THE ASSOCIATION OF BIOMARKERS OF ENDOTHELIAL DYSFUNCTION AND DISORDERS OF MYOCARDIAL PERFUSION

*Jelena Lilić[1], Boris Đinđić [1,2], Tomislav Kostić [1,2], Dragana Stanojević[2],
Gorana Nedin Ranković[1], Marija Cvetkvić[1], Aneta Jovanović[3]*

Atherosclerosis is a process associated with a number of risk factors which via their cumulative action accelerate atherogenesis. It is believed that endothelial dysfunction, associated with inflammation and increased oxidative stress in the blood vessel wall, is in its basis. The aim of the study was to analyze the association of myocardial ischemia with the parameters of endothelial dysfunction.

We analyzed 120 patients of both sexes. The first group consisted of 70 dyslipidemic patients with type 2 diabetes mellitus and manifest atherosclerosis on a hygienic-dietary regime and statin therapy. The second group consisted of 50 dyslipidemic patients with type 2 diabetes mellitus, with no verified atherosclerotic complications. Patients in both groups were similar in age and had a similar duration of diabetes.

The analyses suggested a positive correlation of myocardial ischemia induced by exercise stress test demands with the values of citrulline, but not with the values of highly sensitive C-reactive protein and nitric oxide. In the group with clinically manifest atherosclerosis, there were significantly more positive stress test results when myocardial ischemia was concerned. *Acta Medica Medianae 2017;56(2):25-31*

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University of Niš, Faculty of Medicine, Niš, Serbia[1]
Clinical of Cardiology, Clinical Center, Niš, Serbia[2]
Clinic of Thoracic Surgery, Niš, Serbia[3]

Contact: Jelena Lilić
Boul. Nemajića 83/37, 18000 Niš, Serbia
E-mail: jjeca8451@gmail.com

Introduction

Cardiovascular (CV) diseases provoked by atherosclerosis are now the most common cause of death in the world (57.3% of total mortality), with malignant tumors occupying the second place with 22%, and pulmonary diseases at the third place with 10%. Ischemic heart disease is present basically in 30% of patients with lethal outcome in the total mortality percentage (1). In the structure of mortality in the Republic of Serbia in 2007, heart and blood vessel diseases were present basically in more than half of all lethal outcomes (56.0%). Serbia is in the third place in Europe in the number of patients and mortality due to CVDs, and prevention and healthy lifestyles can certainly help in the prevention of heart diseases. In the territory of our country in 2012, the incidence of CVDs was five times higher than in 1990 and three times higher than in 2000. The average age of cardiovascular patients was previously 60 years, but today this limit dropped to 40 and the cases of young people in their twenties and thirties with a myocardial infarction are not rare now (2).

Atherogenic lesions occur primarily within the intimal blood vessel layer, its development starting from fatty streaks (lesions type I-III) and diffuse intimal thickening (lesion type IV), through fibrolipid plaque (lesion type V and VI), to the developed lesions complicated by thrombosis, hemorrhage or calcification ("complicated lesion"). Atherogenic lesions typically occur in the so-called predilection places (artery bifurcation, the areas of "natural" stenosis). The aforementioned lesions primarily affect the elastic artery (aorta, common carotid and iliac arteries), hybrid (internal carotid artery), and large and medium-sized muscular arteries (coronary artery and popliteal artery).

Oxidation of LDL particles, the formation of fatty streaks and proliferation of smooth muscle cells constitute the basis for the formation of an atheromatous fibrolipid plaque. Several cell forms from the arterial wall and blood are involved in the process of atherogenesis, such as endothelial cells, smooth-muscle cells, macrophages, platelets, and numerous growth factors (3). Potential interactions of cells, cytokines and growth regulator molecules with different cells of atherosclerotic lesions provide an opportunity for numerous changes in the lesion and its progression (4).

What is now known is that the immune system is very early involved in the initiation of atherosclerosis, playing a dominant role in the development of inflammatory reaction in the plaque. Therefore, it is considered that the development of atherosclerosis begins with morphologically invisible damage to the endothelium, which may be caused by physical, mechanical, chemical, toxic, infectious and immunological factors. After the development

of endothelial dysfunction, lipid uptake and its deposition in the intima of the vessel occur. Macrophages are the cells most responsible for the process, performing pinocytosis of modified lipid particles thanks to CD36 receptors on their surface (5).

After their migration to the intima, monocytes are transformed into macrophages, which are not normal components of the arterial wall. Migrated monocytes can release cytotoxic substances (hydrolytic enzymes and reactive oxygen metabolites), cytokines (TNF), growth factors, and procoagulant substances that cause metabolic and functional changes of proliferative processes in the development of atherosclerosis, vasculature remodeling, and plaque destabilization (6).

Normal functioning of the arterial endothelium is essential for the development of atherosclerotic process to be effectively suppressed. The endothelium plays an important role in vascular homeostasis, regulation of plasma lipoproteins uptake, the adhesion of leukocytes, release of procoagulant and anticoagulant factors, growth factors and vasoactive substances (1, 4).

Microtrauma and arterial endothelial dysfunction are the initial event that leads to the development of atherosclerosis, followed by an increased influx of macromolecules into the blood vessel intima (1, 7).

Endothelial dysfunction can be caused by chronic minimal damage of endothelial cells caused by systemic factors such as hypercholesterolemia (specially modified LDL), active and passive smoking (increased superoxide production in endothelial cells, which leads to nitric oxide inactivation and increased lipoprotein oxidation), abnormal vasoconstriction and others (7) (Table 1).

Table 1. Factors causing endothelial damage or dysfunction

Hypercholesterolemia	Obesity/insulin resistance
Minimally modified or Ox LDL	Age
Active and passive smoking	Male
Hypertension	Family history of prematurity
A diet rich in saturated fats	Circulating vasoactive amines
Physical inactivity	Immune complexes
AGE products in diabetes	Some viral infections

Today we know that the initial lesion of atherosclerosis occurs when leukocytes and monocytes pass through the endothelial barrier in the intimacy of an intact or activated endothelium. In fact, in physiological conditions, endothelial cells are found in the so-called "resting" or "quiescent" state – in the standby mode of a kind.

The aim of the study was to analyze the association of myocardial ischemia with the parameters of endothelial dysfunction.

Methods

Our general method was the comparison of the data obtained from prospective and retrospective analysis of patient histories and biochemical parameters. We analyzed 120 patients with type 2 diabetes mellitus, tested in the day-ward of the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center Niš, and the Institute for the Prevention, Treatment and Rehabilitation of Cardiovascular Patients "Niska Banja"- Niska Banja. All the patients started their hygienic-dietary or antidiabetic medicamentous treatment. Atherosclerotic disease (coronary artery disease, peripheral vascular disease and cerebrovascular accidents) was verified in all patients using the functional tests for the detection of cardiovascular manifest atherosclerosis.

Patients were divided into two groups, depending on the presence of clinical manifestations of atherosclerosis and in relation to the type of lipid therapy.

Group I included 70 dyslipidemic patients with type 2 diabetes mellitus and manifest atherosclerosis, on a hygienic-dietetic regime and drug-lipid statin therapy.

Group II included 50 dyslipidemic patients with type 2 diabetes mellitus without verified atherosclerotic complications. Patients in this group were similar in age and duration of diabetes to the patients from the first group. Detailed history data were collected in accordance with the study protocol directly from the patients and from their medical histories.

Mandatory clinical examination consisted of several procedures.

• Determination of body mass index (BMI) was performed by the calculation based on the formula BMI = TT (body weight) / TV2 (height). The values were expressed in kg/m2, and BMI was evaluated based on the criteria of the World Health Organization from 1998 (8).

• Measurement of arterial tension was done in a sitting position after a short rest of at least 5 minutes in the course of a routine clinical examination, and the mean value of three successive measurements was taken. To determine a five-year absolute risk, systolic blood pressure was used. The criteria for the diagnosis of hypertension were systolic TA >140 mmHg and diastolic >90 mmHg, according to the WHO criteria from 1999 (9).

• Clinically manifest atherosclerotic coronary disease was established on the basis of functional tests (ECG and ergometric trial - test load on a treadmill bar).

Methods for the assessment of endothelial dysfunction:

• Determination of fasting plasma glucose was done on a fasting capillary blood sample after fasting for 12 hours. Determination was conducted by MONO analyzer Beckman, based on oxygen consumption. Glycemic values were expressed in mmol/l, and the reference values were 3.6-6.1 mmol/l.

• NO values were determined using an indirect method, measuring the nitrate and nitrite. Oxidation of NO generate nitrates and nitrites, so that their concentrations in the body fluids were considered an indicator of NO production. The concentration of nitrate and nitrite was determined by the spectrophotometric method according to Navarro-Gonzalvez et al. (1998), based on the Gries reaction (10). Concentrations of nitrate and nitrite were expressed in nmol/mg protein.

• Determination of the amount of citrulline was performed colorimetrically, with a diacetyl monoxime reaction, following the Boyd method (1980) (11). The values were expressed in mmol/l.

• Determining the value of a high-sensitive C-reactive protein (hsCRP), was performed using a commercial test of the company Dade Behring on the Dimension Expand analyzer. The values were expressed in mg/l.

Methods for the assessment of myocardial ischemia

For the assessment of myocardial ischemia, a load test on a treadmill was used, whereby the protocol by Bruce was applied. The test was performed to achieve a submaximal heart frequency or was interrupted by the occurrence of subjective symptoms of fatigue or ECG signs of ischemia (ST-segment and T-wave changes). Laboratory tests were carried out in the biochemical laboratory of the Military Hospital Niš, and the Institute of Biochemistry, Faculty of Medicine Niš. The stress test was carried out at the Military Hospital Niš. Data analysis was performed at the Institute of Pathophysiology, Faculty of Medicine, Niš.

Table 2. Characteristics of the formed groups

	Total		Women		Men	
	n	(%)	n	(%)	n	(%)
Without atherosclerosis	70	60.0	32	27.0	38	31.0
Atherosclerosis	50	40.0	30	25.0	20	17.0
Total	120	100.0	62	52.0	58	48.0

The data were processed using standard descriptive statistical methods (mean, standard deviation and percentage). The results were analyzed using the appropriate tests, depending on the group size, type, and type of data. The statistical analysis was performed within and among the defined groups. The importance of endothelial dysfunction in the development of clinically manifest atherosclerotic disease of the coronary arteries and perfusion disorders were analyzed by comparing the data between defined groups of patients based on the presence or absence of manifest atherosclerotic disease.

In this paper several test types were performed:
• Student t-test for independent samples,
• Chi-square
• Fisher Exact probability test
• Pearson coefficient of linear correlation
• Model of binary logistic regression

Statistical analysis was done in Excel 7.0 and SPSS 16.0 in Windows XP environment, and the results are presented in tables and graphs.

Results

The study included 120 patients with dyslipidemia and diabetes mellitus type 2. The basic characteristics of patients are shown in Tables 2 and 3. In relation to the presence or absence of clinically manifest atherosclerotic disease, all the patients were divided into two groups. The characteristics of the examined groups are presented in Table 1. The first group consisted of 70 patients with type 2 diabetes mellitus (T2DM), and with dyslipidemia and atherosclerotic complications. Among them, 32 (27%) were female and 38 (31.0%) were male. The second group consisted of 50 patients with DM type 2 with dyslipidemia, without the presence of atherosclerosis, whereas 30 (25%) were women and 20 (17%) were men (Table 2).

The average age and duration of diabetes mellitus in the studied patients are shown in Table 3. Average age of the patients was 60.8±7.32 years, and there were no statistically significant differences in age between the sexes. The duration of diabetes was significantly higher in men than in women 10.5±8.1 vs. 7.08±6.9 years of age (p<0.05). Men had a shorter duration of laboratory verified dyslipidemia compared to women (p<0.05). The average values of BMI and fasting plasma glucose were not significantly different between the genders (Table 3).

Table 4 shows the general characteristics of the patients studied in relation to the presence

of atherosclerosis. The average age and duration of diabetes were significantly longer in patients with atherosclerosis (* p <0.05).

The prevalence of risk factors for athero-

Table 3. General characteristics of the studied patients

	Age (years)	Duration of Dyslipidemia	DM duration (years)	BMI (kg/m2)	Glucose (mmol / l)
Women	61.8±5.92	5.8±4.9	7.08±6.9	29.79±4.92	7.1±2.65
Men	59.8±8.53	6.4±5.5	10.3±8.1*	28.92±3.2	7.93±2.51
Total	60.8±7.32	6.2±5.2	8.56±7.66	29.2±4.23	7.42±2.6

* p<0.05

Table 4. General characteristics of the tested patients in relation to atherosclerosis

	Age (years)	Duration of Dyslipidaemia	DM duration (years)	BMI (kg/m2)	Glucose (mmol / l)
No atherosclerosis	58.7±8.1	5.9±5.1	6.3±6.7	29.7±4.5	7.6±2.0
Atherosclerosis	63.5±5.7*	7.0±5.6	10.9±8.0*	30.1±4.1	7.3±2.5
Total	60.8±7.32	6.2±5.2	8.56±7.66	28.9±4.23	7.42±2.6

* P <0.05 versus no atherosclerosis

Table 5. Risk factors for cardiovascular disease in the studied groups

	No atherosclerosis (%)	Atherosclerosis (%)	Total (%)
Sedentary lifestyle	15.9	16.0	16.0
Failure to comply with a diet	18.2	14.0	16.0
Hypertension	68.2	100.0**	85.1
Smoking	13.6	6.0	9.6
Alchocol consuming	27.3	38.0	33.0
Obesity	70.5	82.0*	76.6
Family history of early CVD	65.9	70.0*	68.1

*p<0.05, **p<0.01

sclerosis in the examined groups of patients is shown in Table 5. The completed analysis showed a significantly higher incidence of hypertension, obesity and family history of early CV disease (in males before the age of 55, and in women before the age of 65 years).

Markers of endothelial dysfunction in the studied groups are shown in Table 6. The analysis showed that between two groups of patients (with and without manifest atherosclerosis), there were no significant differences in the values of citrulline and highly sensitive C-reactive protein, but the concentration of NO was significantly higher in patients with clinically manifest atherosclerosis (p<0.05).

Table 6. Biochemical indicators of endothelial dysfunction

	No atherosclerosis	Atherosclerosis	Total
NO (nmol/mg prot.)	66.20±25.0	74.4±24.43*	70.39±25.0
Citrulin (mmol/l)	2.98±2.34	2.87±2.32	2.92±2.31
hsCRP (mg/L)	4.25±3.88	4.06±2.49	4.15±3.23

NO-nitrogen monoxide, hsCRP-high-sensitivity C-reactive protein   *p<0.05

The characteristics of the load test in the examined groups of patients are shown in Table 7. In the group with clinically manifest atherosclerosis, there were significantly more positive load test results suggestive of myocardial ischemia (p <0.01).

Table 8 shows the connection of load test myocardial ischemia with the markers of endo-thelial dysfunction. The analysis performed shows the importance of positive correlation of load test myocardial ischemia with the values of citrulline (p <0.05), but not with the values of highly sensitive C-reactive protein and nitric oxide.

Table 7. Characteristics of the load test

	No atherosclerosis n (%)	Atherosclerosis n (%)	Total n (%)
Positive test to ischemia	13 / 18.8	40 / 79.4**	60 / 50.0
Negative test to ischemia	57 / 81.2	10 / 20.6	60 / 50.0

**p<0.01 compared without atherosclerosis

Table 8. Correlation between the markers of endothelial dysfunction with the appearance of ischemia during the load test

A positive load test on myocardial ischemia	hsCRP	NO2+NO3	Citrulin
Correlation coefficient	0.160	0.168	0.315
p	0.211	0.188	**0.049**

Discusion

Atherosclerosis is a disease with a number of risk factors which accelerates atherogenesis via their cumulative effects. It is believed that together with this process there is also endothelial dysfunction, associated with inflammation and increased oxidative stress in blood vessel walls (12).

Diabetes mellitus is one of the leading causes of cardiovascular disorders. Over 50% of the patients with newly diagnosed type 2 diabetes have signs of CVD, suggesting that an increased CV risk had existed for many years before clinically manifest type 2 DM was detected. Since most patients with diabetes mellitus type 2 have a long history of metabolic syndrome, the focus of the treatment of atherosclerotic complications in type 2 diabetes should be shifted to the prevention of this condition (13).

Metabolic syndrome is a condition of an increased risk of CV morbidity and mortality (14). The increasing presence of metabolic syndrome in certain populations is a consequence of modern life. Insulin resistance is a major component of the syndrome and is the basic pathogenic mechanism. Reaven concluded back in 1988 that in certain individuals there was a connection between obesity, diabetes mellitus, hypertension, hyperlipidemia and clinically manifest atherosclerosis (15).

These analyses show that there was no statistically significant difference in age between the genders. Similar age of men and women involved in the study indicates that gender-related differences disappear at the time of onset of CVD in type 2 DM. This is another indirect indicator of increased atherosclerotic risk in women with diabetes. The duration of diabetes was significantly longer in men, but they had shorter laboratory verified dyslipidemia.

The average age and duration of diabetes were significantly longer in patients with atherosclerosis. The performed analysis showed a statistically significantly higher prevalence of hypertension, obesity and family history of early CV disease (in males before the age of 55, and in women before the age of 65 years) in patients with manifest atherosclerosis, which was consistent with the literature findings. These risk factors have a cumulative effect on the incidence and progression of atherosclerosis.

Obesity with hypertension is the most common component of metabolic syndrome and is one of 6 major factors for CV disease, with a global load of 15% (16). Obesity, defined as BMI>30 kg/m^2, was present in a high percentage of the respondents. It should be noted that it was more frequent in patients with atherosclerosis. Average values of BMI and fasting plasma glucose were not significantly different between the genders.

Hypertension is the most common component of the metabolic syndrome. It is one of six major factors for CV disease, with a global load of 45% (16). In the study patients, hypertension (defined according to the WHO criteria) (9) was the most common component of metabolic syndrome, with a prevalence of 100% in the group of patients with clinically manifest atherosclerosis and 60% in the group without manifest atherosclerosis. The prevalence did not vary in relation to gender. In addition to obesity and hypertension, positive family history for the presence of CV disease (present in about 68.1% of the surveyed patients) and inadequate diet (present in about 63% of the surveyed patients) were the most common risk factors in all groups of patients.

The importance of non-lipid risk factors for manifest atherosclerosis was tested by comparing dyslipidemic patients with and without manifest atherosclerotic disease. Smoking was present with about 9.6%, alcohol with 33%, with no significant difference between the patients with and without manifest atherosclerosis, which did not agree with previously published studies. In our patients, other, so-called "major" risk factors, probably had a significant role in the pathogenesis of atherosclerotic process.

Between the two groups of patients with and without manifest atherosclerosis, there was no significant difference in the values of citrulline

and highly sensitive C-reactive protein, but the concentration of NO was significantly higher in patients with clinically manifest atherosclerosis. It is possible that this is a compensatory increase of the potent vasodilator and modulator of endothelial and smooth-muscle cells in the context of the so-called post-ischemic postconditioning (17).

In the group with clinically manifest athe-rosclerosis, as expected, significantly more positive load tests to myocardial ischemia were registered. There was a positive correlation between ischemia induced by exercise stress and the concentration of citrulline. This paradoxical phenomenon could be explained by a compensatory increase in the conce-ntration of citrulline, a precursor in the synthesis of the natural L-arginine, which is a substrate for the enzyme NO synthase (18).

Conclusion

Endothelial dysfunction and impaired myo-cardial perfusion are important factors in the deve-lopment of atherosclerosis. In the group of patients with clinically manifest atherosclerosis, positive test load on myocardial ischemia was registered in a significantly higher number of cases. Biomarker analysis indicates the correlation of myocardial ischemia during the load test with the values of citrulline, but not with the values of highly sensitive C-reactive protein and nitric oxide. It is possible that this is a compensatory increase of the precu-rsors in the synthesis of NO, in the course of a load test induced ischemia.

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UDRUŽENOST BIOMARKERA ENDOTELNE DISFUNKCIJE I POREMEĆAJA MIOKARDNE PERFUZIJE

Jelena Lilić[1], Boris Đinđić[1,2], Tomislav Kostić[1,2], Dragana Stanojević[2],
Gorana Nedin Ranković[1], Marija Cvetkvić[1], Aneta Jovanović[3]

Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija[1];
Klinika za kardiovaskularne bolesti, Klinički centar Niš, Srbija[2]
Klinika za grudnu hirurgiju, Klinički centar Niš, Serbia[3]

Kontakt: Jelena Lilić
Bul. dr Zorana Đinđića 83/37, 18000 Niš, Srbija
E-mail: jjeca8451@gmail.com

Ateroskleroza je proces udružen sa većim brojem faktora rizika koji svojim kumulativnim delovanjem ubrzavaju aterogenezu. Smatra se da u je u njenoj osnovi endotelna disfunkcija, koja je povezana sa inflamacijom i povećanim intenzitetom oksidativnog stresa u zidu krvnog suda. Cilj rada bio je da se analizira povezanost miokardne ishemije sa parametrima endotelne disfunkcije.

Analizirano je 120 bolesnika oba pola. Prvu grupu činilo je 70 dislipidemičnih bolesnika sa dijabetesom melitusom tip 2 i manifestnom aterosklerozom na higijensko-dijetetskom režimu i na terapiji statinima. Druga grupa je obuhvatala 50 dislipidemičnih bolesnika sa dijabetesom melitusom tip 2, bez verifikovanih aterosklerotskih komplikacija. Bolesnici iz obe grupe bili su slične starosti i imali sličnu dužinu trajanja dijabetesa.

Urađene analize ukazale su na postojanje pozitivne povezanosti miokardne ishemije indukovane testom fizičkim opterećenjem sa vrednostima citrulina, ali ne i sa vrednostima visokosenzitivnog C reaktivnog proteina i azot monoksida. U grupi sa klinički manifestnom aterosklerozom registrovana je značajno češća pojava pozitivnog testa opterećenja na miokardnu ishemiju. *Acta Medica Medianae 2017;56(2):25-31.*

Ključne reči: *: ateroskleroza, dijabetes melitus, miokardna ishemija*