

# **Diagnostic and prognostic value of immune indicators of inflammation in the course and progression of gastroesophageal reflux disease and autoimmune thyroiditis in young people**

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**Key words:** gastroesophageal reflux disease, autoimmune thyroiditis, pathogenesis, TNF- $\alpha$ , interleukin-1 $\beta$ , interleukin-18

For many years, the role of the immune system has been viewed from the standpoint of its involvement in anti-infective protection. However, in the early 1960s, a hypothesis was raised about the central role of immunity in cell elimination. A great deal of material has now been accumulated to view the immune system as a regulatory one that is closely linked to the nervous and endocrine systems, whose functions are not only to protect the body against infectious agent but also to preserve homeostasis. Thus, there is a close relationship between the immune system and other regulatory systems of the body [6]. Cytokines are one of the universal mediators that provide links between existing systems. Unlike exogenous modulators (chemical, bacterial or plant origin), the effects of cytokines are achieved through specific receptors, i.e. they are natural regulators of the functional activity of different cell types [13]. Thus, one of the important functions of the cytokine system is to ensure the coordinated action of the immune, endocrine and nervous systems in response to stress [9].

Currently, the existence of more than hundreds of cytokines, which are involved in many processes in the body, has been proven [12]. Cytokines are closely interconnected and form a coherent system of interacting elements, the cytokine network, which has some common features in order to function. The cytokine network functions mainly after antigenic stimulation. This is due to the nature of the functioning of its genes: all genes are inducible, i.e. their activation occurs under the influence of inducers, which act as transcription factors that interact with the enhanced sequences of the regulatory region of the gene. Inductors of cytokine synthesis and expression of its receptor are the same factors that predominantly determine the local nature of the action of cytokines [8, 10].

Cytokines are regarded as a "microendocrine system" due to the fact that they have a triple mechanism of action. First, they affect the producer cell (autocrine effect); second, they affect the neighboring (adjacent) to the cell-producing cells (paracrine exposure). Third, they affect the distant cells of organs and tissues (endocrine exposure) [6]. Most cytokines have a wide range of biological activity, which is associated with their synthesis and secretion by different cell types [13].

One of the conditionally divided groups is proinflammatory cytokines, which include tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 1 $\beta$  (IL-1 $\beta$ ). Tumor necrosis factors (- $\alpha$  and -R) and IL-1 $\beta$  are cytokines with cytotoxic and regulatory actions [10]. They are one of the major mediators of apoptosis, inflammation, and the immune response. Their producers are mainly monocytes and macrophages, but their production is possible by other types of cells — endothelial, mast, dendritic cells,

fibroblasts, cardiomyocytes, stromal cells of the red bone marrow, cells of neuroglia and adipose tissue (13, adipocytes). At the same time, lipopolysaccharides of the cell wall and antigens of various microorganisms, tumor cells, viruses, mitogens, activators of protein kinase C, and the like are stimulators of synthesis. In turn, TNF- $\alpha$  stimulates the secretion of a cascade of endogenous inflammatory mediators (IL-1, IL-6, IL-8, colony-stimulating factors, interferons, etc.) from different cells. It also enhances the phagocytic activity and cytotoxicity of polymorphonuclear leukocytes and has a direct effect on T- and B-cell differentiation [23].

In addition, TNF- $\alpha$  has been shown to have a direct inhibitory effect on thyroid hormone secretion and deiodinase activity in the thyroid gland. TNF- $\alpha$  expression is increased in obesity and correlates positively with adipose tissue mass and insulin resistance.

Among the immunoregulatory mediators, interleukin-18 occupies a special place; it is one of the key cytokines that is involved in the formation of acquired and innate immunity [14]. That is, IL-18 participates in the activation of cytotoxic T lymphocytes, NK cells, macrophages, dendritic cells and promotes the formation of an effective anti-infective and antitumor immune response [18]. In general, it should be noted that due to the presence of various directions of action of this cytokine, it is involved not only in the body's protective reactions, but also in the pathogenesis of many diseases accompanied by chronic inflammation, autoimmune component and tissue destruction [14]. It has been proved that excess IL-18 in vitro can stimulate the expression of adhesion molecules (ICAM-1 and VCAM), i.e. it participates in the process of tissue infiltration by immunocompetent cells [18].

Thus, the non-specificity and many directionality of the action of cytokines allows to determine their diagnostic value and prognostic value in the course of many diseases of internal organs.

In this case, it is appropriate to determine the role of TNF- $\alpha$ , IL-1 $\beta$ , and IL-18 in patients with gastroesophageal reflux disease (GERD), which occurs in young patients with autoimmune thyroiditis (AIT).

The selection of these diseases and the contingent of patients is due to a number of factors. Thus, the pathology of the endocrine system AIT is the leading. The key to the pathogenesis of the disease is the dysfunction of immunoregulatory mechanisms, in particular, the imbalance in the cytokine system [3, 9, 21]. Autoimmune diseases of the thyroid gland occur in 2-5% of cases in the general population. The prevalence of antibodies to thyroperoxidase (AT-TPO) in the population is about 12% [21]. Thyroid hyperfunction is defined in 2% of women; among men it is registered about 10 times less often [7]. According to G.A. Brent et al., Up to 80% of all thyrotoxicosis cases are caused by diffuse toxic goiter [16]. The pathogenesis of the disease is based on genetic factors and the impact of environmental triggers, which leads to impaired gene expression to specific immune cells [9, 11]. At the same time, it has been proven that a key step in the pathogenesis of the autoimmune process in the thyroid gland is the synthesis of antibodies that stimulate it, bind to and activate thyroid-stimulating hormone receptors. One of the leading roles in this process belongs to the cytokine system. A number of studies have demonstrated a positive relationship between the degree of activity of autoimmune processes in thyroid gland

and the content of proinflammatory serum (IL-1 $\alpha$ , IL-8, IL-12, IL-18, INF- $\gamma$ , etc.) and anti-inflammatory (IL-4, IL-10) of cytokines, as well as the content of antibodies to the thyroid-stimulating hormone receptor (AT-rTTH) [1, 2, 3, 15, 22].

In the study of J.A. Zhang et al. (2006) found that mean IL-12 and IL-8 levels in patients with crashes were significantly higher than in the control group. The authors also proved positive correlations between the content of IL-12, IL-8 and the level of thyroid-stimulating antibodies. There are data on the effect of individual cytokines directly on thyroid cells: the ability of TNF- $\alpha$  to inhibit thyroid metabolism has been demonstrated [4, 5, 19]. A link between TNF- $\alpha$  gene polymorphism and an accident has also been established [22].

Jung J.H. et al. (2016) provided the results of a meta-analysis of 10 studies that found a relationship between IL-10 gene polymorphism and susceptibility to autoimmune thyroid disease. It is possible that changes in the activity of some cytokines depend in most cases on the functional state of the thyroid gland, and not on the activity of the autoimmune process. At the same time, changes in the cytokine cascade may depend on concomitant pathology, especially when this pathology has a chronic course and immune mechanisms of formation [1, 3, 10, 17].

**Aim of study** was to determine the role and prognostic values of TNF- $\alpha$ , IL-1 $\beta$  and IL-18 in young patients with autoimmune thyroiditis and gastroesophageal reflux disease.

**Materials and methods.** 113 patients with GERD were involved in the work, which in 83 cases occurred in combination with AIT and in 30 cases isolated. Patients' age ranged from 18 to 25 years (mean age 22.1 $\pm$ 2.11 years) with gender — women predominated: 61 individuals (73.5%) main group and 22 (73.3%) comparison group. The duration of GERD and AIT ranged from "first established" to three years. The young age of the patients and the short history of the disease were the result of involvement in the work of the student community, whose representatives studied in different universities of the city.

Patients were surveyed and examined according to the standard standard procedure. The Montreal Consensus Guidelines (2006) were used in the diagnosis of GERD. The form of the disease, taking into account visual changes (non-erosive or erosive), was evaluated during the FGDS (Fuginon system); while relying on the recommendations of the Los Angeles Classification. Taking 3-4 pieces of biopsy specimens from the esophagus mucosa allowed us to perform histomorphological examination.

The diagnosis of AIT was evaluated by palpation and instrumental changes in the thyroid gland, indicators of the test for antibodies to thyroperoxidase and thyroglobulin, its function — based on the content of thyrotropic hormone (TSH), free thyroxine (T4) and free three (tron). Ultrasound examination of thyroid gland was performed according to the standard method.

The cytokine content of interleukin 1 $\beta$  (IL-1 $\beta$ ), TNF- $\alpha$  and interleukin 18 (IL-18) was determined in the peripheral blood by ELISA using commercial Bender MedSystems GmbH kits (Austria) according to the methods provided.

The indicators of the norm were obtained in the survey of 20 practically healthy persons of the same age, sex and social identity (students).

Each patient received written consent to conduct the study, in accordance with the recommendations of the Ethics Committees on Biomedical Research, Ukrainian

Health Law and the 2000 Declaration of Helsinki, EU Directive 86/609 on the Participation of People in Biomedical Research.

Statistical processing of the measurement results was performed by variational statistics methods using Stata 12.1 licensed software. To assess the statistical significance of the differences between the mean values of the parameters in the compared groups were performed by analyzing the distribution of the studied indicators using the W-Shapiro-Wilk criterion, and the homogeneity of variances by the Leuven criterion. The level of statistical significance was assumed to be at least 95% ( $p < 0.05$ ).

**Results and discussion.** When assessing patients' complaints, it was found that the main manifestation of GERD was heartburn of varying degrees of severity, duration and frequency of onset (Table 1).

Table 1

Characteristics and frequency of occurrence of the main clinical symptoms of GERD in patients of the main group and the comparison group

Clinical signs	Main group (n=83)	Comparison group (n=30)
Heartburn	83 — 100%	30 — 100%
Epigastric pain	9 — 10,8%	2 — 6,7%
Dysphagia	7 — 8,4%	2 — 6,7%
Nausea	11 — 13,3%	3 — 10,0%
Eructation	41 — 49,4%	4 — 13,3%
Hoarseness of voice	5 — 6%	1 — 3,3%

Moreover, in characterizing the intensity of heartburn, it should be determined that in 32 cases (38.6%) of the main group and 11 (36.7%) of the comparison group, it had a moderate intensity; 37 (44.6%) and 15 (50.0%) respectively are weak. Heartburn was reported in 14 (16.9%) and 4 (13.3%) patients in the study groups. The occurrence of heartburn did not depend on the time of day: in the daytime it was recorded in 71.1% and 63.3%, respectively; at night, 49.4% and 36.7% of patients, respectively, complained of it. Regarding the frequency of the onset of the main symptom, in 54.2% and 56.7% of patients, respectively, it was observed every day, otherwise — 2-3 times a week.

The FGDS study showed two main forms of GERD: erosive (22.9% in the main group and 30.0% in the comparison group) and non-erosive (77.1% and 70.0%, respectively).

Antibodies to thyroid peroxidase and thyroglobulin were increased more than 3-fold in all patients with AIT; however, the levels of thyroid-stimulating hormone free T3 and T4 did not exceed normal. That is, AIT had a euthyroid state at the stage of patient observation. In our opinion, the absence of changes in the thyroid hormone indices in these patients was the result of a short history of the disease and a short period of exacerbation of the process.

The content of individual proinflammatory cytokines in the serum was increased in all patients, but their fluctuations differed between groups (Table 2).

Table 2

Levels of immune inflammatory indicators in patients with GERD and AIT comorbidity and isolated GERD

Cytokine (пг/мл)	Main group (n=83)	Comparison group (n=30)	Control group (n=20)
TNF- $\alpha$	7,6 (5,9; 9,8)	5,2 (4,2; 6,9)	1,7 (0,91; 2,4)
IL-1 $\beta$	29,8 (21,9; 35,4)	17,3 (15,9; 19,1)	4,5 (3,1; 6,3)
IL-18	1761,5 (1451,7; 2876,9)	614,6 (521,9; 721,8)	229,4 (198,31; 269,37)

That is, in the active stage of the disease increased levels of proinflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  due to persistence of systemic inflammatory process in the mucosa of the esophagus. The likely increase in the content of these indicators when joining AIT can be explained by the presence of an inflammatory process in the thyroid gland, even with a latent course of the disease. In this case, the difference between the indicators of proinflammatory cytokines is a consequence of the additional activation of the immune chain of the inflammatory process, which arises against the background of immunological pathology.

In the erosive form of esophagitis, the content of TNF- $\alpha$  and IL-1 $\beta$  exceeded the group mean values and amounted to 37.4 (30.7; 53.2) pg/ml and 21.4 (17.3; 25.1) pg/ml respectively for IL-1 $\beta$  and 8.9 (7.4; 9.8) and 6.7 (5.9; 6.9) pg/ml respectively for TNF- $\alpha$ . These results can be explained by the fact that the presence of erosive process in the esophagus is the result of involvement not only of the mucous membrane, but also the submucosal layer of the wall of the organ, that is, more tissue involvement in the pathological process. In addition, an inflammatory shaft is formed around the erosion, consisting of macrophages and leukocytes; the latter are producers of these interleukins.

At the same time, the content of IL-1 $\beta$  and TNF- $\alpha$  was independent of the amount of erosion in the mucosa.

Interleukin 1 $\beta$  and TNF- $\alpha$  are major mediators of local inflammatory responses and general acute phase responses associated with microbial invasion, immune inflammation, and tissue damage. The biological action of IL-1 $\beta$  and TNF- $\alpha$  is ensured by their active involvement in the development of a complex of protective reactions of the organism, which are aimed at limiting infection, eliminating microorganisms, restoring the integrity of damaged tissues [1, 4]. That is, there is a cascade of events that provokes pyroptosis and inflammatory cell death. In this case, on the one hand, enhancing the content of these cytokines is a nonspecific protective reaction of the body, that is, they are the main mediators of the acute-phase response; on the other — with tissue damage and inadequacy of local defense mechanisms their systemic action joins: they stimulate the function of leukocytes (T and B lymphocytes), enhance the synthesis of other interleukins, modulate reparative processes [4, 22]. In this case, the increase in the content of IL-1 $\beta$  and TNF- $\alpha$  in our patients is both a natural reaction to the inflammatory process in the esophageal mucosa at GERD, and the result of an increase in their synthesis in immune inflammation in the thyroid gland. On the other hand, the high activity of these cytokines can be explained by the age of the patients — young people. This age category is characterized by the maximum manifestation of all systems of the triangle

of homeostasis of the body (hyper-reactive response), thus the inflammatory process is not only highly active, but also actively stimulates anti-inflammatory mechanisms, i.e. tissue repair.

The IL-18 content of individuals with combined GERD and AIT was 1761.5 (1451.7; 2876.9) pg/ml, which exceeded the norm by almost 8 times ( $p < 0.05$ ) and, in our opinion, was the result of a stratification of the autoimmune component of inflammation in AIT. In patients with isolated GERD, the IL-18 content also exceeded the norm by almost 2.7 times, which can be explained by its pro-inflammatory properties and the immune system's response. At the same time, the content of IL-18 did not depend on the shape of the esophageal mucosa.

IL-1 $\beta$ , TNF- $\alpha$ , and IL-18 did not correlate with age, gender, and disease duration.

The dependence between TNF- $\alpha$  level in peripheral blood and thyrotropic hormone content was studied. However, unlike the results of other scientists, we have not found such dependence. This is probably due to the lack of fluctuations in our patients (euthyroid state) due to a short history of the disease. At the same time, it can be expected that the progression of AIT on the background of chronic GERD, may contribute to the disruption of hormone synthesis, thereby further leading to the formation of organ hypofunction. That is, impaired thyroid function will occur not only due to the inflammatory process in the gland, but also due to the inflammatory process in the esophagus, accompanied by an increase in TNF- $\alpha$ , IL-1 $\beta$  and IL-18. This thesis requires further study and control of the activity of the inflammatory process on both the side of the esophageal mucosa and the thyroid gland.

Since chronic systemic inflammation is a mechanism for the progression of such combined nosology, it is also important to reduce or lose the tolerance of the immune system, which needs further study.

**Conclusion.** The course of gastroesophageal reflux disease in young people is accompanied by increased synthesis of TNF- $\alpha$  and IL-1 $\beta$  due to the development of systemic inflammation, whose rates are significantly increased when autoimmune thyroiditis is associated.

Increasing the content of proinflammatory cytokines and their dependence on morphological changes in the esophageal mucosa in patients with young GERD and AIT are the result of the development of a common acute-phase response and its local enhancement in the formation of erosions.

In patients with isolated GERD there is an increase in the content of IL-18 — a cytokine that mediates systemic inflammatory process in the esophageal mucosa. When autoimmune thyroiditis is attached, the IL-18 level is likely to increase, which is caused by the participation of this cytokine in immune responses, namely, in the formation of an autoimmune response.

The prospect of further studies is to deepen the study of the combined course of gastroesophageal reflux disease and autoimmune thyroiditis with subsequent prediction of their course and the impact of proteolytic activation of proinflammatory cytokines on clinical and morphological manifestations of the disease.

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**Aim of study** was to determine the role and prognostic values of TNF- $\alpha$ , IL-1 $\beta$  and IL-18 in young patients with autoimmune thyroiditis and gastroesophageal reflux disease.

**Materials and methods.** Study involved 83 patient patients (students) with gastroesophageal reflux disease (GERD) and autoimmune thyroiditis (AIT). The average age for the group was 22.1 $\pm$ 2.11 years. The comparison group was represented by 30 patients of similar age with isolated GERD. The enzyme immunoassay was used to study the content of TNF- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-18 (IL-18).

**Results.** Upon evaluating the complaints of patients, it was found that the main manifestation of GERD was heartburn of varying severity, duration and frequency of occurrence. It has been shown that the course of GERD occurs against the background of the development of a systemic inflammatory reaction (increased synthesis of pro-inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ ), and also depends on the form of esophagitis: more pronounced in the erosive variant of the mucous membrane of the esophagus. At the same time, there was an increase in the synthesis of IL-18, which, with isolated GERD, is associated with a general inflammatory reaction, and with the addition of AIT, the inclusion of immune mechanisms. Relationship between the level of TNF- $\alpha$  in peripheral blood and the content of thyroid-stimulating hormone was studied. However, unlike the results of other scientists, the authors have not identified such a relationship.