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IMMUNO-INFLAMMATORY MARKERS ASSOCIATED WITH LEFT VENTRICULAR REMODELING IN ISCHEMIC HEART DISEASE

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Abstract
The article explores endothelial damage factors in arterial hypertension and ischemic heart disease, forming a cardiovascular syntropy. The cytokines considered as markers of endothelial dysfunction include IGF-I, VEGF, TGF-β1, and serum procalcitonin. The study found that patients with elevated VEGF levels have a high risk of developing and progressing cardiovascular pathology—particularly myocardial fibrosis and hypertrophy—against the background of arterial hypertension, regardless of its severity.

Keywords: Cardiovascular diseases, ischemic heart disease, arterial hypertension, cytokines, immunological markers

Introduction

The immune system functions through the release of cytokines—small signaling molecules essential for cellular communication. Cytokines act as key regulatory mediators of immunity and serve as critical messengers between the nervous and immune systems. Notably, cytokines, like certain neuropeptides, have the ability to cross the blood-brain barrier. Numerous studies have highlighted the role of neuropeptides and substance P, alongside various cytokines, in the modulation of cardiovascular diseases (CVD). This evidence supports the potential involvement of these molecules in both the development and persistence of hypertensive conditions. The widespread presence of cytokines and substance P in peripheral tissues and blood, combined with their capacity to cross the blood-brain barrier, strongly suggests that these molecules facilitate communication between the

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central nervous system (CNS), immune cells, and the cardiovascular system, thereby playing a significant role in maintaining blood pressure homeostasis [2]. Currently, it is well established that the pathogenesis of many cardiovascular and metabolic disorders—such as dyslipidemia, arterial hypertension (AH), ischemic heart disease (IHD), angina pectoris, diabetes mellitus, and obesity—is closely linked to systemic inflammation and oxidative stress. It is hypothesized that these pathological processes share common pathogenic mechanisms across these diseases [1, 3].

Materials and Methods

The study involved 234 middle-aged patients with a mean age of 52.4 ± 1.27 years. Arterial hypertension (AH) was diagnosed in accordance with the World Health Organization (WHO) criteria and classified according to the International Classification of Diseases (ICD-10). The study followed the ACC/AHA Hypertension Guidelines (2017).

Inclusion criteria encompassed patients aged 45 to 59 years diagnosed with hypertensive disease (HD), ischemic heart disease (IHD), and stable exertional angina (SEA), confirmed through clinical and laboratory-instrumental assessments, and admitted for inpatient treatment. The patient groups were matched for age, sex, and cardiovascular risk factors.

Exclusion criteria comprised individuals with acute myocardial infarction, acute coronary syndrome, acute infectious diseases, myocarditis, cardiomyopathies, chronic renal or hepatic failure, pulmonary hypertension, congenital or acquired heart defects, systemic diseases, as well as oncological and hematological disorders.

The study was conducted in compliance with the principles outlined in the Helsinki.

Declaration

Patient Grouping: Group 1 included 64 patients with hypertensive disease, stage 1, grade 1, risk II; Group 2 included 52 patients with ischemic heart disease: stable exertional angina, functional class II, hypertensive disease stage 2, grade 2, risk

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III; Group 3 included 58 patients with ischemic heart disease: stable exertional angina, functional class III, hypertensive disease stage 3, grade 3, risk IV;
The control group consisted of 60 practically healthy individuals without cardiovascular pathology.
All patients underwent necessary functional assessments including electrocardiography (ECG), echocardiography, coronary angiography, abdominal ultrasound, and chest X-ray. Laboratory analyses comprised protein, lipid, and carbohydrate blood profiles, coagulation studies, as well as measurements of cytokines and growth factors in serum.
Statistical analysis was performed using Microsoft Excel from the Microsoft Office XP suite (Microsoft, USA).

Results and Discussion

Immunological blood markers in cardiovascular syntropy demonstrated a trend of proportional increases in cytokine concentrations corresponding with disease severity. Patients in Group 1 showed a 1.3-fold increase in IL-17A and a 1.25-fold increase in IL-1β compared to the control group, while other cytokine levels remained comparable to controls. In Group 2, IL-17A levels (99.9 ± 2.71 pg/mL) were approximately twice those of controls (49.9 ± 2.65 pg/mL), accompanied by a 1.4-fold increase in complement component C3. In Group 3, IL-17A levels were doubled, with IL-6 and C3 levels increasing by 1.5 times. This proportional rise in cytokine levels with disease progression highlights the pathogenetic importance of immunological alterations in cardiovascular pathology (see Table 1).

Cytokine Status in Cardiovascular Syntropy

Cytokines	Group 1 (n=64)	Group 2 (n=52)	Group 3 (n=58)	Control Group (n=60)
IL-1β, pg/mL	54.1 ± 1.97**	58.2 ± 2.07**	67.5 ± 0.89***	43.2 ± 1.57
IL-6, pg/mL	31.0 ± 13.8*	35.8 ± 0.84***	45.2 ± 0.86***	29.8 ± 0.59
IL-17A, pg/mL	62.8 ± 1.61**	99.9 ± 2.71***	105.5 ± 1.08***	49.9 ± 2.65
TNF-α, pg/mL	32.1 ± 1.89*	50.2 ± 1.0**	50.4 ± 1.74**	30.2 ± 1.17
C3, ng/mL	53.2 ± 5.4*	68.2 ± 2.07***	73.0 ± 1.15***	50.2 ± 1.34

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Note: Values are statistically significant compared to control (*P<0.05; **P<0.01; ***P<0.001).

In the study of growth factors IGF-1, VEGF-A, and TGF-β1, patients in Group 3 exhibited an increased level of IGF-1 at 134.0 ± 0.05, which was higher compared to 127.7 ± 2.59 and 124.8 ± 2.18 observed in Groups 1 and 2, respectively (see Table 2). The elevated IGF-1 concentration in ischemic heart disease may reflect mechanisms that both trigger vascular wall injury and initiate protective responses. Additionally, it can serve as a marker of "atherosclerotic plaque instability," indicating an increased risk of myocardial infarction.

Table 2. Immunological Growth and Injury Factors in the Progression of Arterial Hypertension to Ischemic Heart Disease

Blood Parameters	Group 1 (n=64)	Group 2 (n=52)	Group 3 (n=58)	Control Group
IGF-1	127.7 ± 2.59	124.8 ± 2.18	134.0 ± 0.05*	120.9 ± 1.44
VEGF-A	95.9 ± 7.1*	193.8 ± 0.05***	318.7 ± 16.52***	88.4 ± 1.61
TGF-β1	21.9 ± 1.84	25.2 ± 0.05*	20.8 ± 0.90	22.7 ± 1.52

Note: Values are statistically significant compared to the control group (*P<0.05; **P<0.01; ***P<0.001).

Considering the pathogenetic mechanisms involved in the development of hypertensive disease (HD) and its progression to ischemic heart disease (IHD), vascular endothelial growth factor (VEGF) levels were measured across the selected patient groups. The results revealed a significant increase in VEGF levels in Group 3 patients, reaching 318.7 ± 16.52 pg/mL, compared to 95.9 ± 7.1 ng/mL and 193.8 ± 0.05 ng/mL in Groups 1 and 2, respectively ($p < 0.001–0.05$). VEGF levels in Group 3 were elevated approximately 3.6-fold, and in Group 2 by 2.4-fold, indicating substantial pathogenetically significant endothelial damage.

Transforming growth factor-beta 1 (TGF-β1) is recognized as a key pathogenetic factor driving myocardial fibrosis and hypertrophy. Experimental studies on cardiomyocyte cultures have confirmed its role in hypertrophic development. The activation of TGF-β1 is associated with the phenotypic diversity of myofibroblasts and their capacity to synthesize connective tissue components, including glycoproteins, all collagen types, and matrix-modifying proteins. This

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growth factor contributes to interstitial fibrosis and reduces the elastic properties of both myocardium and blood vessels.

Thus, the progression from arterial hypertension (AH) to ischemic heart disease is closely linked to vascular endothelial dysfunction. The activity of growth factors and inflammatory markers holds important prognostic significance in assessing cardiovascular disease progression and related complications.

Correlation analysis demonstrated associations between immunological parameters and coronary artery diameter: complement C3 (r = -0.56) and IL-17A (r = -0.62) exhibited strong negative correlations, whereas procalcitonin (r = 0.28), TNF-α (r = 0.22), and VEGF-A (r = 0.35) showed weak to moderate positive correlations with coronary vessel diameter (see Fig. 1). The inverse relationships between complement C3 and IL-17A levels and coronary artery diameter underscore the diagnostic importance of these cytokines in endothelial injury and suggest an increased risk of atherothrombosis.

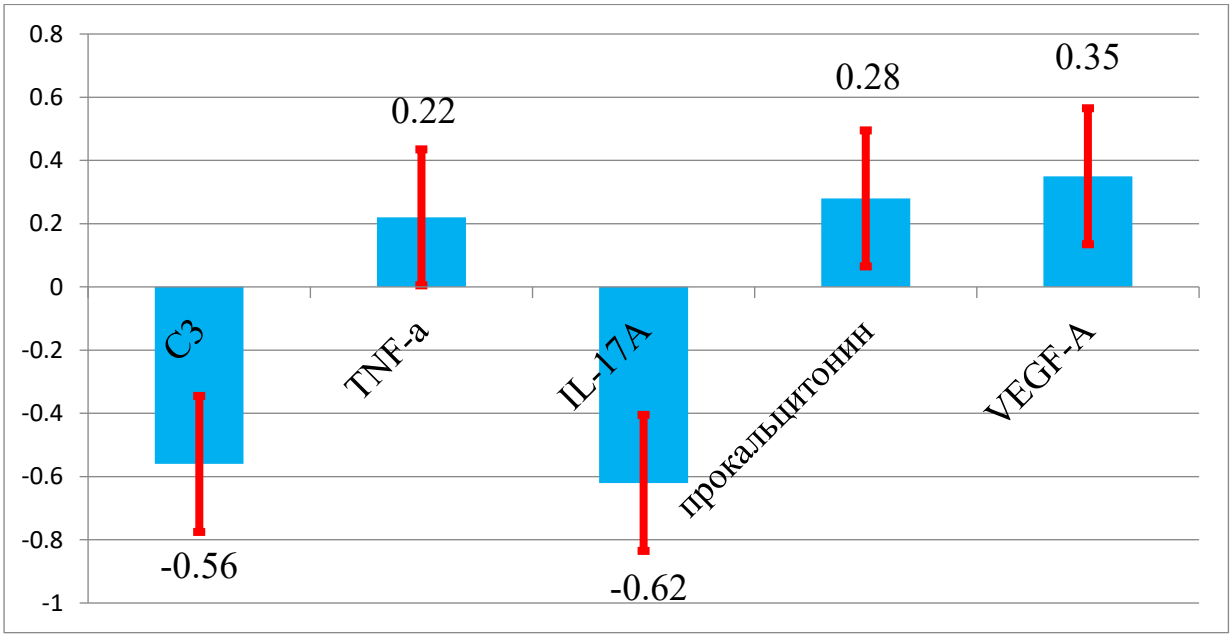

Figure 1. Correlation between coronary artery diameter in ischemic heart disease (IHD) and blood cytokine levels.

During duplex angioscanning of the carotid arteries in 41 patients (23.6%), signs of atherosclerosis of the common carotid artery accompanied by a significant increase in intima-media thickness (IMT) were identified. This condition was

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observed in 12 patients (18.7%) in Group 1, 13 patients (24.6%) in Group 2, and 16 patients (27.6%) in Group 3. Correlation analysis demonstrated a moderate positive association between IMT and blood fibrinogen (r = 0.38) and creatinine (r = 0.36), as well as a statistically significant strong positive correlation with procalcitonin (r = 0.52) and IL-6 (r = 0.64) (see Fig. 2).

The significant correlations between procalcitonin and the proinflammatory cytokine IL-6, both key mediators of systemic inflammatory response, suggest that vascular wall inflammation plays a predominant role in the progression of atherosclerosis and atherothrombosis.

Further correlation analysis involving immunological growth factors IGF-1, TGF-β1, and VEGF-A, alongside cytokines IL-1β, IL-6, IL-17A, TNF-α, left ventricular ejection fraction, and left ventricular myocardial mass revealed the following relationships (see Fig. 3).

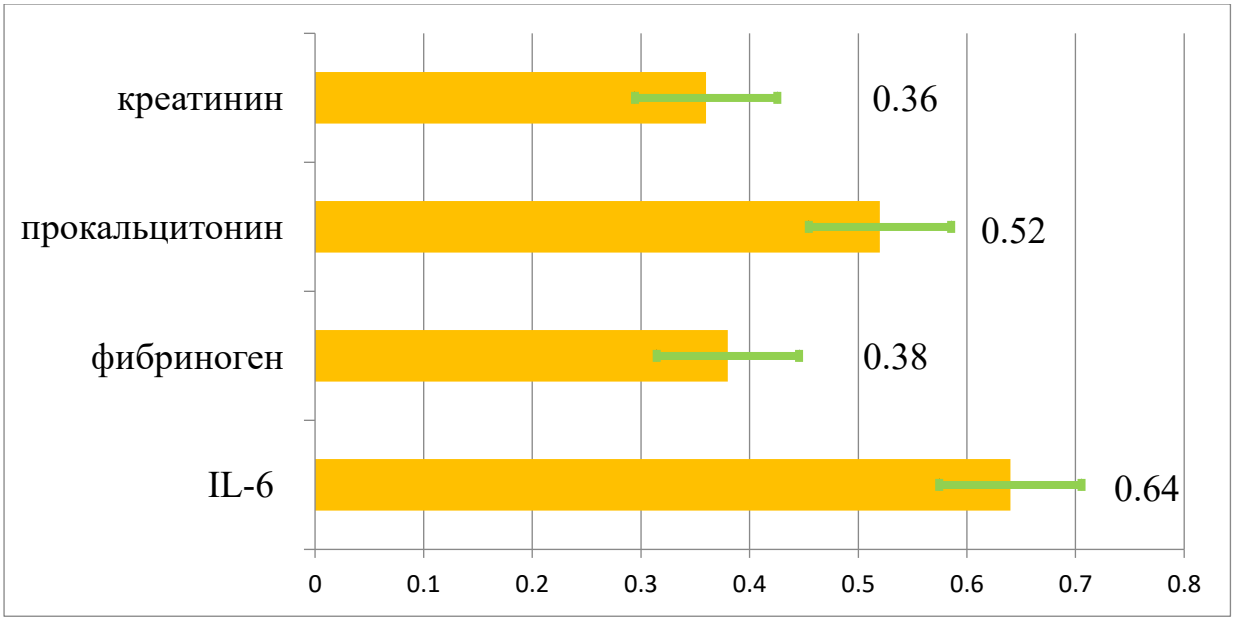

Figure 2. Correlation analysis of immunoinflammatory markers and intima-media thickness (IMT) of the common carotid artery

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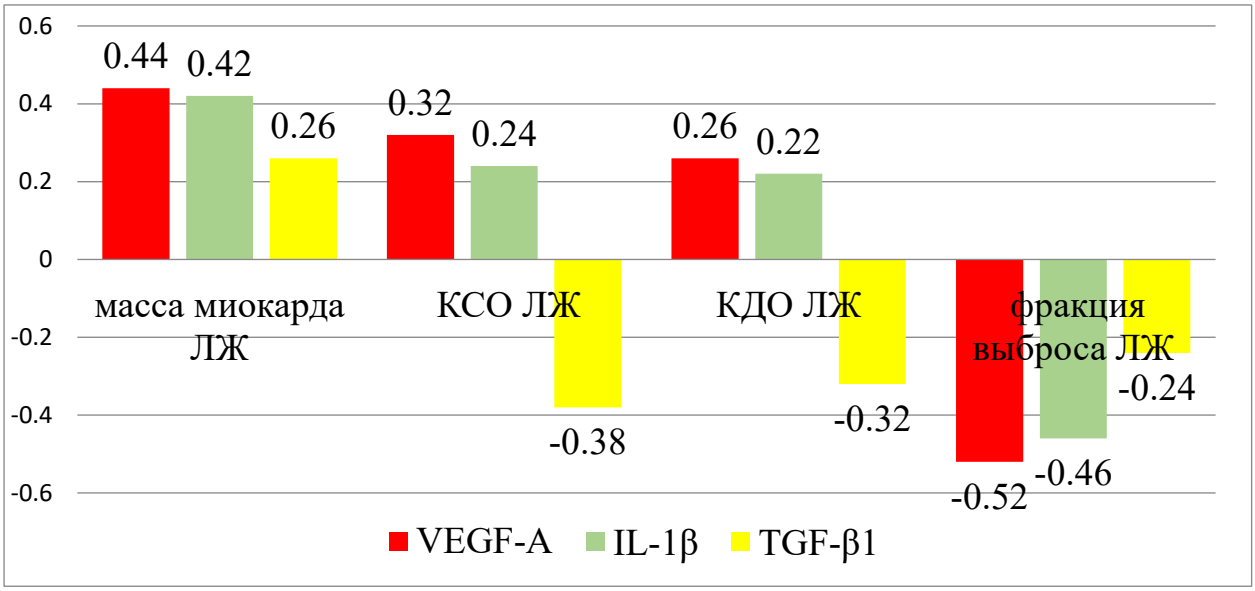

Fig.3. Correlation analysis of immunological growth factors, cytokines, and hemodynamic parameters

Elevated levels of VEGF-A and IL-1β, together with strong positive correlations with left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular myocardial mass (LVMM), as well as strong negative correlations with left ventricular ejection fraction (LVEF) in ischemic heart disease (IHD), indicate a high risk of left ventricular dysfunction. Notably, significant prognostic correlations were observed between VEGF-A and LVMM (r = 0.44), and VEGF-A and LVEF (r = -0.52). Similarly, IL-1β demonstrated a strong positive correlation with LVMM (r = 0.44) and a negative correlation with LVEF (r = -0.46). These findings suggest an increased risk of developing left ventricular dysfunction.

Echocardiographic parameters further revealed notable negative correlations between IL-6 and LVMM (r = -0.31), and a strong negative correlation between IL-6 and LVEF (r = -0.41). Additionally, LVESV showed a strong positive correlation with IL-1β (r = 0.40), while LVEF was positively correlated with serum complement C3 concentration (r = 0.41) (see Fig. 4).

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Thus, LVEF decreases with rising IL-6 levels, whereas LVESV increases with higher IL-1β levels. Both cytokines are pro-inflammatory and underscore the role of immune inflammation in cardiac and vascular pathology in IHD.

Further analysis demonstrated that systolic arterial pressure (SAP) is positively correlated with fibrinogen concentration (r = 0.30) and negatively correlated with procalcitonin (r = -0.30) and IL-6 (r = -0.26). Additionally, heart rate (HR) showed a significant positive correlation with serum creatinine (r = 0.35).

These relationships highlight the contribution of inflammatory (immune) syndrome to the progression of arterial hypertension (AH). Specifically, creatinine, fibrinogen, procalcitonin, and IL-6 serve as important indicators of AH progression in patients with IHD (see Fig. 5).

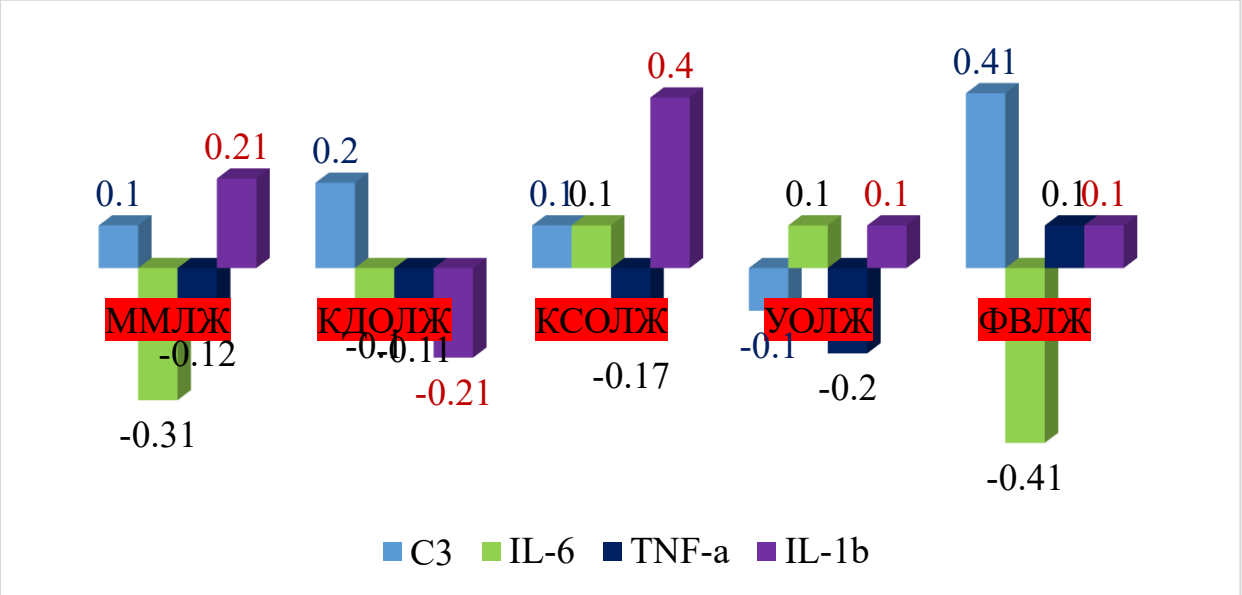

Fig. 5. Correlation between echocardiographic parameters and cytokine levels in ischemic heart disease (IHD)

Therefore, the observed correlations between blood biomarkers and cardiac function underscore the pivotal role of inflammatory syndrome in the progression of arterial hypertension (AH) to ischemic heart disease (IHD).

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The progression of cardiac remodeling highlights the importance of identifying immunological and biochemical markers to predict the transition from arterial hypertension (AH) to ischemic heart disease (IHD) in middle-aged patients.

It has been demonstrated that dynamic monitoring of these immunological and biochemical blood markers improves management of arterial hypertension, enhances diagnostic precision, and facilitates the implementation of effective treatment strategies in patients experiencing cardiac remodeling.

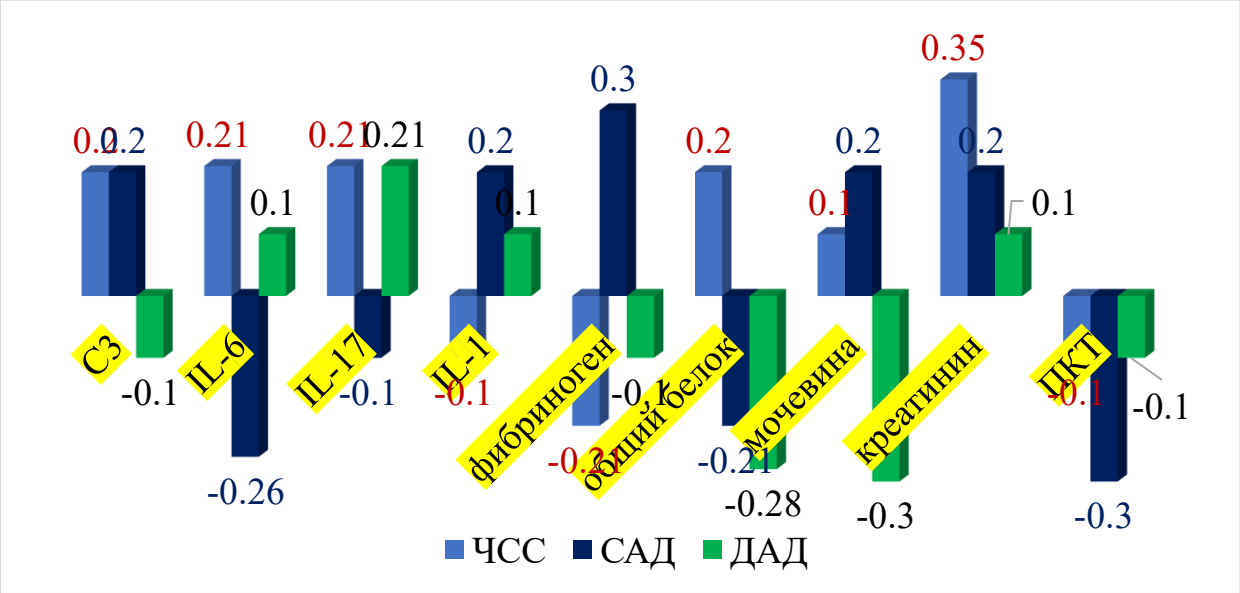

Fig.6. Correlation between immuno-biochemical parameters in ischemic heart disease (IHD)

Conclusions

Elevated blood levels of creatinine, fibrinogen, procalcitonin, and IL-6 were identified as predictors for the development of ischemic heart disease (IHD) in patients with arterial hypertension (AH). These markers were notably increased in patients presenting with carotid atherosclerosis detected by duplex carotid ultrasound, alongside pathological lipid profile changes.

A strong positive correlation between low-density lipoproteins (LDL), procalcitonin, IL-6, and carotid intima-media thickness (IMT) confirms that atherosclerotic vascular changes are driven by destructive inflammatory

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processes, characterized by elevated proinflammatory cytokines and the systemic inflammatory mediator procalcitonin.

In patients with IHD, significant positive correlations were found between VEGF-A and IL-1β levels and increased left ventricular myocardial mass and dimensions, coupled with a strong negative correlation with left ventricular ejection fraction (LVEF). These results indicate a high risk of left ventricular dysfunction.

Additionally, increased levels of complement C3 and IL-17 were inversely correlated with coronary vessel diameter, suggesting a heightened risk of endothelial injury and coronary atherothrombosis.

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