP of various etiologies. There is evidence of an increase in the level of TNF- $\alpha$  not only during the

exacerbation, but also in the phase of remission, which indicates the continuation of the inflammatory process in the pancreas [1, 3, 31].

This is of fundamental importance from the standpoint of diagnosis and assessment of the severity of the disease, as well as treatment of patients in the inter-relapse period and the prevention of subsequent exacerbation of CP. It should be noted that our data are quite consistent and do not conflict with the works of other authors in this direction of research [7, 11, 13, 36, 39].

The positive picture of changes in the immune system in most cases was combined with an improvement in the clinical course of CP, which was expressed in a decrease in intoxication, a decrease in the intensity of pain, and an improvement in the condition of patients.

#### 4. CONCLUSIONS:

- 1) In patients with CP significant changes were observed in the functioning of most parameters of the immune system, namely, the deep suppression of T (CD3+)–lymphocytes and its subpopulations, and the tension of humoral immunity.
- 2) In patients with CP, there was a tendency towards an increase in the pro- and anti-inflammatory cytokines, which to a certain extent characterizes the pathological process that occurs in the pancreas.
- 3) The combination of traditional treatment and Thymoptinum was effective in patients with CP, as it contributed to the restoration and stabilization of most parameters of the immune system.

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