Asymptomatic Cardiovascular Manifestations in Diabetes Mellitus: Left Ventricular Diastolic Dysfunction and Silent Myocardial Ischemia

Jelena P. Seferović-Mitrović[1], Nebojša M. Lalić[1,2], Bosiljka Vujisić-Tešić[2,3], Katarina Lalić[1,2], Aleksandra Jotić[1,2], Arsen D. Ristić[2,3], Vojislav Giga[3], Milorad Tešić[3], Nataša Milić[4], Ljiljana Lukić[1], Tanja Miličić[1], Sandra Singh[1], Petar M. Seferović[2,3]

[1]Department of Endocrinology, Diabetes, and Metabolic Disorders, Clinical Centre of Serbia, Belgrade, Serbia;
[2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
[3]Department of Cardiology, Clinical Centre of Serbia, Belgrade, Serbia;
[4]Institute for Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction Several cardiovascular manifestations in patients with diabetes may be asymptomatic. Left ventricular diastolic dysfunction (LVDD) is considered to be the earliest metabolic myocardial lesion in these patients, and can be diagnosed with tissue Doppler echocardiography. Silent myocardial ischemia (SMI) is a characteristic and frequently described form of ischemic heart disease in patients with diabetes.

Objective The aim of the study was to assess the prevalence of LVDD and SMI in patients with type 2 diabetes, as well as to compare demographic, clinical, and metabolic data among defined groups (patients with LVDD, patients with SMI and patients with type 2 diabetes, without LVDD and SMI).

Methods We investigated 104 type 2 diabetic patients (mean age 55.4±9.1 years, 64.4% males) with normal blood pressure, prehypertension and arterial hypertension stage I. Study design included basic laboratory assessment and cardiological workup (transthoracic echocardiography and tissue Doppler, as well as the exercise stress echocardiography).

Results LVDD was diagnosed in twelve patients (11.5%), while SMI was revealed in six patients (5.8%). Less patients with LVDD were using metformin, in comparison to other two groups ($\chi 2 = 12.152$; $p=0.002$). Values of HDL cholesterol ($F=4.515$; $p=0.013$) and apolipoprotein A1 ($F=5.128$; $p= 0.008$) were significantly higher in patients with LVDD.

Conclusion The study confirmed asymptomatic cardiovascular complications in 17.3% patients with type 2 diabetes.

Keywords: type 2 diabetes mellitus; asymptomatic cardiovascular manifestations; left ventricular diastolic dysfunction; silent myocardial ischemia

INTRODUCTION

Numerous epidemiological and clinical observations have indicated that patients with diabetes are prone to develop various forms of cardiovascular disease. One of the landmark investigations, Framingham study, confirmed that patients with diabetes have significantly higher morbidity and mortality from cardiovascular disease than patients without diabetes [1, 2]. Such findings, confirmed by several subsequent studies have led to the development of the modern medical dogma that diabetes and cardiovascular disease are two sides of one coin.

It has been recently recognized that the term cardiometabolic continuum can be used to describe the changes in the cardiovascular system that develop as a consequence of type 2 diabetes and metabolic syndrome. The initial lesions can usually be identified in the third and fourth decade, while the onset of overt clinical manifestations depends on the duration and severity of diabetes, as well as other risk factors for cardiovascular disease.

Direct metabolic effect of diabetes on myocites may induce early myocardial dysfunction, and is often asymptomatic and unrecognized by both patients and the physician [3]. These changes can be diagnosed by echocardiography as left ventricular diastolic dysfunction (LVDD), which may be considered as a precursor of systolic heart failure. Further progression of these metabolic disturbances may lead to the development of coronary atherosclerosis which is, in patients with diabetes, also often associated with mild symptoms or asymptomatic.

In addition, acute myocardial infarction may occur with minimal or without symptoms in 40% of patients with diabetes. Also, clinically well recognized form of ischemic heart disease in patients with diabetes is silent myocardial ischemia (SMI), occurring 2-6 times more frequently than in those without diabetes. SMI can be defined as transitory impairment of myocardial flow without anginal pain or other symptoms.

As stated, one of the major clinical features of cardiovascular disease in patients with diabe-

Correspondence to:
Jelena P. SEFEROVIĆ-MITROVIĆ
Department of Endocrinology, Diabetes and Metabolic Disorders
Clinical Centre of Serbia
Dr Subotića 13, 11000 Belgrade
Serbia
jpseferovic@yahoo.com

tes is mild intensity or absence of symptoms. A significant number of patients, up to 50%, are not aware of the disease, because they do not have any symptoms [4, 5]. The most important clinical implication of these findings in patients with diabetes is a risk of developing major or even fatal cardiovascular complications despite being asymptomatic.

OBJECTIVE

The objective of the study was to assess the prevalence of asymptomatic cardiovascular manifestations, LVDD and SMI in patients with type 2 diabetes, as well as to compare demographic, clinical and metabolic parameters among the defined groups.

METHODS

Study population

One hundred and four patients (mean age 55.4±9.1 years, 64.4% males) with type 2 diabetes were investigated from October 2007 to January 2011. The medical treatment consisted of diet and/or oral antihyperglycaemic agents (fasting glycaemia <15 mmol/l and glycosylated haemoglobin – HbA1c <9%). The studied patients had normal blood pressure, prehypertension or arterial hypertension stage I. None of the patients had prior history or symptoms of ischemic heart disease, myocardial infarction, cerebrovascular disease, renal disease and microvascular diabetic complications.

The local Ethics Committee approved the study protocol and written informed consent was obtained from all patients.

Study protocol

Demographic data and information on the duration of diabetes, and anthropometric measurements were acquired from all patients. Blood samples were collected after 12-hour fasting for the following analysis: serum glucose, HbA1c, total-, LDL- and HDL-cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, apolipoprotein AII, apolipoprotein E, and lipoprotein(a).

Cardiologic assessment included blood pressure measurements, electrocardiography, echocardiography, as well as stress echocardiography.

Arterial blood pressure was measured in the sitting position, and after five minutes of rest on the hand with a registered higher blood pressure rate, using a sphygmomanometer. Prehypertension was considered as systolic pressure from 120 to 139 mm Hg or diastolic pressure from 80 to 89 mm Hg. Hypertension stage I was defined as systolic pressure from 140 to 159 mm Hg or a diastolic pressure from 90 to 99 mm Hg [6].

Electrocardiography was performed using a 12-lead Schiller Cardiovit CS-200.

Echocardiography

All patients underwent transthoracic 2D, Doppler and tissue Doppler echocardiography using Sequoia c256 Acuson (Siemens Mountain View, California, USA). LVDD was assessed using the criteria defined in a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology (ESC) [7]. According to this statement, LVDD was diagnosed when early mitral valve flow velocity (E) and early diastolic lengthening velocity (E') ratio was E/E'≥15.

If the E/E' is suggestive of LVDD [8-15], additional non-invasive investigations were applied. The abovementioned Consensus considers the left atrial volume index (LAVI) >40 ml/m^2 to provide sufficient evidence of LVDD (excluded by LAVI <29 ml/m^2). Another parameter which can be used to confirm LVDD is the left ventricular wall mass index (LVMI) >122 g/m^2 (women) or >149 g/m^2 (men) [8]. Ratio of maximal early filling velocity (E-wave) and maximal late (atrial) filling velocity (A-wave), E/A >0.5 was also used to confirm LVDD. Elevated plasma levels of BNP can be used as additional diagnostic tool. The same experienced investigator, blinded for the clinical data, performed all echo-Doppler recordings.

Stress echocardiography

In order to detect the presence of ischemic heart disease, all patients underwent stress echocardiograhy test (Del Mar and Agilent Image Point, USA) using Bruce protocol [9]. Myocardial ischemia was established if horizontal, descending or slow ascending ST segment depression ≥1 mm, with duration of 0.08 seconds, or segmental hypokinesia (stress echocardiography) were detected.

Statistical analysis

Continuous data are presented as mean ± SD and as percentages, as appropriate. The unpaired t-test (two-tailed) was used to assess differences between continuous variables. The chi-square test was used to compare categorical variables between groups. Uni- and multiple linear regression analysis were applied to identify the independent correlates of LVDD. A value of $p < 0.05$ was considered significant.

The sample size needed for the study was 99 patients, calculated based on the literature data [10, 11] and the presumed proportion of LVDD of 0.30 (30%), with an alpha error of 0.05 (Z=1.96) and accuracy of E=0.09 (9%).

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RESULTS

Demographic data, anthropometric measurements, duration of diabetes and arterial hypertension

The mean age of studied patients was 55.4±9.1 years, with the predominance of males (64.4% males). The median duration of diabetes was 4 (4) years, while the mean value of body mass index (BMI) in this patient cohort was 27.5±4.4 kg/m^2. Average systolic blood pressure was found to be 132.6±11.0 mm Hg, and diastolic blood pressure was 82.6±6.3 mm Hg. Arterial hypertension stage I was detected in 24 patients (23.1%), with median duration of 3 (4) years.

Prevalence of left ventricular diastolic dysfunction and silent myocardial ischemia

After analysing the results of the study, patients were divided into three groups: 1) patients diagnosed with LVDD; 2) patients suffering from SMI; and 3) patients with type 2 diabetes, but without LVDD and SMI. The diagnosis of LVDD was established in 12 patients (11.5%), while SMI was detected in 6 patients (5.8%).

Comparative analysis of demographic data, anthropometric measurements, duration of diabetes and arterial hypertension in investigated groups

Comparative analysis of demographic data, anthropometric measurements, duration of diabetes and arterial hypertension, as well as patients' therapy is summarized in Table 1. There were no significant differences in age (F=2.627; p>0.05), duration of diabetes (χ^2=3.579; p>0.05) and values of BMI (F=0.252; p>0.05). Furthermore, no significant difference was detected in the values of systolic and diastolic blood pressure (systolic F=0.465; p>0.05, diastolic F=0.827; p>0.05), or duration of arterial hypertension (χ^2=3.558; p>0.05) among the investigated groups. However, less patients with LVDD were using metformin, in comparison to other two groups (χ^2=12.152; p=0.002).

Comparison of laboratory parameters

Table 2 depicts the comparison of parameters of glycoregulation (fasting plasma glucose and HbA1c), lipid parameters and lipid subfractions among the groups. Although the values of fasting plasma glucose and HbA1c were elevated in all patients, there were no statistically significant differences in glycaemia (F=0.428; p>0.05) or HbA1c (F=0.437; p >0.05) among the groups. Mean values of tryglicerides were elevated in all groups, while the values of apolipoprotein A1, B, AII, E and lipoprotein(a) were normal in all patients. There were no significant differences in the values of total (F=0.513; p>0.05) and LDL cholesterol (F=0.001; p>0.05), tryglicerides (χ^2=2.029; p>0.05), apolipoprotein B (F=1.160; p>0.05), apolipoprotein AII (F=1.023; p>0.05), apolipoprotein E (χ^2=0.063; p>0.05) and lipoprotein(a) (χ^2=1.180; p>0.05) among investigated groups.

However, the values of HDL cholesterol (F=4.515; p=0.013) and apolipoprotein A1 (F=5.128; p=0.008) were significantly higher in patients with LVDD when compared to other two groups. Furthermore, significantly higher values of HDL cholesterol (p=0.004) and apolipoprotein A1 (p=0.003) were revealed in patients with LVDD in comparison to those without LVDD and SMI. Also, significantly higher values of apolipoprotein A1 were detected in patients with LVDD than with SMI (p=0.015).

DISCUSSION

Asymptomatic/oligosymptomatic cardiovascular manifestations of diabetes

As confirmed in various studies, a significant number of patients with type 2 diabetes are not aware to have metabolic disorder [4, 5]. This occurrence is more often described in females, who also have a higher glycaemia at the end of the oral glucose tolerance test, particularly if older than 70 years. Seemingly, as with diabetes, cardiovascular symptoms in these patients may be very discrete

Table 1. Comparison of demographic data, antropometric measurements, duration of diabetes/hypertension and treatment

Parameter		LVDD	SMI	T2D, no LVDD, SMI	p
Number of patients		12	6	86	
Age (years)		59.3±9.1	60.7±7.6	54.4±9.0	>0.05
Gender	Male	7 (58.3%)	5 (83.3%)	55 (64.0%)	>0.05
	Female	5 (41.7%)	1 (16.7%)	31 (36.0%)	
BMI (kg/m^2)		27.1±3.1	26.6±2.3	27.7±4.6	>0.05
Duration of diabetes* (years)		2 (4)	7 (13)	4 (4)	>0.05
Diabetes therapy	Metformin	9 (75.0 %)	6 (100.0%)	84 (97.7%)	0.002
	Sulfonylurea	8 (66.7 %)	5 (83.3%)	45 (52.3%)	>0.05
Blood pressure (mm Hg)	Systolic	131.7±9.4	136.7±12.1	132.4±11.1	>0.05
	Diastolic	82.5±4.5	85.8±4.9	82.4±6.6	>0.05
Arterial hypertension stage I		4 (33.3%)	3 (50.0%)	17 (19.8%)	>0.05
Duration of hypertension* (years)		5 (13)	3 (0)	3 (5)	>0.05

Values are expressed as $\bar{X}$±SD and n (%).
*median (interquartile range); T2D – type 2 diabetes; LVDD – left ventricular diastolic dysfunction; SMI – silent myocardial ischemia

Table 2. Comparison of parameters of glycoregulation, lipids and subfractions

Parameter	LVDD	SMI	T2D, no LVDD, SMI	p
Glycaemia (mmol/l)	7.7±1.8	8.7±1.6	8.2±2.3	>0.05
HbA1c (%)	7.1±0.8	7.7±1.6	7.2±1.3	>0.05
Total cholesterol (mmol/l)	5.7±0.8	5.1±1.1	5.7±1.3	>0.05
LDL cholesterol (mmol/l)	3.4±0.9	2.9±1.1	3.5±1.1	>0.05
HDL cholesterol (mmol/l)	1.3±0.3	1.0±0.2	1.0±0.3	0.013
Tryglicerides* (mmol/l)	2.6 (2.4)	2.9 (2.5)	1.9 (1.8)	>0.05
Apolipoprotein A-1 (g/l)	2.1±0.5	1.6±0.3	1.7±0.4	0.008
Apolipoprotein B (g/l)	1.0±0.3	1.1±0.2	1.21±0.3	>0.05
Apolipoprotein AII (mg/l)	359.2±85.0	346.4±44.0	333.3±58.2	>0.05
Apolipoprotein E* (mg/l)	46.0 (17.2)	42.5 (54.8)	45.1 (22.9)	>0.05
Lipoprotein(a)* (g/l)	0.1 (0.05)	0.1 (0.2)	0.1 (0.1)	>0.05

Values are expressed as $\bar{X}$±SD.
* median (interquartile range); HbA1c – glycated haemoglobin

[12]. The duration of the asymptomatic period in patients with diabetes and cardiovascular diseases is unpredictable, varying with gender, age and co-morbidities. Furthermore, the rate of the detection of asymptomatic cardiovascular disease is higher in more developed healthcare systems resulting in increased detection of diabetes, arterial hypertension, and dyslipidemia.

Slow progression of cardiovascular and metabolic changes in patients with diabetes is one of the key reasons for the absence or delayed clinical manifestations.

The scarce symptoms of cardiovascular complications in diabetes prevent timely diagnosis, and thus the successful prevention and treatment. Therefore, early detection of asymptomatic forms of cardiovascular manifestations in patients with diabetes may be crucial not only in preventing fatal complications, but also to improve outcome and survival.

The causes of the absence of symptoms in patients with diabetes and cardiovascular lesions

There are several explanations for the absence of cardiovascular symptoms (including anginal pain) in patients with diabetes. The most common causes can be listed as cardiac autonomic neuropathy, elevated concentrations of endogenous endorphins and dissimulation of anginal pain.

Experimental studies and autopsy reports of patients who died after an asymptomatic myocardial infarction [13] indicated that cardiac autonomic neuropathy could be commonly revealed in patients with diabetes. Cardiac autonomic neuropathy leads to sensory denervation, which increases the threshold for the occurrence of anginal pain [14]. Imaging method with m-iodine benzylguanidine confirmed sympathetic denervation causing diminished sensitivity for anginal pain and abnormal perception of painful stimuli [15]. Various investigations have demonstrated that vagal activity is reduced, while the sympathetic activity is enhanced in patients with diabetes and associated SMI, with expressed morning peak [16]. In addition, significant clinical correlation between autonomic neuropathy and insulin resistance was revealed, as well as the possible etiological role of insulin resistance in developing SMI [17, 18].

High concentration of endogenous endorphins can be listed as a possible cause of asymptomatic cardiovascular events in patients with diabetes. The same is true for dissimulation of anginal pain demonstrated in experimental setting as a reason for the absence of cardiovascular symptoms.

Diastolic left ventricular dysfunction

In this study, LVDD was revealed in twelve (11.5%) patients. Higher proportion of patients with LVDD in comparison to patients with SMI could be explained with early development of myocardial changes during the development of cardiovascular continuum, while atherosclerotic lesions causing SMI can be seen later. Direct negative metabolic effect of diabetes on the myocardium, due to hyperglycemia and insulin resistance, causes the impairment of myocardial relaxation presented on echocardiography as LVDD [19]. Arterial hypertension, as a cause of LVDD, is ruled out by patient selection, since only patients with prehypertension and hypertension stage I were included in the study.

It has been shown that the prevalence of LVDD in various studies showed considerable variability. The results of this study revealed lower proportion of LVDD in comparison to the literature data. This difference could be explained by the strict selection of patients who were in initial stages of cardiovascular continuum with early myocardial changes.

Furthermore, they had a relatively short duration of diabetes (median 4 (4) years) treated with diet and/or oral antihyperglycemic agents, without diabetic complications and had prehypertension and hypertension stage I. Additional reason for the low prevalence of LVDD in this study is that used criteria are ones defined by the Consensus statement of the Heart Failure and Echocardiography Associations of the ESC [7] which are considered to be precise and strict.

From the clinical point of view, LVDD is often asymptomatic or with minimal symptoms and frequently overlooked by the patient [20]. When the symptoms occur, they are discrete and variable in intensity and duration, presenting mostly as dyspnea. In the current study, patients were free of symptoms related to the cardiovascular system.

The major drawback in detecting LVDD includes the lack of precise diagnostic parameters, as well as various technical features of echocardiographic equipment. In-depth review of the literature data, wide heterogeneity of diagnostic parameters for LVDD was demonstrated. In general, the diagnostic approach to LVDD was improved and standardized by using both, the parameters defined in the Consensus statement [7] and tissue Doppler. Good clinical applicability and accuracy were the reasons that these parameters were used in the current study.

Several studies demonstrated a huge variation and heterogeneity among cohorts investigated for the prevalence of LVDD in patients with diabetes. Studies using the criteria defined in the Consensus statement revealed lower, but similar prevalence of LVDD. The prevalence of LVDD in DADD study (Diabetes Mellitus and Diastolic Dysfunction) [21], which investigated the influence of strict glycaemic control on diastolic dysfunction in 39 patients with type 2 diabetes, without ischemic heart disease or heart failure, was 33%.

From et al. [22] investigated 486 patients with type 2 diabetes, without hypertension and ischemic heart disease and revealed that E/E'>15 had 21% of patients. Research of Sharman et al. [23] that included 155 patients with type 2 diabetes without other cardiovascular diseases demonstrated LVDD (E/E'>15) in 51% of subjects.

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Silent myocardial ischemia

In our study cohort, SMI was confirmed in six (5.8%) patients, which was significantly lower than the prevalence of LVDD. Since SMI in patients with diabetes indicates atherosclerotic (coronary artery) diabetic involvement, which develops in the later stage of the cardiometabolic continuum, this complication was unexpected. The majority of patients with diabetes and SMI suffer from ischemic heart disease, presenting as angina pectoris or prior myocardial infarction. In only a few patients, SMI could be confirmed without atherosclerotic coronary disease.

In comparison to the anginal episodes of ischemia, in SMI coronary flow impairments are of shorter duration and/or mild intensity. Several studies demonstrated significant correlation of SMI and increased risk for cardiovascular events, independently of other risk factors for ischemic heart disease [24]. Jacqueminet et al. [25] confirmed that SMI could be considered as an independent risk factor for cardiovascular events.

The diagnosis of SMI in asymptomatic patients with diabetes can be established using several methods. Exercise stress test has a sensitivity of 50-67%, specificity of 75% and significant positive (46%) and negative predictive value (87%). Although imprecise in diagnosing single coronary artery disease, its diagnostic accuracy is much higher in patients with multivessel coronary disease. Due to clinical applicability and low cost, this test is widely used. Echocardiographic stress test, which was used in our study, is more reliable in detecting SMI and its sensitivity, specificity, diagnostic accuracy and predictive value are high. The segmental wall motion abnormality caused by the physical activity and recorded echocardiographically indicates a narrowed coronary artery.

In patients unable to perform the exercise test, dobutamine stress test is indicated. Cosson et al. [26] revealed that SMI, diagnosed by non-invasive tests, could be found in 20-35% of patients with type 2 diabetes. The prevalence of SMI in patients with type 2 diabetes detected in different studies varied between 12 and 62%, depending on the patient selection and diagnostic tests used [27].

In MiSAD study (Milan Study on Atherosclerosis and Diabetes) [28], which included 735 asymptomatic patients with type 2 diabetes, the prevalence of SMI established by echocardiography stress test was only 12%. This could be explained by the absence of other risk factors for cardiovascular disease in these patients. In the study of Cosson et al. [29], computerized tomography was employed for the diagnosis of SMI, which was revealed in 33% of patients. The results of this study confirmed the significance of SMI as a predictor for the development of cardiovascular events, while the worst prognosis was proved in patients with SMI and coronary atherosclerosis.

DIAD study (Detection of Ischemia in Asymptomatic Diabetics) [30] analysed the importance of screening for the SMI by radionuclide adenosine stress test in patients with diabetes, and clinical value for the cardiovascular events risk assessment. Final conclusions were that screening for SMI had no prognostic significance, and that it was associated with several drawbacks, such as a large number of patients and high costs.

In the current study, all patients in whom SMI was detected underwent selective coronary angiography. The angiographic findings included two vessel disease in four patients and three vessel disease in two patients. Diagnosing SMI in 5.8% of patients indicates that the chronological progression of cardiovascular lesions in diabetes might not be always longitudinal, and that the vascular (coronary) changes may develop early causing life-threatening complications even before the individual is aware to have diabetes.

CONCLUSION

This study confirmed asymptomatic cardiovascular complications in 17.3% patients with diabetes. LVDD was diagnosed in 11.5% patients, while SMI was revealed in 5.8% patients. Diagnosing LVDD using tissue Doppler echocardiography and SMI by stress echocardiograhy allow timely detection of these diseases and therefore their treatment and prevention of complications.

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Асимптоматска оштећења срца код особа оболелих од дијабетеса: дијастолна дисфункција леве коморе и нема исхемија миокарда

Јелена П. Сеферовић-Митровић[1], Небојша М. Лалић[1,2], Босиљка Вујисић-Тешић[2,3], Катарина Лалић[1,2], Александра Јотић[1,2], Арсен Д. Ристић[2,3], Војислав Гига[3], Милорад Тешић[3], Наташа Милић[4], Љиљана Лукић[1], Тања Миличић[1], Сандра Сингх[1], Петар М. Сеферовић[2,3]

[1]Клиника за ендокринологију, дијабетес и болести метаболизма, Клинички центар Србије, Београд, Србија;
[2]Медицински факултет, Универзитет у Београду, Београд, Србија;
[3]Клиника за кардиологију, Клинички центар Србије, Београд, Србија;
[4]Институт за медицинску статистику и информатику, Медицински факултет, Универзитет у Београду, Београд, Србија

КРАТАК САДРЖАЈ

Увод Оштећења срца код особа оболелих од дијабетеса обично су асимптоматска. Дијастолна дисфункција леве коморе (ДДЛК) настаје као последица лошег метаболичког утицаја дијабетеса на миокард. Чест и типичан начин клиничког испољавања исхемијске болести срца код болесника са дијабетесом јесте нема исхемија миокарда (НИМ).

Циљ рада Циљ истраживања био је да се утврди учесталост ДДЛК и НИМ код болесника са дијабетесом тип 2 и упореде демографски, клинички и метаболички подаци између испитиваних група болесника (болесника са ДДЛК, болесника са НИМ и болесника без ове две манифестације).

Методе рада У студију су била укључена 104 болесника (64,4% мушкараца), средње старости 55,4±9,1 годину, која су боловала од дијабетеса тип 2 и била лечена дијетом и оралним антихипергликемицима. Испитаници су имали нормалан крвни притисак, прехипертензију или артеријску хипертензију првог степена. Протокол испитивања подразумевао је основне лабораторијске анализе и кардиолошке прегледе (електрокардиограм, дводимензионални ехокардиограм и ткивни доплер и ехокардиографски стрес-тест на покретној траци).

Резултати Код дванаест болесника утврђена је ДДЛК (11,5%), док је код шест испитаника постављена дијагноза НИМ (5,8%). Статистички значајно мањи број болесника са ДДЛК лечен је метформином у односу на друге две групе испитаника (χ^2=12,152; p=0,002). Вредности *HDL*-холестерола (F=4,515; p=0,013) и аполипопротеина А1 (F=5,128; p=0,008) биле су статистички значајно веће у групи болесника са ДДЛК.

Закључак Истраживање је показало да се асимптоматска оштећења срца јављају код 17,3% болесника са дијабетесом тип 2.

Кључне речи: дијабетес мелитус тип 2; асимптоматске кардиоваскуларне манифестације; дијастолна дисфункција леве коморе; нема исхемија миокарда

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