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Correlation of Serum Endocan Level With Apoptosis Indicators and Severity of Atherosclerotic Lesions of Coronary Arteries in Patients With Coronary Heart Disease

Aim	To study the relationship of blood serum concentration of endocan with indexes of apoptosis and clinical and instrumental characteristics of patients with ischemic heart disease (IHD).
Material and methods	The study included 176 subjects (105 men and 71 women). 150 of them were diagnosed with IHD and 26 were healthy volunteers. Anthropometric measurements, coronary angiography, echocardiography, duplex ultrasound scanning of extracranial parts of the brachiocephalic arteries were performed for all patients. Concentrations of endocan (ng/ml), glucose (mmol/l), and apoptotic markers Bcl-2 (ng/ml), Bax (ng/ml), Bcl-2/Bax, TRAIL (pg/ml), and p53 (ng/ml) were measured in blood serum. Patients were divided into groups based on their SYNTAX scores: group 1 with moderate atherosclerotic lesions of the coronary arteries (CA) (score <22, 78 patients); group 2 with severe CA atherosclerosis (score 23–32, 37 patients); and group 3 with extremely severe CA lesions (score >33, 35 patients). The control group consisted of healthy volunteers (26 subjects). All groups were age- and sex-matched. Differences were considered statistically significant at $p<0.05$.
Results	A correlation was found between endocan concentration and IHD severity ($r=0.32$, $p<0.001$). In group 1, the median endocan concentration was 14.57 ng/ml [8.21; 23.66], in group 2, 19.34 ng/ml [8.425; 26.645], in group 3, 32.13 ng/ml [18.2; 39.12], and in the control group, 6.92 ng/ml [4.62; 9.18]. Correlations of varying strength and significance were observed between the endocan concentration and a number of clinical and instrumental characteristics. Endocan concentrations significantly differed in groups of patients with multifocal atherosclerosis ($p<0.01$), angina pectoris ($p<0.01$), a history of myocardial infarction ($p<0.001$), and obesity ($p<0.05$) from patients without these signs. Also, a correlation was found between serum endocan concentration and apoptotic markers: TRAIL ($r= –0.448$, $p<0.001$); BCL-2 ($r= –0.552$, $p<0.001$), Bax ($r= –0.519$, $p<0.001$), Bcl-2/Bax ($r= –0.576$, $p<0.001$) and p53 ($r= –0.520$, $p <0.001$).
Conclusion	The study demonstrated a potential role of endocan as a promising biomarker for risk stratification, prognosis and therapeutic monitoring of IHD patients.

Keywords	Endocan; atherosclerosis; ischemic heart disease; apoptosis
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Introduction

Endocan was found more than 20 years ago, and this biomarker for inflammation and endothelial dysfunction (ED) is still being actively researched [1]. Sometimes referred to as endothelial cell-specific molecule 1 (ESM1), endocan is a soluble dermatan sulfate proteoglycan produced by endothelial cells. It is expressed in actively proliferating tissues and detected in cultured endothelial cells of the skin, fatty tissue, hepatocytes, pulmonary and coronary arteries, etc. [2]. The role of endocan was studied in many diseases associated with inflammation and ED, such as type 2 diabetes mellitus (T2DM) [3, 4], arterial hypertension [5–7], atherosclerotic cardiovascular diseases [2, 8–10], kidney diseases [11], obesity [12, 13], polycystic ovary syndrome [14], metabolic syndrome [4], non-alcoholic fatty liver disease [15], sleep apnea syndrome [16]. Given the known

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Central illustration. Relationship of serum levels of endocan with apoptosis and severity of atherosclerotic coronary artery lesions in patients with coronary artery disease

150 PATIENTS WITH CAD

26 HEALTHY VOLUNTEERS

– Anthropomorphic measurements
– CAG
– Echocardiography
– BCA ultrasound
– Serum endocan, glucose, Bcl-2, Bax, Bcl-2/Bax, TRAIL, p53

Patient groups (SYNTAX score):
Group 1 ≤ 22 (n = 78); Group 2 – 23–32 (n = 37); Group 3 ≥ 33 (n = 35).
Control group-healthy volunteers (n = 26)

- ☑ The concentrations of endocan and the severity of coronary artery lesions were found to be correlated.
- ☑ Correlations of various strength and significance between serum concentration of endocan and some clinical and laboratory characteristics of patients were also established.
- ☑ The levels of endocan were shown statistically significantly different between patients with multivessel disease, angina pectoris, restenosis after previous revascularization, history of myocardial infarction, and obesity, compared to patients without such signs.
- ☑ Endocan concentration was found to be correlated with apoptosis markers TRAIL, Bcl-2, Bax, Bcl-2/Bax, p53.

CAD, coronary artery disease; CAG, coronary artery angiography; BCA, brachiocephalic arteries; Bax, apoptosis regulator protein encoded by the Bax gene; Bcl-2, intracellular protein regulator of apoptosis, the main representative of the Bcl 2 family; TRAIL, cytokine of the tumor necrosis factor family, apoptosis-causing ligand; p53, product of the tumor suppressor gene TP53, transcription factor regulating the cell cycle.

association of inflammatory and apoptotic processes of atherogenesis [17], it would appear relevant to study the relationship between endocan concentration and apoptosis marker levels in patients with coronary artery disease (CAD) within clinical examination and laboratory test context.

Objective

Explore the relationship of serum concentration of endocan with the indicators of apoptosis and clinical and laboratory characteristics of patients with CAD.

Material and Methods

The exclusion criteria were less than 6-week history myocardial infarction (MI) or acute cerebrovascular accident; massive pulmonary embolism with high pulmonary hypertension; any acute inflammatory disease; severe liver and kidney dysfunction [chronic kidney disease stage ≥III (glomerular filtration rate < 60 mL/min/1.73 m^2)], the need for hemodialysis or peritoneal dialysis; diabetes mellitus of both types with glycated hemoglobin > 11% or glucose levels within 24 hours ≥11.0 mmol/L; hypertrophic or dilated cardiomyopathy; cancer; blood and immune system diseases; pregnancy or lactation; mental disorders that prevent contact with the patient during the follow-up period; protocol deviations, and patient's refusal to participate in the study.

The study included 176 people (105 males and 71 females), of whom 150 patients had documented CAD, and 26 subjects were healthy volunteers (control group).

The study was approved by the ethics committee of V. I. Vernadsky Crimean Federal University (Minutes No. 5 dated 19/05/2022). Patients signed the informed consent to be included in the study.

Coronary artery angiography was conducted for all patients in General Electric Optima IGS 330 angiographic system. The SYNTAX score was used as an objective quantification tool to assess the severity of coronary artery atherosclerotic lesions (https://officialsyntaxscore.com). This scale is a reliable tool for determining the severity of coronary atherosclerosis [18], and all patients were divided into the following groups: Group 1 – moderate coronary artery atherosclerotic lesions, SYNTAX score≤22 (n=78); Group 2 – severe coronary artery atherosclerosis, SYNTAX score 23–32 (n=37); Group 3 – extremely severe coronary artery atherosclerotic lesion SYNTAX score≥33 (n=35). Patients with CAD were divided into subgroups of subjects with history of percutaneous coronary intervention (stenting) from 4 months to 6 years (n=41), multivessel disease (n=33), history of myocardial infarction (n=80), angina pectoris (n=109), and obesity (n=8). Group 4 included healthy volunteers – cardiovascular pathology was excluded based on the absence of clinical, anamnestic, and electrocardiographic signs of a heart disease (n=26). All groups were comparable in sex and age composition.

Chronic heart failure was established according to the 2020 Russian Society of Cardiology clinical guidelines. Echocardiographic examinations were carried out using the Samsung Accuvix A30 ultrasound system in the two-dimensional mode, pulsed and continuous wave Doppler, and color Doppler scan. The standard structural parameters of the ventricles and atria, the contractile and diastolic function of the left ventricle (LV), and normal valvular structure and function.

Multivessel disease is a hemodynamically significant atherosclerotic lesion of multiple major vascular beds and thickening of the intima-media complex of the carotid arteries; it often determines the severity of patient's condition and further prognosis. Duplex ultrasound scanning of extracranial brachiocephalic arteries in the Samsung UGEO H60 ultrasound system was used in this study to measure the thickness of the intima-media complex (IMT).

We also studied serum glucose concentrations, serum levels of endocan and apoptosis markers Bcl-2 (intracellular protein factor – a regulator of apoptosis), Bax (apoptosis regulator protein encoded by the BAX gene), Bcl-2/Bax ratio, TRAIL (cytokine of the tumor necrosis factor family, apoptosis-inducing ligand, product of the TNFSF10 gene), and p53 (product of tumor suppressor gene TP53, transcription factor regulating the cell cycle). Venous blood was taken on an empty stomach before coronary angiography. The following direct enzyme immunoassay kits were used according to the manufacturer's instructions: Human Endothelial-cell specific molecule-1 (ESM-1) (AviseraBioscience, USA) for endocan (ng/mL), Human Bcl-2 ELISA Kit (Cloud Clone Corp., China) for Bcl-2 (ng/mL), Human ELISA Kit for Bcl-2 associated X protein (Bax) (Cloud Clone Corp., China) Bax (ng/mL), Human p53 ELISA Kit (RayBiotech, Inc., USA) for p53 (ng/mL), Human TRAIL ELISA Kit (RayBiotech, Inc., USA) for TRAIL (pg/mL).

All patients underwent a standard examination: height, weight, waist circumference, body mass index (kg/m^2).

Absolute and relative frequencies were used as descriptive statistics for statistical processing of dichotomous data. Ordinal or quantitative data were described as the medians (Me) and interquartile ranges [Q25; Q75]. The statistical significance of any differences between two groups was assessed using the Mann-Whitney test. Spearman's rank correlation coefficient was used, and its significance was estimated to assess the statistical relationship between two attributes. The differences were statistically significant at $p < 0.05$. The Kruskal-Wallis test was used for multiple comparisons of central trends in independent samples for quantitative or ordinal

Table 1. Clinical, anamnestic, and laboratory characteristics of patients

Parameter	Group 1 (n = 78)	Group 2 (n = 37)	Group 3 (n = 35)	p
Age, years	64.0 [59.0; 69.0]	66.0 [60.0; 70.0]	66 [60.0; 70.0]	0.696
Male, n (%)	40 (51.3)	22 (59.5)	21 (60)	0.582
SYNTAX, score	12.5 [5.0; 17.0]	27.5 [24.75; 29.5]	36.25 [34.0; 42.5]	3.88*10–26
Multivessel disease, n (%)	14 (18)	10 (27)	9 (25.7)	0.456
CHF class 2 (NYHA), n (%)	26 (33.3)	10 (27)	5 (14.3)	0.110
CHF class 3 (NYHA), n (%)	52 (66.7)	27 (73)	24 (68.6)	0.793
CHF class 4 (NYHA), n (%)	–	–	6 (17.1)	0.00002
History of PCI, n (%)	15 (19.2)	13 (35.1)	13 (37.1)	0.067
Angina pectoris class 2, n (%)	12 (15.4)	9 (24.3)	4 (11.4)	0.309
Angina pectoris class 3, n (%)	38 (48.7)	22 (59.5)	21 (60.0)	0.401
Angina pectoris class 4, n (%)	–	–	3 (8.6)	0.007
LVEF, %	56.0 [48.0; 62.0]	54.0 [49.0; 58.0]	54.0 [45.0; 61.0]	0.403
History of MI, n (%)	32 (41)	28 (75.7)	20 (57.1)	0.002
Carotid artery IMT, cm	0.8 [0.75; 0.9]	0.8 [0.6; 1.1]	0.9 [0.7; 1.2]	0.420
Obesity, n (%)	2 (2.6)	5 (13.5)	1 (2.9)	0.039
Serum glucose, mmol/L	5.5 [4.7; 6.5]	5.9 [5.3; 7.2]	5.9 [5.3; 6.9]	0.075

Data are presented as the medians and interquartile ranges (Me [Q25; Q75]), number of patients (n (%)); MI, myocardial infarction; HF, heart failure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; IMT, intima-media thickness. The percentages were compared using the Pearson chi-squared test; quantitative and ordinal data were compared using the Kruskal–Wallis test.

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Table 2. Statistical relationship between clinical examination and laboratory test parameters and endocan levels using the Spearman rank correlation coefficient

Parameter	r	p
Age	0.256	0.0009
SYNTAX score	0.409	0.0001
IMT	0.450	0.0059
Angina pectoris class	0.399	0.0001
LVEF	-0.153	0.0651
CHF class (NYHA)	0.113	0.1718
Glucose	0.229	0.0053

HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; IMT, intima-media thickness.

Table 3. Values of endocan in patients depending on the presence of multivessel disease, coronary artery restenosis, history of myocardial infarction, angina pectoris, and obesity

Patients	Parameter, Me [Q25; Q75]	p
Patients with multivessel disease (n = 35)	29.26 [12.75; 33.21]	0.0026
Patients without multivessel disease (n = 115)	13.23 [7.12; 24.1]	
Patients with coronary artery restenosis (n = 25)	24.75 [18.225; 31.91]	0.3023
Patients without coronary artery restenosis (n = 16)	19.28 [13.76; 30.92]	
Patients with history of MI (n = 80)	20.78 [11.89; 31.83]	0.0001
Patients without history of MI (n = 70)	10.27 [5.88; 22.10]	
Patients with angina pectoris (n = 108)	20.89 [11.95; 30.1]	0.0001
Patients without angina pectoris (n = 42)	10.66 [6.78; 20.67]	
Patients with obesity (n = 17)	28.68 [23.725; 31.83]	0.0459
Patients without obesity (n = 133)	18.2 [8.65; 29.33]	

MI, myocardial infarction.

Table 4. Serum levels of apoptosis markers depending on the severity of atherosclerotic coronary artery lesions

Parameter, Me [Q25; Q75]	Group 1 (n=78)	Group 2 (n=37)	Group 3 (n=35)	Group 4, (n=26)	p
Bcl-2, ng/mL	3,10 [2,60; 3,95]	2,60 [2,10; 2,90]	2,30 [2,17; 2,60]	5 [4,40; 5,40]	KW: p<0,0001 p_{1-2}<0,0001 p_{1-3}<0,0001 p_{1-4}<0,0001 p_{2-3}=0,289 p_{2-4}<0,0001 p_{3-4}<0,0001
Bax, ng/mL	31,0 [25,25; 34,70]	35,15 [34,20; 36,20]	36,30 [34,70; 37,10]	15,60 [15,00; 16,20]	KW: p<0,0001 p_{1-2}<0,0001 p_{1-3}<0,0001 p_{1-4}<0,0001 p_{2-3}=0,28 p_{2-4}<0,0001 p_{3-4}<0,0001
p53, ng/mL	7,46 [6,22; 8,12]	8,62 [8,12; 9,15]	9,49 [9,10; 10,12]	2,91 [2,20; 3,25]	KW: p<0,0001 p_{1-2}<0,0001 p_{1-3}<0,0001 p_{1-4}<0,0001 p_{2-3}=0,026 p_{2-4}<0,0001 p_{3-4}<0,0001
TRAIL, pg/mL	452,10 [379,20; 591,90]	310,80 [215,10; 375,15]	258,20 [182,60; 299,18]	1749,60 [982,50; 2300,10]	KW: p<0,0001 p_{1-2}<0,0001 p_{1-3}<0,0001 p_{1-4}<0,0001 p_{2-3}=0,105 p_{2-4}<0,0001 p_{3-4}<0,0001
Bcl-2/ Bax	0,10 [0,08; 0,15]	0,07 [0,06; 0,08]	0,06 [0,05; 0,08]	0,32 [0,28; 0,36]	K-У: p<0,0001 p_{1-2}<0,0001 p_{1-3}<0,0001 p_{1-4}<0,0001 p_{2-3}=0,323 p_{2-4}<0,0001 p_{3-4}<0,0001

KW, statistical significance of differences according to the Kruskal–Wallis test. p_{1-2}, p_{1-3}, p_{1-4}, p_{2-3}, p_{2-4}, p_{3-4}, statistical significance of pairwise comparisons according to post-hoc Dunn's test.

data; the post-hoc Dunn test was used for subsequent pairwise comparisons. Nominal data were compared using Pearson's chi-squared test. The critical area was considered bilateral in all cases. The Kruskal–Wallis and Dunn test were calculated in the Past statistical suite, all other calculations were main in Statistica Statsoft.

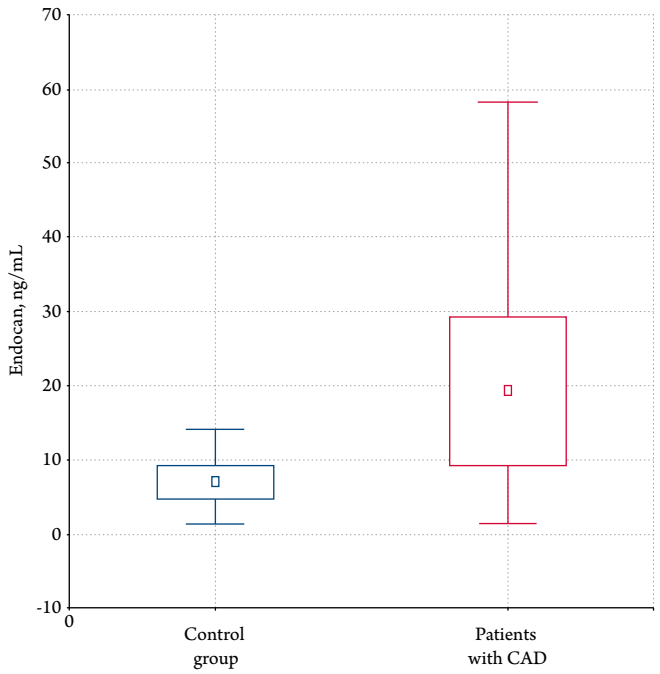
Results

Clinical and anamnestic characteristics of subjects are given in Table 1.

Patients with CAD had higher levels of endocan compared to the control group ($p < 0.001$). The median endocan levels were 19.14 [9.01; 29.4] ng/mL and 6.92 [4.62; 9.18] ng/mL in the CAD group and the control group, respectively (Figure 1).

Statistically significant moderate correlation was found between serum concentrations of endocan and the severity of coronary artery lesions (SYNTAX) in patients of the three groups ($r=0.32$, $p < 0.001$). At the same time, the median endocan levels were 14.57 [8.21; 23.66] ng/mL in Group 1, 19.34 [8.425; 26.645] ng/mL in Group 2, and 32.13 [18.2; 39.12] ng/mL in Group 3 ($p=1.37\times10-5$). Correlations of different strength and significance between serum concentration of endocan and some clinical and

Figure 1. Serum concentrations of endocan in patients with CAD and the control group ($p < 0.001$)



CAD, coronary artery disease.

laboratory characteristics of were also detected (Table 2).

It should be noted that statistically significant differences were found in serum concentrations of endocan between the groups of patients with multivessel disease and patients with coronary artery lesions only ($p < 0.01$), patients with MI and patients without history of acute coronary events ($p < 0.001$), patients with angina and without angina attacks ($p < 0.01$), and between the groups of patients with obesity and without metabolic disorders ($p < 0.05$) (Table 3). At the same time, 29 of 45 patients with history of percutaneous coronary interventions (stenting) developed coronary artery restenosis: the median endocan levels was 24.75 [18.225; 31.91] ng/mL in patients with restenosis and 19.28 [13.76; 30.92] ng/mL in the group without restenosis. However, the differences between these groups were not statistically significant (Table 3).

Statistically significant differences were found between some indicators of apoptosis and the severity of coronary artery lesions (Table 4). Correlations were found between serum concentration of endocan and apoptosis markers: moderate negative correlation between endocan and TRAIL ($r=-0.448$, $p < 0.001$); moderate negative correlation between Bcl-2 ($r=-0.552$, $p < 0.001$), Bcl-2/Bax ($r=-0.576$, $p < 0.001$); moderate positive correlation between Bax ($r=-0.519$, $p < 0.001$) and p53 ($r=-0.520$, $p < 0.001$).

Discussion

The literature indicates that endocan is involved in the regulation of proliferation and neovasculogenesis and is also a surrogate marker of inflammation and ED, which are the root causes of many cardiovascular diseases [17]. Numerous studies described the role of ED as the basis for the pathogenesis of arterial hypertension (AH). At the same time, abnormal endothelial-dependent vasodilation was shown in both essential and secondary AH [17, 19–21].

Noteworthy, Balta et al. (2014) and Oktar et al. (2019) showed that patients with early-stage AH demonstrated a positive correlation between the blood concentrations of endocan and carotid IMT, and high-sensitivity C-reactive protein levels [6, 7]. We also detected a moderate direct highly significant correlation between serum endocan levels and carotid IMT ($r=0.45$, $p < 0.01$).

However, it should be noted that there is a significant degree of heterogeneity in endocan concentrations in the groups of normotensive patients and patients with AH across various studies. We think this may be due to differences in the populations of interest, the nature of the samples tested (e.g., serum or plasma samples; anticoagulant types used for plasma collection), and/or the methods of quantification (sets by different manufacturers).

ED is known to be involved in the pathogenesis of atherosclerosis and affects the outcome of patients with CAD. Patients with impaired vasomotor endothelial response, including an abnormal constrictive reaction to acetylcholine in coronary arteries, face increased risk of developing coronary complications. Moreover, improved endothelial function is associated with better overall outcomes in patients with CAD due to enhanced myocardial perfusion and reduced duration and severity of transient myocardial ischemia, reduced severity of angina pectoris and lower risk of cardiovascular complications in future [17, 19–22]. Several studies investigated the role of endocan as a potential biomarker in CAD.

Higher serum concentrations of endocan were detected in patients with chronic forms of CAD compared to healthy subjects of the control groups [8, 9], including in the presence of AH [2], diabetes mellitus [3, 4] and sleep apnea syndrome [16, 23]. It was also elevated in the group of patients with coronary stent restenosis [24].

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БЕРЛИН-ХЕМИ
МЕНАРИНИ

The present work revealed a higher level of endocan in the group of patients with coronary artery disease compared to the control group ($p<0.001$), and also demonstrated that high serum concentrations of endocan are associated with the presence of MPa ($p=0.0026$), obesity ($p=0.0459$), angina pectoris ($p=0.0001$), a history of MI ($p=0.0001$).

Attention should be paid to the relationship between inflammatory and apoptotic mechanisms of atherosclerotic plaque formation and evolution – there are several papers that confirm delay, defective phagocytosis, and active release of pro-inflammatory mediators and signaling molecules in hyperlipidemia [25]. We found a moderate negative correlation between endocan and TRAIL ($r=-0.448$, $p < 0.001$); moderate negative correlation between anti-apoptotic factor Bcl-2 ($r=-0.552$, $p < 0.001$) and Bcl-2/Bax ratio ($r=-0.576$, $p<0.001$), moderate positive correlation between factors that enhance apoptosis: Bax ($r=-0.519$, $p < 0.001$) and p53 ($r=-0.520$, $p < 0.001$).

Several studies also investigated the role of endocan as a biomarker predicting the severity of CAD using the Gensini and SYNTAX scores, which assess the anatomy, morphology, and severity of coronary artery stenosis and are commonly used in clinical practice to select the best possible treatment and predict the overall cardiovascular risk. Contradictory findings were obtained regarding the correlation between endocan and both scores. While some research indicated significant, independent, and positive correlations [9, 10], others found no significant relationships [26, 27]. At the same time, we found a direct moderate highly significant correlation between serum concentration of endocan and the SYNTAX score ($r=0.409$, $p < 0.001$), which allows considering this indicator as a possible laboratory marker of the severity of atherosclerotic coronary artery lesions.

Since obesity is associated with persistent subclinical inflammation, which causes atherogenesis [28], it is expected that serum levels of endocan as a pro-inflammatory mediator will be increased in this category of individuals, which is confirmed by our findings that demonstrate the statistical significance of differences in endocan levels between patients with obesity and without metabolic disorders ($p < 0.05$). However, the published data on the nature of this relationship are very contradictory: while some research also showed higher levels of endocan in obesity [12] and a positive correlation between anthropometric measurements of both total [13] and abdominal obesity [29], others reported lower levels of endocan in this pathology [30] and a negative correlation with anthropometric indicators [14]. Such contradictions can be explained by different phenotypes, duration and degree of obesity, sample size, ethnicity, and differences in age and sex [12].

Klisic et al. (2019) showed in their observational study by that serum levels of endocan were significantly higher in the T2DM cohort compared to the prediabetes and control groups [31]. Interestingly, multivariate logistic sequential regression analysis showed that a one-unit increase in serum levels of endocan resulted in a two-fold increase in the likelihood of increased glycated hemoglobin [31], suggesting a relationship between this biomarker of ED and poor glycemic control. Another study showed that endocan can be a prognostic marker of a decrease in β-cell function and the development of impaired glucose tolerance and T2DM [32].

The data obtained in this paper demonstrate a statistically significant direct correlation between the levels of endocan and serum concentrations of glucose ($r=0.229$, $p < 0.01$) in the studied patients.

The study was limited by a small sample of patients, a small number of cases of restenosis after previous coronary myocardial revascularization, Multivessel disease, and obesity, which may restrict the interpretation of the data obtained.

Conclusion

The international scientific community has been actively searching for novel laboratory markers of the progression of atherosclerosis processes in recent decades. We found that there is a statistically significant increase in serum concentrations of endocan in patients with coronary artery disease as coronary atherosclerosis becomes more severe. We also revealed correlations of varying strengths between the levels of endocan and some clinical examination and laboratory indicators. The data obtained suggest that endocan can be used as a diagnostic marker of the severity of atherosclerotic processes in patients with coronary artery disease.

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No conflict of interest is reported.

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