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SOLUBLE MOLECULES OF IMMUNOGLOBULINS SUPERFAMILY IN RHEUMATOID ARTHRITIS

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РАСТВОРИМЫЕ МОЛЕКУЛЫ СУПЕРСЕМЕЙСТВА ИММУНОГЛОБУЛИНОВ ПРИ РЕВМАТОИДНОМ АРТРИТЕ

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Relationship of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and platelet-endothelial cell adhesion molecule-1 (PECAM-1) blood levels with features of course of rheumatoid arthritis was studied. 134 patients with rheumatoid arthritis (104 women, 30 men) at age from 20 to 66 years included in study. Duration of joint syndrome was 11.06±0.72 years. In majority of patients high degree of activity, III radiological stage, II and III functional classes of rheumatoid arthritis were diagnosed. Plasma concentration of adhesion molecules was studied by means of ELISA.

Increase of levels of all adhesion molecules was observed ($p<0.05$). concentration of VCAM-1 and PECAM-1 in plasma was higher in seropositive patients or in presence of antibodies to cyclic citrullinated protein ($p<0.05$). In patients with late clinical stage levels of ICAM-1 and PECAM-1 were higher, than in early rheumatoid arthritis ($p<0.05$). High activity of disease was combined with raised plasma levels of ICAM-1 ($p<0.05$). Presense of systemic manifestations of disease and hematological disorders (hyperthrombocytosis) was accompanied by higher blood levels of all adhesion molecules ($p<0.05$). In values of SCORE scale of 5 and more points concentration of ICAM-1 and VCAM-1 in blood was higher ($p<0.05$), than in cases of low and moderated cardiovascular risk.

Thus, the pathogenetic importance of immunoglobulins superfamily molecules in formation and progressing of rheumatoid arthritis is proved. Strengthening of adhesive function of endothelium is interfaced to increased cardiovascular risk.

Keywords: rheumatoid arthritis, immunoglobulins superfamily molecules, activity, systemic manifestations, cardiovascular risk

Изучена взаимосвязь плазменного содержания молекул межклеточной адгезии-1 (ICAM-1), адгезии сосудистого эндотелия-1 (VCAM-1), адгезии эндотелия и тромбоцитов-1 (PECAM-1) с особенностями течения ревматоидного артрита. Обследовано 134 больных ревматоидным артритом (104 женщины, 30 мужчин) в возрасте от 20 до 66 лет. Длительность суставного синдрома составила 11,06±0,72 лет. У большинства пациентов диагностированы высокая степень активности, III рентгенологическая стадия, II и III функциональные классы ревматоидного артрита. Концентрация изучаемых молекул в плазме определялась методом ИФА.

Установлено увеличение содержания всех молекул адгезии ($p<0,05$). Концентрация VCAM-1 и PECAM-1 в плазме была выше у серопозитивных пациентов или при наличии антител к циклическому цитруллинированному пептиду ($p<0,05$). У больных с поздней клинической стадией значения ICAM-1 и PECAM-1 были выше,

чем при раннем ревматоидном артрите (p<0,05). Высокая активность процесса сочеталась с ростом плазменных уровней ICAM-1. Наличие системных проявлений или гематологических отклонений (гипертромбоцитоза) сопровождалось более высоким содержанием всех молекул адгезии в крови (p<0,05). При значениях шкалы SCORE в 5 и более баллов концентрация ICAM-1 и VCAM-1 в крови была достоверно выше (p<0,05), чем в случаях низкого и умеренного кардиоваскулярного риска.

Таким образом, доказана патогенетическая значимость молекул суперсемейства иммуноглобулинов в формировании и прогрессировании ревматоидного артрита. Усиление адгезивной функции эндотелия сопряжено с увеличенным сердечно-сосудистым риском.

Ключевые слова: ревматоидный артрит, молекулы суперсемейства иммуноглобулинов, активность, системные проявления, сердечно-сосудистый риск

Rheumatoid arthritis (RA) is characterized by the development of inflammatory destructive changes of joints as well as systemic manifestations to visceral organs, on the basis of severe immune disorders.

Basis of inflammatory reaction in RA lies in cellular migration and accumulation of macrophages, lymphocytes and fibroblasts, which are involved in the processes of destruction, angiogenesis, and proliferation of synovial membrane. Activation and migration of immunocompetent cells to the focus of inflammation is implemented with the participation of adhesion molecules, expressed by the endotheliocytes, leucocytes and provided their interrelation as a response on inflammatory stimulation [1].

Integrins, selectins, as well as mediators of immunoglobulins superfamily, belonging to adhesion molecules, initiate the rolling of leucocytes on the surface of endotheliocytes, activation of cells, their adhesion to endothelium and their penetration through the subendothelial space to the zone of inflammation [1].

Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet/endothelial cell adhesion molecule-1 (PECAM-1), representing immunoglobulins superfamily provides transendothelial migration of cells to the focus of inflammation, in interaction of antigen presenting cells with T-lymphocytes, participate in the adhesion of leucocytes out of vascular bed, as well as in angiogenesis [21]. In RA hyperexpression of ICAM-1 and VCAM-1 on endotheliocytes, macrophages and fibroblasts, provided by the stimulation of pro-inflammatory cytokines, favors chronisation of inflammatory reaction in joint tissues [8, 20].

In patients with RA, increased concentrations of ICAM-1 and VCAM-1in blood is observed [13, 14, 16], even many researchers had evaluated normal or even decreased levels of circulating adhesins [19]. Increased serum levels of ICAM-1, VCAM-1 and endothelial growth factor in RA, depend on the histological manifestations of synovitis and were correlated with laboratory markers of activity of disease, number of painful and inflamed joints [6, 13, 16]. Soluble forms of adhesion molecules probably regulate contact of leucocytes with membranous form of mediators or modulate leucocyte activation until their interaction with endotheliocytes.

However, probable interrelation of mediators of intercellular interaction with clinical conditions of RA as duration of disease, activity, immunological and systemic manifestations, and complications of RA were not specified yet [7, 11, 13]. It is supposed that the identified discrepancies are may associated with joint pathology by genetic polymorphism of certain adhesion molecules [16].

Aim of our research was the assessment of interrelation of soluble molecules of immunoglobulins superfamily with features of course of RA.

Material and Methods. 134 patients with RA (104 women, 30 men) of age from 20 to 66 years (mean age 50.08±0.97 years) were included in the research. Inclusion criteria were patients with RA of age 18 years and elder, acceptance of participation in research and intake of non-steroid anti-inflammatory drugs or glucocorticoids in stable doses for not less than 4 weeks. Exclusion criteria were intake of genetically engineered biological drugs, joint disorder of other etiology, acute and chronic somatic diseases in the stage of exacerbation, tumors and refusal for participating in the research. Control group constituted of 70 practically healthy individuals, comparable to age, sex and physical development.

Diagnosis of RA was established according to the classification criteria of ACR/EULAR (2010). Clinical characteristics of patients were made in accordance with the classification adopted by Russian association of rheumatologists. Among patients prevailed women (77.6 %) elder than 45 years, with late stage of the disease (81.4 %) and severe stage of disease activity (67.2 %). Duration of joint syndrome was 11.06±0.72 years. Mean values of index DAS 28 were 5.37±0.07. Rheumatoid factor (RF) and antibody to cyclic citrullinated peptide (ACCP) in blood was identified in 89.6 % and 76.8 % patients respectively. Mean serum levels of RF IgM and ACCP were reached 173.67±21.76 ME/ml and 332.53±38.88 IU/ml respectively. Most of the patients were diagnosed with erosive variant of the disease (87.3 %), III X-ray stage (70.9 %), II and III functional class (49.2 % and 47.8 % respectively). In 17.2 % of the patients systemic manifestations (mainly rheumatoid nodules) were noticed and 66.4 % of the cases had secondary osteoarthrosis.

While including in the research in 112 patients, who were above 40 years of age, total cardiovascular risk was studied with the help of SCORE chart modified by EULAR (Peters M. J. L. et al., 2010; Agca R. et al., 2017). Mean values of index SCORE were 2.69±0.31 (moderate risk), but in 22.3 % of the patients high and very high cardiovascular risk was evaluated. In 26.9 % of the cases hypercholesterinemia was present and in 41 % of the examined, arterial hypertension was observed.

A complex clinical, functional, laboratory, instrumental and immunochemical analysis was performed for the examined patients. Plasma concentrations of molecules of immunoglobulins superfamily were studied by the method of enzyme linked immunosorbent assay using kits of company «Bender MedSystems GmbH» (Austria) in accordance with the provided instructions.

Research was corresponded with the requirements of Helsinki declaration of the world medical association on ethical principles for medical research involving human subjects. Patients and individuals in control group gave information consent on their participation in the research, which had been approved by ethical committee of the University.

Statistical analysis of the obtained results was performed using program adapted for medico-biological research (IBM SPSS Statistics 24). Two sample Student's

t-criteria, Newman-Keuls criteria were evaluated, correlation analysis with application of Pearson (r) and Spearman (r_s) criteria were used. Results were considered significant when the range of difference $p<0.05$.

Results and Discussion. A significant increase in the concentrations of molecules of immunoglobulins superfamily in blood ($p<0.05$) was determined, independent of sex and age of the patients (Figure).

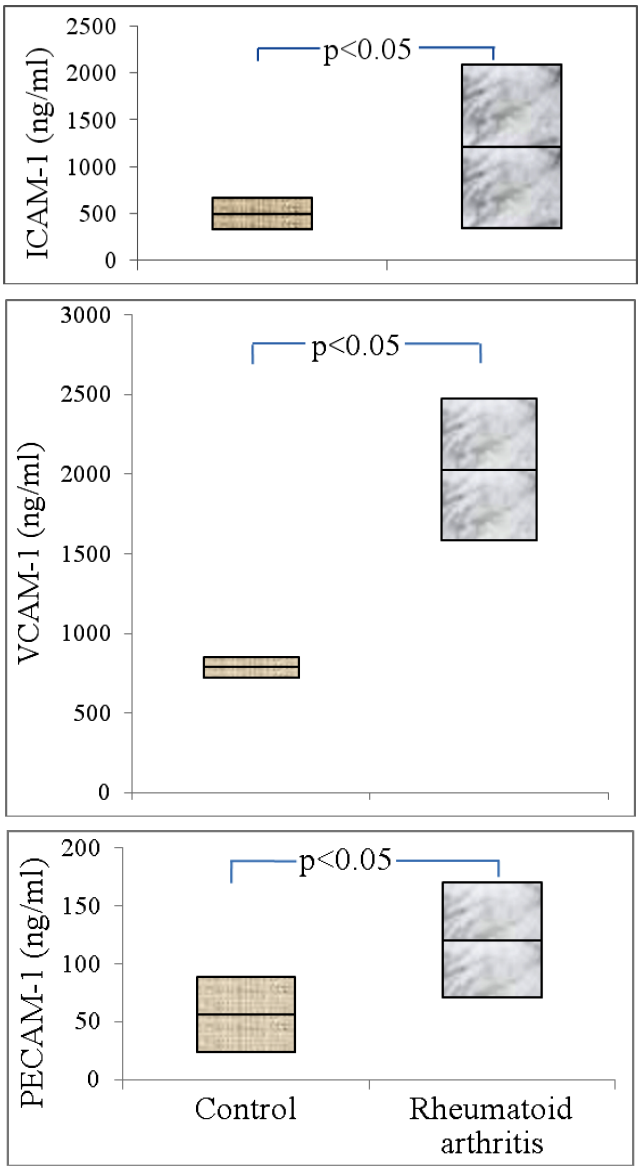

Fig. Blood concentration of immunoglobulins superfamily molecules in rheumatoid arthritis

Overall, being increased, plasma concentration of ICAM-1 in patients with RA was independent of immunological manifestations of arthritis. Whereas, cases with the presence of RF and ACCP characterized by significantly very high levels of VCAM-1 and PECAM-1 in blood ($p<0.05$), compared to seronegative variants of the disease. In patients with absence of RF and ACCP, levels of VCAM-1 in blood were of normal range. A positive correlation of VCAM-1 with the values of RF was also observed ($r=+0.21$; $p<0.05$).

Clinical stage of the disease had no effect on the plasma concentrations of VCAM-1, even when values of ICAM-1 and PECAM-1 in patients with late clinical stage were higher than in early stage of RA ($p<0.05$). Values of ICAM-1, VCAM-1 and PECAM-1 positively correlated with clinical stage of RA ($r_s=+0.36$; $p<0.05$; $r_s=+0.28$; $p<0.05$; $r_s=+0.36$; $p<0.05$ respectively).

Independent of the degree of activity of RA (by index DAS 28), increased levels of adhesion molecules in blood was observed. However, high activity of the disease was associated with very high plasma concentrations of ICAM-1 in comparison with cases of moderate activity ($p<0.05$). Levels of ICAM-1 were interrelated with the values of ESR and C-reactive protein ($r=+0.18$; $p<0.05$; $r=+0.24$; $p<0.05$ respectively). Concentrations of soluble VCAM-1 positively correlated with values of index DAS28 and C-reactive protein ($r=+0.17$; $p<0.05$; $r=+0.22$; $p<0.05$ respectively). Whereas, correlation of VCAM-1 with number of painful and inflamed joints was of insignificant character ($r=+0.16$; $p=0.07$; $r=+0.15$; $p=0.08$ respectively).

Mediators of intercellular interactions were not connected with severity of X-ray changes of joints, including the presence or absence of erosions, and also were independent of functional class or complications of RA. At the same time, in patients with III-IV X-ray stage or with erosive form of the disease, plasma concentrations of PECAM-1 were higher than in cases with less pronounced X-ray picture ($p<0.05$). Concentrations of ICAM-1, VCAM-1 and PECAM-1 in blood had a positive correlation with severity of bone destructive changes ($r_s=+0.32$; $p<0.05$; $r_s=+0.27$; $p<0.05$; $r_s=+0.36$; $p<0.05$ respectively), and indicators of ICAM-1 and VCAM-1 had a positive correlation with functional class of arthritis ($r_s=+0.19$; $p<0.05$ and $r_s=+0.24$; $p<0.05$).

Systemic manifestations of RA bought a significant rise in levels of all adhesion molecules ($p<0.05$) (Table 1). In patients with hyperthrombocytosis, values of adhesins were higher ($p<0.05$) than in cases with normal level of platelets. A positive correlation of values of VCAM-1 with amount of circulating platelets was observed ($r=+0.36$; $p<0.05$).

Table 1

Blood levels of adhesion molecules and systemic manifestations of rheumatoid arthritis ($X \pm s_{\bar{x}}$)

Groups	Adhesion molecules (ng/ml)		
	ICAM-1	VCAM-1	PECAM-1
Control	499.04 ±20.24	889.59 ±63.41	55.90 ±3.87
RA without SM	1160.12 ±79.46 *	3459.96 ±419.50 *	115.75 ±4.36 *
RA with SM	1497.22 ±212.77 */**	5858.26 ±1563.79 */**	143.48 ±12.57 */**

The note: SM – systemic manifestations, * – $p<0.05$ in comparison with control, ** – $p<0.05$ in comparison between groups of patients.

Comorbidity of RA and arterial hypertension/ hypercholesterinemia as well as cases with duration of disease for more than 10 years characterized by significantly very high concentrations of VCAM-1 ($p<0.05$). In patients with RA, with values of modified EULAR SCORE scale ≥5 points, concentrations of ICAM-1 and VCAM-1 were significantly higher ($p<0.05$) than in group of patients with low and moderate 10 year cardiovascular mortality risk (Table 2). Indicators of VCAM-1 were positively correlated with the values of systolic arterial pressure, levels of cholesterol and values of modified SCORE scale ($r=+0.23$; $p<0.05$; $r=+0.21$; $p<0.05$; $r=+0.30$; $p<0.05$ respectively).

Table 2

Relationship of adhesion molecules with SCORE in rheumatoid arthritis ($\overline{X} \pm s_{\overline{x}}$)

Groups	Adhesion molecules (ng/ml)		
	ICAM-1	VCAM-1	PECAM-1
Control	499.04 ±20.24	889.59 ±63.41	55.90 ±3.87
SCORE <5 p.	1126.89 ±85.83 *	3599.60 ±456.02 *	124.77 ±5.65 *
SCORE ≥5 p.	1524.96 ±219.00 */**	6338.76 ±1652.14 */**	114.12 ±9.68 *

The note: * – p<0.05 in comparison with control, ** – p<0.05 in comparison between groups of patients.

Results of the research confirm the key role of endothelial activation and dysfunction in progression of RA [4, 13, 14, 16]. At the same time, a possibility of normal or even decreased production of adhesion molecules in patients with RA is supposed [19].

Interrelation of rise in VCAM-1 and PECAM-1 with the presence of RF may related with the ability of the later causing damage to the endothelium [7], which explains the normal levels of VCAM-1 in seronegative forms of disease. Correlation of ICAM-1 and VCAM-1 with immunological deviations suggests a very fast progression of the disease and the development of complications [4, 16].

Relation of increased activity of RA with raised values of ICAM-1 in blood confirms its significance in inflammatory mechanism in RA. Increased plasma concentrations of ICAM-1 and E-selectin with activation of inflammatory process [3, 4, 13, 19] and interrelation of ICAM-1, VCAM-1 and E-selectin with inflammatory proteins, values of index DAS28 as well as with number of painful and inflamed joints were observed in previous researches [6, 16]. There are many opinions on prevailing role of VCAM-1 in inflammatory process in patients with RA [16]. Whereas the probable correlation of adhesion molecules with number of inflamed joints may be due to the excess production of adhesion molecules by hypertrophied and vascularized synovial membrane, as well as intensification (under the impact of C-reactive protein) of endothelial expression of adhesion molecules and secretion of pro-inflammatory cytokines and nuclear factor-kB by endotheliocytes [5].

At the same time, a point of view on absence of correlation between mediators of intercellular interactions and values of DAS28, ESR, serum levels of C-reactive protein and pro-inflammatory cytokines in RA was stated [7, 11], which witnesses the decisive role of RA itself in the formation of endothelial dysfunction, but not induced by pro-inflammatory cytokines [13].

In previous reports, it was stated that serum concentrations of the studied mediators increases with the presence of rheumatoid nodules [16]; comorbidity of RA with polyneuropathy was characterized with very high levels of VCAM-1 and E-selectin in blood, which may approve that indicators of soluble ICAM-1 and E-selectin not at all related with extraarticular manifestations of arthritis or even decrease in patients with symptoms of cutaneous vasculitis [6, 16]. Interrelation which had been established in our study between adhesion molecules and visceral manifestations was obvious, it may be due to the expression of VCAM-1 *de novo* and intensified expression of ICAM-1 on endothelium under the effect of pro-inflammatory cytokines, partially tumor necrosis factor-α, increase of which had been identified in the given group of patients [6, 9].

In patients with RA and thrombocytosis, very high concentration of adhesins suggests a correlation of adhesion molecules with hematological abnormalities. Even in juvenile rheumatoid arthritis, correlation of PECAM-1, ICAM-1 and vascular endothelial growth factor with number of circulating leucocytes and platelets was observed [2, 12]. But, possible association of mediators of intercellular interaction with deviations in cellular composition of blood in RA was not shared by all the researchers [7].

It is well known that risk of development of cardiovascular diseases in RA increased by 50 %, and mortality by them increased by twice than that of in general population [15, 18]. Manifestation of cardiovascular events explains the intensification of atherosclerosis, associated not only with the traditional risk factors [17], but also with endothelial dysfunction and chronic systemic inflammation [10, 15] – common link of pathogenesis in comorbid diseases.

According to our data, arterial hypertension and hypercholesterinemia in RA were associated with increased values of VCAM-1 in blood. High and very high cardiovascular risk was characterized with very high levels of soluble ICAM-1 and VCAM-1. In RA, interrelation of increased concentrations of ICAM-1 in blood with decreased endothelial dependent and independent vasodilation, correlation of VCAM-1 with thickness of intima media of common carotid arteries were observed in earlier studies and there is a lack of such data for ICAM-1 and E-selectin [3].

Thus, intensification of adhesive function of endothelium in RA was conditioned by very severe course of disease, through the impact of adhesion molecules on immunological disorders, activity of the process, visceral and hematological manifestations. In patents with RA, adhesion molecules were associated not only with damage to synovial tissue, but also were involved as negative markers of increased cardiovascular risk.

Conclusions. In RA, increased concentration of molecules of immunoglobulins superfamily, independently of sex and age of the patients was observed. Rise in values of adhesion molecules were seen in seropositive variants of disease, severe degree of disease activity, presence of systemic and hematological manifestations, which confirms their pathogenic role in formation and progression of RA. In RA, interrelation of circulating ICAM-1 and VCAM-1 with values of SCORE scale characterizes the negative role of endothelial adhesive function in development of cardiovascular diseases.

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SOME PECULIARITIES OF ACUTE MYOCARDIAL INFARCTION PATHOGENESIS IN NON-OBSTRUCTIVE CORONARY ARTERIES

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НЕКОТОРЫЕ ОСОБЕННОСТИ ПАТОГЕНЕЗА ОСТРОГО ИНФАРКТА МИОКАРДА ПРИ НЕОБСТРУКТИВНОМ ПОРАЖЕНИИ КОРОНАРНЫХ АРТЕРИЙ

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Myocardial infarctions (MI) in case of non-obstructive atherosclerosis or intact coronary arteries are set apart into a separate group – myocardial infarction with no-obstructive coronary atherosclerosis – MINOCA. 1240 patients were included. The first group comprised the patients with single-vessel disease and complete acute occlusion –