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Early Diagnosis of Structural and Functional Changes in the Heart with Metabolic Syndrome: A Relationship with Insulin Resistance

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Abstract

Despite the fact that the relationship of metabolic syndrome (MS) with structurally functional changes in the heart is well established, the role of metabolic disorders, the main of which is insulin resistance (IR), is not completely defined. The role of IR in the development of coronary disease (CD) against the background of MS requires further study, IR plays, elucidation of predictors of functional heart disorders. The aim of the research is to study the effect of IR and metabolic disturbances on early structural and functional changes in the heart in patients with MS and to evaluate the course of coronary disease in the presence of MS. The study included 63 patients, including 47 men (74%) and 15 women (25%) aged 39–53 years. The main group (n=38) consisted of patients with stable angina (SA) of FC I, FC II and MS, with a disease duration of not more than 5 years. A comparison group (n = 25) was presented by patients with MS without SA. The parameters of the lipid spectrum and blood glucose were determined, echocardiography was performed using traditional and tissue myocardial dopplerography (TMD), and a stress test was performed with an ECG on a bicycle ergometer. More pronounced signs of remodeling by the type of concentric LV hypertrophy were determined in patients with SA on the background of MS; in patients with MS, concentric remodeling was more common. The use of TMD revealed the diastolic heart failure of the left ventricle in a larger number of patients compared to traditional Doppler echocardiography. The most sensitive indicator was the E/e´ average ratio, which had a pronounced relationship with the HOMA IR index> 2.77 in patients with SA and MS. Reduced exercise tolerance in patients with metabolic syndrome is closely related to the insulin resistance index and the ratio of TG / HDL cholesterol> 1.32. Early structural and functional changes in the heart in patients with MS are closely related to the insulin resistance index: HOMA IR index> 2.77 in patients with SA and MS; the ratio of TG / HDL cholesterol> 1.32 in all patients with and without SA. When conducting stress

ECG tests, it is necessary to pay attention to the recovery period of the study. In patients with SA, MS slows down the restoration of blood pressure and heart rate due to the low level of adaptive reactions of the cardiovascular system, which allows the attending physician to take into account the choice of drug therapy.

Keywords: *Metabolic Syndrome; Insulin Resistance; Angina; Stable; Heart Failure; Diastolic*

Introduction

The results of many studies have shown that metabolic syndrome (MS) is one of the main causes of the development of ischemic heart disease (IHD) and a cluster of risk factors complicating its course. In Uzbekistan, as in all countries of the world, there is a growth of cardiovascular diseases (CVDs), which take the first place in the structure of mortality and disability of the population. Global Research on the Prevalence of the Most Socially Significant and Widely Prevalent Diseases – "Global Burden of Disease Study" – held from 1990 to 2017 in cooperation with researchers from the University of Washington with specialists from 195 different countries. The objectives of the project were to track trends in morbidity and mortality from IHD by region and to identify the association of specific factors with the development of the disease. According to the results for 2015, the average mortality rate per 100,000 of the male population in Central Asia (425.2) was twice as high as that in Central Europe (234.0). A similar trend was observed among women: 271.1 in Central Asia and almost twice as little – 141.3 – in Central Europe. Over the 25-year period, the most pronounced reductions in IHD mortality were among males (average – 43.5%) and females (–42.9%) in the Central European population. Less significant success in preventing the disease was seen in Central Asia (–11.9% and –16.5% for men and women, respectively). Among the leading risk factors, arterial hypertension (AH) and dyslipidemia (DLP) were mentioned; smoking and high body mass index (BMI) ranked third in importance in the development of CHD (Global Study 2017). In 2018, CVDs in the total structure of the causes of death in Uzbekistan amounted to 59.7%, the main of which are CHD, AH and their complications (myocardial infarction, cerebral stroke, etc.) [2]. Practical aspects of early diagnostics and prevention of CVD in MS are of great interest also in our country and are one of the priority directions of today's health care in Uzbekistan. Wide use and correct choice of diagnostic methods in clinical practice for detection of early cardiac abnormalities, which is one of clinical manifestations of MS and the most widespread and actual in terms of high disability of population, will allow to identify both MS patients and persons with increased coronary risk, subjected to MS as much as possible.

The nature of cardiac remodeling in MS is determined not only by the BP level, but also by the state of multiple neurogenic, humoral–metabolic and cellular mechanisms of cardiovascular regulation, all of which exhibit synergistic effects on accelerating myocardial remodeling. When assessing diastolic function (DF) in patients with MS, it should be taken into account that obesity is accompanied by an increase in circulating blood volume, which increases preload on the left ventricle (LV) and can mask its relaxation disorders, that is, cause "pseudonormalization" of LV filling character. In this connection traditional methods of LV DF assessment (relaxation time, transmittral flow, etc.) do not always reflect the objective picture, which depends on peculiarities of intracardiac hemodynamics, pre– and postload, changes in the valve apparatus. According to the literature, tissue myocardial Doppler echocardiography (TMDE) is acceptable for the most accurate diagnostics of LV DF changes. To date, LV DF in CHD patients with the presence of MS has been poorly studied. Despite the fact that association of MS with structural –functional cardiac changes is well established, the role of metabolic disorders, the main of which is insulin resistance (IR) in the development and progression of these changes is not fully defined. The problem of what role of IR, metabolic and early functional heart disorders play in the development of CHD against the background of MS requires further study.

Aim to study the effect of IR and metabolic disorders on early structural and functional changes of the heart in patients with MS and to assess the course of CHD against the background of MS. The study was conducted as a one–stage case–control study; it included patients matched by age, sex and body mass index (BMI), with clinically and laboratory–confirmed diagnoses of SAP and MS, who were under investigation at the Department of Cardiology 1 of the Tashkent Medical Academy clinic. Overall 63 patients were studied including 25 patients with MS, 38 patients with SAP and MS. Lipid spectrum parameters, fasting glucose and after 75 g glucose load, blood insulin were determined in all patients, echocardiography using traditional and tissue myocardial Doppler, exercise test with ECG on cycle ergometer were carried out.

63 patients, 47 men and 16 women at the age of 39–53 years old were included in the study.

The main group (n=38) consisted of patients with stable angina pectoris (SAP) of fibrous ring I, fibrous ring II (the fibrous ring of SAP was defined according to the Canadian classification, 1978) and MS, with the duration of the disease not more than 5 years. The comparison group (n=25) was represented by patients with MS without CHD. The diagnosis of metabolic syndrome was made according to the International Diabetes Federation (IDF, 2005) recommendations: the main indication was abdominal obesity (AO) + 2 additional criteria.

Exclusion criteria for the study were heart failure with reduced ejection fraction, type 2 diabetes mellitus, persistent rhythm disturbances, and chronic obstructive pulmonary disease.

All clinical, laboratory and instrumental studies performed in the present study were carried out on the basis of two institutions: 1 clinic of Tashkent Medical Academy, 1 Republican Clinical Hospital, Tashkent city, Uzbekistan. The study participants were recruited among the patients attached to the outpatient and polyclinic network of the institution and the departments of cardiology No.1 and No.2. No specific factors, which could affect the external generalizability of the study findings, were identified.

Material was collected from September 2019 to October 2021. Blood tests and instrumental studies were performed as the study progressed.

All patients underwent general clinical and instrumental examination, which included echocardiographic (EchoCG) examination with TMDE. Averaged indices of three cardiac cycles were calculated. All data measured and calculated by formulas were divided into groups characterizing the structure, systolic and diastolic function of the left ventricle. EchoCG study was performed according to the recommendations of American Society of Echocardiography. To study LV structural and systolic function, we determined LV end–systolic and diastolic volumes (ESV and DV); LV end–systolic and diastolic volumes (ESR, DEV); stroke and minute volumes (SM and MV); LV ejection fraction (EF) according to Simpson, thickness of interventricular septum and posterior wall of LV (TIS and PW) in systole and diastole, LV myocardial mass (MM), LV myocardial mass index (LVMMI), volume and volume index of left atrium (LV). To study diastolic function of LV in apical 4–chamber position in pulse–wave mode we studied diastolic flow through mitral valve (MV), flow acceleration time (FAT). Maximum velocities of early diastolic filling (E, cm/s) and atrial systole (A, cm/s), their ratio, tricuspid regurgitation rate (TRR) were calculated. In pulse–wave TMD mode at the level of lateral and septal portions of the mitral valve fibrous ring (MVFR), the maximum early diastolic EF velocities (E′, cm/s) were calculated and the ratio of early diastolic filling rate to mean mitral ring velocity E/e´ mean was determined. Verification of LV diastolic dysfunction (LVDD) was performed on the basis of the supplemented guidelines published in 2016 “Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography” on the use of echocardiographic techniques for this purpose.

ECG with stress testing was performed on a bicycle ergometer (Kettler, Germany), with computer ECG and VEM software by Neurosoft Poli–SPECTr, Russia.

At the beginning of the test the initial ECG examination and BP measurement were performed. During the period of unloaded pedaling (the "Warm–up" phase lasting 1 minute) the subject pedaled with an initial load step of 25 W. The goal of the no–load pedaling was to maximize the patient's adaptation to the ergometer, as well as to teach him to maintain an optimal pedaling speed (60 rpm) at all times. The main "Load" period, with stepping–up load, lasted until the submaximal heart rate was reached or other test termination criteria were met. The duration of each load step was 2 min. The load was recorded by the researcher through a computer program.

Exercise tolerance was determined by the maximum power of the load performed by the patient in Watts.

The type of cardiovascular system reaction was defined as hypertensive if systolic blood pressure (SBP) increased by more than 70 mmHg, diastolic blood pressure (DBP) - by more than 10–20 mmHg (or in absolute numbers – more than 220/95 mmHg) with normal heart rate increase, if the patient performed low or medium power load.

The recovery period (recovery phase) lasted for 10 minutes: 5 minutes of pedaling at 50–60 rpm with 25 W of power, and 5 minutes of resting state. During the recovery period, the patient was closely monitored, ECG monitoring was continued, BP was measured every minute, and the rate of HR recovery was taken into account.

Main Outcome of the Study

Structural and functional parameters of LV were studied; tolerance to physical load and type of CSS response to load were determined. Additional outcomes of the study.

Correlation relations between BP indices (TG/HDL> 1.32, HOMA IR) and cardiac structural and functional parameters were determined.

All examined patients were divided into two groups. The main group (n=38) consisted of patients with stable angina pectoris (SAP) FR I, FR II (fibrous ring SAP was determined according to the Canadian classification, 1978) and MS, with disease duration not more than 5 years. The comparison group (n=25) was represented by patients with MS without CHD.

The sample size was not pre–calculated. Statistical processing of the obtained clinical research results was carried out by the method of variation statistics using the Microsoft Excel 2007 for Windows application package. The study defined the main statistical characteristics: mean (M), average error (m) and the quantitative values were represented as M. The qualitative variables were described by absolute and relative values (%). The validity of the mean value differences was estimated using parametric and non–parametric criteria. The validity of the differences was assumed at $p<0.05$.

Correlation, one–factor and multi–factor variance and regression analyses were used to determine the coupling strength between indicators. The Spearman rank correlation coefficient was also used. The validity of the differences between the groups was estimated using the Mann–Whitney criterion.

Results and discussion

The study included 63 patients, of whom 47 were men and 16 were women aged 39–53.

The main group (n=38) was made up of patients with SAP FR I, FR II and MS, with a duration of the disease no more than 5 years. The comparison group (n=25) was represented by patients with MS

without CHD. All subjects studied had AG, DLP: total cholesterol 4.2–4.97 mmol/l, triglycerides (TG) – from 1.47 mmol/l to 2.58 mmol/l, HDL (high–density lipoprotein) – from 0.81 mmol/l to 1.27 mmol, LDL (low–density lipoprotein) – from 2.58 mmol/l to 65/ol. The presence of AGs was observed in 33 patients, 9 patients suffered from indigestion and 7 from a glucose tolerance disorder.

The analysis of structurally functional parameters of the heart in SAV patients by FR did not reveal reliable differences and for comparison the main group is presented without division into FR. The study of the systolic function showed in all the surveyed preserved EF and RF LWH, in FDS and CEB LW reliable differences were not identified (Table. 1). In the group of SAV and MS patients, the thickness of PWLW, VCS and higher LVMMI were determined.

Table 1. Structural and Functional Parameters of the Heart in the Subjects

Parameters	Basic Group (SAV+MS) N=38	Group of comparison (MC) N=25
FE, %	58,7±0,43	59,6±1,2
SF, %	35,7±0,9	39,4±1,03
CDR LV	5,61±0,52	5,32±0,9
CSS LV	3,84±0,37	3,87±0,21
BWLV, cm	1,11±0,016*	1,01±0,06
VS, cm	1,1±0,01*	1,0±0,12
LVMMI, g/m^2	138,2±1,9*	132,4±4,7

MS – metabolic syndrome, SAB – stable angina tension, EF – ejection fraction, SF – shortening fraction, CDR LV – of course–diastolic size of left ventricle, CSS – of course–systolic size of left ventricle, BWLV – back wall of left ventricle, VS – ventricular septum, LVMMI – left ventricular myocardial mass index

The data are presented as average values (M) and standard error average (±m)

*–validity of differences between groups ($p<0,1$).

A high frequency of concentric remodeling of PLH (COL) was observed in 9 (36%) cases. In 12 (31%) patients of the core group (SAP FR II+MS), concentric hypertrophy LV (CHT) was noted, in the group with MS CHT was detected only in 2 patients. It should be noted that in all cases, the patients were IR ID according to HOMA IR (r=0.29) and the ratio of TG/HS HDL>1.32 (r=0.32).

A study of DHFLV in patients with MS (comparison group) based on the algorithm of diagnosis of DHF with a normal fraction of LW ejection showed the presence of DHFLV in 14 patients (56%). The most sensitive were: mean ratio E/e´ mean>14, speed of diastolic movement of the mitral valve fibrosis ring during tissue dopplerography.

The main indicators that were used to estimate LF in the group of patients SAP+MS: ratio of transmitral flow velocities (E/A), ratio E/E mean, peak velocity of TP and index of LP volume, according to algorithm of estimation of LF in patients with preserved fraction of ejection. The first and second degrees of DHFLV were determined for all of the study groups. Ten patients had the first degree of DHFLV, with E/A ratios of 0.8 and E 50 cm/s, indicating normal pressure in LA (left atrium). In 1 patient, DHFLV of the first degree was noted with E/A≤0.8 and E>50 cm/s, but with an insufficient number of positive criteria (TR>2.8 m/s). The ratio of 0.8<E/A<2 was noted in the remaining 27 subjects, of which 15 had first–degree DHFLV due to insufficient positive criteria for DHF (only one criterion – E/e´>14), 12 patients with DHFLV of the second degree, which was characterized by FR>2.8 m/s, E/e´>14 and volume index LA>34 ml/m^2.

The correlation analysis performed to assess the effect of MS on the development of DHFLV confirmed a direct correlation between IR and indicators of LV diastolic function (Table 2).

Table 2. Indicators of LV Diastolic Function and Correlation Between IR (HOMA IR>2.77) in Subjects

Index	IR (HOMA IR>2,77)		IR (HOMA IR>2,77)	
	SAP+MS N=38	r	MS N=25	r
E/e´ avarage	9,04±0,46	0,632**	8,3±0,26	0,531**
DT ms	213±0,89	0,243*	213±0,72	0,164*
Volume index LA, ml/m2	34,08±1,03	0,576**	32,05±1,2	0,492**
TR	2,7±0,67	0,613**	2,21±0,32	0,544**
E cm/s	63,9±3,06	0,217*	54,6±6,06	0,261*

DT – flow deceleration time, LA – left atrium, TR – tricuspid regurgitation

Data are presented as means (M) and standard error of the mean (± m)

*–reliability of results between indicators ($p<0.001$)

**–reliability of results between indicators ($p<0.0001$).

Statistically significant correlation dependences between the Homa IR> 2.77 index and the main indicators of echocardiography and TMDs in the main group and in the comparison group are identified: E/E´ average (R = 0.632; P = 0.0001) and (R = 0.531; p = 0.0001); LP volume index, ml/m2 (r = 0.576; p = 0.0001) and (r = 0.492; p = 0.0001); TR (R = 0.613; P = 0.0001) and (R = 0.544; P = 0.0001).

When assessing exercise tolerance in patients, the threshold load power was taken into account, at which patients reached submaximal heart rate (80% of the maximum age – related heart rate) or the test was terminated due to other criteria for stopping the test: AH> 220/120 mmHg.st., rhythm disturbances, ischemic depression of the ST segment and clinical signs: dizziness, headache, severe shortness of breath. Initially, the mean systolic blood pressure in the comparison group (MS) and in the main group (CHF+MS) did not differ significantly. DBP exceeded 90 mm Hg in both groups in more than half of the patients. There was no significant difference between SBP versus DBP ($p < 0.05$) in FC I and FC II CHF patients. Patients of the groups with MS and SSN+MS did not differ in the mean baseline heart rate (Table 3).

Table 3. Hemodynamic Parameters in the Initial Period in the Examined Groups

Index	MS N=25	SAP+MS	
		FR I (N=17)	FR II (N=21)
SBP, mm Hg.	135,9±5,5	139,2±6,8	134,6±7,4
DBP, mm Hg.	87,2±4,9	89,1±2,1	96,6±3,75*‡
HR per minute	84,7±1,4	82,5±1,9	89,7±3,8*‡

SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate;

Data are presented as means (M) and standard error of the mean (± m);

*–significance of differences between groups ($p<0.05$);

‡– significance of differences between FC ($p<0.05$).

In the comparison group, the average power of the performed load was 85 W. At the height of the load, most patients complained of severe shortness of breath, dizziness, severe weakness. The type of CVS response to exercise in 11 (44%) patients was defined as hypertensive; given the start of the test with high SBP and in 6 (24%) patients a rapid increase in SBP in the initial stages and middle stages of exercise.

In 4 patients during the recovery period, a single ventricular extrasystole was observed, in the 1st sinoauricular blockade of the 2nd degree. It should be noted that in these 5 patients with MS during ECHO CG with TDH, DHFLV, changes in echo geometry in the form of CRLV (n=2) and CRLV (n=2) were detected. In the recovery period, 8 patients (32%) showed a slowdown in the decrease in heart rate and blood pressure.

In the main group, in 12 (32%) patients, according to the results of the BE test at a load of more than 100 W, oblique ascending ST segment depression by 1.5 mm (n=7), horizontal ST depression by 1.0 mm (n=5) was registered. In 13 (37%) patients, ischemic changes were observed at a load height of 75-100 W, in the form of a horizontal depression of the ST segment by 1.5 mm (n=6) in the lateral ECG leads.

Conclusions

More pronounced signs of LV remodeling of concentric hypertrophy type were detected in CHD patients against MS background, concentric remodeling was more frequent in MS patients. The use of Tissue myocardial Doppler echocardiography allowed to detect DHFLV in a greater number of patients compared to traditional Doppler echocardiography. The most sensitive index was E/e´ averaged ratio, which had a pronounced correlation with HOMA index IR>2.77 in CHD and MS patients. Reduced exercise tolerance in patients with metabolic syndrome is closely related to insulin resistance index, HDL TG/CHL ratio> 1.32. When performing stress ECG tests it is necessary to pay attention to the recovery period of the study. In patients with CHD against the background of MS there is a delayed recovery of BP and HR, due to the low level of adaptive reactions of the cardiovascular system, which allows the attending physician to consider the choice of drug therapy.

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