DOI: 10.38096/2181-5674.2020.2.00075

УДК: 616-002-(612.014.464)+616.13.002.2-004.6

THE LINK BETWEEN INTENSITY OF INFLAMMATION, DISLIPIDEMYA AND REACTIVE OXYGEN SPECIES GENERATION AT ATHEROSCLEROSIS


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АТЕРОСКЛЕРОЗ ЯЛЛИҒЛАНИШНИНГ РИВОЖЛАНИШИ УЗЛУКСИЗЛИГИДА, ДИСЛИПИДЕМИЯ ВА ФАОЛ КИСЛОРОД ТУРЛАРИНИНГ ЎЗАРО БОҒЛИҚЛИГИ

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ВЗАИМОСВЯЗЬ ВОСПАЛЕНИЯ, ДИСЛИПИДЕМИИ И УРОВНЯ АКТИВНЫХ ФОРМ КИСЛОРОДА ПРИ АТЕРОСКЛЕРОЗЕ

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Аннотация. *АСА/АНА маълумотларига кўра юрак қон -томир кассаликлари ва атеросклероз, ўлим кўрсаткичлари бўйича дунё миёқсида биринчи ўринни эгаллайди. Текшириш усуллари: 120 нафар атеросклероз беморлар текширилди, 60,2± 1,5 ўрта ёш ида, аёллар - 19 (15,8%), эркаклар - 101 (84,2%). 30 нафар беморларда атеросклероз илео-феморал ховузида-перифирик атеросклероз (1 гурух), 80 нафар беморларда тож артериялар атеросклерози, юракишимик кассаликлар (2-гурух). С – реактив оқсил даражасини баҳолаш (СРБ), интерлейкин-6 (ИЛ-6), некроз ўсма омили альфа (ФНО-а), фибриноген, умумий лейкоцитлар сони ва уларнинг тури, оксидлаш стресс маркерлари-малондеальдегид ва активлашган каталаза, пролифератив маркерлар ва эндотелий дисфункцияси-васкулоэндотелиал ўсиш омиллари (VEGF). Натижалар: ЮИК (юрак ишимик касаллиги) ҳамда перефирик атеросклерозда яллиғланиш интенсивлиги, солиштирма таҳлили шуни кўрсатдики, яллиғланиш олди цитокинлари ИЛ-6, ФНО-а, ўткир яллиғланиш оқсиллари концентрациясига тенг – СРБ ва фибриноген. Юқорида келтирилган текширув гуруҳига нисбатан иккала атеросклероз бемор гуруҳларида деярлик баландроқ. Периферик атеросклероз беморларини фарқли белгилари ўткир яллиғланиш, умумий лейкоцитларни кўтарилиши ЛИИ, СРБ фибриноген, оксидлаш стресс яллиғланиши, ушбу беморларда қисман камайди,(VEGF) эса кўтарилди. ЮИК оксидлаш стресси декомпенсацияси билан тавсифланиши ва яллиғланиш паст интенсивлиги ЛИИни даражасига нисбатан олинди. Перифирик атеросклерозда яллиғланиш гипергликемия фонида кечади. Ёғлар алмашинувининг бузилиши (дислипидемия) иккала гуруҳда ҳам бир хил, яққол кўринишда кечди.*

Калит сўзлар: *юрак қон-томир касалликлари, атеросклероз, илеофеморал бассейн, периферик атеросклероз, коронар атеросклероз.*

Abstract. *According ACA/AHA data (2019) Cardiovascular diseases (CVD) owing to an atherosclerosis are in the first place among the reasons of morbidity and mortality rate all over the world. Methods. It is surveyed 120 patients with an atherosclerosis, middle age 60,2±1,5; 19 women (15,8%) and 101 men (84,2%). There were 30 patients with an atherosclerosis in the iliac-femoral arterial pool - the peripheral atherosclerosis (PA), accompanying with chronic limb ischemia and 80 patients with coronary atherosclerosis (CHD). C-reactive protein (CRP), interleykin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), fibrinogen, general*

blood count, markers of oxidative stress (OS) – malondialdehyde (MDA) and catalase activity, marker of endothelial proliferation and migration – vascular endothelial growth factor (VEGF) were analyzed. Results. Comparative analysis of intensity of inflammation at peripherical atherosclerosis and CHD shows, that concentration of proinflammatory cytokines IL-6 and TNF-a were increased versus control (p<0,05) both at PA and CHD patients. Acute inflammation reactants proteins – CRP, fibrinogen also were increased versus control (p<0,05) both at PA and CHD patients. The character signs of inflammation at PA were the prevalence of acute inflammation with WBS, LSI, CRP, fibrinogen increasing and partly compensated oxidative stress accompanied with VEGF increasing. CHD was associated with decompensate OS and low-grade inflammatory reaction, accompanied with metabolic disorders. Inflammation at PA was associated with increase immature neutrophils, hypoalbuminemia. In contrast, inflammation at CHD was associated with hyperglycemia. Dyslipidemya was common both CHD and PA.

Keywords: *cardiovascular diseases, atherosclerosis, ileofemoral pool, peripheral atherosclerosis, coronary atherosclerosis.*

Urgency of problem. According ACA/AHA data (2019) Cardiovascular diseases (CVD) owing to an atherosclerosis are in the first place among the reasons of morbidity and mortality rate all over the world [1]. The economical loss from disability and expenses for treatment of atherosclerosis is more than 200 million dollars per one year in USA [8]. According WHO forecasts, mortality rate from CVD will increase, a part of coronary heart disease (CHD) in CVD takes of 28,7% for today, and it has trend to increase up to 50% [17]. Nowadays the heart can be considered as a psycho-neuro-endocrine-immunitary structure that constantly interacts with other organs through a dynamic dialogue made of neuro-peptides, hormones and cytokines [18].

The exploration of microvascular function is important as predictive tool and as prognosis of cardiovascular risk and progression of heart failure. The coronary circulation is regulated by four main factors: anatomical (left ventricular wall thickness and the presence of collateral circulation), mechanical (systemic flow, vascular resistance, systolic compression, myogenic reflection and blood viscosity or hemolysis and platelet aggregation), neuro-immune (through alpha and beta2 receptors, vagal action) and endocrine-metabolic (pO2, pH, K+, adenosine, prostaglandins, tromboxane, hyperlipemia and nitric oxide (NO)) [16].

Endocrine – metabolic component includes both reactive oxygen and nitrogen species, cytokines and lipidomic fraction of blood serum. The activity of endothelial NO depends on the balance between synthesis of NO and its breakdown by superoxide anion (O2-) [10]. Increased production of reactive oxygen species (ROS) is regarded as major determinant of reduced levels of NO. The loss of NO due to enhanced oxidative stress in the vessel wall might be considered the central mediator of all different aspects related to endothelial dysfunction, critically contributing to plaque destabilization in traditional atherosclerosis [11]. The loss of endothelium-derived NO permits increased activity of the pro-inflammatory transcription factor nuclear factor kappa B (NF-kB), resulting in expression of leukocyte adhesion molecules and production of chemokines and cytokines [6, 15]. These actions promote monocytes and vascular SMCs migration into the intima and formation of macrophage foam cells, characterizing the initial morphological changes of atherosclerosis [5]. The activity of the endothelium, thus, extends far beyond the control of vascular tone and reactivity, and the release of vasodilating mediators is only one aspect of its homeostatic and protective roles. An impaired NO bioavailability, leading to endothelial dysfunction, is a key pathological condition which is associated with most, if not all, cardiovascular diseases and risk factors [14].

The inflammation is a pathogenesis basis of an atherosclerosis from the beginning up to a final stage – vulnerable atherosclerotic plaque formation [4]. The data of recent researches have proved an essential role of CRP, interleukins (IL)-6,-8,-1,-10, 12, tumor necrosis factor alpha (TNF-a) in progressing an atherosclerosis, in an estimation of risk of sudden death, development of acute coronary events and its complications [2]. In research GISSI among 11 324 patients with a acute heart attack of a myocardium and the contents of WBC less than 6000 mortality during 4 years has made 6,9 %, and at the contents of leukocytes more than 9000 – mortality has made 17,7%. Thus prognostic value and the importance of WBC number did not depend on expressiveness of other factors of atherogenesis [12, 16]. There is now considerable biochemical, physiological and pharmacological data to support a connection between free radical reactions and cardiovascular tissue injury that share common mechanisms of molecular and cellular damage. Overproduction of reactive oxygen species (ROS) such as superoxide radical, hydrogen peroxide, and the hydroxyl radical leading to lipid peroxidation, denaturation of proteins or enzymes or mutagenic damage to nucleic acid and caused oxidative stress [9]. As these mechanisms are elucidated, it can be possible to improve the techniques for clinical and pharmacological intervention. Ways of liquidation of inflammatory process and oxidative stress at an atherosclerosis have not found yet, probably, since of heterogeneity of trigger factors of the systemic inflammatory response and ROS generation. In this view, research of factors of an inflammation and oxi-

dative stress and its correlation with traditional metabolic disorders is in the area of interest at an atherosclerosis of various localization, as was the purpose of this work.

Materials and methods. It is surveyed 120 patients with an atherosclerosis, middle age 60,2±1,5; 19 women (15,8%) and 101 men (84,2%). There were 30 patients with an atherosclerosis in the iliac-femoral arterial pool - the peripheral atherosclerosis (PA), accompanying with chronic limb ischemia and 80 patients with coronary atherosclerosis (CHD). The diagnosis established on the basis of clinical, ultrasound and Doppler data, multi scanning computer tomography, percutaneous coronary angiography. As a control group, we accessed 18 volunteers of same age (14 men, 4 women) without atherosclerosis. Laboratory tests included C-reactive protein (CRP) and routine biochemical tests (lipidomic panel, total protein, albumin, glucose, uric acid), which were made in automatic biochemical analyzer "VITROS-350" (USA). Interleykin-6 (IL-6), tumor necrosis factor alpha (TNF-a), vascular endothelial growth factor (VEGF) were measured in the blood serum using commercially available ELISA kits (VECTOR-BEST, Russia) in immunoassay analyzer ST-360, (China). General blood count was made by automatic hematological analyzer BC 5800 (Mindray, China), qualitative white cell-associated signs; such as immature granulocytes and left shift were identified by manual differential leukocyte count in blood smears. White blood cells (WBC), neutrophils (Neu), immature granulocytes (INeu), monocytes (Mon), Bazophils (Baz), Eozinophils (Eoz), lymphocytes (Lymph) were identified. Left shift index (LSI) was calculated as immature granulocytes and blasts to mature neutrophils ratio. Studies support a decision threshold of 0,069 for LSI. Marker of oxidizing stress – malondialdehyde (MDA) was analyzed according to procedure of Ohkawa on reaction with thiobarbituric acid in Al-Gayyar's modifications [15]. In brief, serum proteins are precipitated by the addition of trichloroacetic acid. Then, thiobarbituric acid reacts with MDA to form thiobarbituric acid-reactive substance that is measured at 532 nm. Catalase activity was determined by the speed of hydrogen peroxide degradation in the semi-automatic analyzer "Screen Master Plus" (Hospitex Diagnostics, Italy). The results are presented as the M ± m, independent student t-test was applied to find out the statistically significant difference ($p<0,05$) between the groups, Pearson's correlation was used to figure out the correlation among the circulating biomarkers.

Results and discussion. The blood count and blood smear examination results in the patients with PA and CHD were different. There was increasing of WBC, Neu and the left shift at the PA patients (table 1). There were statistically significant difference between control group and CHD patients in the blood count and blood smear parameters, include WBC, immature neutrophils, monocytes and LSI. WBC was increased in 1,5, LSI – in 1,4 times in compare with control at CHD patients. But this differences were in reference interval for WBC. Amount of WBC were increased in 1,7 times versus control in PA patients and statistically significant ($p<0,05$) versus CHD patients. Monocytes and eozinophils at PA patients was in reference value [5], but it were higher, than in control in 1,9 and 3,4 times.

Our study supports a decision threshold of 0,069 and the reference value 0,050 - 0,070 for LSI.

LSI characterizes the intensity of inflammation, the intensity of inflammation is middle if LSI is 0,080 – 0,099 and is high if LSI is more 0,100 [16]. Our data shows, that LSI was increased in 1,6 and 1,4 times concerning the control at PA and CHD patients respectively. This data shows that intensity of inflammation, according to LSI, is middle at the CHD patients and is high at the PA patients. High LSI and WBC amount was accompanied with increasing of CRP in 2,5 times, fibrinogen on 16%, decreasing of albumin on 25% concerning the control at PA patients (table 2).

Comparative analysis of intensity of inflammation at peripherical and coronary atherosclerosis shows, that concentration of proinflammatory cytokines IL-6 and TNF-a were increased versus control ($p<0,05$) both at PA and CHD patients. CRP was increased in contrast with control in 2,3 at PA and in 2,9 times at CHD patients; TNF-a concentration was increased in 1,6 and 1,9 times respectively. But there were no significant difference in CRP, TNF-a, IL-6 levels between PA and CHD groups ($p>0,05$). Fibrinogen concentration was statistically significant increased at PA patients, while at CHD patients it does not differ from the control ($p>0,05$).

Markers of oxidative stress (OS) – MDA and catalase were changed greater at CHD patients. There were high MDA level (increased in 2,1 times compare with control) with increasing of catalase activity in the blood on 52% ($p<0,05$) at CHD patients. At PA patients MDA level was increased in 1,5 time, catalase activity was comparable to the control, that specifies on compensated OS. Probably, the chronic ischemia / hypoxia of heart is accompanied by activation of generation of reactive oxygen species and accumulation of MDA in blood greater, rather than an ischemia of peripheral muscles at PA [11]. It may be caused by specific properties and differs of bloodstream and metabolism intensity, different value of drainage function of micro vascular system and activity of endogenous antioxidative capacity of the heart and skeletal muscles.

At CHD patients CRP was higher, then control in 2,9 times, and it was associated with metabolic disorders such as increasing of glucose concentration up to 6,1±0,3 mmol/L and body mass index (BMI) up

to 30,3±1,6 kg/m^2. Concentration of the uric acid (UA) was increased concerning to the control at 1,4 times both at PA and CHD patient, but it was in the reference value 360 mkmol/L, determined by EULAR. Changes of plasma lipidomic profile were similar at the PA and CHD patients and included increasing of the triglycerides (TG) with decreasing of high density lipoproteins (HDL), but at PA patients serum glucose concentration was significantly lower, than at CHD patients (p<0,05) (table3).

Table 1. The blood count and blood smear parameters at patients with atherosclerosis

Groups of patients	WBC, 10^9/L	Neu, %	INeu, %	Mon %	Baz, %	Eoz, %	Lymph %	LSI
The control, n=18	4,8±0,3	56,7± 3,7	3,9± 0,4	3,5± 0,3	0,40± 0,01	1,6± 0,4	30,7± 0,6	0,068± 0,003
1 group - PA, n=30	8,3±0,4*	54,7±1,9	5,9± 0,4*	6,8± 0,4*	0,50± 0,10	5,4± 0,7*	26,7± 1,8	0,108 ± 0,007*
2 group - CHD, n=80	7,4±0,3 *, **	56,2± 2,9	3,3± 0,6 *, **	7,1± 0,6 *	0,52± 0,08	2,2± 0,3	30,6± 3,1	0,098± 0,005 *

*Note: * - statistically significant difference at p<0,05 versus the control;*
*** - statistically significant difference at p<0,05 versus 1 group.*

Table 2. Pro-inflammatory cytokines, markers of oxidative stress at patients with atherosclerosis

Groups of patients	The control	1 group - PA	2 group - CHD
IL-6, pg/ml	8,7±1,1	35,5±13,1*	24,4±4,6*
CRP, mg /L	4,4±0,8	10,3±0,5*	12,8±1,4*
TNF-a, pg/ml	4,3±1,2	7,1±0,8*	8,1±1,3*
Fibrinogen, mg/L	3294±252	3829±199*	3263±127 **
Albumin, g/L	44,2±1,2	35,5±0,7*	42,2±1,5**
MDA, nmol/mg protein*h	4,7±0,25	7,33±0,3*	9,8±0,6 *,**
Catalase, U/L	19,2±1,8	23,3±0,9	41,2±0,9*,**

*Note: * - statistically significant difference at p<0,05 versus the control;*
*** - statistically significant difference at p<0,05 versus 1 group.*

Table 3. Lipidomic profile at patients with atherosclerosis.

Groups of patients	The control	1 group - PA	2 group - CHD
Glucose, mmol/l	4,7±0,1	4,8 ±0,4	6,1 ±0,3*,**
Trigliserides, mmol/l	0,93±0,19	1,98 ±0,11*	2,1 ±0,13*
VLDL, mmol/l	0,44±0,11	0,90 ±0,05*	0,84 ±0,09*
Cholesterol, mmol/l	4,4±0,1	5,0 ±0,5*	4,3 ±0,2*
HDL, mmol/l	1,34±0,03	0,97 ±0,04*	1,08 ±0,06*
LDL, mmol/l	2,80±0,17	3,12± 0,12*	3,12 ±0,15*
AK	2,3±0,2	4,24 ±0,18	3,0± 0,2

*Note: * - statistically significant difference at p<0,05 versus the control;*
*** - statistically significant difference at p<0,05 versus 1 group.*

Discussion of the results. Comparative analysis of intensity of inflammation at peripherical and coronary atherosclerosis shows, that concentration of both proinflammatory cytokines IL-6, TNF-a and acute inflammation reactants proteins – CRP, fibrinogen were increased versus control (p<0,05) both at PA and CHD patients. But inflammation at PA was associated with increase immature neutrophils, hypoalbuminemia. In contrast, inflammation at CHD was associated with hyperglycemia. The high level of fibrinogen at PA patients specifies not only activation of an inflammation, but also predisposition for thrombosis and microcirculation disturbances [4, 13]. It has established, that a change of coagulation at the patients with PA includes a high level of fibrinogen with increasing of thrombin and fibrinolytical activities. All of this exhausts reserve capacity of the coagulation system and can lead thrombosis [3].

It is known that IL-6 - is mediator of the cell damages, produced by monocytes, macrophages, endotheliocytes, its high-level triggers syntheses of fibrinogen, CRP, haptoglobin, amiloid A and inhibits the TNF-a production. Also IL-6 can induce increasing of the glucose concentrations due to hypothalamic - pituitary stimulation [17, 18]. We assume, that high concentrations of CRP and fibrinogen at PA patients are linked with exactly increasing of IL-6, which triggered synthesis of those proinflammatory proteins in the liver. High level of IL-6 occurs together with high TNF-a concentration, hyperglycemia and BMI increasing at the CHD patients. This allows to expect the contribution of visceral adipose tissue in IL-6 and TNF-a production. There is indeed evidence that obesity is associated with macrophage accumulation in adipose tissue and it is directly linked with inflammatory response. Obesity associated TNF-a is primarily

secreted from macrophages, accumulated in adipose tissue, whereas the adipocytes, predominantly produce unsecreted, membrane-bound TNF-a [18].

Our data shows that at CHD inflammation is closely connected with metabolic disorders and oxidative stress. Increasing of the UA level may be explained controversial. Several mechanisms have been postulated for explaining perceived endothelial abnormalities induced by UA. Incubation of vascular smooth muscle cells with UA has been found to stimulate proliferation, angiotensin II production, and oxidative stress; human aortic smooth muscle cells exposed to different concentrations of UA experienced dose-dependent cell proliferation and phosphorylation-dependent endothelin-1 expression, along with an increased activity of NADPH-oxidase - mechanism of production of ROS. Interestingly, those effects were reversible after treatment with antioxidants, such as N-acetylcysteine [7]. On the other hand, UA has the highest concentration of any blood antioxidant and provides over half of the total antioxidant capacity of human serum at levels as high as 285 μmol/L; it does act against peroxynitrite, peroxides, and hypochlorous acid. The effects of UA in atherosclerosis are still not well understood, with some studies linking higher levels of UA with increased mortality [4]. In the best way this contradiction has characterized by Proctor P.H.: "the well-established association between high urate levels and atherosclerosis could be a protective reaction (antioxidant) or a primary cause (pro-oxidant)", so it might be due to uric acid being activated as a defense mechanism against oxidative stress, but instead acting as a pro-oxidant in cases where metabolic derangements shift its production well outside of normal levels. Our data show, that at PA patients UA level is higher and oxidative stress is less expressed in contrast with CHD patients, probably due antioxidant properties of UA. We assume that extracellular antioxidant capacity and total antioxidant system activity is compensated at PA patients (catalase activity is normal) and strongly mobilized at the heart ischemia at CHD patients. Oxidative stress is developed in atherosclerosis due to disturbance in the pro-oxidant / antioxidant balance and impairment of antioxidant mechanisms in the ischemic tissue [10]. The main sources of oxidative substances and ROS in atherosclerotic vessels are macrophages and smooth muscle cell. ROS production, in turn, induces endothelial dysfunction [18]. So, ROS generation and inflammation are closely connected at atherosclerosis.

Our data confirm that ischemia of peripheral muscles at acute inflammation at PA patients leads endothelial proliferation and collateral bloodstream, which are more intensive in contrast with CHD patients due to VEGF concentration increasing. VEGF level was increased at PA patients at 2,2 times concerning the CHD patients. This data can be used in therapeutic angiogenesis conception development, because high level of VEGF is associated with stimulation of collateral bloodstream and endothelial proliferation [3,5,6]. On different models has shown that administration of vascular endothelial growth factor induced dose-dependent collateral artery augmentation of persistent ischemia [13].

As have shown our researches, the peripheral atherosclerosis is closely accompanied by inflammatory reaction, and a coronary atherosclerosis is closely connected with metabolic disorders and oxidative stress. The certain contribution to it development can bring co morbidity, in particular presence of metabolic syndrome [9]. This data suggests that inflammation at PA is acute, due to local inflammatory reaction of peripheral tissues after chronic ischemia. At CHD inflammation is low grade, closely connected with metabolic disorders and ROS generation.

Conclusion. Thus, studying of factors of an inflammation and ROS generation at a peripheral and coronary atherosclerosis has allowed revealing characteristic distinctions. This study shows, that concentration of both proinflammatory cytokines IL-6, TNF-a and acute inflammation reactants proteins – CRP, fibrinogen were increased versus control ($p<0,05$) both at PA and CHD patients. Prevalence of acute inflammation with WBS, LSI, CRP, fibrinogen increasing and partly compensated oxidative stress accompanied with VEGF increasing observed at PA patients. CHD is associated with decompensate OS and low grade inflammatory reaction and metabolic disorders. Inflammation at PA was associated with increase immature neutrophils, hypoalbuminemia. In contrast, inflammation at CHD was associated with hyperglycemia. Dyslipidemya was common both CHD and PA.

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ВЗАИМОСВЯЗЬ ВОСПАЛЕНИЯ, ДИСЛИПИДЕМИИ И УРОВНЯ АКТИВНЫХ ФОРМ КИСЛОРОДА ПРИ АТЕРОСКЛЕРОЗЕ

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Аннотация. По данным ACA/AHA, сердечно-сосудистые заболевания и атеросклероз занимают первое место в структуре смертности от всех причин во всем мире. Материалы и методы. Было обследовано 120 пациентов с атеросклерозом, средний возраст составил 60,2±1,5 лет; женщин было 19 (15,8%), мужчин - 101 (84,2%). У 30 больных был атеросклероз в илеофеморальном бассейне – периферический атеросклероз (1 группа), у 80 больных – коронарный атеросклероз – ишемическая болезнь сердца (2 группа). Оценивали уровень С-реактивного белка, интерлейкина-6 (ИЛ-6), фактора некроза опухолей альфа (ФНО-а), фибриноген, общее количество лейкоцитов и их типы, маркеры окислительного стресса – малоновый диальдегид и активность каталазы, маркер пролиферации и эндотелиальной дисфункции – васкулоэндотелиальный фактор роста (VEGF). Результаты. Сравнительный анализ интенсивности воспаления при периферическом атеросклерозе и ИБС показал, что концентрация провоспалительных цитокинов – ИЛ-6, ФНО-а, равно как и концентрация белков острой фазы - СРБ и фибриногена, была статистически значимо выше относительно контроля у пациентов с атеросклерозом обеих групп. Отличительной особенностью воспаления у больных с периферическим атеросклерозом был острый характер воспаления с увеличением общих лейкоцитов, ЛИИ, СРБ, фибриногена, а окислительный стресс у этих пациентов был частично компенсирован, VEGF был увеличен. Выводы. Воспаление при периферическом атеросклерозе сопровождается сдвигом лейкоцитарной формулы влево, гипоальбуминемией, компенсированным окислительным стрессом. ИБС характеризовалась декомпенсированным окислительным стрессом и низкой интенсивностью воспаления по уровню ЛИИ. При ИБС воспаление протекает на фоне гипергликемии. Дислипидемия была одинаково выражена у пациентов обеих групп.

Ключевые слова: сердечно-сосудистые заболевания, атеросклероз, илеофеморальный бассейн, периферический атеросклероз, коронарный атеросклероз.