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Abstract **УДК 616.12-008.311.1+613.25+616.379-008.64]-071-055.2**

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EFFECTS OF TYPE 2 DIABETES MELLITUS ON CLINICAL AND LABORATORY STATUS OF WOMEN WITH ARTERIAL HYPERTENSION, OBESITY, AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Patients with type 2 diabetes mellitus (DM) may develop cardiomyopathy independently of such risk factors as arterial hypertension and coronary heart disease. Myocardial dysfunction in diabetes mellitus may vary from subclinical forms of left ventricular dysfunction to heart failure. It was suggested that diastolic left ventricular dysfunction is one of the earliest signs of myocardial injury in diabetes mellitus and plays a key role in the formation of diabetic cardiomyopathy.

The **aim** of our study was to evaluate the effect of diabetes on the clinical and laboratory status of women with hypertension, obesity, and left ventricular diastolic dysfunction (LVDD).

Materials and methods. We examined 80 patients aged 40 to 60 years with stage 2, grade II and grade III hypertension, class I–III obesity, grade 1 LVDD and preserved ejection fraction. Depending on the presence or absence of diabetes, the cohort of patients was divided into two groups: patients with diabetes were assigned to group 1 and non-diabetes patients – to group 2. Statistical processing was performed using Statistica for Windows version 6.0.

Results. Patients had tendency to increased body mass index (BMI) in the DM group, but without significant differences. The results of the 6-minute walk test showed a tendency to decreased distance in the group of patients with diabetes. There was an increase in leptin levels and a decrease in adiponectin in patients with diabetes without significant differences. Levels of IL-6, glycosylated hemoglobin, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index were significantly higher in the cohort of patients with diabetes ($p < 0.05$).

Conclusions. Women aged 40–60 years with LVDD with hypertension, class I–III obesity and type 2 diabetes mellitus differ from similar cohorts of patients without diabetes with a tendency to increased BMI levels, leptinemia, and decrease in distance of 6-minute walk test, LV ejection fraction and blood adiponectin level; they have significantly higher blood levels of interleukin-6, glycosylated hemoglobin (HbA1c) and HOMA-IR; indicators of diastolic function in the group of patients with diabetes tend to worsen the parameters of diastolic filling of the LV even in grade 1 DD.

Key words: diabetes mellitus, arterial hypertension, obesity, left ventricular diastolic dysfunction.

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Резюме

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ВПЛИВ СУПУТНЬОГО ЦУКРОВОГО ДІАБЕТУ НА КЛІНІКО-ЛАБОРАТОРНИЙ СТАТУС ЖІНОК З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ, ОЖИРІННЯМ ТА ДІАСТОЛІЧНОЮ ДИСФУНКЦІЄЮ ЛІВОГО ШЛУНОЧКА

Дисфункція міокарда при цукровому діабеті (ЦД) може варіювати від субклінічних форм дисфункції лівого шлуночка до явної серцевої недостатності. Діастолічна дисфункція лівого шлуночка (ДДЛШ) є однією з найбільш ранніх ознак ураження міокарда при ЦД та відіграє ключову роль у формуванні діабетичної кардіоміопатії.

Метою нашого дослідження було оцінити вплив супутнього цукрового діабету на клініко-лабораторний статус жінок з артеріальною гіпертензією (АГ), ожирінням і ДДЛШ.

Матеріали та методи. Обстежено 80 пацієнток у віці від 40 до 60 років з АГ 2 стадії, II і III ступеня, ожирінням I–III ступенів, ДДЛШ 1 ступеня і збереженою фракцією викиду лівого шлуночка (ФВЛШ). Залежно від наявності або відсутності ЦД когорта пацієнтів була розділена на дві групи: до групи 1 були віднесені пацієнти з наявністю ЦД, а до групи 2 – без ЦД. Статистична обробка даних проводилася з використанням Statistica for Windows версії 6.0.

Результати. Пацієнти мали тенденцією до збільшення індексу маси тіла (ІМТ) в групі з ЦД, але без достовірних відмінностей. Результати тесту з 6-хвилинною ходьбою виявили тенденцію до зниження пройденої дистанції в групі пацієнтів з ЦД. Спостерігалося збільшення показників рівня лептину та зниження адипонектину у пацієнтів з ЦД без достовірних відмінностей. Рівні інтерлейкіну-6 (ІЛ-6), глікозильованого гемоглобіну та індексу Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) були достовірно вище в групі пацієнтів із супутнім ЦД ($p < 0,05$). Спостерігалася тенденція до погіршення параметрів діастолічного наповнення ЛШ у хворих з ЦД.

Висновки. Жінки у віці 40–60 років з ДДЛШ, які страждають на АГ з ожирінням I–III ступенів і супутнім ЦД 2 типу відрізняються від аналогічної когорти пацієнток без ЦД тенденціями до збільшення рівнів ІМТ, лептинемії і зниженням величин дистанції тесту з 6-хвилинною ходьбою, ФВЛШ і вмісту в крові адипонектину; мають достовірно більш високі рівні в крові ІЛ-6, глікозильованого гемоглобіну (HbA1c) та індексу HOMA-IR; показники діастолічної функції у групі пацієнтів з ЦД мають тенденцію до погіршення параметрів діастолічного наповнення ЛШ навіть в умовах 1 ступеня ДД.

Ключові слова: цукровий діабет, артеріальна гіпертензія, ожиріння, діастолічна дисфункція лівого шлуночка.

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Introduction

In patients with type II diabetes mellitus (DM), cardiomyopathy may develop independently of risk factors, such as arterial hypertension (AH) and coronary heart disease (CHD). There is an undeniable link between DM and cardiovascular diseases, which acts as a vicious circle, whereby the former increases the risk of the latter, and the latter are an important complication, comorbidity and mortality factor for the former [1]. Myocardial dysfunction in DM can range from subclinical forms of the dysfunction of left ventricle (LV) to

apparent heart failure (HF). At the initial stage, myocardial disorders may have an asymptomatic course, progressing initially to shortness of breath during exercise, followed by severe symptomatic HF in the later stages of the disease. Increased LV filling pressure is the main pathophysiological component, which leads to shortness of breath during exercise in patients with systolic or diastolic LV dysfunction (DLVD).

DLVD is an important predictor of HF [2]. In the current guidelines on HF, special attention is paid to the early detection of asymptomatic changes in LV function. Epidemiological studies show relationship of diastolic dysfunction with age, sex, AH and myocardial ischemia. In addition, there is data that demonstrates a strong relationship between diastolic function and obesity, especially abdominal, and visceral fat mass [3]. Insulin resistance may be one of the important pathophysiological links involved in these associations. Metabolic syndrome, or insulin resistance syndrome, is a group of cardiovascular risk factors that act synergistically to increase the risk of adverse cardiovascular events [4] and induce subclinical changes in heart structure and function. Indeed, patients with metabolic syndrome also have an increased prevalence of DLVD, often with a subclinical course [5]. There is an assumption that DLVD is one of the earliest signs of myocardial damage in DM and plays a key role in the formation of diabetic cardiomyopathy [3].

Considering the fact that DLVD is an important predictor of HF and predominates in the female population, and the associations between DM and the development of preclinical DLVD are not fully understood, we attempted to assess the impact of concomitant DM on the clinical and laboratory status of women with hypertension, obesity and DLVD.

Materials and methods. We examined 80 patients aged 40 to 60 years with stage 2, degree II and III hypertension, class I–III obesity, degree I DLVD (relaxation disorder) and preserved left ventricular ejection fraction (LVEF >50%). Depending on the presence or absence of DM the cohort of patients was divided into two groups: group 1 included patients with DM (n=40), and group – 2 without DM (n = 40). The study was carried out in accordance with the principles of the Helsinki Declaration. The study Protocol was approved by the local Ethics Committee for all participants. Informed consent was obtained from all patients included in the study.

Patients with LVEF <50%, symptomatic forms of hypertension, congenital and acquired heart disease, chronic HF, heart and vascular surgery in history, systemic connective tissue diseases, acute or exacerbations of chronic kidney disease, autoimmune diseases, cancer, mental illness, alcohol abuse were excluded from the study.

All groups of patients underwent a comprehensive clinical examination. The diagnosis was established based on complaints, anamnesis, objective examination data, results of laboratory and instrumental examination methods. The diagnosis AH was established according to the recommendations of the European Society of Cardiology and the European Society of Hypertension for the diagnosis and treatment of hypertension [6]. The diagnosis and degree of obesity were established in accordance with WHO recommendations (1997). Serum levels of adipokines (leptin and adiponectin) were determined by enzyme immunoassay. Glycosylated haemoglobin (HbA1c) was determined in serum by turbidimetric method. Interleukin-6 (IL-6) levels were determined by immunochemical method with electrochemiluminescent detection. Heart ultrasound studies were carried out in one-, two-dimensional and Doppler modes with color mapping on an ultrasound scanner Siemens USA Acuson X300 Premium Edition according to generally accepted methods. Diastolic function was evaluated according to the recommendations of the Working group on functional diagnostics of the Association of Cardiologists of Ukraine and the all-Ukrainian Association of Echocardiography Specialists [7, 8]. Diastolic function of the left ventricle was assessed by the results of determining the following parameters: the maximum rate of early LV filling in the spectral mode (E), maximum rate of late (atrial) LV filling in the spectral mode (A), ratio of maximum rates of early and late LV filling in the spectral mode (E/A), maximum rate of early LV filling in tissue mode (e'), the average pressure in the pulmonary artery according to Kitabatake, the ratio of E and E' peaks on the mitral valve in the spectral and tissue Doppler modes (E/e'). Statistical processing of the obtained digital data was carried out using the software package Statistica for Windows version 6.0. Continuous data are provided as mean ± standard deviation.

Results. The average age of the cohort was 51.2±4.4 years. Patients in the groups were comparable by age, body mass index (BMI) as well as systolic (SBP) and diastolic blood pressure

(DBP) with a tendency to BMI increase in the group with DM, but without significant differences. Table 1 shows the data of clinical and laboratory parameters of comparison groups (n=80). Prior to conducting laboratory tests in order to determine exercise tolerance, all patients were tested with a 6-minute walk. The results of the test revealed a tendency distance decrease in the group of patients with DM compared to the group without DM, but there was no significant difference in the indicators.

Table 1 – Characteristics of study population values in comparison groups

	Group 1 (n=40, without DM)	**Group 2 (n=40, with DM)**
Age, years	53.5±3.2	52.8±3.6
BMI, kg/m^2	37.8±3.6	38.6±4.2
T6min, m	610.5±27.5	589.2±16.8
SBP, mm Hg	151.8±9.1	157.6±7.3
DBP, mm Hg	100.5±6.2	101.9±
HOMA-IR*	4.24±1.32	7.89±1.69
HbA_1C, %*	5.42±0.49	7.72±0.24
IL-6, pg/ml*	136.48±8.23	152.94±11.12
Adiponectin, µg/ml	6.22±0.62	5.04±0.83
Leptin, ng/ml	17.83±2.53	19.22±1.68
EF, %	63.8±6.1	60.1±4.3
E/A, RU	0.61±0.08	0.67±0.06
DT, ms	249.1±21.2	243.1±20.6
IVRT, ms	107.2±8.3	102.5±6.8
E/e', RU	7.27±0.36	7.12±0.41
LAP, mm Hg	18.1±1.8	16.3±2.2

T6min – 6-minute walking test; E/A – the ratio of rates in the phase of early diastolic and late diastolic LV filling; DT – time of decrease of the flow rate in the phase of early diastolic filling; IVRT – time of isovolumetric relaxation of LV; E/e` – ratio of rates of early LV diastolic filling according to spectral and tissue Doppler studies; LAP – lung artery pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; Index* indicates values with statistically significant differences ($p < 0.05$)

When comparing the blood levels of adipokines in patients with concomitant DM, an increase of leptin and decrease of adiponectin without any significant differences were observed. IL-6 content was significantly higher in the group of patients with concomitant DM ($p < 0.05$). Level of HbA1c and HOMA-IR index were significantly higher in the group of patients with DM ($p < 0.05$).

Even taking into account that only patients with preserved LVEF participated in the study, there was a downward trend in this indicator in the group of women with concomitant DM. A comparative analysis of LV diastolic function revealed a tendency in worsening of the LV diastolic filling parameters even within one stage of DD (relaxation disorder).

Discussion. In this study, we showed progressive deterioration of diastolic function parameters (E/A ratio, IVRT, DT, E/e' ratio, LAP) in individuals with DM compared to patients without DM. Levels of IL-6, HbA1c and HOMA-IR were also shown to be significantly higher in patients with concomitant DM than in those without it.

In most patients, insulin resistance is a key pathophysiological mechanism of impaired glucose metabolism. We have found that people with higher insulin resistance had worse diastolic function parameters. Several studies have analyzed the relationship between insulin resistance and DD. Dinh et al. in the group of patients without diabetes found out that insulin resistance independently associated with DLVD [9], and the same association was observed in the study of patients with aortic valve sclerosis [10]. Another two studies demonstrated changes in diastolic function in both patients with DM and persons with prediabetes [3, 11]. In general, this data suggests that subclinical changes in myocardial diastolic function are already present before the DM onset and are mainly associated with insulin resistance, and not only with persistent hyperglycemia.

Several pathophysiological mechanisms may be involved in the relationship between insulin resistance, diabetes and DLVD [12]. In the heart, insulin stimulates the absorption and oxidation of glucose, which is necessary for energy production, along with the use of fatty acids. Disorders of the use of substrates in energy production can lead to a violation of energy synthesis in the myocardium [13, 14]. Other mechanisms of insulin resistance are expressed in increased interstitial fibrosis of the myocardium, activation of the sympathetic nervous system, increased postload, endothelial dysfunction, increased oxidative stress of the myocardium [3].

It is considered that diabetes can affect the structure and function of the heart in the absence of changes in blood pressure or coronary artery disease. This condition is called diabetic cardiomyopathy [13, 15]. It is assumed that DLVD is the earliest manifestation of diabetic cardiomyopathy, preceding the development of systolic dysfunction [13]. In our study, we observed a difference in diastolic function parameters between individuals without DM and patients with DM even within the same DD stage with a tendency to worsening in the latter group. The pathogenesis of diabetic cardiomyopathy is known to be multifactorial [13] and in addition to changes, associated with insulin resistance, persistent hyperglycemia also increases the glycosylation of interstitial proteins, such as collagen, by depositing the end products of non-enzymatic glycosylation in the extracellular matrix [16], which leads to a further increase in myocardial stiffness.

Subclinical DLVD is recognized as an important HF predictor. Therefore, early detection and correction of major determinants of subclinical DD, such as insulin resistance, is essential morbidity and mortality decrease. This is especially important in preventing the development of HF with preserved FV (also known as diastolic HF). The above data indicates that the decrease of diastolic function is observed already in the early stages of glucose metabolism disorders and in the state of insulin resistance, and not only in stable hyperglycemia. Several studies have shown that insulin resistance with or without DM predetermined the development of HF independently of other risk factors [17, 18]. Insulin resistance as well as metabolic syndrome is closely related to obesity. Recent data have demonstrated a strong relation between DLVD and obesity [19], especially with abdominal [19] and visceral fat mass [21]. Therefore, it was suggested that insulin resistance was one of the important pathophysiological components, implicated in the relation between obesity and DLVD [22, 23].

DM is a comprehensive disorder that can develop due to acquired and genetic factors. Inflammation plays an important role in DM progression. High levels of proinflammatory IL-6 were observed in persons with prediabetes and patients, diagnosed with DM [24–27]. In our study we obtained similar results: in patients with DM significantly higher levels of IL-6 were observed compared to those without DM.

Chronic delayed inflammation in obesity, which is reflected in an increase in the systemic level of cytokines, including IL-6, apparently precedes and is a risk factor for the subsequent development of insulin resistance and diabetes [28–30]. IL-6 was identified as an independent predictor of DM and related cardiovascular events [28, 30]. Adipocytes and macrophages, located in adipose tissue, are the main sources of increasing IL-6 concentration in plasma in patients with obesity and diabetes [28, 31], however, there are insufficient data for establishing a causal relationship between IL-6 levels and the development of metabolic and cardiovascular disorders. Due to its pleiotropic action in various tissues and organs, the exact role of IL-6 in the pathogenesis of diabetes should be carefully studied, but with the possibility of cross-reactions between affected tissues and organs.

Conclusions

Women aged 40–60 years with DLVD, suffering from hypertension with I–III degree obesity and concomitant type II DM differ from a similar cohort of patients without DM tendencies in increase of the BMI, SBP, DBP, leptinemia levels and a decrease in the distance of the 6-minute walk test, LVEF and blood adiponectin. The presence of concomitant DM in women aged 40–60 years with hypertension and obesity is associated with significantly higher blood levels of IL-6, HbA1c and HOMA-IR index. A comparative analysis of LV diastolic function in women aged 40–60 years, suffering from hypertension and obesity, depending on the presence or absence of DM, revealed a tendency to worsening of LV diastolic filling parameters even in conditions of degree I DD (relaxation disorder).

Prospects for future research

The prospect of further research will be the development of measures to reduce the manifestations of DLVD as a sign of early heart disease in DM in women with hypertension and obesity.

Conflict of interest

The authors declare no conflict of interest.

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