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Review Article

Immune-metabolic genesis of pathological processes

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Abstract

This article deals with metabolic-immune processes at rest and under stress conditions, which, in turn, results in the development of immune-dependent and immune-associated disorders. The article analyzes study results and conclusions of various literature sources and experimental data in healthy individuals and patients suffering from non-specific inflammatory lung diseases; purulent-inflammatory diseases and their combinations, primary and secondary progressive multiple sclerosis in the acute stage and remission. Research studies investigated the impact of the type, stage, combination of diseases on the parameters of the immunologic and metabolic statuses, as well as their correlations. The authors also analyzed metabolic effects of immunomodulators. Based on the analysis of the literature and own clinical and experimental data, the authors identified the ability of metabolic factors to regulate immunological processes. A correlative analysis of examination results of the patients with various diseases helped detect the unity of the immune-metabolic mechanisms of pathology. The data on the therapeutic effect of various modulators through differentiated biochemical chains and vice versa – the metabolic effect through immunological mechanisms –were analyzed in the study. Thus, one can testify that there is the phenomenon of a mediated effect of some immunocorrectors on the reactivity through metabolic chains. The fact that a number of modulators and metabolics can simultaneously affect the biochemical and immunological parameters of patients proved the above phenomenon. There was revealed a significant correlation interaction of the immune-metabolic parameters with various types of purulent-inflammatory diseases, which proves the formation of a single mechanism of pathology.

Keywords

immunomodulators, immunotropic effect, immuno-metabolic parameters, metabolics.

Introduction

The last decade has been characterized by an increase in purulent-inflammatory diseases (Ditkoff et al. 2018, Falconi-McCahill 2019). This regularity results from reduced herd immunity of the population due to a number of objective reasons, mutations of microorganisms, hygiene violations, and complications (Majdan 2016). Disorders of nonspecific and specific, regional and systemic mechanisms of anti-infectious resistance play a significant role in the pathogenesis of diseases.

Persistent imbalance of protective reactions ultimately leads to a decrease in the body's resistance to infections and other factors, the induction of chronic pathological processes and their relapses.

In addition, the problem of purulent-inflammatory diseases remains one of the most important problems in the modern world, since they develop in every tenth patient with a high risk of the development of chronic diseases and their recurrence (Tomassetti and D'Hooghe 2018, Zhang et al. 2018).

Treatment and diagnostic characteristics of patients can play a negative role (Dumesic et al. 2015). Firstly, surgical intervention and its therapeutic support are unconditional immunosuppressive factors. Secondly, all pharmacological and non-drug therapeutic measures actively stimulate or suppress immunological reactivity, which leads to the suppression of anti-infectious resistance or induction of auto-aggressive and allergic reactions. Thirdly, diagnostic invasive and non-invasive procedures, on the one hand, also significantly distort the intensity and nature of protective reactions, whereas on the other hand result in infectious contamination of the examined patients with hospital aggressive or opportunistic microorganisms that cause the chronic course of infectious processes and resistance to treatment (Kapral et al. 2018, Verwijs et al. 2019). These processes exacerbate immunological disorders in patients, form a vicious circle of aggravation of purulent-inflammatory diseases, cause their recurrence, and form a negative background for the development of complications (Bove et al. 2018). As a result, the immune system of patients is under multiple (stimulating, suppressing) pressure from the pathological inflammatory process itself due to impaired metabolic immunity (lipid and protein peroxidation, and antioxidant resistance disorders) (Goktas et al. 2019).

The phenomenon of metabolic immunity is intended to mean nonspecific regulation of immunogenesis by biochemical mechanisms (Forti et al. 2019). At rest, the immune-metabolic processes are well balanced, but this balance is disturbed under stress conditions, which leads to the development of immune-related or immune-associated diseases (Zemskov et al. 2018). Various methods, including the correlation analysis of laboratory findings in healthy volunteers and patients suffering from multiple diseases, helped detect a wide range of metabolic factors responsible for immunological phenomena and vice versa (Zemskov et al. 2017).

Metabolic regulation of immunological reactions

Cyclic nucleotides

There is a single mechanism in the body that regulates the biochemical processes and functions of cells belonging to various organs, including the immune system: 3’5’ adenosine monophosphate (3’5’ – AMP) and 3’5’ guanosine monophosphate (3’5’ – GMP). These compounds can be considered as secondary intracellular messengers mediating the action of extracellular factors. The formation of cyclic nucleotides is associated with the activity of enzymes – adenylyl and guanylate cyclase, being components of cell membranes (Aronsson et al. 2014, Soto-Velasquez et al. 2018).

b2-adrenergic stimulants, catecholamines, hormones of the anterior pituitary, glucagon, vasopressin, prostaglandins E, parathyroid hormone, histamine and other biologically active substances appear to be adenylyl cyclase activators. Guanylate cyclase is activated by cholinergic stimulants: acetylcholine, prostaglandins E, steroid hormones and a number of other compounds. Phosphodiesterase is the enzyme that hydrolyzes cyclic nucleotides to inactive 5′-AMP and 5′- GMP. In this system, significant disorders are registered in various diseases, at the same time cAMP inhibits the immune system reactions, whereas cGMP stimulates them.

Thus, deficient adenylyl cyclase system is revealed in leukocytes in patients with bronchial asthma. A lower concentration of 3′5′-AMP is detected in the urine of the patients compared to that of the healthy individuals. The content of cAMP in the blood plasma increases during “acute bronchial asthma” and decreases in the remission stage of bronchial asthma, which indicates constantly predominant intracellular mediator of the cholinergic system. The low coefficient of cAMP/cGMP in the period of remission of bronchial asthma results in a decrease in control over the synthesis of reaginic antibodies of class E and leads to their excessive formation. Therefore, a 3′5′-AMP deficiency in patients with lung diseases is reported to be an unfavorable factor. It should be also noted that this system through certain hormones, for example, the pancreatic produce glucagon, regulates carbohydrate and lipid exchanges, which also play a part in non-inflammatory pulmonary desease pathogenesis (Zemskov et al. 2017).

Nucleic acid exchange

The involvement of nucleic acids in the regulation of cells functioning, including cells of the immune system, is evidenced by the pronounced dynamics of the ribonucleotide content in various pathological conditions: thyrotoxicosis, rheumatic heart disease, various infections, poisoning, radiation injuries, ulcers, bronchopulmonary disease, etc. (Zemskov et al. 2017). Multitude pathological and physiological processes in the body result in the constant destruction of cells of various tissues, the release of nucleic acids, primarily RNA, which are destroyed into low-molecular oligonucleotides under the influence of endogenous nucleases; these low-molecular oligonucleotides do not carry any genetic information, but have a general biological effect. For example, several hours later, under the influence of RNA, there is activated motility, absorption, metabolic ability of monocytes/macrophages, production of humoral protection factors (lysozyme, complement, interferon, etc.) are observed in.

Later, there follows stem cell differentiation, T-B cells and macrophages cooperation, antibodies generation, the body desensitization via the enzymatic and cellular mechanisms, the derepression of immune memory cells, antigen redeposition, etc. As a result, the body reproduces a number of immunological phenomena: tachyphylaxis, which is a rapid non-specific antimicrobial resistance; formation of antiviral interferons; adjuvance, which is a non-specific enhancement of specific immune responses; a revaccinating effect due to antigens redeposition; and immunomodulation, which is normalization of perverted

defense reactions. Additional evidence of the immunotropy of low-molecular-weight nucleic acids is the detection of the direct correlative dependence of the serum RNA content on the level of undifferentiated leukocytes, T-cells and immunoglobulins of class A, and the reverse correlative dependence – on "zero" lymphocytes in ulcers and bronchial asthma (Jung et al. 2018, Shi et al. 2019).

Protein exchange

C-reactive protein (CRP), a marker of an acute inflammatory process, released when various cells are destroyed, is an important factor of the protein exchange. This protein first recruits into the affected area granulocytes, then monocytes/macrophages; binding to ligands, it accelerates the recognition of foreign antigens, activates phagocytosis as the initial phase of the cellular immunity, promotes the development of humoral protection, and stimulates T-cytotoxic lymphocytes (Zemskov et al. 2017).

Other factors of protein metabolism are also immunotropic, which is documented by a strong correlation between the patients' immunological and metabolic parameters. Thus, the dependence of the number of B cells on albumin, and the phagocytic number on α-1 and β-fractions was registered in children suffering from serous meningitis. In the cases of a more severe damage to the meninges (in purulent meningitis), the formation of strong T-cell correlations and their regulatory subpopulations with blood protein fractions was demonstrated. HbsAg carriers had a positive association of total protein concentration with IgM and IgA (Zemskov et al. 2017).

Statistically significant associations were found between the level of total protein and tests characterizing the functional activity of phagocytes (nitro blue tetrazolium spontaneous (NBT_{spont}) and nitro blue tetrazolium activated (NBT_{active})), concentrations of serum Ig A and Ig M in patients with superficial angiitis. The CRP concentration before treatment had a significant positive correlation with T-cells, and a negative correlation with the phagocytic number and immunoglobulins of classes A and M. In patients with deep angiitis, the total protein was positively associated with the phagocytic number, spontaneous and activated by NBT tests, negatively – with IgA and IgG. In these patients, albumin formed positive links with the level of immunoglobulins of classes A, M, and negative – with the CIC, NBT_{active}; while CRP formed positive links with T cells, phagocytic number, zero lymphocytes, and negative – with IgG and IgA, respectively (Zemskov et al. 2017).

Lipid metabolism

The effect of lipid levels on the main parts of the immune system was documented (Genest 2017). Hypercholesterinemia was associated with an increased number of T-helper cells (T-helpers), and a decreased number of T-suppressors/killer cells (T-killers). The accumulation of cholesterol in blood was associated with an increase in the number of B cells (B), and its deficiency was due to their insufficiency (Alvarez-Curto and Milligan 2016). High levels of cytotoxic antibodies and T lymphocytes (T) with Fas/Apo-1 apoptosis antigen expression, which were detected in patients with coronary heart disease, obesity and dyslipidemia; were significantly different from the corresponding parameters in patients without obesity (Ogden et al. 2013, Shahwan et al. 2019). The concentration of aggressive circulating immune complexes (CIC) and IgM was also higher in patients with obesity (Kunz et al. 2019). At the same time, significant correlations were found between the number of cells with apoptosis markers and the body mass index, atherogenic lipid metabolism parameters and creatinine phosphokinase.

On this basis, the directed modification of the components of immunological reactivity through the regulation of lipid metabolism seems to be a real possibility (Waldmann 2015). Vascular sclerosis is an example of the immunopathological condition based on lipid metabolism disorders. The formation of autoantibodies to the transport forms of cholesterol and its esters – high/low density lipoproteins – results in imbibition of the vessel walls. In patients with chronic bronchitis and bronchial asthma, there was recorded an increase in the β-level of lipoproteins and cholesterol, which, on the one hand, compensated for lipid metabolism disorders, and, on the other hand, was a toxic factor of cell proliferation. At the same time, a direct correlative connection of hyperlipidemia with an increased concentration of auto-aggressive medium-weight molecules (MWM) was formed.

Carbohydrate metabolism

Three groups of regulators – catecholamines and thyroid hormones, stimulating glycolysis, and insulin, inhibiting it – appear to be the key participants in carbohydrate metabolism. It was found that a change in glycogenolysis, damage to insulin receptors resulted in the development of autoimmune diseases with involvement of the thyroid gland, pancreas, and other organs (Xavier and Rutter 2019). In patients with diabetes mellitus (DM), there was an increase in the level of immunoglobulins (Ig) and the CIC with a simultaneous decrease in the proliferative activity of lymphocytes in response to mitogen. In patients with type 2 diabetes, the release of a factor that inhibits macrophage migration was reduced; in patients with both types of diabetes, the chemotaxis of neutrophils and their adhesive functions were weakened, and with ketoacidosis, phagocytosis was affected. There was a frequent combination of diabetes with thyroid pathology, which indicated the involvement of the immune system in an autoimmune pathology (Desai and Brinton 2019). Glycaemia reduction restored the function of immunocompetent cells. In patients with insulin-dependent diabetes, there was revealed a positive dependence of the content of lymphocytes expressing CD11b on the level of ceruleoplasmin (CP), glutathione reductase (GR), plasma antioxidant activity, and peroxide resistance (PR); natural killers (NK) were positively dependent on CP; T-cells were negatively depen-

dent on glutathione peroxidase (GPx) and positively dependent on superoxide dismutase (SOD), and the number of B-lymphocytes, respectively, was dependent on SOD. Phagocytic absorption capacity was positively associated with malonic dialdehyde (MDA), negatively with PR, systemic thiols, lipoproteins (LP), cholesterol, whereas oxygen metabolism of neutrophils – with plasma antioxidant activity (Waldman 2015, Zemskov et al. 2017).

Metabolic syndrome

Metabolic syndrome (MS) is an example of a pathological process combining lipid and carbohydrate metabolism disorders (Parikh and Mohan 2012). Metabolic syndrome includes: abdominal (visceral, android) obesity; type 2 diabetes, or impaired glucose tolerance; hypertension; and dyslipidemia. Examination of patients with MS revealed disorders of the immune system which were evident in a decrease in the number of T-lymphocytes, disimmunoglobulinemia with increased levels of IgA and IgG. When metabolic syndrome was combined with a thyroid gland pathology and chronic infectious diseases, an inversion of the immune status was observed with the development of deficiency in T_{cyt}, T-helpers, NK, and an IgG level (Bhargava et al. 2017).

According to (Mazloomzadeh et al. 2019), clinical models of psoriasis, ischemic heart disease (IHD), and their combinations (psoriasis + MS, IHD + MS) revealed the ability of the metabolic syndrome to determine: quantitative aggravation of changes in the parameters of carbohydrate, lipid, and cytokine metabolism, free-radical oxidation of lipids, proteins, the endogenous antioxidant system and endocrinological factors, mainly, with a stimulating effect against the background of stimulating the pro- and anti-inflammatory cytokine formation. Using the coefficient of diagnostic consideration, the offset formulas for sentinel laboratory tests in patients suffering from the combined disorders – psoriasis + MS and IHD + MS – compared to solely psoriasis and IHD: $SOD^{-}_{2}IL4^{+}_{3}HOMAIR^{+}_{3}$ and $HOMAIR^{+}_{3}$ IL $l\beta^{+}_{3}$ thyroid hormone (TH^{+}_{3}). In the first case, in patients with psoriasis, the metabolic syndrome caused a decrease in the activity of the antioxidant superoxide dismutase enzyme, an increase in the concentration of anti-inflammatory IL4, and an insulin resistance index; in the second - stimulation of HOMA IR, IL-lβ and thyroid hormone levels.

The state of the detoxifying function of the liver largely determines the level of immunological reactivity. Hepatocytes, being under constant pressure of stimuli of various chemical nature – xenobiotics – change metabolism and enter the vascular bed of immunomodulating compounds, for example, proteolytic and glycolytic enzymes (Liaskou et al. 2012). Healthy individuals demonstrated a positive correlation of cellular immune parameters with total bilirubin (tBili), conjugated bilirubins (conjBili), amylase, thymol test, ASAT; humoral parameters had a positive correlation with tBili, unbound (free) bilirubin, and a negative correlation with conjBili. In patients with diabetes mellitus, B-cells were associated with thymol test, and IgM – with thymol test, conjBili, and tBili. In Australian antigen carriers and patients with chronic viral hepatitis, these connections were progressively simplified according to an increase in the severity of immunological disorders (Bogdanos et al. 2013, Zemskov et al. 2017).

Enzyme immunomodulation is determined by proteolytic and glycolytic enzymes of medical purposes. Endogenous and exogenous protease activation provides regulation of a T-dependent immune response. This is expressed in the *in vivo* reduction of T-and B-lymphocytes migration (Fig. 1), changes in the structure of the surface of lymphocytes and cell metabolism stimulating the incorporation of 3H-thymidine into the DNA of lymphocytes, an increased mitogenic effect of concanavalin A, and the removal of blocking factors from receptors of lymphoid cells (Zemskov et al. 2017).

Free-radical oxidation of lipids, proteins and antioxidant protection

The treatment of immune-metabolic disorders in various pathological processes is based on the fact that free-radical oxidation (FRO) processes are central to cell metabolism, serve as a source of energy necessary for vital activity, prepare plastic material for creating and updating cellular structures, regulate reactions associated with metabolism of carbohydrates, lipids and proteins. During stepwise degradation of polyunsaturated lipids in FRO reactions, primary, secondary and final molecular products playing an important role in the processes of structural modification of biomembranes and changes in their physicochemical properties are formed. The primary products include diene conjugates, ketodienes; the secondary products are malonic dialdehyde, bityrosine, and the end products are Schiff bases (Vilhardt et al. 2017).

Normally, the content of free-radical oxidation products is small, which is achieved by the presence of the constantly functioning endogenous antioxidant protection system in the body, limiting the processes of free-radical oxidation of lipids and proteins by enzymatic mechanisms (superoxide dismutase, catalase, peroxidase, glutathione peroxidase, proteins with mixed valence (transferrin, ceruleoplasmin), non-enzymatic factors (reduced glutathione, systemic thiols, antiradical activity of blood lipids), as well as β-carotene, retinol, α-tocopherol, polyunsaturated phospholipids, and ascorbic acid (Kiljan et al. 2019).

Combined immuno-metabolic modulation effects

The above data suggest the phenomenon of mediated action on the reactivity of some immunomodulators through metabolic chains. The above phenomenon is evidenced by the implementation of simultaneous action by a number of modulators and metabolic agents on the biochemical and immunological parameters of patients (Zemskov et al. 2017).

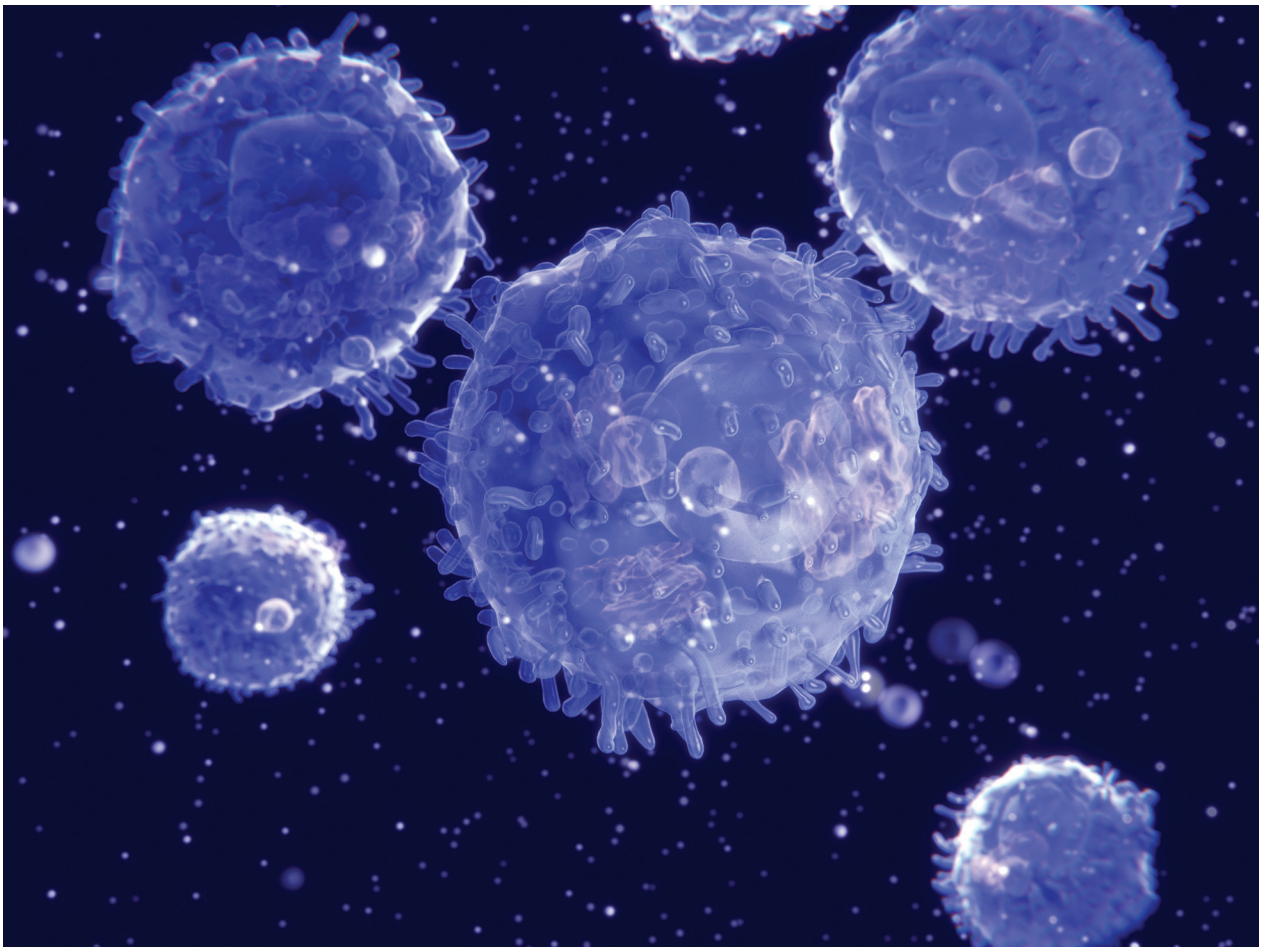

Figure 1. T-lymphocytes.

Metabolic effects of immunomodulators

After combining and analyzing the data of the studies on immunotropic drugs, it was identifed that they had a certain metabolic effect; perhaps in some cases it has not been studied yet (Kuzmenko et al. 2019). Thus, the metabolic effect of **poly- and lipopolysaccharides** was expressed in the intensification of protein synthesis, activation of the adenyl cyclase – cAMP system, and the ^{3}H-thymidine incorporation into the spleen cells. P**rodigiozan** significantly stimulated the activity of the glycolytic dehydrogenase, a key enzyme of the hexose monophosphate shunt (G-6-PD), as well as succinate dehydrogenase, glutamate dehydrogenase, NADH-NADRN diaphorase, and lysosomal enzymes. The metabolic effect of **levamisole** was expressed in stimulating the enzymatic activity of the hexose monophosphate shunt, protein iodization in neutrophils, synthesis of DNA and protein in lymphocytes and macrophages, increased secretion of alpha-gluconidase and cathepsin D in phagocytes, accumulation of intracellular cGMP in lymphocytes and granulocytes. **Muramildipeptide** was able to activate various lysosomal enzymes and to determine an increase in the levels of cAMP, prostaglandins, and DNA. **Polyelectrolytes** (**PAA and P-4VP**) in tissue culture contributed to the formation of DNA and RNA. **Synthetic double-stranded RNA (dsRNA) - poly I:C, poly A:U, poly G:C** increased the ^{3}H-thymidine incorporation into lymphoid and other cells, stimulated the formation of adenylate cyclase, and cAMP. **Thymus derivatives, myelopeptides,** potentiated the synthesis of protein and nucleic acids in various cells. Thymomimetic agents turned out to be lipid metabolism regulators, reduced blood glucose levels, and normalized liver function indicators. In patients with chronic pyelonephritis, **galavit** resulted in the normalization of creatinine and bilirubin; **super lymph** – creatinine; **derinat** – urea, creatinine, ALAT and ASAT (Hsu et al. 2015). **Nucleic acid preparations** – sodium nucleinate, ridostin, derinat, poludan, isoprinosine – manifested not only differentiated immunocorrective, but also metabolic effects (Daniels et al. 2018). Thus, in the experimental models, monoribonucleotide – AMP – reduced 10 times the amount of antibody formomg cells (AFCs) , whereas cytidine monophosphate (CMP), uridine monophosphate (UMP) increased the amount of antibody-forming cells 9–19 times. At the same time, AMP activated antigen-specific suppressors and slowed down hormone replacement therapy (HRT). The maximum stimulation of the metabolism of macrophages is determined by UMP, guanosine monophosphate (GMP), the minimum – by cMP and AMP. Purine nucleo-

tides contributed, whereas pyrimidine nucleotides inhibited the expression of lymphocyte receptors (Dellis and Papatsoris 2018). On the other hand, nucleotides and their components are part of ATP, GTP, UTP, CMP, a number of coenzymes and phospholipids necessary for the normal course of metabolic reactions (Yen et al. 2015). ATP is a source of energy; cytosine nucleotides are involved in lipid synthesis; uridine and guanine nucleotides – in the exchange of polysaccharides; guanine nucleotides – in the synthesis of proteins (Bhargava et al. 2017).

Immunological effects of metabolics

Hypoxen additionally prescribed to patients with chronic pyelonephritis determined the preferential normalization of immunological parameters with the standard formula of immunocorrection targets (FIT) - IgM-$_2$ CIC-$_3$ MWM $^+_3$) – the reduced levels of IgM, CIC, and MWM. The same agent resulted in the modification of various key targets in the immune system – leukocytes, lymphocytes, T-helpers, NK, Ig of the three main classes, phagocyte absorption activity, pro-inflammatory cytokine concentration – IL4 – in patients with mixed, exogenous, endogenous asthma, and chronic obstructive pulmonary disease (Malik et al. 2018). Stimulation was the predominant vector of changes in these parameters (Zemskov et al. 2017). The similar results were obtained with the additional administration of **food supplements:** patients with chronic pyelonephritis and chronic salpingo-oophoritis were given cigapan; patients with chronic salpingo-oophoritis+ bacterial vaginitis were given tykveol; and patients with acute salpingo-oophoritis were given limontar. For example, the FIT of cigapan in chronic salpingo-oophoritis ($NBT_{active}{}^+{}_3PhN^+{}_2PhI^+{}_2$) was made of tests characterizing the absorbing and metabolic capacity of phagocytes; the FIT of cigapan in chronic pyelonephritis ($NK_{regulatory}{}^+{}_3NK_{T\text{-}dependent}{}^+{}_3IL4^+{}_3$) – of tests characterizing two subpopulations of natural killers, IL4, etc. Cigapan in patients with herpetic keratitis had a differentiated effect on the immune system depending on the type of concomitant therapy: on the metabolic and absorbing capacity of phagocytes, CIC or -–on T-helpers, CIC, NBT_{active} or – on CIC, $T_{cytotoxic}$, B cells; or – on T-helpers, IgA, and NK (Zemskov et al. 2018). Native **protein drugs**: amino acids – glutamic acid, methionine, cysteine, viceine, aminalon, hypophenate; human blood products = albumin, protein (albumin, α, β-globulins), aminocrovins (a solution of amino acids and low molecular weight peptides); protein hydrolysis products, casein, liver of cattle and pigs – hydrolysin (L-103), amopeptide, casein hydrolyzate, syrepar, fibrinosol were effective in treating the immunopathology of the cellular, humoral, and phagocytic immunity. **Energizers** (riboflavin, nicotinamide), **glycolysis activators** (thiamine, riboxin), **stimulants of the tricarboxylic acid cycle** (biotin, lipoate), **proteolytic and glycolytic enzymes** (trypsin, terrilitina, lysozyme, hyaluronidase), **vitamins** (β-carotene, retinol, α-tocopherol); **hepatoprotectors** (essentiale, carsil, phosphoglyph); **adaptogens** (pantocrin, eleutherococcus, esberitox); **metabolics** (potassium orotate, pentoxyl, methyluracil); **eubiotics** (acipol, acilact, baktisubtil) had a pronounced correcting effect on immunological disorders (Hauser et al. 2016).

Cyclic nucleotides inducing or inhibiting enzyme systems and functions of the elements of the immune system seem to be the mediating mechanism of the action of metabolic processes on immunocompetent cells. It is known that 3,5-AMP inhibits neutrophil phagocytosis, proliferation and differentiation of lymphocytes, T-B-effector cells, cell-humoral reactions, and 3,5-GMP stimulates these processes, as well as hypothetical receptors for nucleic acids on lymphoid and other cells.

Changes in immunological and metabolic parameters in various diseases

The subjects of studying the literature data and clinical and experimental research data were healthy individuals and patients suffering from nonspecific inflammatory lung diseases (NSILD – bronchial asthma, bronchitis, obstructive pulmonary disease); purulent-inflammatory diseases – acute and chronic cystitis, acute and chronic pyelonephritis, acute and chronic salpingo-oophoritis, deep pyoderma, purulent soft tissue infection; combinations of chronic cystitis + chronic pyelonephritis, chronic cystitis + chronic salpingo-oophoritis; chronic pyelonephritis + urinary stone disease (USD), chronic pyelonephritis + benign prostatic hyperplasia (BPH); chronic salpingo-oophoritis + bacterial vaginosis (BV), chronic salpingo-oophoritis + cervicitis, chronic salpingo-oophoritis + endometritis, deep pyoderma with skin allergies, purulent infection of soft tissues with true eczema; multiple sclerosis with primary and secondary progressive forms (PPMS, SPMS) (Kaymakamzade et al. 2019), in the acute stage and remission. The authors studied the impact of the type, stage, combination of diseases on the parameters of the immunologic and metabolic statuses, as well as their correlations (Geijer et al. 2015, Germano et al. 2019, Huang et al. 2019).

Investigating the data from clinical and experimental studies of various foreign and Russian researchers, the following parameters were analyzed: the number of leukocytes (L), lymphocytes (Lymph), mature and immature granulocytes (stabs and segmented), monocytes (M), ESR; clones and subclones of lymphocytes (T-cells – T, T-helper cells – T-helpers, T-cytotoxic cells – T-cytotoxic, T-regulators - Tr, T-activated cells – T-activated, T-cell-dependent natural killers– $NK_{T\text{-}dependent}$, regulatory natural killer cells – $NK_{regulatory}$, cytotoxic natural killer cells – $NK_{cytotoxic}$, B-lymphocytes – B) were evaluated using flow cytofluorometry NAVIOS Beckman Coulter and monoclonal antibodies CYTO-STAT tetra CHROM, a biochemical analyzer Chospitec, Holland, spectrophotometric, turbodimetric, and immunoenzymatic methods; the absorbing and oxygen-producing capacity of phagocytes (phagocytic index – PhI, phagocytic number – PhN, nitro blue tetrozolium

spontaneous – NBT_{spont}, nitro blue tetrozolium activated – NBT_{active}), concentration of circulating immune complexes (CIC), serum immune globulins of the main classes (IgM, G, A), medium-weight molecules (MWM), pro-and anti-inflammatory cytokines (IL-2, 4,6,6,8,10, TNF) were evaluated using sets by Protein Contour Company (Cruz 2014, Ermishina et al. 2014, Malik et al. 2018).

The parameters of free-radical oxidation of lipids and proteins – diene conjugates, ketodienes, malonic dialdehyde (MDA), bi-tyrosine linkages, Schiff bases and indicators of the antioxidant protection system – superoxide dismutase (SOD), catalase (K), vitamin E (VE), systemic, protein, non-protein thiols, plasma antioxidant activity – were determined using methods of UV spectrophotometry, fluorescence, reaction with 2-thiobarbituric acid, etc.

The analysis of the literature data on the problem revealed that a number of researchers applied the modern panel of planning methods to support the relevance of the results obtained – randomization, representativeness of the sample according to L.E. Kholodov, V.P. Yakovlev formula (Zemskov et al. 2017), statistical analysis of the laboratory findings using parametric (Student's) and non-parametric (Wilcoxon-Mann-Whitney) criteria depending on the normal distribution of the parameters. The coefficient of diagnostic consideration (Kj) was calculated according to the formula (Gorelik, Skripkin):

$$Kj = \frac{2 \cdot \left(\delta_1^2 + \delta_2^2\right)}{\left(M_2 - M_1\right)^2},$$

where δ^2_1 и δ^2_2 are mean root square deviations, M_1, M_2 – mean values of the parameters of the compared groups; the sentinel tests were determined with the following interpretation: the lower the Kj module was, the more the parameter deviated from the target level.

All the analyzed data of the previous studies were comnined to formalize the key laboratory tests into the standard formulas of the immune system disorders and metabolic disorders and to reveal the specific regularity with reference to normal values in healthy people (See Tables 1 and 2).

Cystitis

With all thefindings on immunological and metabolic parameters from various scientific literature being combined in a single table (see Table 1), it can be seen that the following parameters were the key parameters of the standard formula of the immune system disorders **in acute cystitis**: $T_{cytotoxic}$, Ig M, MWM, all with a stimulating vector of the 3rddegree. **Chronic cystitis** was characterized by a decrease in the number of T-helpers, IgA with the accumulation of pro-inflammatory interleukin 8 (Lai et al. 2014). **The complication of chronic cystitis with chronic pyelonephritis** resulted in leukocytosis, T-cell deficiency, inhibition of the phagocyte absorption function of the 3rd-degree (Amano and Shimizu 2014). **The combination of chronic cystitis with chronic salpingo-oophoritis** contributed mainly to class A hyperimmunoglobulinemia, stimulation of the $T_{activated}$ lymphocyte count, and inhibition of neutrophil oxygen metabolism of maximum or average severity. Specific features were detected when determining the reference metabolic parameters selected in patients for the formula of metabolic disorders. In this case, according to the criteria – the order, vector and degree of changes from the norm of the indicators – the composition of standard formulas was original in all cases. Thus**, in acute cystitis,** there was a medium decrease in the antioxidant parameter – anti-oxidant plasma activity against the background of the suppression of two enzymatic mechanisms of the antioxidant protection – catalase and superoxide dismutase. **In chronic cystitis,** stimulation of the enzyme ceruleoplasmin, reduction of non-enzymatic systemic thiols and anti-oxidant plasma activity played the leading role (Keagy 2018). **In chronic cystitis + chronic pyelonephritis,** there was observed a predominant accumulation of free-radical oxidation parameters – ketodienes, MDA combined with inhibition of the concentration of the antioxidant enzyme SOD. **In chronic cystitis + chronic salpingo-oophoritis,** there was a significant increase in the level of MDA, inhibition of the enzymatic and non-enzymatic mechanisms of anti-oxidant protection – SOD and anti-oxidant plasma activity of the 2nddegree (Bollestad et al. 2018).

Pyelonephritis

In patients with **acute pyelonephritis**, the key factors were: stimulation of the PhI, MWM, $T_{cytotoxic}$ level, and the reduction of catalase, plasma anti-oxidant activity, and vitamin E. **In chronic pyelonephritis**, accumulation of B-cells, MWM, Schiff bases, MDA was observed along with inhibition of neutrophil metabolism and SOD. In the combination of **chronic pyelonephritis with chronic cystitis,** the key factors were: leukocytosis, T-cell deficiency, phagocytic number combined with an increase in the ketodienes, MDA concentration, and SOD deficiency. **The combination of chronic pyelonephritis + chronic salpingo-oophoritis** resulted in monocytosis, an excess of B-lymphocytes, a decrease in NBT_{sp}, with stimulation of the bi-tyrosine linkages formation, and a decrease in SOD and protein thiols. **The combination of chronic pyelonephritis with USD** resulted in the activation of the B-lymphocyte formation, CIC, $T_{cytotoxic}$ suppressors, MDA, Schiff bases with a decrease in plasma anti-oxidant activity. In chronic pyelonephritis + benign prostatic hyperplasia, there was a $T_{cytotoxic}$deficiency, CIC overproduction, a deficiency of pro-inflammatory IL6, diene conjugates, MDA, and systemic thiols.

Salpingo-oophoritis

An analysis of various clinical and experimental studies helped reveal that in patients with acute salpingo-oophoritis the sentinel tests of the standard formulas of the immu-

Table 1. Sentinel Tests of the Key Formulas of Immune-metabolic Disorders and Their Correlations in Purulent-inflammatory and Other Diseases.

Disorders	Formulas of immune system disorders	Formulas of metabolic disorders	Correlations
Mono purulent-inflammatory diseases			
GP	CIC^{+}_{3} $NKcyt^{+}_{3}$ $IL6^{+}_{3}$	VE^{+}_{3} MDA^{+}_{2} plasma anti-oxidant $activity^{-}_{2}$	CIC^{+}_{3}+**Schiff bases,-ceruleoplasmin**; $NKcyt^{+}_{3}$ **–plasma anti-oxidant activity**; $IL6^{+}_{3}$**-systemic thiols**
Acute pyelonephritis	PhI^{+}_{2} MWM^{+}_{3} $T_{cyt}{}^{+}_{3}$	K^{-}_{1} plasma anti-oxidant $activity^{-}_{2}$ VE^{-}_{1}	PhI^{+}_{2}**-MDA,+Schiff bases;** MWM^{+}_{3}**-plasma anti-oxidant activity**
Chronic pyelonephritis	B^{+}_{3} MWM^{+}_{3} $NBTsp^{-}_{2}$	$Schiff\ bases^{+}_{2}$ SOD^{-}_{2} MDA^{+}_{3}	B^{+}_{3}**+MDA**; $T_{cyt}{}^{+}_{3}$**-VE,-SOD**
Acute salpingo-oophoritis	TNF^{+}_{3} CIC^{+}_{3} IgM^{+}_{3}	MDA^{+}_{2} plasma anti-oxidant $activity^{-}_{1}$ bi-tyrosine linkages T^{-}_{1}	CIC^{+}_{3}**-ceruleoplasmin**; IgM^{+}_{3}**+bi-tyrosine linkages**
Chronic salpingo-oophoritis	T^{-}_{3} IgM^{+}_{3} $IL6^{+}_{3}$	VE^{+}_{1} plasma anti-oxidant $activity^{-}_{1}$ $Schiff\ bases^{+}_{2}$	T^{-}_{3}**+Schiff bases**; IgM^{+}_{3}**+ceruleoplasmin**; $IL6^{+}_{3}$**+catalase**
Acute cystitis	$T_{cyt}{}^{+}_{3}$ IgM^{+}_{3} MWM^{+}_{3}	plasma anti-oxidant $activity^{-}_{2}$ $catalase^{-}_{1}$ SOD^{-}_{1}	$T_{cyt}{}^{+}_{3}$**–bi-tyrosine linkages,-ketodienes**; MWM^{+}_{3} **–VE**
Chronic cystitis	$T\text{-}helpers^{-}_{2}$ IgA^{-}_{2} $IL8^{+}_{3}$	$ceruleoplasmin^{+}_{2}$ $systemic\ thiols^{-}_{3}$ plasma anti-oxidant $activity^{-}_{2}$	$T\text{-}helpers^{+}_{2}$**+diene conjugates;** $IL8^{+}_{3}$**-VE,-systemic thiols**.
Purulent infections of soft tissues	$T_{cyt}{}^{+}_{3}$ $IL8^{+}_{3}$ B^{-}_{2}	plasma anti-oxidant $activity^{-}_{3}$ $ketodienes^{+}_{2}MDA^{-}_{1}$	$T_{cyt}{}^{+}_{3}$**+MDA;** B^{-}_{2}**+plasma anti-oxidant activity + catalase**
Combined purulent-inflammatory diseases			
Chronic cystitis+chronic pyelonephritis	L^{+}_{3} T^{-}_{3} PhN^{-}_{3}	$ketodienes^{+}_{2}$ MDA^{+}_{2} SOD^{-}_{2}	L^{+}_{3}**+diene conjugates**; T_{3}+**Schiff bases,-SOD**; PhN^{-}_{3}**-catalase,-non-protein thiols**
Chronic cystitis +chronic salpingo-oophoritis	IgA^{+}_{3} Tac^{+}_{2} $NBT_{active\ 3}{}^{-}$	MDA^{+}_{3} SOD^{-}_{2} plasma anti-oxidant $activity^{-}_{2}$	IgA^{+}_{3}**–MDA,+plasma anti-oxidant activity**;$T_{activated\ 2}{}^{+}$**+ceruleoplasmin,+systemic thiols**; $NBT_{active\ 3}{}^{-}$**+bi-tyrosine linkages,+SOD, +catalase**
Chronic salpingo-oophoritis +endometritis	T^{-}_{2} NK^{+}_{3} IgA^{+}_{3}	$systemic\ thiols^{-}_{2}$ VE^{-}_{3} plasma anti-oxidant $activity^{-}_{2}$	T^{-}_{2}**+VE,+ceruleoplasmin,+catalase**;NK^{+}_{3}**-ketodienes;** IgA^{+}_{3}**+MDA,+plasma anti-oxidant activity**
Chronic salpingo-oophoritis+bacterial vaginitis	$T\text{-}helpers^{-}_{2}$ CIC^{+}_{3} $T_{activated}{}^{+}_{3}$	$ceruleoplasmin^{+}_{2}$ $systemic\ thiols^{-}_{2}$ plasma anti-oxidant $activity^{-}_{2}$	CIC^{+}_{3}**+ketodienes, +Schiff bases, +bi-tyrosine linkages**;$T_{activated}{}^{+}_{3}$**+SOD,+systemic thiols**
Chronic salpingo-oophoritis+cervicitis	IgG^{+}_{2} $NKcyt^{+}_{2}$ IgM^{+}_{2}	$ketodienes^{+}_{2}$ $bi\text{-}tyrosine\ linkages^{-}_{2}$ $catalase^{-}_{2}$	IgG^{+}_{2}**-ketodienes,-plasma anti-oxidant activity**; IgM^{+}_{3}**-diene conjugates, +non-protein thiols, +bi-tyrosine linkages**
Chronic salpingo-oophoritis+chronic pyelonephritis	M^{+}_{3} B^{+}_{3} $NBTsp^{-}_{2}$	$bi\text{-}tyrosine\ linkages^{+}_{2}$ SOD^{-}_{2} $systemic\ thiols^{-}_{2}$	M^{+}_{2}**-VE,-systemic thiols**; B^{+}_{3}**–MDA,-bi-tyrosine linkages**,**-catalase, +SOD**; $NBTsp^{-}_{2}$**+ketodienes,-ceruleoplasmin**
Chronic pyelonephritis+USD	B^{+}_{3} CIC^{+}_{3} $Tcyt^{+}_{2}$	MDA^{+}_{3} $Schiff\ bases^{+}_{2}$ plasma anti-oxidant $activity^{-}_{3}$	B^{+}_{3}**-Schiff bases,+plasma anti-oxidant activity, +MDA, -catalase**; CIC^{+}**ceruleoplasmin, -systemic thiols**
Chronic pyelonephritis +BPH	$Tcyt^{-}_{3}$ CIC^{+}_{3} $IL6^{-}_{2}$	$diene\ conjugates^{-}_{2}$ MDA^{-}_{1} $systemic\ thiols^{-}_{3}$	$T_{cyt}{}^{+}_{3}$**+ketodienes.-MDA, +bi-tyrosine linkages**; CIC^{+}_{3}**-ceruleoplasmin;** IL^{-}_{2}**-ketodienes,+plasma anti-oxidant activity**
Deep pyoderma +skinallergies	$eosinophils^{+}_{3}$ B^{+}_{3} TNF^{+}_{3}	$systemic\ thiols^{-}2$ MDA^{+}_{2} plasma anti-oxidant $activity^{-}_{2}$	$eosinophils^{+}_{3}$**+ketodienes,-plasma anti-oxidant activity**; B^{+}_{3} **+VE,-Schiff bases**; TNF^{+}_{3}**+bi-tyrosine linkages-,MDA,-systemic thiols**
Purulent infections of soft tissues+true eczema	$T\text{-}helpers^{-}_{3}$ $T_{cyt}{}^{+}_{3}$ CIC^{+}_{3}	$schiff\ bases^{+}_{2}$ SOD^{-}_{2} VE^{+}_{3}	$T\text{-}helpers^{-}_{3}$ **+MDA,+diene conjugates,-SOD**; $T_{cyt}{}^{+}_{3}$ –bi-tyrosine linkages**,-ceruleoplasmin**; CIC^{+}_{3}**+bi-tyrosine linkages,-plasma anti-oxidant activity**

Note: GP – glutathione reductase, CIC – circulating immune complexes, VE – vitamin E, NK – natural killers, SOD – superoxide dismutase, MDA – malonic dialdehyde, Ig – immunoglobulin; TNF – tumor necrosis factor.

Table 2. Signaling Immuno-metabolic Risk Factors for Clinical Variants of Multiple Sclerosis (MS).

Clinical forms of MS	Parameters	
	Immunologic	**Metabolic**
PPMS	**T, T-helpers,** $NK_{T\text{-}dependent}$, CIC, PhI, NBT_{spont}	**MDA**, **Schiff bases**, systemic thiols, **VE**, ceruleoplasmin, GP, **GR**
SPMS	**T-helpers,**$NK_{cytotoxic}$, HLA, B, PhI, NBT_{spont}	**MDA**, **Schiff bases**, systemic thiols, GP, GR
Acute stage	T, T-helpers, $NK_{T\text{-}dependent}$, $NK_{cytotoxic}$, B, NBT_{spont}	**MDA**, **systemic thiols**, VE, catalase, GP
Remission	HLA, **CIC**, B, **IgA**, NBT_{spont}	**MDA**, diene conjugates, Schiff bases, **systemic thiols**, VE, **catalase**

Note: parameters of the standard formulas of the immune system disorders and metabolic disorders included in the key risk factors are given **in bold**; GP - glutathione reductase, GR - glutathione reductase, CIC - circulating immune complexes, VE - vitamin E, NK -natural killers, MDA - malonic dialdehyde, PPMS - primary progressive forms, SPMS - secondary progressive forms.

ne system disorders and metabolic disorders, respectively, were: TNF α, auto-aggressive CIC, IgM and MDA, plasma anti-oxidant activity and bi-tyrosine linkages. Chronic inflammation of the uterine appendages caused a predominant decrease in the level of T-cells with accumulation of IgM and pro-inflammatory IL6. At the same time, in the patients there was the activation of vitamin B and Schiff bases formation and a decrease in plasma anti-oxidant activity. Chronic salpingo-oophoritis complicated by chronic cystitis modified the qualitative composition of the formulas of immuno-metabolic disorders (MacLean et al. 2013). Accordingly, patients were diagnosed with hyperimmunoglobulinemia A, an excess of T_{active} lymphocytes, a decreased amount of the neutrophil oxygen metabolism, and a stimulation of the MDA concentration with a decrease in SOD and plasma anti-oxidant activity. Bacterial vaginosis caused a predominant decrease in the T-helpers level, an increase in CIC, T_{active}, the free-radical oxidation-ceruleoplasmin factor, suppression of the antioxidant protection factor – SOD parameters and plasma anti-oxidant activity (Desai and Brinton 2019, Faught and Reyes 2019).

In general, the above data demonstrate that as pathological inflammatory processes in the urogenital organs transform from acute to chronic, from mono to combined, a quantitative and qualitative increase and differentiation of changes in the immunological parameters can be observed, which is combined with pronounced variations in the metabolic components of the oxidative stress or vice versa (Kicha et al. 2018). To prove the correlations between these mechanisms, the authors applied methods to identify the key parameters of the disorders and their correlation relationships.

Consistent changes in immuno-metabolic parameters in various diseases

To prove the presence of a functional relationship between the immunological and metabolic parameters in patients with a wide range of pathological processes, a number of researchers used a correlation analysis determining the presence of strong relationships, with the coefficient of the above laboratory tests being > 0.6.

The clinical model of NSILD demonstrated that the content of T-cells, $T_{cytotoxic}$ and T-helpers is inversely correlated with the level of free-radical oxidation products, which can be explained by the suppressive effect of this mechanism on the immune system, mainly, on the cellular link. Thus, the absolute amount of $T_{cytotoxic}$ correlates with the content of MDA, GP, SOD, while T-helpers – with the concentration of MDA, GP, and SOD (Mikalsen et al. 2018). The authors suggested that free-radical oxidation products have a toxic effect on T-lymphocytes, inhibit their proliferation, cause membrane destruction via damage to the lipid layer, contribute to the formation of autoantigens and autoimmune reactions. At the same time, hyperlipidemia developing in patients causes inhibition of T-cell proliferation processes and distortion of intracellular metabolism with impaired functioning. A correlation analysis demonstrated that the investigated antioxidant protection values of blood were inversely interdependent on free-radical oxidation products, which shows the accumulation of toxic peroxide products that inhibit the activity of enzymatic and non-enzymatic mechanisms of anti-oxidant protection (Natsume 2019).

Additional information is provided by the analysis of strong correlations between the key immuno-metabolic indicators formalized into the typical formulas for immune system disorders and metabolic disorders in patients with purulent-inflammatory diseases and multiple sclerosis (Tables 1 and 2).

The data in Table 1 indicate the presence of a significant correlation interaction among the immune-metabolic parameters in patients with various types of purulent-inflammatory diseases of the bladder, kidneys and uterus appendages, which proves the formation of a single mechanism of pathology – immune-oxidant stress.

A different picture of the immune-biochemical correlations was revealed with **purulent-inflammatory diseases.** Thus, in **acute cystitis**, an increased number of $T_{cytotoxic}$ was negatively associated with the free-radical oxidation parameter — bi-tyrosine linkages, whereas immune-active MWM — with the non-enzymatic antioxidant defense factor – vitamin E. In chronic cystitis, the character of correlations was different: a reduced number of T-helpers consistently varied along with the level of diene conjugates, whereas an excessive amount of IL-8 was negatively dependent on the concentration of vitamin E and systemic thiols. **In combination of chronic cystitis + chronic pyelonephritis,** leukocytes formed a positive correlation with diene conjugates, T-cells formed a negative correlation with Schiff bases and SOD, the phagocytic number also formed a negative correlation with catalase and non-protein thiols. **In chronic cystitis complicated by chronic salpingo-oophoritis,** the number of strong bonds turned out to be maximal – 7. The content of IgA was negatively dependent on the amount of MDA and positively – on plasma anti-oxidant activity, whereas the number $T_{activated}$ consistently positively changed along with the levels of ceruleoplasmin, systemic thiols, bi-tyrosine linkages, SOD, and catalase (Bollestad et al. 2018).

In patients with **acute pyelonephritis**, the absorbing capacity of phagocytes was associated with free-radical oxidation factors (MDA, Schiff bases), and MWM – with plasma anti-oxidant activity. **In chronic pyelonephritis**, the reverse dynamics was observed – B cells were associated with one free-radical oxidation parameter (malonic dialdehyde), and MWMs were associated with two anti-oxidant protection tests – vitamin E and SOD. The combination of **chronic pyelonephritis + chronic cystitis** contributed to the correlation of leukocytosis with diene conjugates; T cells – with Schiff bases and SOD; PhN – with catalase and non-protein thiols. In **chronic pyelonephritis + chronic salpingo-oophoritis**, the number of monocytes depended

on the level of non-enzymatic mechanisms of anti-oxidant protection, vitamin E, and non-protein thiols; the number of B-lymphocytes depended on markers of the lipid free-radical oxidation, MDA proteins, bi-tyrosinelinkages, anti-oxidant protection enzymes – catalase, SOD; operational oxygen-dependent neutrophil metabolism depended on free-radical oxidation and anti-oxidant protection factors –ketodienes and ceruleoplasmin (Aronsson et al. 2014). **In patients with a combination of chronic pyelonephritis and USD**, the number of B-cells consistently was changed in dependence on two free-radical oxidation parameters – Schiff bases and MDA, two anti-oxidant protection parameters – on plasma anti-oxidant activity and catalase; CIC concentration – on non-enzymatic mechanisms of the anti-oxidant system – ceruleoplasmin and systemic thiols. In patients with complex pathology – **chronic pyelonephritis + BPH**, the $T_{cytotoxic}$ content correlated with three tests of free-radical oxidation – ketodienes, MDA, and bi-tyrosine linkages; the content of auto-active CICs correlated with ceruleoplasmin activity; the content of anti-inflammatory IL 2 correlated with free-radical oxidation and anti-oxidant protection mechanisms – catalase and plasma anti-oxidant activity.

In acute salpingo-oophoritis, the correlation analysis revealed a strong correlation between the level of CIC and the non-drug factor of the anti-oxidant protection ceruleoplasmin, as well as the correlation between immune globulins M and the free-radical oxidation parameter – bi-tyrosine linkages. **In chronic inflammation of uterine appendages,** the key tests of formulas of the immune system disorders were associated with two free-radical oxidation parameters – Schiff bases, ketodienes and ceruleoplasmin (an anti-oxidant protection parameter).

Chronic salpingo-oophoritis complicated by chronic cystitis modified the qualitative composition of the formulas of immunological and metabolic disorders. Thus, hyperimmunoglobulinemia A, an excess of $T_{activated}$ lymphocytes, a decrease in the neutrophilic oxygen metabolism, and a stimulation of malondialdegyde concentration along with a decrease in superoxide dismutase and plasma anti-oxidant activity were diagnosed in patients. The reference immunological tests of the formulas of the immune system disorders were consistently modified: IgA^{+}_{3} – along with the level of MDA, +plasma anti-oxidant activity; $T_{activ\ 2}^{+}$ – along with +ceruleoplasmin and +systemic thiols; $NBT_{activ\ 3}^{-}$ – along with +bi-tyrosine linkages, +SOD, and +catalase (Amano and Shimizu 2014). **Bacterial vaginosis** resulted in a significant dependence of the CIC concentration on the content of free-radical oxidation products – ketodienes, Schiff bases, and bi-tyrosine linkages, whereas T_{activ} – on the anti-oxidant protection factors: superoxide dismutase and systemic thiols (Amano and Shimizu 2014).

Table 2 demonstrates mathematically distinguished immuno-metabolic risk factors for the formation of individual forms and stages of **multiple sclerosis** (Kiljan et al. 2019). The fact that the key parameters of the formulas of the immune system disorders and metabolic disorders are included in the range of risk factors in the clinical forms of MS appears to be an indirect evidence of a certain unity of the immune-metabolic mechanisms of the pathology: in the primary progressive form – T, T-helpers, MDA, vitamin E, and GR; in the secondary progressive form – T-helpers, PhI, MDA, and Schiff bases; in the acute remittent stage – $NK_{T\text{-dependent}}$, $NK_{cytotoxic}$and MDA, Schiff bases; and also in the remission stage – CIC, IgA, MDA, and catalase.

Conclusion

Based on the analysis of various literature and clinical and experimental data, the authors determined the ability of metabolic factors – cyclic nucleotides, nucleic acid, protein, lipid, carbohydrate metabolism, metabolic syndrome, free-radical oxidation of substrates, antioxidant system, detoxifying systems of the liver, exogenous and endogenous enzymes – to regulate immunological processes. A correlative analysis of the examination results of patients with various diseases – NSILD, purulent-inflammatory diseases, multiple sclerosis in primary and secondary progressive forms in acute stages and in remission stages – supported the unity of the immune-metabolic mechanisms of pathology. The data on the therapeutic effect of modulators of various origins were analyzed through differentiated biochemical chains and vice versa – the realization of the effect of metabolics through immunological mechanisms.

Conflict of interest

The authors have no conflict of interest to declare.

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