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LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS WITH METABOLIC SYNDROME

DIJASTOLNA DISFUNKCIJA LEVE KOMORE KOD PACIJENATA S METABOLIČKIM SINDROMOM

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Summary – Metabolic syndrome (MetS), which is a cluster of medical disorders, is common and it is associated with increased cardiovascular morbidity and mortality. The aim of this study was to evaluate the relationship between characteristics of metabolic syndrome and the grade of diastolic dysfunction. The study included 72 patients (29 male and 43 female), who had central obesity and at least two of the other four characteristics of metabolic syndrome according to IDF (International Diabetes Federation) criteria. The exclusion criteria were age above 65, impaired systolic function (left ventricular ejection fraction <55%), atrial fibrillation, valvular and pericardial heart disease. Diastolic function was determined according to the criteria of the American Society of Echocardiography. There was a positive correlation between the number of characteristics of metabolic syndrome and the diastolic dysfunction grade ($p < 0.0001$). The positive correlation was found between the grade of diastolic dysfunction and the waist circumference ($p < 0.0001$), arterial hypertension ($p < 0.001$), impaired glucose tolerance/diabetes ($P = 0.0063$), and hypertriglyceridemia ($p = 0.0262$). A low level of high-density lipoprotein did not show a statistically significant correlation. The presence of metabolic syndrome is associated with the presence of diastolic dysfunction. The grade of diastolic dysfunction is dependent on the number of coexisting characteristics of metabolic syndrome. Arterial hypertension, central obesity, hyperglycemia and hypertriglyceridemia showed a significant correlation with the degree of diastolic dysfunction.

Key words: Heart Failure, Diastolic; Ventricular Dysfunction, Left; Metabolic Syndrome X; Echocardiography; Male; Female

Introduction

Metabolic syndrome (MetS), which is a cluster of medical disorders, is common and it is associated with increased cardiovascular morbidity and mortality as well as with increased risk of heart failure. According to International Diabetes Federation (IDF) metabolic syndrome is defined as the presence of central obesity plus any two of the following four factors: a low level of high-density lipoprotein (HDL) (or specific treatment for this lipid abnormality), high triglycerides (or specific treatment for this lipid abnormality), arterial hypertension (or treatment of previously diagnosed hypertension) and fasting hyperglycemia (or previously diagnosed diabetes) [1]. The prevalence of MetS in industrial countries is about 22% of adult population, and over 40% of those aged 50 and more [2-4]. It is also well known that the prevalence of MetS is dependent on the sex and ethnicity. There are no data of MetS prevalence for Serbia, but a research performed in the city of Niš in 2005, which included subjects aged 46.6 on average, showed the prevalence of 43.3% [5].

The risk factors clustering MetS have been shown to act both individually and synergistically, via mechanisms poorly defined, to increase the risk of adverse cardiovascular events including coronary artery disease and congestive heart failure, and they are associated with high cardiovascular morbidity and mortality [3,6]. Although studies have shown that hypertension, diabetes mellitus, and obesity adversely affect cardiac structure and function, the ex-

tent to which individual and clustering components of metabolic syndrome predict subclinical left ventricular (LV) systolic and/or diastolic dysfunction has not been characterized well [7-10].

The purpose of the study is to assess the association between the increasing number of characteristics of metabolic syndrome and the grade of left ventricular diastolic dysfunction in our population.

Material and Methods

The research included 72 subjects, both males and females, without clinically manifested symptoms and signs of congestive heart failure. All of them had central obesity and at least two of four characteristics of MetS according to the IDF criteria. The exclusion criteria were age over 65, reduced systolic function (left ventricular ejection fraction <55%), valvular and pericardial heart disease. All subjects underwent history and physical examination. Central obesity was determined according to the IDF criteria for the Europeans as the waist circumference ≥ 94 cm for men and ≥ 80 cm for women. The waist circumference was measured with flexible, non-distensible measuring tape at the middle point between the inferior margin of the ribs and the anterior superior iliac crest taking the nearest round centimeter [11,12].

Other characteristics of metabolic syndrome were considered positive if were as follows:

Hypertriglyceridemia: $> (1.7 \text{ mmol/L, or specific treatment for this lipid abnormality,}$

Abbreviations

MetS	– metabolic syndrome
IDF	– International diabetes foundation
LV	– left ventricle/left ventricular

Low level of HDL cholesterol: <1.03 mmol/L) in males and <1.3 mmol/L in females, or specific treatment for this lipid abnormality,

Arterial hypertension: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension,

Impaired glucose tolerance: blood sugar ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes.

Blood samples for laboratory measurement were taken after 12h fasting period. Blood pressure was measured by mercury sphygmomanometer after ten minutes rest using the mean value of two consecutive measurements. Echocardiographic examination was performed using General Electric Vivid 4 ultrasound system. Left ventricular diastolic function was assessed by pulse wave (PW) doppler measurement of E wave, A wave velocity and E wave deceleration time of mitral inflow in four chambers apical view placing sample volume at the tip of mitral leaflets. Velocity e' was assessed by tissue doppler (TDI) in four chamber apical view with 2mm sample volume placed at septal mitral annulus. Values of E/A and E/ e' were calculated. The grade of diastolic dysfunction was determined according to the American Society of Echocardiography criteria [13] (**Table 1**).

Table 1. Diastolic dysfunction grading criteria

Tabela 1. Kriterijumi za stepenovanje dijastolne disfunkcije

	Normal (adults) <i>Normalno (odložena) relaksacija (odrasli)</i>	Impaired relaxation/Pseudonormal mitral inflow pattern/ <i>Impaired relaxation/Pseudonormalni profil protoka Grade 1 Prvi stepen</i>	Pseudo-normal mitral inflow pattern/ <i>Pseudonormalni profil protoka Grade 2 Drugi stepen</i>	Restrictive mitral inflow pattern/ <i>Restriktivni profil protoka Grade 3 Treći stepen</i>
E/A	>1	<0.8	$0.8-1.5$	>2
E wave deceleration time (ms)/ <i>Deceleracijsko vreme E-talasa (ms)</i>	<200	>200	$160-200$	<160
IVRT (ms)*	<100	>100	$60-100$	<60
Septal e' (cm/s) <i>Septalno e' (cm/s)</i>	$>8-10$	<8	<8	<8
E/ e'		≤ 8	$9-12$	≥ 13

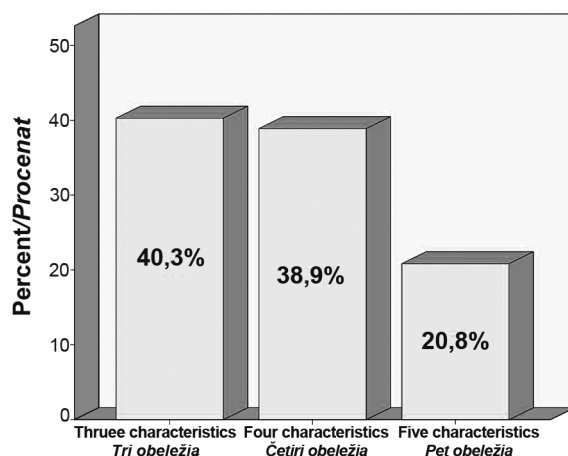
*IVRT - isovolumetric relaxation time

All subjects were categorized into appropriate groups according to the number of characteristics of metabolic syndrome. The grouping was done by the presence of three, four, or five characteristics. The grouping by diastolic function was as follows: no diastolic dysfunction, diastolic dysfunction grade 1 (delayed relaxation), grade 2 (pseudonormal pattern of transmitral inflow) and grade 3 (restrictive pattern of transmitral inflow).

The data were processed by SPSS v17 software (SPSS inc, Chicago, Illinois, USA) and they were presented as mean values $\pm$ SD for quantitative values, and as proportions for qualitative values. Chi square was used to calculate p value. P value less than 0.05 was considered statistically significant.

Results

The investigation was performed in the period from Mart 1st, 2009 to April 30th, 2009. Among 375 examined patients, 162 were diagnosed with metabolic syndrome. Ninety six of those patients matched the age criteria (≤ 65 y). After echocardiographic examination 72 of 96 met all inclusion criteria. In the study cohort there were 29 male (40.2%) and 43 female (59.8%), their average age being 54.8 ± 7.1 . All of the subjects had central obesity (100%) as an obligate inclusion criterion. High blood pressure was found in 70.8%, raised fasting glucose or diabetes in 43.1%, low level of HDL cholesterol in 80.6% and high level of triglycerides in 86.1%. There were 40.3% subjects with three, 38.9% with four and 20.8% with all five characteristics of MetS (**Graph 1**).



Number of characteristics of Mets/Broj obeležja MetS

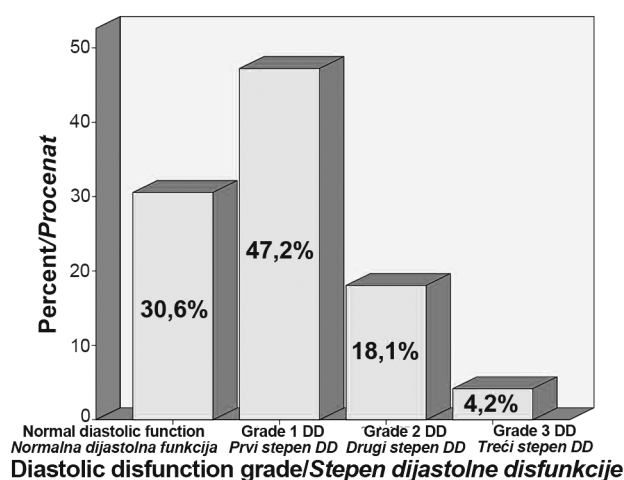
Graph 1. Metabolic syndrome characteristics in percent

Grafikon 1. Procenatna zastupljenost broja obeležja metaboličkog sindroma

Twenty two of 72 subjects (30.6%) did not meet criteria for diastolic dysfunction (normal diastolic function), 34 (47.2%) subjects had Grade 1 diastolic dysfunction, 13 subjects (18.1%) had Grade 2 diastolic dysfunction and 3 (4.2%) had Grade 3 diastolic dysfunction (**Graph 2**).

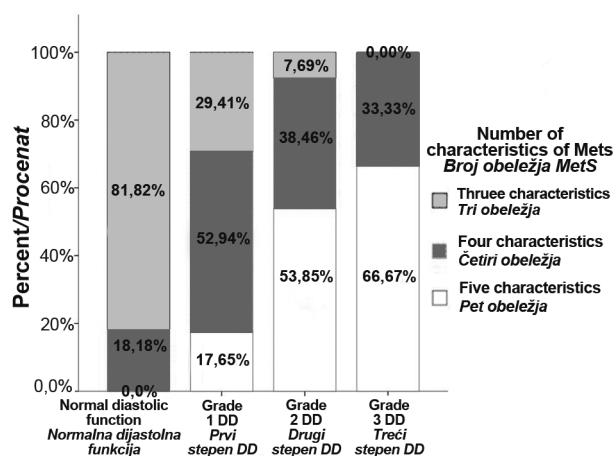
In the group with normal diastolic function, there were 81.8% with three presented characteristics, 18.2% with four characteristics, and none (0%) with five characteristics of MetS. In the group with first grade of diastolic dysfunction, there were 29.4% subjects with three characteristics, 62.8% with four, and 17.6% with five characteristics of MetS. In the group with second grade of diastolic dysfunction, there were 7.7% with three, 38.5% with four, and 53.8% with five characteristics of MetS. Finally, in the group with third grade of diastolic dysfunction there were no subjects with three criteria, 33.3% with four and 66.7% with five criteria for MetS (**Graph 3**).

A statistically significant correlation was found between the number of existing characteristics of MetS and the grade of diastolic dysfunction ($p < 0.0001$). In



Graph 2. Diastolic dysfunction grade among subjects

Grafikon 2. Procentualna zastupljenost stepena dijastolne disfunkcije kod ispitanika



Graph 3. Characteristics of metabolic syndrome according to the degree of diastolic dysfunction

Grafikon 3. Zastupljenost broja obeležja metaboličkog sindroma prema stepenu dijastolne disfunkcije

Table 2. Distribution of frequencies of metabolic syndrome according to diastolic dysfunction grade and level of positive correlation
Tabela 2. Raspodela frekvencija obeležja metaboličkog sindroma prema stepenu dijastolne disfunkcije i nivo njihove pozitivne povezanosti

	Grade of diastolic dysfunction Stepen dijastolne disfunkcije				p – value vrednost p
	0	1	2	3	
Waist circumference/Obim struka (+/-)	22/0	34/0	13/0	3/0	p<0,0001
Arterial hypertension (+/-)	5/17	30/4	13/0	3/0	p<0,0001
Arterijska hipertenzija (+/-)	20/2	25/9	10/3	3/0	p=0,3325
Low HDL/Nizak HDL (+/-)	12/10	28/6	12/1	3/0	p=0,0262
Hypertriglyceridaemia (+/-)	4/18	15/19	10/3	2/1	p=0,0063
Hipertigliceridemija (+/-)					
Hyperglycemia/diabetes (+/-)					
Hiperglikemija/dijabetes (+/-)					

addition, the positive correlation was found between the grade of diastolic dysfunction and central obesity ($p<0.0001$), arterial hypertension ($p<0.0001$), impaired glucose tolerance/diabetes ($p<0.0063$) and high level of triglycerides ($p<0.0262$) as the separate criteria. No statistically significant correlation was found between the grade of diastolic dysfunction and low level of HDL cholesterol ($p=0.3325$) (Table 2).

Discussion

Cardiovascular diseases associated with metabolic syndrome comprise vascular and myocardial abnormalities that are usually manifested as impaired relaxation of the left ventricle. This myocardial dysfunction is characterized predominantly by diastolic dysfunction consisting of relaxation abnormalities that are prevalent and have prognostic importance [14]. The correlation between the intensity of metabolic syndrome and the presence of diastolic dysfunction is well documented [15-17], as well as the fact that the grade of diastolic dysfunction is associated with the intensity of metabolic syndrome [15,18].

Obesity prevalence is rising all over the world and makes an important risk for morbidity and mortality of cardiovascular diseases. Some earlier studies have pointed that central obesity contributes to structural and functional cardiovascular abnormalities directly by disproportional increase of cardiac output mediated by adrenergic stimulation and indirectly by increasing left ventricular mass [19-21].

The results of PROCAM (Prospective Cardiovascular Münster) study, performed on a sample of 2754 males aged 40-65 years followed over a four-year period, indicate that patients who had hypertension only or diabetes only, had a 2.5 times increased risk of cardiovascular morbidity. The patients with diagnosis of both diabetes mellitus and hypertensive disease had an eight-fold increase in their risk. There was a twenty-fold increase in the risk of cardiovascular events in the patients with diabetes mellitus and coexistent hypertensive disease and associated abdominal lipid profile [22]. Strong Heart Study data have indicated that diabetes has independent adverse cardiac effects which may contribute to cardiovascular events in diabetic patients [23]. There is a documented association between the duration of diabetes mellitus and the degree of LV diastolic dysfunction [24]. In the same paper, it is pointed that not only microvascular disease plays a role in the development of decreased LV compliance, but also autonomic deregulation and cardiac fibrosis, which are the well known consequences of diabetes, are involved in evolving LV diastolic dysfunction.

Hypertriglyceridemia, as an independent risk factor influencing diastolic function, was also previously documented [15,16,25]. It has been shown by experimental models that the accumulation of triglycerides in cardiac myocytes is related to diastolic dysfunction in obese mice [26].

Low levels of HDL cholesterol in some studies were associated with left-ventricular diastolic dys-

function [15], but in others were not [27]. There is no explanation for that difference, but it could be related to ethnic differences of studied subjects.

The results of our study on the population aged 65 and less, without clinical signs of congestive heart failure confirms the existence of relationship between the intensity of metabolic syndrome (rated by the number of coexisting characteristics of MetS) and left ventricular diastolic dysfunction as a parameter of subclinical organ damage. First grade of diastolic dysfunction (impaired relaxation) was the most common disorder. Central obesity, arterial hypertension, impaired glucose tolerance and hypertriglyceridemia were related to the grade of diastolic dysfunction, and these results are consistent with the results of previously published studies.

Our results are consistent with the findings of other studies which have not confirmed that low levels of HDL cholesterol are associated with an increased risk of diastolic dysfunction.

Conclusion

The presence of metabolic syndrome is related to the presence of diastolic dysfunction. The diastolic dysfunction grade is associated with the number of characteristics of metabolic syndrome. Central obesity, hypertension, hyperglycemia and hypertriglyceridemia showed a statistically significant correlation with the degree of diastolic dysfunction.

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Sažetak

Uvod

Metabolički sindrom povezan je s povećanim kardiovaskularnim morbiditetom i mortalitetom, kao i s povećanim rizikom od insuficijencije srca. Cilj ovog rada bio je da se proceni odnos između broja istovremeno postojećih obeležja metaboličkog sindroma i stepena dijastolne disfunkcije.

Materijal i metode

Studija je obuhvatila 72 ispitanika (29 muškog i 43 ženskog pola), koja su imala centralnu gojaznost i najmanje dva od preostala četiri obeležja metaboličkog sindroma. Kriterijumi za isključenje iz studije bili su starost preko 65 godina (ejekciona frakcija leve komore < 55%), atrijska fibrilacija, valvularna i perikardna bolest srca. Dijastolna funkcija je određivana transtorakalnom ehokardiografijom.

Rezultati

Normalnu dijastolnu funkciju leve komore imalo je 30,6%, a najveći deo njih imao je samo tri obeležja metaboličkog sindroma (81,8%).

Glavne reči: Dijastolna disfunkcija srca; Disfunkcija leve komore; Metabolički sindrom; Ehokardiografija; Muško; Žensko

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Većina ispitanika imala je dijastolnu disfunkciju prvog stepena (49%) od kojih je 52,9% njih imalo četiri udružena obeležja metaboličkog sindroma. Drugi stepen dijastolne disfunkcije imalo je 18% ispitanika, a samo 4,2% treći stepen, dok je većina u obe grupe imala svih pet obeležja ovog sindroma. Pozitivna korelacija nađena je između broja obeležja metaboličkog sindroma i stepena dijastolne disfunkcije. Dobijena je pozitivna korelacija stepena dijastolne disfunkcije i zasebno centralne gojaznosti, arterijske hipertenzije, poremećene glikozne tolerancije/dijabetesa i hipertrigliceridemije.

Zaključak

Stepen dijastolne disfunkcije povezan je s brojem obeležja metaboličkog sindroma. Pojedinačno centralna gojaznost, arterijska hipertenzija, hiperglikemija i hipertrigliceridemija pokazale su statistički značajnu povezanost sa stepenom dijastolne disfunkcije.