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E-Selectin as a Marker of Endothelial Dysfunction in Patients with Coronary Artery Disease Including Those with Type 2 Diabetes Mellitus

Aim	To determine concentration of the endothelial dysfunction (ED) marker, serum E-selectine, in patients with ischemic heart disease (IHD) in combination with type 2 diabetes mellitus (DM) and without DM.
Material and methods	The study included 60 IHD patients; 31 of them also had type 2 DM. E-selectin was measured in blood of all patients. In addition, a comprehensive evaluation of the morpho-functional condition of large blood vessels and microvasculature (MV) was performed by laser finger plethysmography (LFP) and nailfold computed videocapillaroscopy (CVC).
Results	Concentration of E-selectin was increased in IHD patients with type 2 DM (35.2 [29.0; 47.35] ng/ml vs. 31.7 [20.85; 36.68] ng/ml for IHD patients; p=0.028). A significant (p=0.018 and 0.016, respectively) decrease in the phase shift was observed in IHD patients with type 2 DM (–4.4 [– 8.7; –2.45] ms) compared to IHD patients (–1.9 [–3.95; – 0.38] ms). The capillary density evaluated in the venous occlusion test was reduced in IHD patients with type 2 DM (67.70 [57.83; 80.69]) compared to IHD patients (80.80 [69.05; 99.08]).
Conclusion	The signs of ED observed in patients of both groups were more pronounced in IHD patients with type 2 DM.

Keywords	Ischemic heart disease; type 2 diabetes mellitus; E-selectin; endothelial dysfunction
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Despite the maturity of modern internal medicine, coronary artery disease (CAD) remains a major cause of death in the world (17.9 million), and its prevalence is increasing according to the WHO [1]. The prevalence of diabetes mellitus (DM) increases at a higher rate: 108 million worldwide suffered from DM in 1980 and 422 million in 2014, which was more than a four-fold increase in less than 35 years [2]. In 2019, DM was diagnosed in as many as 463 million, and according to the International Diabetes Federation, by 2045, the number of patients with DM is likely to increase to 700 million [3]. Type 2 DM (DM2) is the most prevalent type of DM, reaching 90% of all cases [3]. DM2 is a key risk factor for the development and progression of CAD [4]. Specifically, 75% of patients with DM2 die of CAD and other cardiovascular diseases (CVDs) [5]. Patients with CAD and DM2 have more extensive and severe coronary lesions [6, 7]. Thus, it is urgent to increase future funding for the prevention and treatment of these diseases.

Similar to worldwide trends, Russia has a high CAD mortality rate. According to the Federal State Statistics Service, this rate was 386.3 and 453.3 thousand in 2006 and 2008, respectively [8]. The mortality rate due to DM2 was lower in absolute values, 33.1 thousand in 2018, yet equally significant [8]. To interpret the mortality rates due to DM2, it is necessary to highlight its contribution to the mortality associated with CVDs, kidney diseases, infectious complications, etc.

Thus, it is necessary to identify mechanisms by which DM2 contributes additionally to faster and more severe progression of CAD. One of the most relevant mechanisms may be endothelial dysfunction (ED), which underlies the development of macro- and microvascular complications of DM2 [9] and is one of the pathogenetic links of the development of coronary atherosclerosis, primary to the development of CAD. Phenomena observed in chronic hyperglycemia associated with DM, specifically, oxidative stress, insulin resistance, decreased bioavailability of NO, activation of the procoagulant mechanism of hemostasis, increased stress response molecules, are key factors of the development of ED and its consequences. They complete a cycle in which

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relative predominance of vasoconstriction is observed in the presence of impaired vasorelaxation. This results in faster and more pronounced development of macro- and microvascular complications, including CAD [10–14].

Serum E-selectin [15], an adhesion molecule, is an ED marker. Adhesion molecules of the selectin family are glycoproteins, which play a major role in the process of polymorphic leukocyte rolling and attachment to the endothelial wall followed by migration into the intercellular matrix [16, 17].

E-selectin is produced by endothelocytes when the vascular wall is damaged. This results in chronic, non-specific inflammation, e.g., in hyperglycemia, which contributes to the attraction of leukocytes by chemotaxis. The increased concentration of E-selectin is likely to trigger further endothelial damage resulting in the progression of atherosclerosis and the development of CVDs [18, 19].

Data demonstrate opposing views concerning the role of E-selectin in the development and progression of CAD. For example, several studies [20–22] revealed that E-selectin is associated with the development and aggravation of CAD. However, other studies [23, 24] did not found this association. Moreover, it is not known whether DM2 contributes significantly to increased expression of serum E-selectin and whether levels of E-selectin are correlated with structural and functional status of the microcirculatory and large-caliber vessels as assessed using laser finger-photoplethysmography (FPP) and nailfold video capillaroscopy, the key non-invasive methods used to evaluate these changes in patients with CVD [25, 26].

The objective of our study was to determine the levels of serum E-selectin, a marker of endothelial dysfunction (ED), and to perform a correlation analysis of E-selectin levels and the results of instrumental examination of the structural and functional status of the vasculature of patients with CAD with/without DM2.

Material and Methods

The study included 60 patients with CAD divided into two groups: Group 1, 29 patients with CAD including 14 (48.3%) male patients, and Group 2, 31 patients with CAD and DM2 including 15 male (48.4%) patients. The mean age of patients in Group 1 was 65.28 ± 7.20 years, and in Group 2, 65.84 ± 9.34 years. Groups 1 and 2 did not differ by age, sex, body mass index (BMI), and smoking status at the time of the study (Table 1). Moreover, there were no statistically significant differences in their significant clinical and anamnestic characteristics, except for myocardial infarction with a statistically higher incidence in Group 2 (Table 2).

All patients signed an informed consent form before the start of the study. The study was approved by a local Ethics Committee and carried out in accordance with the principles of the Declaration of Helsinki.

All patients underwent laboratory tests and instrumental examinations under the relevant medical and economic standards, including complete blood count, biochemical tests, urinalysis, electrocardiography, 24-hour ambulatory blood pressure monitoring, 24-hour Holter monitoring, transthoracic echocardiography, frontal chest X-ray, and bicycle ergometry. Levels of serum E-selectin were determined by immunoenzymatic analysis using Technoclon kits. Laser FPP was performed using a Angioskan-01 device, and nailfold video capillaroscopy (VCS) was done using a Kapillaroscan-1 device, TU 9442001 82402834 2008.

FPP was used to assess the structural (stiffness index, aSI, m/s) and functional state (phase shift, PS, ms) of large vessels and the structural (reflection index, RI, %) and functional (occlusion index, IO) state of microcirculatory arterioles. VCS was used to estimate capillary density at rest (CDr), capillary density during reactive hyperemia (CDrh), capillary density after venous occlusion test (CDvo), percentage of capillary recovery (PCR), and percentage of perfused capillaries (PPC). The parameters of the functional state of the capillaries were calculated as follows:

$$PCR = (CDrh - CDr)/CDvo \times 100\%, \text{ and}$$
$$PPC = (CDrh/CDvo) \times 100\%.$$

Table 1. Demographic characteristics of the study subjects

Parameter	Group 1 (CAD)	Group 2 (CAD + DM2)	p*
Number of patients	29	31	–
Age, years	65.28 ± 7.20	65.84 ± 9.34	0.871
Sex composition (male / female)	14 (48.3); 15 (51.7)	15 (48.4); 16 (51.6)	0.414
BMI, kg/m^2	28.99 ± 5.08	31.49 ± 5.06	0.076
Smokers (active smoking at the time of the study)	11 (37.93)	12 (38.71)	0.234

Data are expressed as mean ± standard deviation or as absolute and relative (%) values.
*, the statistical significance of intergroup differences was evaluated using the chi-squared test.
CAD, coronary artery disease; DM2, type 2 diabetes mellitus; BMI, body mass index.

Table 2. Clinical characteristics of the study subjects

Parameter	Group 1 (CAD)	Group 2 (CAD + DM2)	p
Dyspnea	18 (62.07)	16 (51.61)	0.642
Heart pains	15 (51.72)	16 (51.61)	0.544
Hypertensive heart disease	22 (75.86)	24 (77.42)	0.452
Obliterating BCA atherosclerosis	8 (27.59)	10 (32.26)	0.186
History of coronary artery stenting	5 (17.24)	6 (19.35)	0.222
History of coronary artery bypass surgery	3 (10.34)	1 (3.22)	0.279
History of myocardial infarction	8 (27.59)	14 (45.16)	0.024
History of atrial fibrillation	1 (3.44)	1 (3.22)	0.324
CHF	4 (13.79)	6 (19.35)	0.102
History of CVA	3 (10.34)	3 (9.67)	0.805
History of gastric and duodenal ulcers	7 (24.14)	5 (16.13)	0.504

The data are expressed as absolute and relative (%) values.
BCA, brachiocephalic arteries; CHF, chronic heart failure; CVA, cerebrovascular accident.

The findings were statistically analyzed with IBM SPSS, version 22.0. Descriptive statistics of the findings are provided as the percentage and standard error for qualitative values and as the mean (M) and standard deviations (σ) for quantitative values. In the absence of normal distribution of characteristics, the median (Me) and quartiles [Q1; Q3] were used for the descriptive statistics. The Pearson's correlation test for normal distributions and the Spearman's correlation test for non-normal distributions were used.

Results

Laboratory and instrumental signs of severe ED were identified in both groups.

There was a statistically significant increase in E-selectin in Group 2 (35.2 [29.0; 47.35] ng/ml) versus Group 1 (31.7 [20.85; 36.68] ng/ml (p=0.028, Figure 1).

FPP detected structural and functional disorders of microcirculatory vessels and dysfunction of large vessels in both groups. A marked decrease in PS versus the mean population value (≥10 ms) was observed in both groups. Significant dysfunction of large vessels was manifested by a significantly lower value of PS in Group 2 (–4.4 [–8.7 [–2.45] ms) versus Group 1 (–1.9 [–3.95; –0.38] ms (p=0.018, Figure 2).

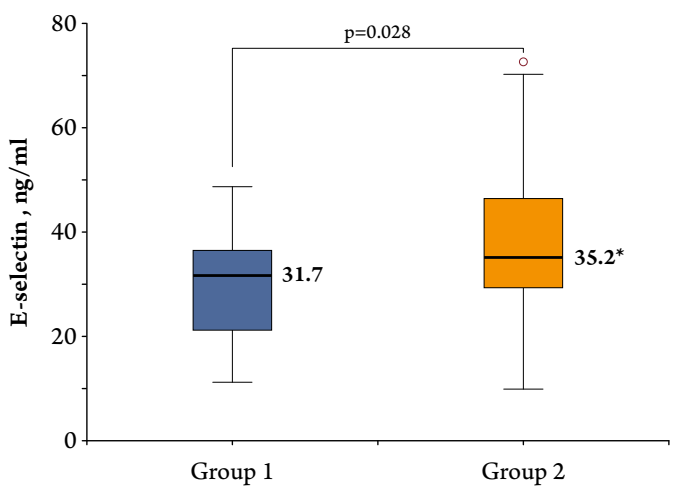
aSI was above the established normal value (5–8 m/s) in Group 2 (8.22 [7.15; 10.80] m/s). In group 1, aSI (7.80 [6.25; 9.78] m/s) was normal and tended to be less than in Group 2, but differences between the groups were not significant (p=0.532). In both groups, RI was above normal population values (up to 30%). RI in Group 2 (41.15 [22.55; 54.38] %) was higher than in Group 1 (36.00 [23.20; 58.50] %), but these structural changes in arterioles were not significant (p=0.92).

In both groups, IO was below normal values, ≥1.8. Values in Group 2 (1.40 [1.20; 1.70]) tended to be lower than in Group 1 (1.52 [1.32; 1.70]), but differences between the groups were not significant (p=0.78).

CDr was at the mean population levels in both groups and did not differ significantly between the groups (p=0.103). However, capillary density measured by the venous occlusion test was lower than the mean population values in both groups. Capillary density was significantly less in Group 2 (67.70 [57.83; 80.69]) than in Group 1 (80.80 [69.05; 99.08] (p=0.016; Figure 3).

The reactive hyperemia test detected no decrease in CDrh in either group, nor was there a significant intergroup difference: (60.33 [49.08; 79.25] in Group 1 versus 67.67 [52.67; 105.33] in Group 2 (p=0.131). PPC in Group 2 (88.56 [79.56; 98.41]) was lower than the mean population levels, ≥92.00 and tended to be less than in Group 1 (93.64 [79.87; 105.67]), but this difference was not significant (p=0.296). PCR in both groups were lower than the mean population levels,

Figure 1. E-selectin levels (ng/ml) in Group 1 and Group 2 patients



*, the increase is statistically significant.

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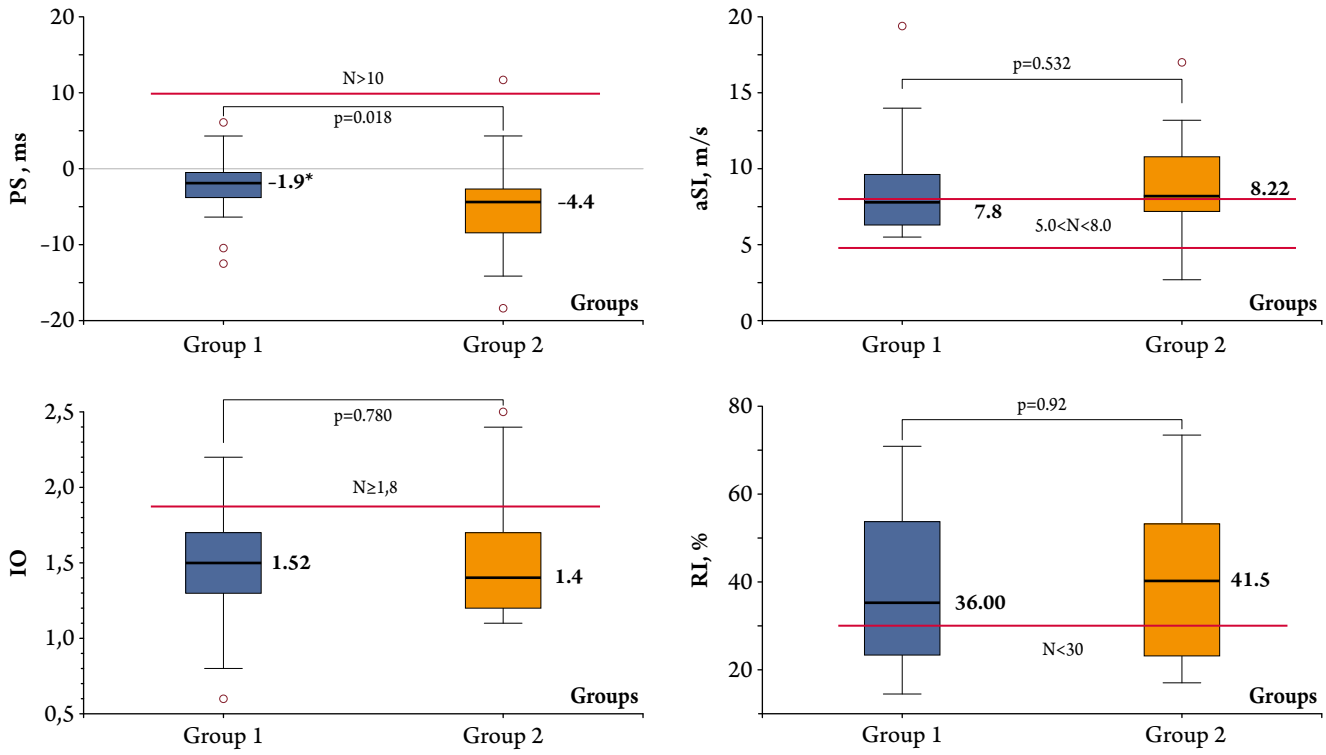
Figure 2. PS, aSI, IO, and RI values in Group 1 and Group 2 patients



PS, phase shift; aSI, stiffness index; IO, occlusion index; RI, reflection index.

≥16.5. Differences in PCR between Group 1 (8.55 [–2.7; 27.31] and Group 2 (10.53 [2.73; 22.55]) were not significant (p=0.867).

Despite the statistically significant differences in E-selectin between the groups and despite the changes identified by in FPP and VCS, no statistically significant correlations were found by inter-group and intra-group analyses.

Discussion

The presence of severe ED in patients with CAD in both groups was confirmed by increased E-selectin and by decreased phase shift and occlusion index. In both groups, structural capillary disorders were indicated by decreased CDvo and functional disorders by decreased PCR. This was true also for structural changes of arterioles as indicated by increased RI. Moreover, E-selectin was significantly higher, and PS and PCS were significantly lower in Group 2 than in Group 1. RI was higher and IO was lower in Group 2, but these differences were not significant. aSI was higher in Group 2 than the general population normal values. In patients with CAD, aSI was below the upper limit of the general population norm. Similarly, PPC was decreased in Group 2 but was normal in Group 1.

All of the above changes show that DM makes a significant additional contribution to the development of endothelial dysfunction. Thus, the study revealed signs of disorders at several stages of the cardiovascular continuum. e g., endothelial dysfunction and later the development of structural vascular disorders at different levels of the microcirculation.

It should be noted that increased serum E-selectin and more severe changes of the FPP parameters were observed in patients with compensated glycosylated hemoglobin: mean level of Hb1Ac was 6.8% [6.15; 7.35], i.e., 93.5% of patients reached individual glycemic targets. Therefore, if patients with DM2 do not reach target levels for Hb1AC, even more severe signs of ED may be expected. Moreover, sugar reducing therapy may have an additional effect on reducing the severity of ED, not only by reducing the direct impact of glucotoxicity, but also due to possible pleiotropic effects. It is also important that cardiovascular therapy reduced the severity of ED in patients in both groups. However, there were no significant intergroup differences in the dosing frequency of major drug groups. The absence of significant correlations among the various parameters may reflect the relatively small number of patients in both groups.

Conclusion

We suggest that chronic hyperglycemia in DM2 patients with coronary artery disease contributes to the

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development and aggravation of EDn. The identified changes require more prolonged and larger studies to assess the increase in E-selectin in patients with coronary artery disease.

These studies should include the use of new sugar-lowering drugs with proven cardionephroprotective effects, such as glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter-2 inhibitors (glyflosins). In addition, the effects of cardiovascular drugs must be considered. In prospective multicenter studies, correlations between cardiovascular death, stroke, and myocardial infarction with E-selectin should be evaluated.

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No conflict of interest is reported.

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