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INTERRELATION OF THE CONTENT OF TRANSFERRIN, ERYTHROCYTES WITH THE FUNCTIONAL ACTIVITY LEUKOCYTES OF PERIPHERAL VENOUS BLOOD IN RESIDENTS OF THE EUROPEAN NORTH OF THE RUSSIAN FEDERATION

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The aim is establish the relationship between the content of transferrin, erythrocytes and the functional activity of leukocytes of peripheral venous blood in residents of the European North of the Russian Federation. Study included analysis of immunological parameters of 765 people, aged 18 to 89 years, living in the Arkhangelsk, of which 553 women aged 18-89 years and 212 men aged 18-84 years. It was found that increase in 49.21% of the examined individuals, the iron-containing protein increases against the background of a decrease in the content of the membrane transferrin receptor (CD71+). An increase in the content of transferrin is associated with an increase in the concentration of circulating IgG immune complexes in 44.21% of cases. With an increase in the concentration of transferrin in the blood in 27.95% of cases it is associated with a decrease in platelet count and in 24.08% - with a decrease in hemoglobin, mainly in men with increasing age. In 8.06% of the examined individuals, an increase in the level of transferrin is interrelated with an increase in the concentration of reagins. In 5.12% of cases, an increase in the transferrin content is associated with the activation of cell-mediated cytotoxicity, which is mainly supported by the pro-inflammatory cytokine IL-6. No association has been established between the increase in transport protein and the concentration of IL-10.

Keywords: transferrin, erythrocytes, hemoglobin, lymphocytes, cytokines, IgE, circulating immune complexes.

Background. The functions of the iron transport protein are not limited to participation in iron homeostasis [1]. Reference range of transferrin on the serum content is 170-340 mg / dL, in the bloodstream it is in a state of apo-, mono-, or bi-iron transferrin [2] and half-life is 8-12 days [3]. Normally, transferrin is saturated with iron by 20-30% [4,5], therefore, the iron-binding capacity is used only by 1/3. Iron transport protein with partial saturation, being a component of the antioxidant system, binds blood plasma iron and protects cell from disrupting membrane structures and reducing cell energy supply when intensifying lipid peroxidation processes [6]. In addition, iron binds to complexes with albumin, low molecular weight organic compounds, forming a pool of nontransferrin-bound iron [7,8]. The content of iron-binding protein is interrelated with the content of cells with a membrane receptor for transferrin [9,10]. In addition, when binding to receptors on the cell surface, transferrin is involved in the transport of metals: Zn, Co, Ga, Al. It should be taken into account that the content of transport proteins in the inhabitants of the North fluctuates within wide limits due to the pronounced photoperiodicity and intensity of the geomagnetic field [11,12].

The aim of the study was to establish the relationship between the content of transferrin and erythrocytes with the functional activity of leukocytes in peripheral venous blood in residents of the European North of the Russian Federation.

Material and methods. The immunological results of preanalytical and analytical stages of examination of 765 people were analyzed, including 553 women aged 18-89 years and 212 men aged 18-84 years, living in Arkhangelsk, who applied to the center of professional diagnostics "Biolam". The inclusion criteria are residence of the examined persons in Arkhangelsk and voluntary consent to the examination.

All stages of clinical laboratory examination were performed by medical workers of the laboratory of the center "Biolam": instruction on the rules of preparation for laboratory research, taking of biomaterial and its preliminary processing, application of analytical technology using appropriate reagents and equipment, obtaining examination results. Clinical and

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diagnostic interpretation of the examination results, identification of risk factors and causes of the disease, the formation of recommendation protocols was carried out by the doctor of medical sciences, professor, immunologist Dobrodeyeva Lilia Konstantinovna. The examination results, protocols of recommendations are kept by the attending physician in compliance with the requirements of the legislation of the Russian Federation on the protection of confidential information and personal data. Before the laboratory examination, all volunteers were informed about the possibility of using the examination results for research purposes by the staff of the Institute of Physiology of Natural Adaptations of the FECIAR UrB RAS while maintaining the confidentiality of the results.

A database was formed, including the data of the volunteer: date of birth, date of examination, age, sex and indicators of the immune background. The immunological study complex included the study of a hemogram (the number of platelets, red blood cells, white blood cells, the total hemoglobin content in the blood, a leukogram with 5-component differentiation of white blood cells), the phagocytic activity of peripheral blood neutrophil leukocytes in blood smears stained according to the Romanovsky-Gimz method. By flow cytometry using the Epics XL apparatus of Beckman Coulter (USA), Immunotech a Beckman Coulter Company (France) reagents studied lymphocyte phenotypes (CD3+, CD4+, CD8+, CD10+, CD16+, CD71+, CD95+). Transferrin, serum immunoglobulins (IgA, IgM, IgG, IgE) and cytokines (TNF-α, INF-γ, IL-6, IL-10) were determined by enzyme immunoassay. The reactions were evaluated using a Multiskan MS photometer (Labsystems, Finland) and a Bio-RAD Evolis automatic enzyme immunoassay analyzer (Germany). The concentration of circulating immune complexes was determined by a standard precipitation method using 3.5%; 4.0%; 7.5% PEG-6000.

Initial analysis of study results was based on the formation of comparison groups by sex and age (18-50 years and 50-89 years relative to median age). The level of transferrin is stable indicator with less pronounced differences by sex and age [13], so further analysis of results of the study was carried out randomly based on statistical analysis of transferrin concentration, followed by the formation of comparison groups based on the distribution of quantitative values relative to the reference range (170-340 mg/dl): 1st group - transferrin content below the reference limit of content <170 mg/dl (n=68), 2nd group - transferrin content within 170-340 mg/dl (n=441), 3rd group - content transferrin above the reference limit> 340 mg/dl, (n=256). The average age in each group was, respectively: 44.73 ± 1.81; 48.02 ± 0.71 and 48.99 ± 0.92 years. The comparison groups are uneven, which is a consequence of different mechanisms of regulation of decreased and increased levels of transferrin content.

The normality check of the distribution of quantitative indicators was carried out using the Kolmogorov-Smirnov single-sample criterion, both with the full sample volume and when dividing observations into comparison groups, since the results of checking the nature of the distribution using statistical criteria are sensitive to the sample size. In the formed comparison groups, the distribution of the values of most indicators obeyed the law of normal distribution. The values of quantitative indicators are presented as M ± δ, the assessment of differences in the comparison groups (1-2; 2-3; 1-3) was carried out using the Student's t-test and Mann-Whitney U-test in cases of asymmetric distribution of indicator values. To study the relationship between the indicators, the correlation coefficient r-Pearson and Spearman was determined depending on the nature of the distribution of the values of the indicators. Statistical analysis of the data was carried out using the Statistics 21.0 software package.

Findings and discussion. It was found that in 27,95% of the examined individuals an increase in the concentration of transferrin in the blood (from 153,56±1,85 to 422,04±2,94 mg /dl) was associated with a decrease in the platelet count (from 232,54±8,09 up to 209,68±3,98 $x10^9$ cells/l; p=0,008). Evidence appears in the literature on the iron-independent function of transferrin in maintaining coagulation balance. An imbalance in coagulation is associated with an increased level of transferrin, which interacts with thrombin and factor XIIa (FXIIa), enhancing their enzymatic activity, and with clotting inhibitors, blocking the inactivating effect, thereby inducing hypercoagulation. [14,15]. With an increase in transferrin in 24.08% of cases, the concentration of hemoglobin decreases (from 134,76±3,01 to 129,34±1,18 g/l; p=0,048) within the reference limits of the content, without changes in the content of erythrocytes (4,53±0,06 and 4,61±0,13$x10^{12}$ cells/l) and leukocytes (6,40±0,17 and 6,20±0,11 $x10^9$ cells/l). At the same time, the most pronounced decrease in hemoglobin content (from 149.13 ± 1.75 to 135.0 ± 1.98, p = 0.01) occurs in men with an increase in age (Table 1) and no change in women (Table 2). A decrease in the level of hemoglobin is associated with a decrease in the concentration of erythrocytes in the blood (r=0,661, p<0,001).

There is a competitive relationship between erythropoiesis and leukopoiesis in the red bone marrow [16], which has become fundamental in establishing the relationship between the transferrin content with leukocytic row. Despite the fact that, depending on the level of transferrin content, no change in the total content of leukocytes in the blood was established, a decrease in the level of lymphocytes was revealed in the structure of the hemogram. So, with an increase in the concentration of iron transport protein in the blood, the content of lymphocytes decreases (from 2,15±0,06 to 1,87±0,03 $\times10^9$ cells/l, p=0,001; r = -0,137, p<0,001), mainly for the count of mature T-lymphocytes (CD3 +) (from 1,03±0,02 to 0,92±0,01, p=0,001; r= -0,160, p <0,001), activated T-lymphocytes to the transferrin receptor (CD71+) (from 0,62±0,01 to 0,37±0,01, p=0,001; r= - 0,644, p <0,001) and cells to programmed cell death (CD95+) (from 0,50±0,01 to 0,41±0,01, p=0,001; r= -0,202, p <0,001). Pays attention that in 49,21% of the examined individuals, an increase in the concentration of iron-containing protein against the background of a decrease in the content of cells with a membrane receptor for transferrin (CD71+) reflects a known pattern of changes in the activity of membrane receptors and a substrate for it by changing expression or shedding into the intercellular environment [17]. Shedding CD71 ensures elimination of excessive accumulation of Fe3 + and reactive oxygen species (ROS) during reticulocyte maturation [18]. Regeneration of superoxide radical in cells increases under hypoxic conditions [19].

Expression of CD71 + receptors depends on the presence of iron in the cell [13] and provides further differentiation and maturation of T-lymphocytes, since CD71 + provides the activated cell with iron. With an increased demand for intracellular iron or iron deficiency, the expression of the receptor for the iron-containing protein increases. In various lymphoproliferative processes, lymphocytes begin autonomous synthesis of CD71 + or utilize iron in a transferrin-independent way [20].

The expression of iron transport protein receptors is negatively affected by proinflammatory cytokines. With an increase in the content of transferrin in the blood, the concentration of pro-inflammatory cyto-

Взаимосвязь содержания трансферрина и параметров гемограммы в зависимости от возраста у мужчин и женщин

Indicators	Reference content limits	Возраст		p – validity of difference
		18-50 years old	50-84 years old	
		n=106	n=106	
Male gender				
Transferrin, mg/dl	170-340	284.06±9.78	299.75±10.01	
Erythrocytes, ×1012 cells/l	4.0-5.1	4.98±0.05	4.59±0.06	
Platelets, ×109 cells/l	180-320	198.02±5.01	197.0±8.24	
Hemoglobin, g/l	130-160	149.13±1.75	135.0±1.98**	0.01
Leukocytes, ×109 cells/l	4.0-8.8	6.30±0.16	6.32±0.16	
Monocytes, ×109 cells/l	0.09-0.6	0.46±0.02	0.50±0.02	
Lymphocytes, ×109 cells/l	1.5-4.0	1.97±0.05	1.98±0.06	
Neutrophils, ×109 cells/l	2.0-5.2	3.68±0.14	3.64±0.11	
Eosinophils, ×109 cells/l	0.02-0.3	0.19±0.01	0.18±0.01	
Female gender				
Transferrin, mg/dl	170-340	296.15±5.84	298.01±6.31	
Erythrocytes, ×1012 cells/l	4.0-5.1	4.35±0.02	4.39±0.03	
Platelets, ×109 cells/l	180-320	228.13±3.53	218.64±4.39	
Hemoglobin, g/l	130-160	124.21±0.97	127.48±0.91	
Leukocytes, ×109 cells/l	4.0-8.8	6.42±0.22	6.21±0.12	
Monocytes, ×109 cells/l	0.09-0.6	0.46±0.01	0.47±0.01	
Lymphocytes, ×109 cells/l	1.5-4.0	1.98±0.03	2.04±0.04	
Neutrophils, ×109 cells/l	2.0-5.2	3.61±0.07	3.53±0.09	
Eosinophils, ×109 cells/l	0.02-0.3	0.17±0.01	0.17±0.01	

kines increases: TNF-α (from 11,23±0,67 to 17,93±1,36 pg/ml, p=0,002), IL-6 (from 9,11±0,76 to 15,28±0,89 pg/ml, p=0,001), INF-γ (from 11,22±0,82 to 13,62±0,53 pg/ml, p=0,026). The strongest correlation is observed between the content of transferrin and IL-6 (r-Spearman = 0,222, p<0,001) and between the content of IL-6 and cells with a membrane receptor for the iron transport protein (r-Spearman = -0,197, p<0,001). The relationship between the iron-containing protein and the anti-inflammatory cytokine IL-10 has not been established, the concentration of which does not change (7,05±0,29 and 6,45±0,26 pg/ml) with an increase in transferrin content.

An increase in the content of iron-containing protein is associated with an increase in the concentration of circulating IgG immune complexes (CIC) in 44,21% of cases. It is known that the formation of CEC is aimed at removing genetically foreign agents from the body [21]. The mechanism for increasing the CEC is the activation of the kinin system, as well as exocytosis of biologically active substances of granulocytes and macrophages. Increasing the formation of various proteolytic enzymes and reactive oxygen species, acid hydrolases, katahepseins and collagenases contributes to strengthening the processes of damage, cell destruction, followed by an increase in components, substances in the intravascular medium, requiring binding and transport [22].

In 8,06% of the examined individuals, an increase in the transferrin concentration was associated with an increase in the IgE content (from 45,58±4,92 to 57,54±5,07 IU/ml, p=0,011) without changes in the IgA content (2,10±0,31 and 2,34±0,56 g/l), IgM (2,70±0.84 and 1,85±0,07 g/l) and IgG (17,93±0,56 and 18,00±0,24 g/l). This pattern is explained by the fact that IgE are the most sensitive and react with very low antigen concentrations, recognizing conformational epitopes, in contrast to immunoglobulins of other classes, which are able to recognize only linear epitopes of proteins [23].

In 5,12% of the examined individuals, an increase in the concentration of transferrin (from 153,56±1,85 to 422,04±2,94 mg/dl) is associated with an increase in the activation of cell-mediated cytotoxicity (CD8+), which is mainly supported by the pro-inflammatory cytokine IL-6 (r-Spearman=0,145, p=0,001).

Conclusion. It was found that in 49.21% of the individuals examined, the content of transferrin increases against the background of a decrease in the level of cells with a membrane receptor to transferrin (CD71+), which reflects the known competing relationships of the receptor and its level of shedding and substrate (transport). It is known that transferrin receptors can react with Fc Ig and even with IgA [24]. Thus, an increase in transferrin content is associated with an increase in the concentration of CIC containing IgG in 44.21% of cases. In 27.95% of the examined individuals, an increase in the concentration of iron-containing protein in the blood is associated with a decrease in platelet content (r = -0.073; p = 0.05), possibly indicating the involvement of transferrin in maintaining coagulation balance. In 24.08% of people, when the level of transferrin increases, the concentration of hemoglobin decreases (r = -0.275; p = 0.043), which confirms the increased iron requirement for erythropoiesis. The most pronounced decrease in hemoglobin was found in men with an increase in age. The remaining relationships given are of little importance and can be random. Thus, in 8.06% of the examined persons, the increase in the level of transferrin is interconnected with an increase in the concentration of reagents (r = 0.084; p=0.011). In 5,12% of cases, an increase in the content of the transferrin transport protein is associated with the activation of cell-mediated cytotoxicity, which is mainly supported by the pro-inflammatory cytokine IL-6 (r=0,195; p<0,001). The relationship between the increase in transport protein and the concentration of IL-10 has not been established. An increase in cytotoxicity enhances the processes of damage, destruction of cells with a subsequent increase in components, substances in the intravascular environment that require binding and transport. An increase in the concentration of not only circulating immune complexes, but also concentration transferrin is aimed at achieving this goal.

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