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Role of markers of inflammation and endothelial dysfunction in the prognosis of the development of cardiovascular complications in patients with coronary artery disease and metabolic syndrome after coronary stenting

Aim	To study the role of inflammation markers and endothelial dysfunction in predicting the risk of cardiovascular event following a percutaneous coronary intervention (PCI) in patients with ischemic heart disease (IHD) and metabolic syndrome (MS).
Material and methods	80 patients (72 men; median age, 56 (50;63) years) with IHD and PCI were evaluated. Based on the presence of MS according to NCEP-ATP III criteria, patients were divided into two groups, group 1 without MS (n=32) and group 2 with MS (n=48). The control age- and sex-matched group included 15 people without cardiovascular diseases. Serum concentrations of tumor necrosis factor α (TNFα), interleukin 6 (IL-6), IL-10, lipoprotein-associated phospholipase A2 (LP-PLA2), and endothelin 1 were measured by enzyme-linked immunosorbent assay (ELISA). Patients were followed up for 12 months after PCI with evaluation of the incidence of adverse cardiovascular events. Statistical analysis was performed with Statistica 10.0 and Medcalc 19.2.6 software. Differences between variables were considered statistically significant at $p<0.05$. Potential predictors were determined by the ROC analysis with construction of ROC curves, calculation of AUC (area under the curve), identification of COP (cut-off point by the Youden's index), and sensitivity (Se) and specificity corresponding to the COP.
Results	Patients with MS had statistically significantly higher serum levels of inflammatory markers than patients of the control group. Concentration of the intravascular inflammation marker, PL-PLA2, was 2.7 times higher in group 1 and 5.1 times higher in group 2 than in the control group ($p<0.001$). Concentrations of endothelin 1 were 1.9 times higher in group 1 and 3.7 times higher in the MS group compared to the control. At one year after PCI, the incidence of adverse outcomes in the form of cardiovascular events was higher for patients with MS: 10 (20.8%) cases of stent restenosis and 13 (27.1%) episodes of coronary atherosclerosis progression according to results of repeated coronarography vs. 2 (6.3%) restenosis cases (χ^2–10.853; p=0.002) and 2 (6.3%) episodes of atherosclerosis progression (χ^2–23.651; p=0.001) for patients without MS. The groups did not differ in rates of myocardial infarction and cardiac death. The most significant predictors of unfavorable prognosis were LP-PLA2 concentration >983.83 ng/ml (area under the ROC curve, 0.867; sensitivity, 80%; specificity, 100%; $p<0.001$) and endothelin 1 overexpression >0.852 fmol/ml (area under the ROC curve, 0.885; sensitivity, 85.5%; specificity, 83.6%; $p<0.001$).
Conclusion	Patients with MS were characterized by more pronounced imbalance of pro- and anti-inflammatory factors. Concentrations of LP-PLA2 >983.83 ng/ml and endothelin 1 >0.852 fmol/ml were shown to be predictors of unfavorable prognosis for patients with IHD and MS after PCI with coronary stenting.

Keywords	Ischemic heart disease; inflammatory markers; lipoprotein-associated phospholipase A2; endothelin 1; metabolic syndrome
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Metabolic syndrome (MS) is a complex of highly atherogenic factors of cardiovascular risk, including abdominal obesity, hypertension, dyslipidemia, insulin resistance (IR), pro-inflammatory, and prothrombotic states [1].

Percutaneous coronary intervention (PCI) with coronary stenting is an effective treatment for coronary artery disease (CAD). The real-world incidence of adverse cardiovascular events in the two year follow-up period after PCI ranged from 2.0% to 6.7% [2]. In recent years, strong evidence has become available that the incidence of cardiovascular complications and coronary in-stent restenosis in patients with CAD associated with MS reduced the time to onset of adverse cardiovascular events [3].

However, the predictive value of MS for CAD is still unclear, as the thresholds of major and contributing cardiovascular risk factors involved in MS are not definitively justified. Thus, it is necessary to find a more careful approach to measuring markers that allow predicting the course of CAD after PCI in this category of patients in order to improve and individualize therapy for each patient.

The pathogenesis of cardiovascular diseases (CVDs) is known to be interrelated, with inflammation being most often a determinant in disease progression and an essential component of the immune response. At the initial stage, it can protect from infections and tissue damage and can be arrested in a timely manner when infectious agents are eliminated, or causes of tissue damage disappear. However, an unsatisfactory inflammatory response may cause endothelial dysfunction that contributes to the onset and progression of CVDs [4–6].

Thus, activating the anti-inflammatory pathway, inhibiting the pro-inflammatory pathway, and maintaining a satisfactory inflammatory response is a promising CVD management strategy.

One of the mechanisms through which chronic inflammation stimulates IR is the synthesis of the main pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), by fat tissue. These inflammatory biomarkers activate the innate immune system and are essential biological factors contributing to the pathogenesis of diabetes mellitus.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a newly identified inflammatory marker. In vivo studies in animals showed that elevated levels of Lp-PLA2 in plasma could slow down atherosclerosis progression [7]. However, other evidence suggests that Lp-PLA2 contributes to the onset and progression of atherosclerosis. The proatherogenic role of Lp-PLA2 is presumably due to pro-inflammatory products of Lp-PLA2 activity for oxidized phospholipids, which can contribute to the development of atherosclerotic plaque and, eventually, lead to the formation of a necrotic nucleus [8]. Lp-PLA2 may be a crucial factor in developing atherosclerosis and plaque instability through inflammatory pathways, yet the ultimate role of this marker is not entirely clear.

According to the literature, high endothelin-1 levels are predictors of disease severity [9]. They are associated with an increased risk of adverse events in patients with stable CAD [10, 11], hypertension [12], chronic heart failure (CHF) with reduced left ventricular ejection fraction [13], and acute coronary syndrome [14]. However, contribution of endothelin-1 levels to the development of long-term adverse cardiovascular complications is still under active study.

This study's objective was to examine the role of the inflammatory markers Lp-PLA2 and epithelin-1 on endothelial dysfunction in the stratification of the risk of post-PCI complications in patients with CAD and MS.

Material and Methods

The local ethics committee approved the protocol of this study. All patients signed an informed consent before being included in the study. We examined 80 male and female patients with CAD (median age 56 [50; 63] years). Depending on the presence of MS, according to the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III [15], patients were divided into two groups: Group 1 included 32 patients without MS, and Group 2 included 48 patients with MS.

The control group comprised 15 individuals without cardiovascular disease comparable in age and sex to patients in the treatment groups. The median age in the control group was 58 [53; 66] years.

Inclusion criteria were documented CAD, scheduled PCI. Exclusion criteria were acute coronary or cerebrovascular events within the past 6 months, uncontrolled hypertension, cancer, hematological and immune diseases, acute inflammatory diseases.

There were no significant differences between the groups in the main clinical and demographic characteristics (Table 1). However, patients in Group 2 were significantly more likely to have carbohydrate disorders (p=0.001), and patients in Group 1 were more likely to smoke (p=0.002).

Drug therapy did not differ statistically significantly between the groups (Table 2).

In addition to an assessment of complaints, medical history, and objective status, all patients underwent standard general clinical and biochemical examinations. Fasting blood samples were collected from the peri-

Table 1. Clinical and demographic characteristics of patients

Parameter	Group 1 (no MS), n = 32	Group 2 (MS), n = 48
Male/female	32/0	40/8
Age, years	55 [50; 62]	57 [50; 63]
Waist-to-hip-ratio	1.01 [1.0; 1.02]	1.04 [1.02; 1.05]
Exertional angina, n (%)		
FC III FC IV Pain-free ischemia	8 (25) 24 (75) –	8 (16.6) 34 (70.8) 3 (6.3)
CHF FC (NYHA), n (%) FC I FC II	1 (3.1) 25 (78.1) 6 (18.8)	– 42 (87.5) 6 (12.5)
History of myocardial infarction, n (%)	14 (43.8)	28 (58.3)
Repeat myocardial infarction, n (%)	2 (6.3)	3 (6.3)
Atrial fibrillation, n (%)	6 (18.8)	11 (22.9)
Hypertension, n (%)	25 (78.1)	42 (87.5)
Carbohydrate disorders, n (%)	8 (25)	18 (37.5)*
Smoking, n (%)	21 (65.6)	22 (45.8)*
Family history of CVDs, n (%)	10 (31.3)	18 (37.8)
GFR (CKD EPI), mL/min/1.73 m2	87.5 [66.3; 95.8]	78.5 [67.1; 91.3]

*, p = 0.001–0.002, differences between the two groups.
The data are expressed as Me [Q25; Q75], n (%).
MS, metabolic syndrome; FC, functional class;
NYHA, New York Heart Association; CHF, chronic heart failure;
GFR, glomerular filtration rate; CVDs, cardiovascular diseases.

Table 2. Comparative evaluation of the drug therapy per groups

Treatment	Group 1 (no MS), n=32	Group 2 (MS), n=48
Beta-blockers	30 (93.8)	47 (97.9)
Nitrates	12 (37.5)	13 (27.1)
ACE inhibitors	29 (90.6)	41 (85.4)
ARBs	3 (9.4)	7 (14.6)
Diuretics	8 (25)	12 (25)
Anticoagulants	6 (18.8)	11 (22.9)
Acetylsalicylic acid	32 (100)	48 (100)
Statins	30 (93.8)	48 (100)
Calcium antagonists	9 (28.1)	15 (31.3)
Mineralocorticoid receptor antagonists	17 (53.1)	20 (41.7)
Clopidogrel	32 (100)	48 (100)

The data are expressed as n (%).
MS, metabolic syndrome;
ACE, angiotensin-converting enzyme;
ARB, angiotensin II receptor blocker.

pheral veins 2–3 days before the PCI. Glycated hemoglobin (HbA1c) levels were measured using immunoturbidimetry (DiaSys Diagnostic Systems, Germany). The concentrations of insulin (Monobind Inc., USA), TNF-α, IL-6, IL-1, interleukin-10 (IL-10) (Vector-BEST, Russia), Lp-PLA2 (Cloud-Clone Corp., USA), and endothelin-1 (Biomedica, Austria) were measured by enzyme-linked immunosorbent assay (ELISA). The lipid profile, apolipoprotein A1 (apo-A1), and apolipoprotein B (apo B) were determined by the enzymatic colorimetric method (DiaSys, Germany). IR was evaluated by Homeostatic Model Assessment for IR (HOMA-IR). IR was diagnosed if the index was more than 2.77.

The groups did not differ in terms of the incidence of coronary lesions, the number of occlusions, or bifurcation lesions (Table 3).

All patients were previously subjected to PCI. The outcomes were assessed 12 months after the index PCI during a repeat hospitalization or an in-person appointment. Repeat coronary angiography was performed in 81.3% of patients in Group 1 and 83.3% of patients in Group 2. In Group 2, three patients died (sudden cardiac death); the remaining patients completed the study. The composite endpoint included cardiovascular death, the progression of CHF, the progression of atherosclerosis, myocardial infarction, unstable angina, cerebrovascular accidents, restenosis, stent thrombosis, repeat coronary revascularization (surgical, endovascular), ventricular rhythm disorders, atrial fibrillation, and pacemaker implantation. Res-

Table 3. Characteristics of the coronary lesions

Coronary lesions	Group 1 (no MS), n=32	Group 2 (MS), n=48
SYNTAX score, Me (Q25; Q75)	13 [9.8; 20.1]	15 [8.7; 21.1]
One coronary artery involved	12 (37.5)	15 (31.3)
Two coronary arteries involved	17 (53.1)	23 (47.9)
Three coronary arteries involved	3 (9.4)	7 (14.6)
Number of coronary occlusions	8 (25)	12 (25)
Type of implanted stents:		
DES BMS DES + BMS	25 (78.1) 3 (9.4) 4 (12.5)	39 (81.3) 5 (10.4) 4 (8.3)
Postintervention complication	3 (9.4)	5 (10.4)
Bifurcation lesion	30 (93.8)	41 (85.4)

Data are expressed as n (%). MS, metabolic syndrome;
DES, drug-eluting stents; BMS, bare-metal stents.

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tenosis was a clinically significant (anginal pain) narrowing of the lumen of a stent by 50% or more or a 70% narrowing of a coronary artery in all cases when not indicative of recurrent angina. Hemodynamically significant narrowing of coronary arteries localized elsewhere were considered as the progression of coronary atherosclerosis.

Results of the study were statistically processed using the Statistica 10.0 and Medcalc 19.2.6 software. The quantitative data were expressed as Me (Q25; Q75) (the median and the interquartile range [25th and 75th percentiles]), and categorical data were presented as the absolute and relative rates (n [%]). The quantitative variables were compared using the Mann-Whitney U-test, and the Fisher's exact test and χ^2 test were used for the categorical data. Spearman's rank correlation test was used for the correlation analysis. Analysis of the receiver operating characteristic curve (ROC) analysis was performed to determine possible predictors. It included the construction of ROC curves, the calculation of the area under a curve (AUC), the definition of a cutoff point using Youden's test, and corresponding sensitivity (Se) and specificity (Sp). The critical significance level was p=0.05.

Results

Patients with MS (Group 2) had higher levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL–C), apolipoprotein B (apo B), apolipoprotein A1 (apo A1), apo-B/apo-A1 ratio, and lipoprotein (a) (Lp (a)) than those in the control group (p<0.001). All above mentioned parameters did not differ between Group 1 and Group 2 (Figure 1).

The mean level of insulin was 2.1 times higher in patients with MS than in the control group and 34.8% (p=0.005) higher than in patients without MS. In addition, IR (HOMA-IR) was 2.3 times higher in Group 2 than in the control group. HbA1 was significantly higher in the MS group than in Group 1 and the control group (Table 4).

In this study, patients with MS had a statistically significant increase in the inflammatory markers versus the control group: TNF-α 2.8 times, IL-15 times, and the levels of anti-inflammatory IL-10 were 1.5 times lower in the control group (Figure 2).

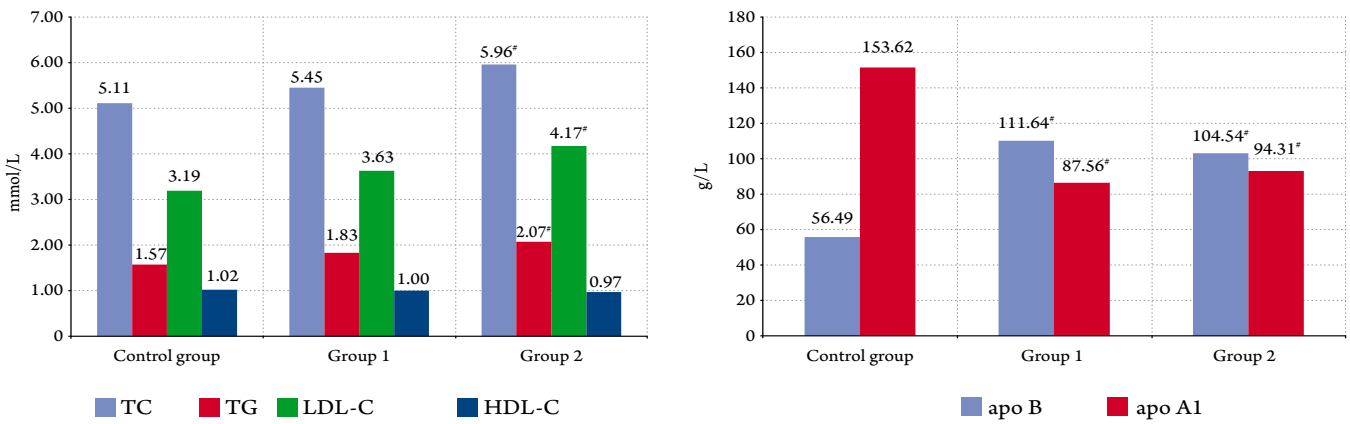
The concentration of intravascular inflammatory marker Lp-PLA2 was 2.7 times higher in Group 1 than in Group 2 and 5.1 times higher than in the control group (p<0.001). The concentration of endothelin-1 was increased 1.9 times in Group 1 and 3.7 times in patients with MS (Table 5).

A correlation analysis was performed to assess the relationship between the parameters studied in patients with CAD who had undergone PCI.

Lp-PLA2 was positively correlated with TC (r=0.45; p=0.001), TG (r=0.36; p=0.005), LDL–C (r=0.35; p=0.005), basal glycemia (r=0.35; p=0.006), and HOMA-IR (r=0.27; p=0.037). In patients with MS, a correlation was established only between endothelin-1 and insulin (r=0.73; p<0.001) (Figure 3).

A year after PCI, adverse outcomes such as cardiovascular events were more common in patients with MS. For example, 10 (20.8%) cases of in-stent restenosis and 13 (27,1%) episodes of the progression of coronary atherosclerosis were reported in this group according to repeat selective coronary angiography, with only 2 (6.3%) cases of restenosis and progression of atherosclerosis in patients without MS. There were no differences in the incidence of myocardial infarction and cardiac death (Table 6).

Figure 1. Lipid profile in patients with CAD



#, differences between Group 2 and the control group, p = 0.001–0.004

#, differences between Groups 1 and 2 and the control group, p = 0.001

TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol, apo B, apolipoprotein B, apo-A1, apolipoprotein A1.

Table 4. Characteristics of carbohydrate metabolism markers

Parameter	Control, n=15	Group 1 (no MS), n=32	Group 2 (MS), n=48	p
Basal glucose, mmol/L	4.77 [4.32; 5.22]	5.15 [4.90; 5.95]	6.15 [5.60; 7.70]	p_{1-2}=ns; $p_{1-к}$=ns; $p_{2-к}$ =ns
Insulin, μU/mL	5.55 [4.54; 7.01]	8.64 [6.99; 9.62]	11.65 [7.29; 17.60]	p_{1-2}=0.005; $p_{1-к}$=0.014; $p_{2-к}$ <0.001
HOMA-IR, units	1.39 [1.02; 1.77]	2.08 [1.58; 2.35]	3.18 [2.03; 4.27]	p_{1-2}=ns; $p_{1-к}$=ns; $p_{2-к}$ <0.001
HbA1c, %	5.41 [4.92; 5.89]	5.90 [5.30; 6.35]	7.70 [6.50; 8.60]	p_{1-2}=0.012; $p_{1-к}$=ns; $p_{2-к}$ <0.001

The data are expressed as Me [Q25; Q75].
MS, metabolic syndrome; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HbA1c, glycated hemoglobin.

Table 5. Parameters of inflammation and endothelial dysfunction

Parameter	Control, n=15	Group 1 (no MS), n=32	Group 2 (MS), n=48	p
Lp-PLA2, ng/mL	190.92 [166.14; 217.89]	525.36 [251.52; 799.21]	990.73 [649.12; 1255.30]	p_{1-2}<0.001; $p_{1-к}$<0.001; $p_{2-к}$ <0.001
Endothelin-1, fmol/mL	0.33 [0.19; 0.37]	0.64 [0.35; 0.92]	1.21 [1.03; 1.91]	p_{1-2}<0.001; $p_{1-к}$=0.014; $p_{2-к}$ <0.001

The data are expressed as Me [Q25; Q75]. MS, metabolic syndrome; Lp-PLA2, lipoprotein-associated phospholipase A2.

ROC analysis was carried out, ROC curves were constructed, and cutoff values were determined to estimate the significance of predictors in predicting the risk of cardiovascular complications and their critical values. The most significant predictors were the concentration of Lp-PLA2 >983.83 ng/mL (AUC 0.867, sensitivity 80%, specificity 100%, p<0.001) and hyperexpression of endothelin-1 >0.852 fmol/mL (AUC 0.885, sensitivity 85.5%, and specificity 83.6%, p<0.001). Patients with MS have a more pronounced imbalance of pro- and anti-inflammatory factors. The levels of Lp-PLA 2>983.83 ng/mL and endothelin-1 >0.852 fmol/mL were found to be predictors of adverse prognosis in patients with CAD and MS after percutaneous intervention with coronary stenting.

Discussion

Atherosclerosis causing most cardiovascular events is a systemic disease involving a combined effect of inflammation and immunological factors.

Finding suitable cardiometabolic biomarkers is a priority in cardiovascular medicine. This is because traditional factors may not always predict the risk of adverse cardiovascular events.

Patients with CAD and MS have hyperexpression of inflammatory markers. According to Teplyakov et al. (2008), chronic low-intensity inflammation is associated with an unfavorable serum profile of pro-inflammatory cytokines in patients with CAD and type 2 diabetes mellitus [16].

Table 6. Comparative evaluation of long-term coronary stenting outcomes in patients with CAD

Parameter	Group 1 (no MS), n=32	Group 2 (MS), n=48	p
Repeat coronary angiography	27 (84.4)	39 (81.3)	ns
Unstable angina	3 (9.3)	4 (8.3)	ns
Q-MI	0	1 (2.1)	ns
Restenosis of the target coronary artery	2 (6.3)	10 (20.8)	p=0.002, df=1, χ^2–10.853
Progression of atherosclerosis	2 (6.3)	13 (27.1)	p=0.001, df=1, χ^2–23.651
Thrombosis of an implanted stent	1 (3.1)	0	ns
Cardiovascular death	0	3 (6.3)	ns
Stroke	0	1 (2.1)	ns
Rhythm disorders	1 (3.1)	0	ns
CABG	0	2 (4.2)	ns
Progression of CHF	1 (3.1)	0	ns
Pacemaker implantation/RFA	0	0	ns

Data are expressed as n (%). MS, metabolic syndrome; MI, myocardial infarction;
CABG, coronary artery bypass grafting; CHF, chronic heart failure; RFA, radiofrequency ablation; ns, nonsignificant.

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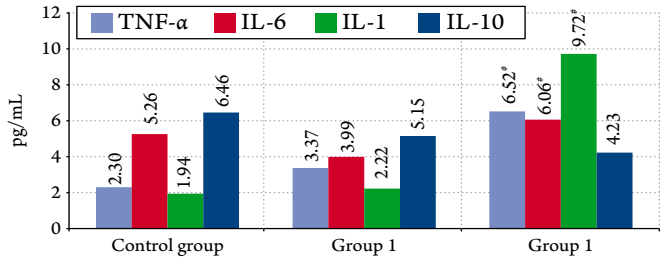
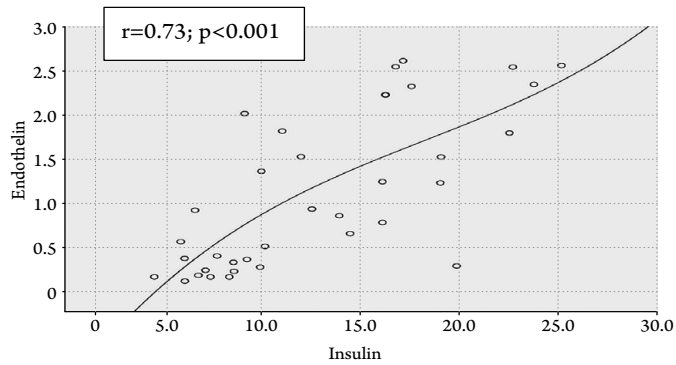
Figure 2. Concentration of inflammation biomarkers



#, differences between Group 1 and Group 2;
#, differences between Group 2 and the control group, p = 0.001

TNF-α, tumor necrosis factor alpha, IL-1, interleukin-1, IL-6, interleukin-6, IL-10, interleukin-10.

Figure 3. Correlations of endothelin-1 in patients with CAD and MS



In this study, the high predictive value of Lp-PLA2 and endothelin-1 for the risk of adverse outcomes after PCI was confirmed in patients with CAD and MS.

Lp-PLA2 is believed to be an important, highly promising cardiovascular marker independent of traditional risk factors (such as highly sensitive C-reactive protein) and contributing to the assessment using major risk factors [17]. According to the literature, Lp-PLA2 is a newly identified biomarker with a pronounced pro-inflammatory effect and an independent risk factor for CAD, ischemic stroke, and the main cardiovascular diseases [18–20]. Lp-PLA2 is directly involved in atherogenesis by causing lipid modification and stimulating inflammation in an atheroma [21]. Lp-PLA2 is actively synthesized in atherosclerotic lesions and has multiple proatherogenic and prothrombotic effects. Therefore it is relevant to determine the marker for the diagnosis and estimation of the severity of coronary atherosclerosis [21].

The role of endothelium dysfunction has been increasingly discussed in recent years as one of the reasons for the rapidly progressing atherosclerotic changes. It is considered to be an early phase of atherosclerosis and atherothrombosis and is defined as a universal mechanism of implementing the atherogenic potential of various risk factors of atherosclerosis [22].

The effect of endothelin-1 is due to its binding to the receptors of vascular smooth muscle cells, which results in a powerful contraction of the arteries, contributing to the development of an acute coronary complication. There is a small amount of endothelin-1 in a healthy person's blood, but its concentration increases proportionally to the severity of a cardiovascular pathology [14]. Our study demonstrated the adverse predictive role of endothelin-1 for the risk of adverse cardiovascular events during the 12-month prospective follow-up after PCI.

Limitations

Small sample size.

Conclusion

Patients with metabolic syndrome have a more pronounced imbalance of pro- and anti-inflammatory factors. The levels of Lp-PLA 2 >983.83 ng/mL and endothelin-1 >0.852 fmol/mL were found to be predictors of adverse prognosis in patients with coronary artery disease and metabolic syndrome after percutaneous intervention with coronary stenting.

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