International Journal of Psychosocial Rehabilitation

ISSN:1475-7192

International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 05, 2020
ISSN: 1475-7192

Contents of Serum P-selectin As An Early Marker of Endothelium Dysfunction and Atherosclerotic Changes in Patients with Chronic Kidney Disease

Rasulova Khurshidakhon Abduboriyevna*, Daminov Botir Turgunpulatovich and Abbasov Aziz Kabilovich

Abstract--- Objective: *to study the content of P-selectin in the blood of patients with chronic kidney disease (CKD) and evaluate its effect on the development of endothelial dysfunction (ED) and atherosclerotic changes.*

Material and methods: *In 65 patients with CKD (average age 61.2 ± 1.7 years), the level of P-selectin in the blood serum was determined. The control group consisted of 20 relatively healthy individuals without CKD, comparable in age and sex with the study group. All patients analyzed the data of clinical, laboratory, instrumental methods of research. The diagnosis of CKD was made in accordance with the recommendations of KDIGO (2012) and ICD-10. The content of P-selectin in the selected and frozen blood sera of patients was determined by the method of enzyme-linked immunosorbent assay.*

Results. *With CKD, a violation of immune homeostasis associated with clinical manifestations was revealed, characterized by significantly higher serum P-selectin values. However, when it is increased, the concentration of P-selectin in the blood depends on the stage and category of CKD: as GFR decreases (59 ml / min / 1.73 m2 or less), the serum level of P-selectin significantly decreases, especially with CKD stage III-V. In patients with CKD with clinical, laboratory and instrumental signs of ED and atherosclerosis, the level of P-selectin increases more significantly compared with patients with CKD without atherosclerotic changes. There is a close relationship between the level of P-selectin and various clinical and biochemical syndromes of kidney pathology. As the inflammatory process, hypercholesterolemia, urinary, nephrotic syndromes, as well as arterial hypertension syndrome, the concentration of P-selectin increases. However, with uremia and hypercreatininemia, serum P-selectin levels decrease.*

Conclusions. *The established abnormalities are based on the inflammatory process in the kidneys and activation / dysfunction of the endothelium and platelets. The deepening imbalance of the mediator of intercellular interactions of P-selectin with the progression of CKD (up to the terminal stage) and the presence of a relationship with various clinical options for renal pathology are evidence of the important clinical and pathogenetic significance of selectin disorders in the progression of the process and the formation of atherosclerotic changes and other complications of CKD.*

Keywords--- *Chronic Kidney Disease, Endothelial Dysfunction, P-selectin, Blood Serum.*

Rasulova Khurshidakhon Abduboriyevna, DSc, Associate Professor of the Department of Faculty of Internal Medicine, Occupational Diseases, Military Field Therapy, Hospital Internal Medicine and Propaedeutics of Internal Medicine, Tashkent Pediatric Medical Institute, Republican Specialized Scientific and Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent, Uzbekistan.*
E-mail: khurshidakhon@gmail.com
Daminov Botir Turgunpulatovich, Tashkent Pediatric Medical Institute, Republican Specialized Scientific and Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent, Uzbekistan.
Abbasov Aziz Kabilovich, Tashkent Pediatric Medical Institute, Republican Specialized Scientific and Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent, Uzbekistan.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

I. INTRODUCTION

Currently, chronic kidney disease (CKD) is understood to mean any structural and / or functional impairment of the kidneys lasting more than 3 months with or without a decrease in glomerular filtration rate (GFR), as well as GFR below 60 ml / min / 1.73 m2 lasting three or more months, regardless of the presence or absence of other signs of kidney damage [14, 15, 26, 37, 32]. CKD with creatinine clearance below 90 ml / min has been proven to be an important factor that causes endothelial dysfunction (ED) and affects endothelial integrity [27]. To date, the effect of reducing GFR on the development of atherosclerosis has been established [25].

The kidneys are a vascular organ; therefore, approximately 80% of the endothelial lining of the vessels of the kidneys is concentrated in the capillaries of the renal glomeruli, including their microvasculature. The complexity of the interpretation of the revealed changes in the functional state of the endothelium in kidney diseases is associated, first of all, with the presence of a large number of factors that can affect the endothelium. ED in patients with CKD is seen as an imbalance between vasoconstrictors and relaxing factors, between anti- and procoagulant mediators, growth factors and their inhibitors [11, 14].

Currently, when studying the mechanisms of CKD progression, a great influence is given to impaired vascular endothelial function locally in the kidney and in the systemic channel. The severity of ED is associated with a progressive decline in renal function and the development of sclerosis, being a predictor of an unfavorable prognosis of CKD. With prolonged exposure to damaging factors (hypoxia, toxins, immune complexes, inflammatory mediators, hemodynamic overload, etc.), activation and damage of endothelial cells occur, leading subsequently to a pathological response even to ordinary stimuli in the form of vasoconstriction, thrombosis, increased cell proliferation, hypercoagulation with intravascular deposition of fibrinogen, a violation of microhemorheology and the production of biological active products [11, 22, 23].

One of the current trends in modern endotheliology is the study of the mechanisms of functional heterogeneity of the endothelium, which, as it turned out, is not only genetically determined. The formation of the endothelial phenotype is influenced by hemodynamic factors, as well as organ function and the interaction of endotheliocytes with other cells [35].

In the pathogenesis of the earliest stages of ED, an increase in the adhesiveness accompanying the activation of endotheliocytes is of great importance [28]. Adhesive molecules of the endothelium of the vascular wall provide intercellular and cell-matrix interactions; they are involved in the regulation of the permeability of the endothelial barrier, adhesion and migration of cells through the endothelium, angiogenesis [6, 36], which determines their role both under normal conditions and in pathology.

Selectins are calcium-dependent transmembrane glycoproteins located on the surface of leukocytes, platelets and endotheliocytes. They provide selective homing of the cell through the vessel wall and stimulate the inflammatory process by facilitating the penetration of leukocytes into the focus of inflammation [5, 17, 24]. The selectin family is represented by E-, P-, and L-selectin. E-selectin (CD62E) is normally not expressed by endothelium, with the exception of skin microvasculature, but is rapidly synthesized under the influence of pro-inflammatory cytokines. P-selectin (CD62P) is contained in the α-granules of platelets and Weibl-Palad bodies of endotheliocytes and moves

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

during activation to their surface. L-selectin (CD62L) is expressed on granulocytes, monocytes and most lymphocytes [3, 18, 24, 35].

Selectins mediate functions unique to blood vessels - the adhesion of leukocytes to the vessel wall with the formation of labile adhesions to the wall, which allow leukocytes to slide in the direction of flow. Damage to the endothelium, an "unstable" atherosclerotic plaque and subsequent platelet activation initiates thrombosis in the coronary vessels and the development of acute coronary syndrome. Platelet activation marker is P-selectin ("P" from the English, platelet - platelet; indicates the initial source of detection of this adhesion molecule) [18, 24]. In response to acute inflammatory mediators, such as histamine or thrombin, P-selectin is rapidly transferred to the plasma membrane and acts as a receptor by which leukocytes bind to activated platelets and endothelium. P-selectin-mediated adhesion is aimed at the adhesion of cells to cells through the binding of molecules and, in all likelihood, is very important in the development of inflammation and hemostasis [13].

It is known that platelet stimulation is manifested by the expression of pro-inflammatory markers on their membrane, such as P-selectin and CD40L. By means of P-selectin and its leukocyte ligand PSGL-1, platelets form platelet-leukocyte aggregates. It has been established that after acute coronary syndrome, the number of circulating monocyte-platelet coaggregates is a more indicative marker of blood plate activation than the determination of the expression of soluble sP-selectin on their surface [2, 13, 16, 18].

However, in the available literature there is insufficient information on changes in the expression of adhesive molecules of the endothelium of the vascular wall in patients with kidney diseases. In the literature, there are practically no studies on the role of P-selectin in the formation and progression of CKD, which proves the need for this study.

The aim of the study is to study the content of P-selectin in the blood of patients with CKD and evaluate its effect on the development of ED and atherosclerotic changes.

II. MATERIAL AND RESEARCH METHODS

65 patients with CKD (26 (40%) men and 39 (60%) women) with an average age of 61.2 ± 1.7 years (from 44 to 81 years old) undergoing examination and treatment in the therapeutic, cardiology department were under observation. Tashkent City Clinical Hospital No. 5 and the Republican Specialized Scientific-Practical Medical Center for Nephrology and Kidney Transplantation. All patients gave written informed consent to participate in the study.

A simultaneous, prospective, case-control study was conducted. Criteria for inclusion in the study: age 18 years and older, chronic kidney disease of various etiologies, or a decrease in GFR lasting more than 3 months. Exclusion criteria: acute heart attack or acute cerebrovascular accident, pregnancy, autoimmune and allergic diseases, atherosclerosis obliterans of the lower extremities, cancer, patient refusal to participate in the study.

The control group consisted of 20 healthy volunteers (9 men and 11 women), who had no acute respiratory viral infections during the 6 months preceding the study, and there were no signs of diseases that could lead to a permanent impairment of the functional state of the kidneys and according to the results imaging research methods were not detected morphological lesions of the kidneys. The average age of the study participants in the control

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

group was 53.7 ± 6.7 years. The diagnosis of CKD was made in accordance with the recommendations of KDIGO (2012) and ICD-10. The diagnosis and variant of kidney damage in the patients included in the study was established on the basis of: complaints, anamnesis, course features and clinical symptoms of the disease; standard examination of a general blood test, which was carried out using an automatic hematological analyzer "Mindray BC-5310" (China) using a commercial kit of reagents from the company "DIRUI" made in China; erythrocyte sedimentation rate was determined by the unified Panchenkov micromethod; standard examination of the general analysis of urine, including using standard test strips from Combina-13 (HUMAN, Germany); urine samples according to Nechiporenko; studies of the main biochemical parameters of blood serum (glucose, total protein, urea, creatinine, uric acid, total cholesterol, lipid profile with the calculation of the atherogenic coefficient, glucose, potassium, sodium, chlorine, calcium ions) using the DIRUI CS-T 240 analyzer manufactured China using a commercial reagent kit from DIRUI (China); study of the main indicators of the coagulogram (coagulation time, prothrombin index, international normalized ratio, prothrombin time).

GFR was calculated using the CKD-EPI formula using a renal calculator [38]. All patients underwent measurement of blood pressure and ECG. Ultrasound examination of the kidneys with the calculation of linear dimensions was performed on a SonoScope SSI-6000 apparatus (China). Dopplerographic examination of brachiocephalic (BCC) and renal vessels with the calculation of the linear blood flow velocity and determination of stenosis, atherosclerotic plaque was performed on a SonoScope SSI-6000 apparatus (China).

All biochemical, hemostasiological and instrumental studies were carried out in clinical diagnostic laboratories of City Clinical Hospital No. 5 and Republican Specialized Scientific and Practical Medical Center of Nephrology and Kidney Transplantation of the Ministry of Health of the Republic of Uzbekistan. A complete clinical and special examination of patients was carried out in the first days of hospitalization or on an outpatient basis until treatment was prescribed.

Determination of the content of P-selectin was carried out in selected and frozen blood sera of patients with CKD and control subjects by enzyme-linked immunosorbent assay (ELISA). The study was carried out at the Interuniversity research laboratory of the Tashkent Medical Academy under the supervision of the head of the laboratory for medicogenetic and enzyme immunoassay, PhD, Senior Researcher A.A. Abduvalieva. To quantify the concentration of P-selectin “Cloud-Clone Corp” reagent kit was used. The minimum detectable concentration of P-selectin was 33 pg / ml. To quantify human P-selectin, the Human SEA569Hu kit from China was used. The optical density was measured on a horizontal scanning photometer at a wavelength of 450 nm. For the calculations we used the formula: $(B-B_t) / (B_0-B_t)$,

Where B is the average optical density in the wells containing calibration or test samples,

B_0 is the average optical density in the wells containing the calibration sample "0 nmol / l",

B_t is the average optical density of the holes A1 and A2.

In the logit-log coordinates, a plot of the concentration of P-selectin (pg / ml) in calibration samples was constructed for calibration samples.

The content of P-selectin (pg / ml) in the samples was determined according to the calibration graph after obtaining the average values in the duplicate wells according to the above formula.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

Statistical processing of quantitative indicators was performed using the program program Microsoft Excel. The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package. Arrays of statistics with normal distribution were presented in the form of mean values (M), standard deviation (σ), error of the mean (m), relative values (frequency, %), linear correlation coefficient (r) Pearson. The statistical significance of the measurements obtained when comparing the average values was determined by the Student t-test with the calculation of the probability of error (P) when checking the normality of the distribution (by the excess criterion) and the equality of the general variances (F is the Fisher test). For statistically significant changes, the confidence level was P <0.05 [10].

III. Results And Discussion

All patients included in the study were divided into 3 groups depending on GFR according to the classification of CKD [15, 32]:

- Group I - 9 (13.8%) patients with stage I CKD (GFR greater than 90 ml / min / 1.73 m2) with the presence of markers of renal damage for more than 3 months;
- Group II - 31 (47.7%) patients with stage II CKD (GFR from 60 to 89 ml / min / 1.73 m2) with the presence of markers of renal damage for more than 3 months;
- Group III - 16 (24.6%) patients with stage III CKD (GFR from 30 to 59 ml / min / 1.73 m2) with the presence of markers of renal damage for more than 3 months; of them, CKD stage IIIA (GFR 45-59) - 10 (15.4%) patients, CKD stage IIIB (GFR 30-44) - 6 (9.3%) patients;
- Group IV - 3 (4.6%) patients with stage 4 CKD (GFR from 15 to 29 ml / min / 1.73 m2) with the presence of markers of renal damage for more than 3 months;
- V group - 6 (9.3%) patients with CKD stage V (GFR <15 ml / min / 1.73 m2) with the presence of markers of renal damage for more than 3 months.

Thus, the majority of those examined with CKD had I-III stages of the disease (86.1%) (Fig. 1).

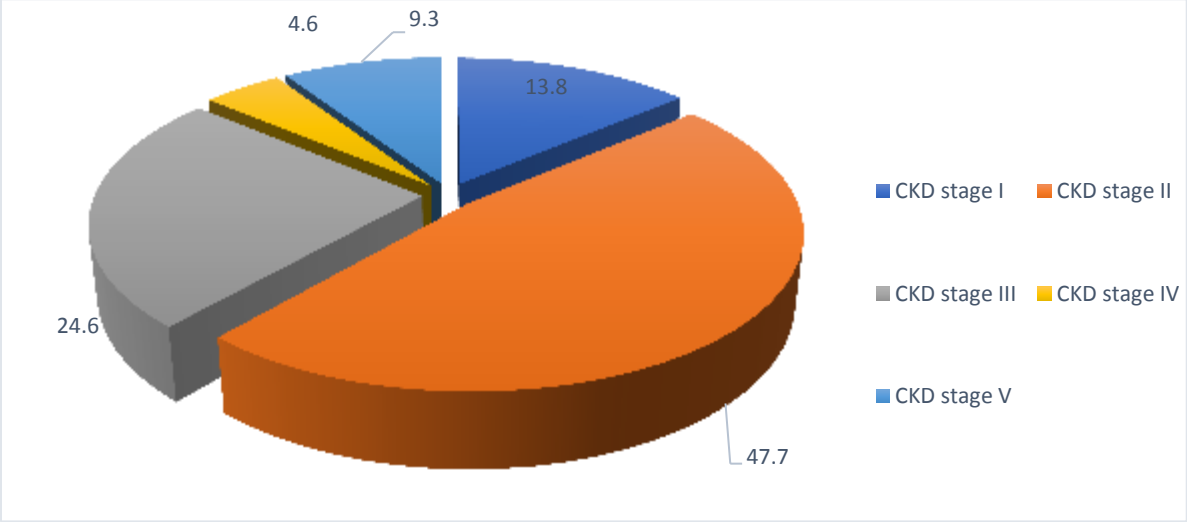

Fig. 1: The Distribution of Patients by Stages of CKD (%)

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

Based on clinical, laboratory and instrumental examination, chronic pyelonephritis (CP) was diagnosed in 20 (30.8%) patients, chronic glomerulonephritis (CGN) in 1 (1.5%) patients, and hypertensive nephropathy in 39 (60%), 5 (7.7%) - diabetic nephropathy. Terminal CKD was determined in 9 (13.8%) patients. So, the main cause of CKD was hypertension with predominant renal failure with renal failure (60%) (Fig. 2).

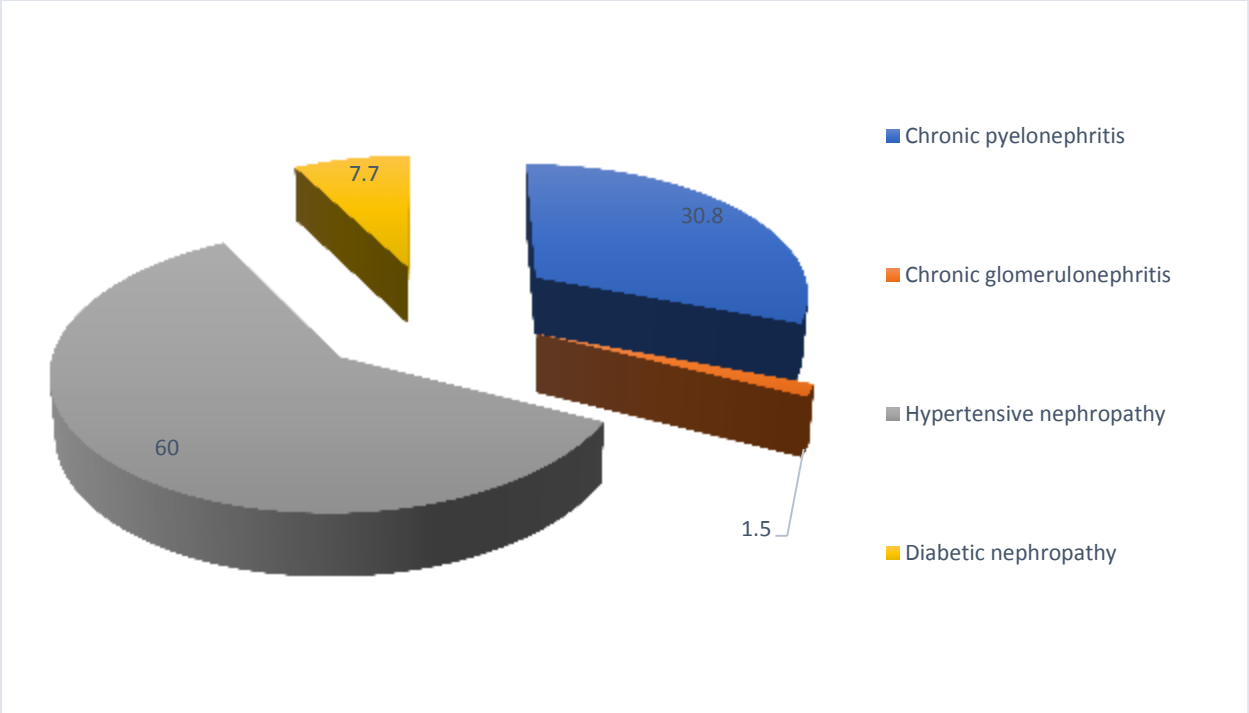

Fig. 2: The Distribution of Patients with CKD by Nosology (%)

Patients mainly complained of shortness of breath, elevated blood pressure, headaches, dizziness, general malaise, general weakness, palpitations, lower back pain, muscle pain, especially legs, numbness and cooling of the extremities, rapid urination, flies before the eyes, chest pains difficulty urinating, swelling on the face and legs, poor appetite and disgust for food, constant thirst, pain and pain during urination, urinary incontinence, itching of the skin. Basically, all these complaints were related to renal and underlying pathology leading to CKD.

Enzyme-linked immunosorbent studies of P-selectin showed a significant increase in the concentration of P-selectin in the blood serum of patients with CKD (96.46 ± 1.38 pg / ml) compared with the control group (89.36-1.52 pg / ml) in 1, 08 times ($p < 0.05$). The highest P-selectin indices were observed in groups 1 and 2 of patients with CKD I (103.88 ± 4.67 pg / ml) and II stage (127.02 ± 2.90 pg / ml), which was higher than the control values, respectively 1.16 and 1.42 times ($p < 0.05$). In the CKD group III (87.57 ± 5.03 pg / ml, $p > 0.05$) and stage IV (74.01 ± 1.44 pg / ml, $p < 0.05$), a decrease in the serum concentration of this marker in 1.02 and 1.21 times lower than the control values, respectively, stage III and IV of the disease. In patients with stage CKD, a sharp decrease in the concentration of P-selectin was observed 2.68 times compared with the control group (33.40 ± 1.38 pg / ml) ($p < 0.05$) (Table 1).

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

Table 1: The Content of P-select in in the Blood of Healthy and CKD Patients Depending on the Stage of the Disease (M ± m), [max; min]

Surveyed groups	**P-selectin, pg / ml**	**P to control**
CKD stage I	103,88±4,67 [123,01; 78,01]	p<0,05
CKD stage II	127,02±2,90 [135,01; 56,01]	p<0,05
CKD stage III	87,57±5,03 [121,01; 50,01]	p>0,05
CKD stage IV	74,01±1,44 [92,01; 50,01]	p<0,05
CKD stage V	33,40±1,38 [78,01; 4,01]	p<0,05
Total number of patients	96,46±1,38 [135,01; 50,01]	p<0,05
The control	89,36±1,52 [99,01; 45,01]	

Thus, in general, patients with CKD had significantly higher serum P-selectin values. However, in cases of severe kidney damage with a decrease in GFR from 59 ml / min / 1.73 m2 or less, the level of P-selectin changed more significantly towards its decrease. The content of P-selectin decreased sharply in cases of CKD stage V with a decrease in GFR <15 ml / min / 1.73 m2. The relationship of P-selectin with GFR in patients with CKD was positive (r = 0.52; p <0.05), which indicates that as the GFR decreases, the serum level of this adhesion molecule decreases (Fig. 3). This may be due to impaired leukocyte migration, a decrease in the sensitivity of receptors to P-selectin due to intoxication, ischemia and hypoxia both in the kidneys themselves and in the body as a whole.

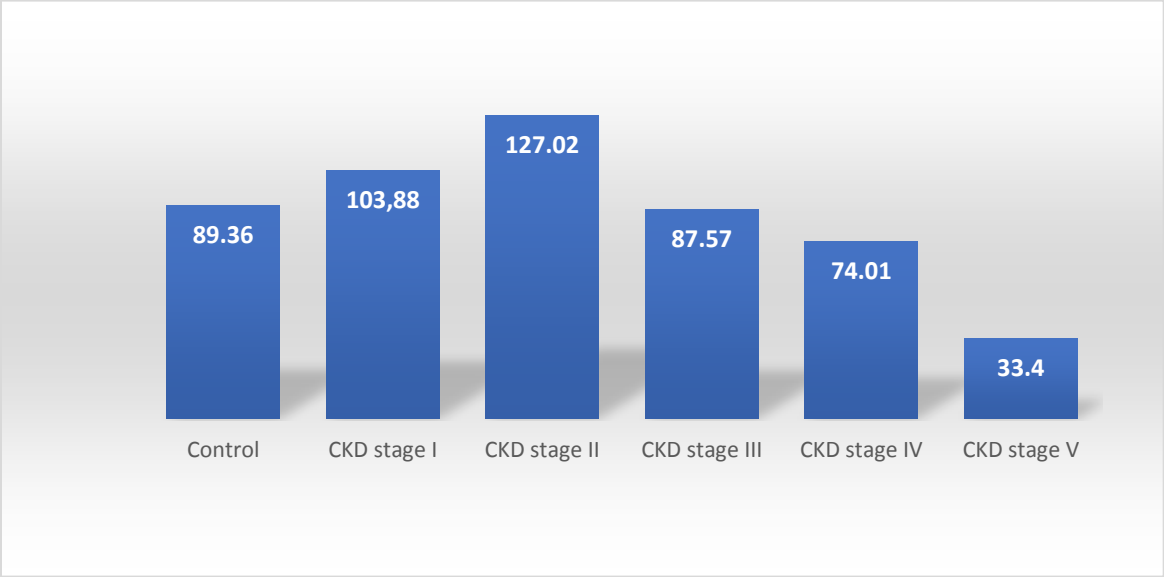

Fig. 3: The Concentration of Serum P-selectin in Healthy and CKD Patients Depending on the Stage of the Disease (PG / ml)

In accordance with the goal, signs of atherosclerotic changes were determined according to clinical data, blood lipid profile and dopplerographic changes in renal arteries. Signs of atherosclerotic lesions included lipid

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

metabolism disorders (hypercholesterolemia, triglyceridemia, increased LDL, decreased HDL, high atherogenicity index), as well as thickening of the intima-media complex, the presence of atherosclerotic plaque with stenosis in brachiocephalic vessels and / or renal arteries during additional doppler arteries. The presence of at least two of these signs may indicate atherosclerotic changes.

Depending on the presence of signs of atherosclerosis, patients with CKD were divided into two groups:

Group 1 - 29 (44.6%) patients with CKD + signs of atherosclerosis (A +);

Group 2 - 36 (55.4%) patients with CKD without signs of atherosclerosis (A–).

In patients with CKD, the level of P-selectin increased more significantly (122.86 ± 16.72 pg / ml, $p < 0.05$) in cases of signs of atherosclerosis compared with patients without atherosclerotic changes (94.66 ± 2.74 pg / ml, $p < 0.05$), which was almost 1.3 times higher than the values of patients with CKD without signs of atherosclerosis and 1.37 times the control values (Fig. 4).

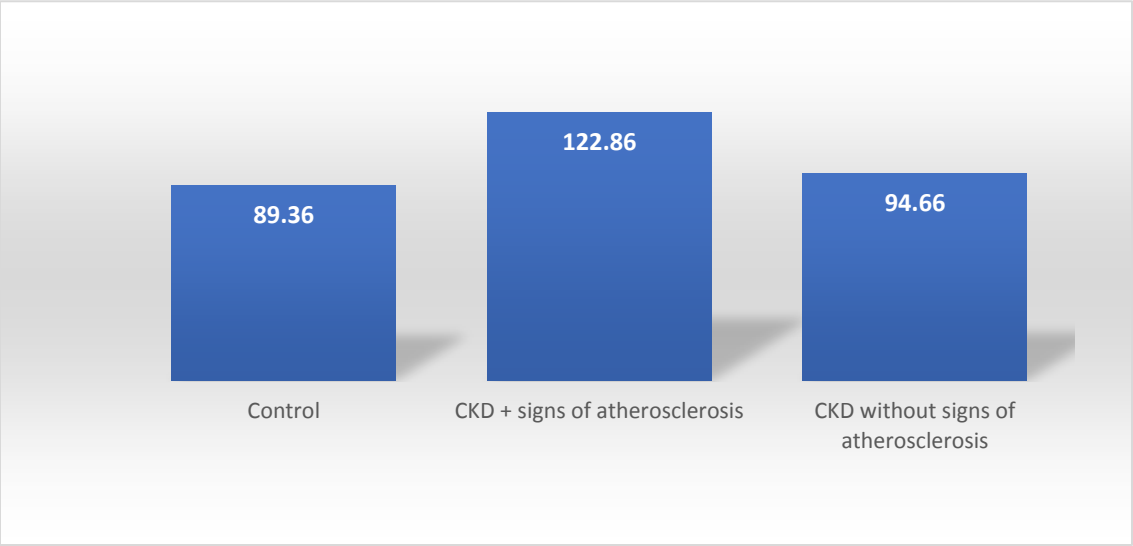

Fig. 4: The Concentration of Serum P-selectin in Healthy and CKD Patients, Taking into Account the Presence of Signs of Atherosclerosis (PG / ml)

A positive correlation of P-selectin with a violation of lipid metabolism (hypercholesterolemia) in CKD ($r = 0.34$; $p < 0.05$) was revealed. The combination of CKD with diabetes mellitus in the decompensation stage was accompanied by higher values of the adhesion mediator in the blood.

The relationship between the imbalance of leukocyte-platelet-endothelial interactions and the course of CKD is confirmed by the close correlation of P-selectin with various clinical and biochemical syndromes of kidney pathology. So, the concentration of P-selectin in the blood of patients increased with increasing severity of urinary and nephrotic syndromes. The content of P-selectin increased in cases of hypertensive nephropathy, arterial hypertension syndrome. CKD with signs of an inflammatory process was also characterized by significantly higher serum P-selectin values.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

The most pronounced negative correlation of the content of P-selectin, on the one hand, and an increase in the level of urea, and especially creatinine, on the other ($r = -0.59$; $r = -0.36$; $p < 0.05$), i.e. . with uremia and hypercreatininemia, serum P-selectin level decreases. Terminal CKD is one of the severe manifestations of renal pathology, in connection with which the priority of early detection and assessment of the state of ED and markers of inflammation in CKD is obvious for the timely implementation of preventive measures for the development of complications and the use of hemodialysis.

In the literature, works devoted to the study of the role of P-selectin in the formation and progression of CKD are few and contradictory. So, Yu.A. Morozov and T.V. Marchenko (2014) reported an increase in P-selectin in the plasma of patients with stages of 3-4 CKD, which indicates intravascular platelet activation. It is believed that this hyperactivity of blood platelets is associated with hyperfibrinogenemia, hypovolemia, hypoalbuminemia, hyperlipidemia [9].

There are studies on changes in the expression of adhesive molecules of the endothelium of the vascular wall in patients with chronic liver diseases, according to which chronic liver pathology with biochemical signs of cholestasis was characterized by significantly higher plasma values of E-selectin, and prognostically severe liver cirrhosis (class C according to Child-Pugh) were accompanied by the maximum values of E- and P-selectins, directly correlating with the Child-Pugh index. The concentration of selectins in the blood, being increased, did not depend on the degree of impaired portal hemodynamics, and the relationship of P-selectin with the values of the prothrombin index was negative. High rates of P-selectin and low levels of L-selectin were associated with an increased risk of high degree esophageal venectasis in patients with cirrhosis. The values of E-, L- and P-selectins were characterized by high diagnostic accuracy in predicting moderate and severe histological activity of the liver [3, 4, 20, 21].

ED is a condition preceding the disruption of the functioning of any vessel, regardless of its caliber and organ affiliation, and an increased level of selectins (E- and P-selectin) is an early sign of endothelial activity [6, 7, 35].

ED is a key element of vascular disorders, and its presence is associated with an unfavorable prognosis of various diseases. So, in patients with coronary heart disease (CHD), the initial content of ICAM-1 and VCAM-1 in the blood determined the appearance of myocardial infarction and the development of a fatal outcome, although this relationship was not found for P-selectin [2]. An increased concentration of soluble E-selectin in patients with diabetes mellitus was associated with an unfavorable prognosis in the form of a manifestation of unstable angina and Q-negative myocardial infarction [1]. Patients with acute coronary syndrome with high levels of adhesion molecules were more likely to develop heart failure [1, 2, 31].

It is believed that the level of soluble forms of cellular adhesion molecules in the blood (intercellular adhesion molecule 1 (slCAM-1), vascular adhesion molecule 1 (sVCAM-1), pE-selectin and sP-selectin), as well as von Willebrand factor, reflect the state of endothelium [8, 11]. According to a study conducted by the Atherosclerosis Risk in Communities Study program, sICAM-1 overproduction shows a significant increase in the risk of coronary heart disease and atherosclerosis of the internal carotid arteries, and an increase in sE-selectin levels is associated with an increased risk of developing atherosclerosis of the internal carotid arteries [31]. An increase in sVCAM-1

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

level correlates with the prevalence of atherosclerosis and atherosclerotic changes in the arteries of the basin of the internal carotid arteries [7]. In the works of M.Yu. Maksimova et al. (2014) discuss the role of endothelial dysfunction in the development of ischemic, in particular atherothrombotic stroke. Data were obtained on an increase in the level of sICAM, sVCAM-1, sE-selectin and sP-selectin in the first hours and days after a stroke and the impact on the prognosis of the disease [8].

As evidence of the role of indicators of the selectin family in inflammatory and immune responses, we established the conjugacy of the adhesion molecule in CKD in the form of an increase in serum P-selectin level with an increase in the intensity of the inflammatory component. In cases of the development of a systemic inflammatory response syndrome, increased circulating E-selectin and immunoglobulin superfamily molecules were associated with increased mortality during the month, especially in cases of the infectious nature of the process [20]. The initial increased values of platelet expression of P-selectin and plasma levels of the mediator in cirrhosis were higher in cases of subsequent development of acute gastrointestinal bleeding [4].

It has been proven that P-selectin plays a critical role in reperfusion and endotoxin-induced migration of leukocytes [3, 17, 18]. Thus, the disturbed production or blockade of the mediator by monoclonal antibodies that we identified was accompanied by a decrease in the adhesion of leukocytes to the renal capillaries, lymphocytic infiltration of the parenchyma and apoptosis of the cells, as well as a decrease in GFR. As a result, perfusion worsened, urea and creatinine levels increased, and P-selectin levels decreased. This may be due to the neutralization of P-selectin receptors [40]. An example of a model of cholestatic liver pathology shows the positive effect of reduced platelet counts or P-selectin receptors on cells on the adhesive and aggregation ability of platelets in the microvasculature of the liver, their cooperation with leukocytes and the rate of biochemical activity of the process [21]. K. Monson et al. (2007) found that the deficiency of the adhesion molecule did not significantly affect the degree of neutrophilic liver infiltration and serum enzymes and pro-inflammatory cytokines, but improved survival rates of mice with reperfusion syndrome [34].

At the same time, the opposite point of view was voiced about the inability of P-selectin, in contrast to the von Willebrand factor, to play a key role in the development of lipopolysaccharide-mediated intravascular thrombosis [7, 8, 9]. The absence of the inhibitory effect of antibodies to P-selectin on concanavalin-induced cytotoxicity was revealed [31]. The point of view is discussed about the limiting role of the mediator in the formation of pneumonia and pulmonary fibrosis. Thus, infection of Schistosoma mansoni in mice lacking the P-selectin gene led to a pronounced increase in necroinflammatory and fibrotic changes in the lungs [30]. Deficiency of P-selectin or its ligand contributed to an increase in fibrosis [30, 39], which was accompanied by a decrease in type 1 T-helpers in tissue, enhancing the expression of PSGL-1 and inhibiting the expression of ICAM-1 ligand [39], or by a decrease in natural killers producing interferon [30].

Thus, the role of selectin family indicators in predicting adverse outcomes of many diseases, including kidneys, has not been fully established. Disorders of intercellular interactions, being involved in the progression of CKD, can affect the prognosis of the disease. One of the least studied issues of the problem is to determine the role of selectins as predictors of the appearance of signs of ED and atherosclerosis, as well as adverse disease events. The selection

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

of markers predicting the development of an adverse outcome will contribute to the timely implementation of preventive and rehabilitation measures.

The results of a study of the problem of intercellular interactions in kidney diseases indicate that, despite the fact that extensive material has been accumulated in recent years, the questions “Are imbalances of selectins in kidney pathology a key element of pathogenesis and prognosis?”, “Can they be early markers ED and atherosclerotic changes? ” no clear answer. The conflicting opinions regarding the significance of deviations of many adhesion molecules are the basis for considering a new clinical paradigm for disorders of intercellular interactions in CKD.

It is quite obvious that the model of the diagnostic process in a patient with CKD should include not only clinical, laboratory and instrumental criteria, but also an assessment of the state of selectins, which will improve the quality of stratification of patients according to the stages of the disease, clinical forms, severity, and, therefore, the risk of development complications.

Studying the various components of ED, immune homeostasis and establishing their relationship with clinical features, prognosis and results of nephroprotective therapy will help to understand clinical CKD polymorphism, which will enrich clinical practice with new differential diagnostic criteria, and will facilitate a timely assessment of the effect of intercellular balance deviations on the course and prognosis of the disease.

Thus, the activation of mediators of intercellular interactions in combination with a change in endothelial function and platelets under the influence of inflammation triggers is the basis for enhancing ED, atherosclerotic, morphological and other changes, closing the vicious cycle of CKD progression.

IV. CONCLUSIONS

1. In CKD, a violation of immune homeostasis associated with clinical manifestations was revealed, characterized by significantly higher serum P-selectin values. The established abnormalities are based on the inflammatory process in the kidneys and activation / dysfunction of the endothelium and platelets. However, when it is increased, the concentration of P-selectin in the blood depends on the stage and category of CKD: as GFR decreases (59 ml / min / 1.73 m2 or less), the serum level of P-selectin significantly decreases, especially with CKD stage III-V.
2. In patients with CKD with clinical, laboratory and instrumental signs of ED and atherosclerosis, the level of P-selectin increases more significantly compared with patients with CKD without atherosclerotic changes.
3. There is a close relationship between the level of P-selectin and various clinical and biochemical syndromes of kidney pathology. As the inflammatory process, hypercholesterolemia, urinary, nephrotic syndromes, as well as arterial hypertension syndrome, the concentration of P-selectin increases. However, with uremia and hypercreatininemia, serum P-selectin levels decrease.
4. The deepening imbalance of the mediator of intercellular interactions of P-selectin as CKD progresses (up to the terminal stage) and the presence of a relationship with various clinical options for renal pathology is evidence of the important clinical and pathogenetic significance of selectin disorders in the progression of the process and the formation of atherosclerotic changes and other complications of the disease.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

5. It is recommended to use the values of P-selectin obtained during the study to state the severity of renal changes and stratification of patients in groups with high cardiovascular risk. Determining the selectin profile in patients with CKD is important for the purposes of differential diagnosis and assessment of prognosis, which is of great importance for the choice of therapeutic tactics.

REFERENCES

[1] Bedelbaeva G.G., Mukhambetyarova S.A., Nurmakhanova Zh.M. Features of the course of myocardial infarction in patients with type 2 diabetes mellitus // *Clinical medicine of Kazakhstan*. - 2013. - No. 3 (29). - S. 16-20.

[2] Belokopytova IS, Moskalets OV, Paleev F.N., Zotova OV The diagnostic value of adhesion molecules sICAM-1 and sVCAM-1 in coronary heart disease // *Atherosclerosis and dyslipidemia*. - 2013. - No. 4 (12). - S. 62-65.

[3] Gilyazova G.I., Koroy P.V. Selectins in chronic liver disease // *Bulletin of a young scientist*. - 2013. - No. 1. - S. 14-18.

[4] Gilyazova G.I., Koroy P.V., Yagoda A.V. Selectins as predictors of the adverse course of liver cirrhosis // *Medical Bulletin of the North Caucasus*. - 2013. - No. 2. - S. 80-81.

[5] Gilyazova G.I., Mukhoramova I.S., Rudenko Yu.A., Koroy P.V. The role of adhesion molecules in the immune response // *Bulletin of a young scientist*. - 2012. - No. 2. - S. 21-27.

[6] Ivanov A.N., Norkin I.A., Puchinyan D.M. and other Adhesive molecules of the endothelium of the vascular wall // *Uspekhi Fiziologicheskikh Nauk*. - 2014. - T. 45, No. 4. - S. 34-49.

[7] Komelkova L.V., Ionova V.G. Adhesion molecules and platelet-vascular hemostasis in patients with stenosis of the internal carotid artery of atherosclerotic origin // *Thrombosis, hemostasis and rheology*. - 2011. - No. 1. - S. 53-60.

[8] Maksimova M.Yu., Komelkova L.V., Okhtova F.R. Factors of intercellular interaction in ischemic stroke // *Zh. nevrol. and a psychiatrist*. - 2014. - No. 2. - S. 15-20.

[9] Morozov Yu.A., Marchenko T.V. Chronic kidney disease and hemostatic disorders // *Hemorrhagic diathesis, thrombosis, thrombophilia*. - 2014. - No. 1.

[10] Petri A., Sabin K. Visual medical statistics: a training manual / Per. from English ed. V.P. Leonov. - *2nd ed., Revised. and add. - M., GEOTAR-Media*, 2010 .-- 169 p.

[11] Rasulova H.A., Ikramova A.Sh. The use of anticoagulants in patients with chronic renal failure // *Internat. Scientific Journal Global Science and Innovations 2019: Central Asia. - Nur-Sultan, Kazakhstan,* Sept.-Oct., 2019 .-- P. 167-171.

[12] Rasulova H.A., Nishonov Sh.Yu., Abbasov A.K., Khusinbaev I.D. Fluctuations in blood pressure in patients with ischemic stroke, depending on the pathogenetic subtypes and functional state of the kidneys // *Neurology. - Mat. conf. "Current issues in the diagnosis and treatment of neurological diseases." - Tashkent,* December 6, 2019.- No. 4 (80). - S. 174.

[13] Romaniuk S.V. Lymphocyte-platelet adhesion and sP-Selectin level in patients with myocardial infarction // *Symbol of science*. - 2017 .-- Vol. 2, No. 1. - R. 174-177.

[14] Sigitova O.N. Chronic kidney disease: current status of the issue // *Diary of Kazan Medical School*. - 2013. - No. 1 (1). - S. 59-62.

[15] Smirnov A.V., Dobronravov V.A., Kayukov I.G. The problem of modifying the classification of chronic kidney disease // *Nephrology*. - 2010. - No. 15 (2). - S. 7-15.

[16] Umarova Z.F., Rasulova H.A. Modern approaches to predicting complications of coronary heart disease // *Electron. periodic peer-reviewed scientific journal "SCI-ARTICLE.RU"*. - 2020. - No. 77 (January). - S. 73-78.

[17] Khaitov P.M., Ignatieva G.A., Sidorovich I.G. Immunology. Norm and pathology. - *The textbook. - 3rd ed., Revised. and add. - M.: Publishing House "Medicine"*, 2010. - 752 p.

[18] Chepel E., Haney M., Misbach S., Snovden N. Fundamentals of clinical immunology. - *Translation from English. - 5th ed. - M .: GEOTAR-Media*, 2008 .-- 416 p.

[19] Chizhova M.A., Hammad E.V., Mursalov S.U., Sedova E.V. Studying the levels of signaling molecules in blood serum with coronary heart disease, iron deficiency anemia and their combination in elderly patients // *Modern problems of science and education*. - 2015. - No. 6.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020

[20] Berry A.V., Koroy P.V., Gilyazova G.I. Selectins as predictors of stable virological clearance in chronic viral hepatitis C // *Medical Bulletin of the North Caucasus*. - 2013. - No. 3. - S. 5-9.

[21] Berry A.V., Koroy P.V., Gilyazova G.I. Selectins and histological picture in chronic viral diseases of the liver // *Medical Herald of the North Caucasus*. - 2013. - No. 1. - S. 29-33.

[22] Abbasov A.K., Rasulova Kh.A. Modern data on modifiable and non-modifiable risk factors of chronic kidney disease // *Internat. Scientific Journal Global Science and Innovations 2019: Central Asia. - Nur-Sultan, Kazakhstan,* Sept.-Oct., 2019 .-- P. 67-70.

[23] Abbasov A.K., Rasulova Kh.A. Changes in lipid metabolism in patients with chronic kidney disease // *XIII International Symposium on the Chemistry of Natural Compounds (ISCNC 2019)*. - Shanghai, China, October 16-19, 2019 .-- P. 40.

[24] Abbasov A.K., Rasulova Kh.A. The role of P-selectin in development and progression of chronic kidney disease // *Bulletin of TMA. - Tashkent*, 2019 .-- No. 4. - S. 181-183.

[25] Arbel Y., Halkin A., Finkelstein A., Revivo M., Berliner S., Herz I., Keren G., Banai S. Impact of estimated glomerular filtration rate on vascular disease extent and adverse cardiovascular events in patients without chronic kidney disease // *J. Cardiol.* - 2013 .-- Vol. 29 (11). - R. 1374–1381.

[26] Daminov B.T., Abdullaev Sh.S. Left Ventricular Structure during Antihypertensive Treatment in Patients with Chronic Kidney Disease // *International Journal of Biomedicine*. - 2016.

[27] Daminov B.T., Ubaydullaeva B.N. Anemia in patients receiving programmed hemodyalisis // *Central Asian J. Pediatrics.* - 2019 .-- Vol. 2 (11) - P. 131-141.

[28] Dimastromatteo J., Broisat A., Perret P. et al. In vivo molecular imaging of atherosclerotic lesions in ApoE - / - mice using VCAM-1-specific, 99mTc-labeled peptidic sequences // *J. Nucl. Med.* - 2013. - V. 54, No. 8. - R. 1442-1449.

[29] Glowinska B., Urban M., Peczynska J., Florys B. Soluble adhesion molecules (sICAM-1, sVCAM-1) and selectins (sE selectin, sP selectin, sL selectin) levels in children and adolescents with obesity, hypertension , and diabetes / // *Metabolism*. - 2005. - V. 54, No. 8. - R. 1020-1026.

[30] Horikawa M., Fujimoto M., Hasegawa M. et al. E- and P-selectins synergistically inhibit bleomycin-induced pulmonary fibrosis // *Am. J. Pathol.* 2006. - Vol. 169, No. 3. - P. 740-749.

[31] Hwang S.J., Ballantyne C.B., Sharrett A.R. et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incidental coronary heart disease cases. The Atherosclerosis risk in communities (ARIC) study // *Circulation*. - 1997. - Vol. 96.- R. 4219-4225. PMID: 9416885.

[32] KDIGO, 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease // *Kidney Int (Suppl.).* - 2013. –Vol. 3. - R. 1–150.

[33] Ling S., Nheu L., Komesaroff P.A. Cell adhesion molecules as pharmaceutical target in atherosclerosis // *Mini. Rev. Med. Chem*. - 2012. - V. 12, No. 2. - P.175-183.

[34] Monson K.M., Dowlatshahi S., Crockett E.T. CXC-chemokine regulation and neutrophil trafficking in hepatic ischemia-reperfusion injury in P-selectin / IC AM-1 deficient mice // *J. Inflamm*. - 2007. - Vol. 24. - P. 4-11.

[35] Rasulova Kh.A, Abbasov A.K. P-selectine is a new marker of endothelial dysfunction // *Neurology. - Mat. conf. "Current issues in the diagnosis and treatment of neurological diseases." - Tashkent,* December 6, 2019.- No. 4 (80). - S. 132.

[36] Smith C.W. Adhesion molecules and receptors // *J. Allergy. Clin. Immunol.* - 2008. - V. 121, No. 2. - R. S375-S379.

[37] Sumagin R., Kuebel J.M., Sarelius I.H. Leukocyte rolling and adhesion both contribute to regulation of microvascular permeability to albumin via ligation of ICAM-1 // *Am. J. Physiol. Cell. Physiol.* - 2011. - V. 301, No. 4. - R. C804-C813.

[38] Van der Velde M., Matsushita K., Coresh J. et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. *A collaborative meta-analysis of high-risk populations cohorts // Kidney Int.* - 2011. - Vol. 79 (12). - P. 1341-1352.

[39] Yoshizaki A., Yanaba K., Iwata Y. et al. Cell adhesion molecules regulate fibrotic process via Thl / Th2 / Thl7 cell balance in a bleomycin-induced scleroderma model // *J. Immunol.* - 2010 .-- Vol. 185, No. 4. - P. 2502-2515.

[40] Yu Z., Otsuka H., Yamaguchi K. et al. Roles of platelets and macrophages in the protective effects of lipopolysaccharide against concanavahn A-induced murine hepatitis // *Biochim. Biophys. Acta*. - 2011. - Vol. 1812, No. 9. - P. 1069-1079.

DOI: 10.37200/IJPR/V24I5/PR2020291
Received: 18 Mar 2020 | Revised: 30 Mar 2020 | Accepted: 08 Apr 2020