OPTIMIZATION OF COMORBIDE PATHOLOGY DIAGNOSTICS: HYPERTENSION AND DIABETES MELLITUS TYPE 2 BASED ON THE EVALUATION OF CARDIAC HEMODYNAMICS AND METABOLIC DISORDERS

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Abstract. **The aim** is to study morpho-functional state of the heart and vascular wall of the common carotid artery, verify the type of left ventricle remodeling in patients with hypertension (HTN) and type 2 diabetes (DM2T) and without it, to explore transmitral blood flow indices of the left ventricle and to clarify the severity of diastolic dysfunction in patients with combination of HTN and DM2T, to make a comparative evaluation of cardiohemodynamic disorders and disorders of carbohydrate metabolism, to determine the dynamic changes in indices of oxidative stress, antioxidant protection, to assess adipokines levels, proinflammatory cytokines, to identify possible correlations between the balance of hormones of adipose tissue, inflammatory markers and indicators of carbohydrate metabolism, anthropometric data and indicators of intracardiac hemodynamics, markers of endothelial dysfunction.

Material and methods. Depending on the presence of DM2T, patients were divided into three groups. In the first group with HTN 20 patients with DM2T were included. Among them, there were 11 (55 %) women and 9 (45 %) men. The second group consisted of 20 patients with exclusively HTN. Among them, there were 10 (50 %) women and 10 (50 %) males.

The control group included 10 practically healthy people (6 men (60%) and 5 women (40 %) of representative age and sex as the main group. According to the set goal, we analyzed clinical features, metabolic and cardiovascular disorders at different course of HTN and DM2T. For this purpose, all patients were examined by a single program, which included:

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physical (blood pressure (BP), body mass index (BMI), clinical, biochemical (glucose, insulin levels, HOMA-IR, hormonal (leptin, adiponectin), proinflammatory markers (tumor necrosis factor (TNF–alpha), interleukin-6 (IL-6), oxidative stress and antioxidative system parametres, and instrumental methods (ultrasound parameters of the carotid artery and the heart) of research.

Results and Conclusions. Prognostically unfavorable variants of hypertrophic remodeling of left ventrecle are determined in patients with HTN and DM2T – concentric (65,3 %) and eccentric (17,01 %) types of left ventricle hypertrophy, whereas in HTN patients without comorbidities there are no statistically significant differences. The progression of diastolic dysfunction is identified with combination HTN and DM2T, which is confirmed by indicators of blood flow in pseudonormal 14, 5 % of patients, higher values of E/A – integral indicator of diastolic function of the LV, while patients with exclusively HTN diastolic dysfunction is presented only by initial changes in the form of excited relaxation. Specific feature of patients with concomitant HTN and DM2T in comparison with patients of HTN are higher values intema-media thickness (TIM), with increased carbohydrate metabolism (blood glucose index and HOMA-IR), confirming the aggressive vascular remodeling in this disease. Pronounced activation of prooxidant system simultaneously with a depressed antioxidant defense system can be observed in patients with the combination of HTN and DM2T, as evidenced by significantly higher malonedialdehyd (MDA) and diene conjugates (DC) (38,7 ± 0,08 nmol/ml and 40.0 ± 0,050 nmol/ml, respectively) while decreases of superoxide dismutase (SOD) and catalase (Cat) (41,9 ± 0,061 u/mg Hb min 0,162 ± 0,018 u/mg Hb min, respectively) compared with exclusively HTN ($p<0.001$). In patients with HTN and DM2T, hyperleptinemia and hypoadiponectinemia were identified, the severity of which depends on the anthropometric indices (BMI). The effect of hyperleptinemia on the severity of IR with the growth of BMI is confirmed by the correlations between the increasing levels of leptin, insulin and increased HOMA-IR. The role of proinflammatory cytokines TNF-α and IL-6 in the formation of endothelial dysfunction (ED), and disorders of carbohydrate metabolism in patients with HTN and DM2T was confirmed, increasing levels of which is associated with increases of TIM, index HOMA-IR, fasting glucose and BMI.

This research optimized differentiated approaches to the diagnosis of patients with HTN and DM2T – based on the study of anthropometric, car-

dioghemodynamic, carbohydrate metabolism, proinflammatory markers, adipose tissue hormones and oxidative stress and antioxidant defense in the aspect of the development of comorbidity. It is promising for improving the diagnosis of metabolic disorders and as early as possible preventing cardiovascular complications and reducing mortality in the presence of comorbid pathology.

1. Introduction

At the turn of the century hypertension (HTN) remains one of the most common diseases not only in our country but in the world [1, p. 3-288; 2, p. 975]. HTN is one of the major risk factors of atherosclerosis, of cardiovascular, cerebral and renal complications, and mortality [2, p. 1-8]. It should be noted that atherogenic classes of lipoproteins are potentially proinflammatory factors, and thus increase the likelihood of developing HTN and the occurrence of cardiovascular accidents[3, P.40]. Modern strategy for modification of cardiovascular risk pays great attention to the condition of lipid metabolism, the cause of dyslipidemia [4, p. 1-87]. In addition, it should be noted that the metabolism of carbohydrates and its relationship with immunoinflammatory markers, endothelial function, are no less important than the increase in blood pressure (BP) [5, p. 54-59]. HTN is detected in almost 80% of patients with diabetes mellitus type 2 (DM2T). In the long HTN due to chronic reduction in peripheral blood flow, tissue sensitivity to insulin is decreased with subsequent development of DM2T. Diabetes and HTN, regardless of what comes first, mutually aggravate the severity of the disease. Patients with disorders of carbohydrate metabolism and HTN very often suffer from excess weight and obesity. In turn, the obesity as a distinct disease of metabolism, is associated with hyperinsulinemia and IR [6, p. 1-416]. The pathogenesis of insulin resistsnce (IR) is heterogeneous in nature and due to the presence of a number of factors: genetic, sex, age, hormonal influences, and so on [7, p. 35-40]. Over the past few years an idea emerged that, adipose tissue is not only a passive form for the accumulation of excess energy, but also is actively involved in the life of the body. The discovery that adipocytes express and enhance the secretion of a large number of proteins and other molecules, including a number of hormones adipokines with various local, peripheral and central effects allowed to consider adipose tissue from a different angle [8, p. 432; 9, p. 122-164]. These effects affect the metabolic processes, the formation of oxidative stress, disorders of the cardiovascular system, etc.

There is evidence that one of the leading mechanisms in the progression of HTN in patients with DM2T is that the hypertrophy of adipocytes leads to overproduction of angiotensinogen and angiotensin-II, which induce systemic vasoconstriction, and direct retention of sodium and water, leading to increased BP [9, p. 67-71; 10, p. 136-149].

Therefore, success in controlling HTN combined with DM2T depends on the clarification of the key pathogenetic mechanisms of development of both diseases and their complications.

2. The purpose of the study

1. To study morpho-functional state of the heart and vascular wall of the common carotid artery,the type of left ventricle remodeling in patients with HTN and DM2T and without it.

2. To explore transmitral blood flow indices of the left ventricle and to clarify the severity of diastolic dysfunction in patients with combination of HTN and DM2T.

3. To make a comparative evaluation of cardiohemodynamic disorders and disorders of carbohydrate metabolism in patients with HTN in the presence and absence of DM2T.

4. To determine the dynamic changes in indices of oxidative stress, antioxidant protection with combination HTN and DM2T, and exclusively in patients with HTN.

5. To assess the levels of adipokines, proinflammatory cytokines in the studied groups and find out their influence on the progression of insulin resistance in HTN patients and in combination with DM2T.

6. To identify possible correlations between the balance of hormones of adipose tissue inflammatory markers and indicators of carbohydrate metabolism, anthropometric data and indicators of intracardiac hemodynamics, markers of endothelial dysfunction.

3. Material and methods

According to the goal in the process of study, 40 patients with stage II hypertension I-II degrees were selected and examined.

Depending on the presence of DM2T, patients were divided into three groups. In the first group with HTN 20 patients with type 2 diabetes were included. The mean age was (56,0 ± 5,5) years. Among them, there were 11 (55 %) women and 9 (45 %) men.

The second group consisted of 20 patients with exclusively HTN. The mean age was (57,2 ± 5,2 years). Among them, there were 10 (50 %) women and 10 (50 %) males.

The control group included 10 practically healthy people (6 men (60%) and 5 women (40 %) of representative age (average age in men and women respectively: 55,2±3,5 and 54.8±4.2 years) and sex as the main group.

According to the set goal, we analyzed clinical features, metabolic and cardiovascular disorders at different course of HTN and DM2T. For this purpose, all patients were examined by a single program, which included: physical, clinical, biochemical, hormonal and instrumental methods of research.

The study excluded patients with refractory and symptomatic hypertension; high functional class of chronic heart failure (CHF) (3-4 functional class according to NYHA); DM1T, acute or chronic inflammatory diseases; patients who have suffered acute myocardial infarction or acute ischemic stroke less than 6 months prior to screening; patients who have a history of having abused alcohol, mental illness; people who did not wish to give voluntary informed consent for participation in the study; as well as patients who anticipated high probability of violations of the study Protocol, people who are not citizens of Ukraine.

Anamnestic survey established the existence of any allergic reactions to antihypertensive, hypolipidemic and hypoglycemic drugs.

All patients with HTN who were selected for the study received basic therapy according to the latest recommendations for treatment of HTN. Diagnosis and treatment of diabetes mellitus was carried out on the basis of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (2015). Abdominal obesity (AO) was diagnosed when the waist circumference/ in men 102 cm, women 88 cm or more, and when waist circumference/ thighs circumference was > 0,85 in women and > 0,93 men. Based on anthropometric measurements, we calculated the body mass index (BMI) and the degree of obesity according to the criteria of International Diabetes Federation (IDF, 2005 p.) based on the calculated BMI by the formula Quetelet:

BMI = body weight (kg) / height² (m²)

BMI within 18,5 – 24,9 kg/m² were assessed as normal, 25 and 29.9 kg/m² as overweight, 30,0 – 34,9 kg/m² as obesity I degree, 35,0 – 39,9 kg/m²– obesity II degree, over 40,0 kg/m²- obesity III degree.

Measurements of systolic (SBP) and diastolic (DBP) pressure were determined as the arithmetic mean value after BP measurements, carried out three times at the intervals of 2 minutes at rest in the sitting position of the patient standard sphygmomanometer. Heart rate (HR) was determined directly after the second measurement of BP.

At the stage of screening the assessment of the morpho-functional state of the myocardium was conducted on the unit Toshiba – SSH – 60 A (Japan) according to standard methods in M and B modes with the recommendations of the American Society of Echocardiography.

Biochemical studies were performed on the analyzer "Humalyser 2000" ("Human", Germany). The concentration of serum glucose fasting blood was determined by glucoseoxidase method using a standard set of reagents "Kit for determination of glucose in biological fluids, the glucose oxidase test" ("FST Diagnostics", Ukraine) on the spectral colorimeter "Spekol-P" (Germany) at a wavelength of (500 – 550) nm. To determine the content of immunoreactive insulin fasting (basal value) used monofermentation method was used with a set of reagents "InsulinELISA" ("DRG-Diagnostics", Germany) on a multi-channel Scrophulariaceae ("Humareader", Germany).

The assessment of insulin resistance (IR) was carried out using the HOMA index (Homeostatic Model Assessment) calculated according to the formula:

HOMA = insulin (mUn/ml) x fasting glucose (mmol/l) / 22,5

At the level of HOMA – IR more than 2.77, IR was diagnosed.

The functional state of the adipose tissue was evaluated on the content of leptin and adiponectin in the serum. Leptin and adiponectin levels were determined by enzyme immunoassay with sets of reagents Leptin (Leptin ELISA" ("DRG Diagnostics", Німеччина), Human Adiponectin ELISA BioVendor (Czech Republic). Optical density measurement was carried out at the photometer-analyzer Humareader (Germany). Measurements of the concentration of TNF-α, IL-6 in the serum of patients were performed using a set of reagents for immunoassay determination in the serum ("Vector – best", Russia). The state of the prooxidant system was evaluated according to the levels of the molecular products of the LP – DK and MDA, and the state of the enzymatic system of antioxidant protection – by the activity of SOD and Kat during spectrophotometry on a Hitachi U-1900 spectrophotometer (Japan).

4. Instrumental studies

The condition of intracardiac hemodynamics was evaluated by a conventional method with the calculation of end-diastolic (EDS) and end-systolic (ESS) size and volume (EDV and ESV) of left ventricle (LV). The thickness of the posterior wall of the LV (LVPWT) and interventricular septum (TIVS) in diastole; the mass of the LV myocardium (LVMM) according to the Penn Convention formula. The index of LVMM was calculated as the ratio of left myocardium mass to the body surface area (criteria of LV hypertrophy was considered LVMM > 125 g/m^2 in men and > 110 g/m^2 in women).

Diastolic LV function was assessed according to the nature of transmitral blood flow by doppler Echocardiography from apical approach in 2-and 4-chamber images of the heart. In pulsed mode, we analyzed the ratio of the velocities of early and late diastolic filling (E/A).

Geometric model of the LV was determined with the evaluation of remodeling types. Phase structure of the LV miocardia and determining the speed characteristics of blood flow were assessed in synchronization with the electrocardiogram (ECG): duration of flow (LVDF), acceleration time (ATLV), maximum (Vmax), mean velocity (Vav) flow, electromechanical systole of the left ventricle (LVEMS).

Research of TIM of carotid arteries (CA) was performed using the ultrasound system "Logic-5" (General Electric, USA) with a linear array probe 5-7.5 MHz according to the standard Protocol. In accordance with the recommendations of the ETG, ETK (2007) normal TIM was considered less than 0.9 mm; the presence of atherosclerotic plaque was identified as a local thickening TIM > 1.3-1.5 mm focal thickening TIM >50% of the volume surrounding TIM.

Standard dimension TIM in the common CA (CCA) was performed on 1-1,5 cm proximal to the bifurcation at the rear relative to the radiating surface of the sensor wall of the artery. The conditional standard for the diagnosis of pathological changes in TIM CCA amounted to 1.0 mm. First one measurement of TIM was performed – the average for the right and left CCA, in the case where the value of TIM did not reflect significant pathology (TIM right – 0.5 mm, and TIM left – 1.0 mm, TIM average – 0.75 mm, at a rate of less than 0.9 mm), maximum of the two values were used.

The registration of the electrocardiogram was performed according to standard methods in 12 chest leads. According to the obtained results, the

presence of LVH was determined on the quantitative criterion Sokolow – Lyon according to the recommendations of the ETG, ETK (2007).

The defeat of target organs were determined in accordance with the European recommendations of the ESC, ESH (2007): 1) from the hypertrophy of LV myocardium (ECG, Echo-CG) criterion for LVH was considered to be the index Sokolow – Lyon >38 mm, the mass index of the LV myocardium (LVMI) in men >125 g/m^2 in women >110 g/m^2; 2) atherosclerotic lesions of blood vessels – the carotid arteries TIM >0.9 mm; focal thickening TIM (1.3-1.5 mm, or the appearance of atherosclerotic plaques; 3) kidney damage – the presence of microalbuminuria (MAU) (30-300) mg/24 h or more or proteinuria, increased serum creatinine in men >(115-133) μmol/l, women>(107-124) μmol/l.

The results obtained were processed by methods of variation statistics using the computer program "STATISTICA". Data were presented in the conventional form (M ± m), where M – arithmetic mean, m – error of mean arithmetic. Results were considered statistically significant at a probability of error less than five per cent ($p<0.05$). In the analysis of significance of differences between two groups according to the severity index, measured by the number of used Student's t-test). To assess the degree of connectedness or synchronicity in the changes in indicators, r-coefficient of linear correlation was calculated – the product of the moments of Pearson.

5. Main findings and discussion

When comparing anthropometric indices of the three groups, no significant differences in BMI, SBP and DBP were detected between 3 and 1 group ((24,0 ± 3,2) kg / m^2 and (32,2 ± 2,2) kg / m^2; (121,4 ± 3,2) mm Hg and (171,2 ± 4,0) mm Hg.; (79,9 ± 4,6) mm Hg and (95,6 ± 5,1) mm Hg, respectively; $p <0.05$), at the same time, there were no differences in age, weight and height between the patients of all three groups. Not significant differences were established in BMI between individuals with HTN and patients with concomitant pathology of DM2T (28,6 ± 2,4) kg / m^2 and (32,2 ± 2,2) kg / m^2, respectively; $p>0.05$), at the same time, the SBP values were statistically different ((of 145, 4 ± 8,9) mm Hg and (171,2 ± 4,0) mm Hg; $p<0.05$) between the two groups (table 1).

The study of carbohydrate metabolism showed pronounced differences in the control group ((of 9.77 ± 2,2) mcUn / ml; $p <0.05$). HOMA-IR

Table 1

Anthropometric data and blood pressure parameters were examined patients and the control group (M ± m)

Indicator, units	1 group (DM2T+HTN) (n = 20)	2 group (HTN) (n=20)	control (n=10)	Statistical indicator (P)p
age, y	59,6 ± 7,2	58,8 ± 6,4	57,0 ± 4,3	3-2 P > 0,05 3-2 P > 0,05 2-1 P > 0,05
W, кg	89,2 ± 8,2	81,0 ± 59,3	78,1 ± 4,9	3-2 P > 0,05 3-1 P > 0,05 2-3 P> 0,05
H,sm	1,69 ± 0,05	1,70 ± 0,05	1,71 ± 0,067	3-2 P > 0,05 3-1 P > 0,05 2-1 P > 0,05
BMI, kg/m^2	32,2 ± 2,4	28,6 ± 2,4	24,0 ± 3,2	3-2 P > 0,05 3-1 P < 0,05* 2-1 P > 0,05
SBP, mm Hg	171,2 ± 4,4	145,4 ± 8,9	122,4 ± 2,2	3-2 P < 0,05* 3-1 P < 0,05* 2-1 P < 0,05*
DBP, mm Hg	95,6 ± 5,1	89,2 ± 5,6	79,9 ± 4,6	3-2 P> 0,05 3-3 P < 0,05* 2-1 P > 0,05

Note. (3-2) – the differences between 2nd and control groups; (3-1) – the differences in the indicators between the control group and patients of the 1st group; (2-1) is a difference between the 1st and 2nd groups; * – reliability of differences between groups, p < 0.05.

index in 2 and 1 level of glucose in the group only with HTN and patients with comorbidity of HTN with DM2T compared with the control group (table 2). The level of fasting insulin was higher by 1.6 times in group 2 (15,5 ± 3,2) mcUn/ ml and 2.2-fold in the group with HTN and type 2 diabetes (20,5 ± 3,1) mcUn/ ml in comparison with groups was significantly different compared with the control group. Between 2 and 1 groups, no significant differences of HOMA – IR was found.

Adhering to the above-mentioned distribution of patients into groups, we analyzed the main structural-functional parameters of the LV with the purpose of studying certain changes in each case (table 3).

Pressure overload (in our research – HTN) leads to an increase in the number of sarcomeres and the thickness of the cardiomyocytes, the thick-

Table 2

Carbohydrate metabolic parameters in patients of investigated groups (M ± m)

Indicator, units	1 group (DM2T+HTN) (n = 20)	2 group (HTN) (n=20)	control (n=10)	Statistical indicator (P)
Fasting glucose, mmol/l	7,4 ± 0,56	5,76 ± 0,18	5,04 ± 0,14	3-2 P < 0,05* 3-1 P < 0,05* 2-1P< 0,05*
Fasting insulin, mcMU/ml	20,5 ± 3,1	15,3 ± 3,5	9,37 ± 2,0	3-2 P > 0,05 3-1 P < 0,05* 2-1P> 0,05
HOMA–IR	5,65 ± 1,02	3,9 ± 1,04	2,1 ± 0,50	3-2 P < 0,05* 3-1 P< 0,05* 2-1P> 0,05

Note. (3-2) – the differences between 2nd and control groups; (3-1) – the differences in the indicators between the control group and patients of the 1st group; (2-1) – differences between the 1st and 2nd groups; * – reliability of differences between groups, $p < 0.05$.

ness of the walls and, as a consequence, the formation of the concentric geometry of the left ventricle. Left ventricular hypertrophy (LVH) is a compensatory reaction under conditions of increased load on the myocardium. It is aimed at maintaining of normal heart function. The results of the Framingham study revealed that cardiovascular risk is highest in patients with concentric LVH. The presence of additional factors in the form of lipid and carbohydrate metabolism observed in type 2 diabetes exacerbates the pathological processes of myocardial remodeling and disorders of endothelial function. In the study of indicators of diastolic LV function, certain changes were identified that are provided in table 3 (E, A, E/A). Violation of relaxation of the myocardium in patients with HTN has shown itself reliable, the reduction in the peak rate E in comparison with the control group.

There were significant differences between patients with HTN and patients with comorbide pathology HTN and DM2T ($p<0.05$), peak velocity and ratio E/A significantly demonstrate a reduction in the elasticity of the myocardium of the left ventricle in patients with first and second groups in comparison with healthy group. The study showed no significant differences between the group of patients with HTN and HTN with DM2T ($p>0.05$). It is known that diastolic LV dysfunction in patients with HTN is

Table 3

Echocardiographic parameters of patients studied groups (M ± m)

Indicator, units	1 group (DM2T+HTN) (n = 20)	2 group (HTN) (n=20)	control (n=10)	Statistical indicator (P)
MMLV, gr	215,2 ± 19,2	171,6 ± 11,2	120,4 ± 4,2	3-1 p < 0,05* 3-2 p > 0,05 2-1 p > 0,05
I MMLV,gr/м^2	136,2 ± 7,0	114,0 ± 10,5	76,4 ± 5,4	3-1 p < 0,05* 3-2 p < 0,05* 2-1 p > 0,05
LVPWT, sm	1,34 ± 0,20	1,28 ± 0,24	1,2 ± 0,03	3-1 p > 0,05 3-2 p > 0,05 2-1 p > 0,05
TIVS, sm	1,33 ± 0,15	1,22 ± 0,11	1,08 ± 0,04	3-1 p < 0,05* 3-2 p > 0,05 2-1 p > 0,05
EF,%	47,9 ±5,1	56,0 ±2,5	65,4 ± 1,4	3-1 p < 0,05* 3-2 p>0,05 2-1 p > 0,05*
E, м/с	0,60 ± 0,03	0,78 ± 0,10	0,68 ± 0,06	3-1 p < 0,05 3-2 p < 0,05 2-1 p <0,05
A, м/с	0,68 ± 0,04	0,81 ± 0,08	0,54 ± 0,04	3-1 p > 0,05 3-2 p > 0,05 2-1 p > 0,05
E/A	0,88 ± 0,03	0,96 ± 0,16	1,25 ± 0,04	3-1 p < 0,05* 1-2 p< 0,05* 2-3 p> 0,05
ESS, sm	4,24 ± 0,04	4,05 ± 0,03	3,3 ± 0,04	1-3 p< 0,05* 1-2 p< 0,05* 2-3 p> 0,05
EDS,sm	5,50 ± 0,05	5,23 ± 0,06	4,87 ± 0,07	1-3 p< 0,05 1-2 p< 0,05 2-3 p<0,05
EDV, ml	151,0 ± 4,2	134,4 ± 6,7	110,6 ± 3,8	1-3 p< 0,05* 1-2 p< 0,05* 2-3 p<0,05*
ESV, ml	80,6 ± 1,6	62,1 ± 8,6	44,4 ± 0,9	1-3 p< 0,05* 1-2 p< 0,05* 2-3 p> 0,05
IEDV,ml/m^2	73,6 ± 2,27	68,6 ± 5,1	58,4 ± 4,2	1-3 p< 0,05* 1-2 p< 0,05* 2-3 p> 0,05
IESV, ml/m^2	41,3 ± 3,7	34,2 ± 4,7	23,8 ± 6,2	1-3 p< 0,05* 1-2 p< 0,05* 2-3 p> 0,05

Note. (3-2) – the differences between 2nd and control groups; (3-1) – the differences in the indicators between the control group and patients of the 1st group; (2-1) – differences between the 1st and 2nd groups; * – reliability of differences between groups, $p < 0.05$.

an early marker of myocardial fibrosis, which leads to a higher rigidity of the myocardial wall of the LV and development of HF.

Structural remodeling reflects EDV diastolic filling LV. Significant differences of this index was observed in patients of the 1st group (HTN with DM2T) (151,0 ± 3,6) and patients with HTN (134,4 ± 4,7) compared with the control group (110,6 ± 3,8; $p < 0.05$).

Similar is the change of the index of end systolic volume (ESV) (table 3), except for the lack of significant differences between the group with HTN or HTN combined with DM2T.

In addition, the dimensions in diastole, and LV volume increased in the patients ofthe group only with HTN or HTN with DM2T in comparison of each group with the control group. There are no differences between the two groups. But amid the thickening of the left ventricle posterior wall and interventricular septum in patients with HTN and DM2T, as well as improving SBP and DBP such changes of indicators point to an increase in venous return to the heart and, accordingly, increase the preload on the left ventricle in patients of the 1st group (tables 1-3).

Noteworthy the fact is that certain changes in the pumping function of the left ventricle between the groups, a decrease in EF with the increase of the action of metabolic components on the background of hypertension. Significant differences were revealed between the control and the 1st groups (65,4 ± 1,4 and 47.9 ± 5,1; $p<0.05$). Between 2nd and 1st groups, no significant differences were revealed.

The result of processes occurring at all levels of the structural organization of the heart changes its size, shape, and functional properties. Violation of relaxation and enhanced stiffness of the LV develops at the stage of HTN, long before the development of diabetes, which reduces the degree of elasticity of the LV. Probably, in patients with HTN against DM2T LVH is developed, the extent of which depends on the severity of diabetes. Changes in intracardiac hemodynamics in patients with HTN and DM2T is characterized by the development of diastolic LV dysfunction.

During the formation and development of HTN there can be observed lesion of organs and systems, due to the onset and progression of structural vascular changes, an increase in the thickness of artery walls and reduction of lumen of the vessels increases peripheral vascular resistance, increases the stiffness of blood vessels. Scientists believe that such changes are possible due to the remodeling and growth of smooth muscle cells. It is important to detect

changes of the vascular wall before clinical symptoms of the disease. A highly informative indicator of such violations is the intima-media (table 4).

In the study of intima media thickness (TIM) in patients with HTN an increase of TIM was detected on the carotid artery by 20% (0,76 ± 0,14 in the control of 0,60 ± 0,06; p <0,05) in patients of the 1st group (HTN and DM2T) – (1,1 ± 0,02), surpassing IMT of the 2nd group 25% (p<0.05). The resulting changes TIM in the 1st group showed an increase in early atheromatous process in carotid arteries.

Table 4

Indicators of intima media in patients of investigated groups (M ± m)

Indicator, units	1 group (DM2T+HTN) (n = 20)	2 group (HTN) (n=20)	control (n=10)	Statistical indicator (P)
TIM, mm	0,60 ± 0,06	0,76± 0,14	1,1± 0,02	3-1 p < 0,05* 3-2 p > 0,05 2-1p< 0,05*

Note. (3-2) – the difference between 2nd and control groups; (3-1) – the difference in the indicators between the control group and patients of the 1st group; (2-1) – difference between the 1st and 2nd groups; * – reliability of differences between groups, p < 0.05.

In addition, the dimensions in diastole, and LV volume is increased in patients 1 and 2 groups, compared each group with the control group. There were no differences between the two groups. But amid the thickening of the LVPW and IVS in patients with HTN and DM2T, as well as improving SBP and DBP such changes of indicators point to an increase in venous return to the heart and, accordingly, increase the preload on the left ventricle in people with HTN and DM2T (tables 1 – 3).

It should be noted that when changing the pumping function of the left ventricle between the groups, a decrease in EF with the increase of the action glucometabolic components on the background of HTN. Significant differences were revealed between the control and the 1st groups (65,4 ± 1,4 and 47.9 ± 5,1; p <0.05). Between 1 and 2 groups, no significant differences were revealed.The results of correlation analysis of anthropometric, biochemical and echocardography indicators in patients with HTN and DM2T are presented in table 5.

The correlation analysis of interrelation of indicators of LV structural-functional state in patients with HTN and DM2T with basic carbohydrate

metabolism showed that with the presence of DM2T certain changes of form and function of the left ventricle are observed, it is determined by the level of glycemia, BMI, and blood pressure.

After the study of anthropometric indices, biochemical and ultrasound studies, and after evaluation of a correlation analysis of the patients groups, the status of oxidative stress was assessed, antioxidant defense in patients of the 1st group (HTN and DM2T).

Table 5

Correlation analysis of anthropometric, biochemical and echocardiographic parameters in patients of the 1st group (HTN with DM2T)

r / p	IMT, mm	IMMLV	E/A	IEDV
Age, years	0,68/<0,05*	0,35/>0,05	0,43/>0,05	0,05/>0,05
BMI, kg/m^2	0,83/<0,05*	0,44/<0,05*	0,08/>0,05	0,06/>0,05
SBP, mmHg	0,05/>0,05	0,74/<0,05*	-0,58/<0,05*	0,81/<0,05*
DBP, mm Hg	0,08/>0,05	0,26/>0,05	-0,77/<0,05*	0,023/>0,05
Fasting glucose, mmol/l	0,68/<0,05*	0,92/<0,05*	0,06/>0,05	0,15/>0,05
Fasting insulin, mcMU/ml	0,78/<0,05*	0,07/>0,05	0,11/>0,05	0,31/>0,05
HOMA–IR	0,32/<0,05*	0,24/>0,05	-0,41/<0,05*	0,06/>0,05
IEDV	0,56/<0,05*	0,22/>0,05	0,21/>0,05	0,18/>0,05
IESV	0,47/<0,05*	0,15/>0,05	0,15/>0,05	0,16/>0,05
IMMLV	0,16/>0,05	0,09/>0,05	-0,39/<0,05*	-0,66/<0,05*

r – coefficient Pearson; p – significance of differences; * – significant differences at $p < 0.05$.

In the process of the study identifies the contents diene conjugates (DC) significantly differed in the studied groups. It was shown that in patients of the 2nd group (HTN) DC were significantly ($p<0.05$) higher than in the control group (38,7±0.08 and of 25.02 ± 0,16 vs 13,6±0,23 nmol/ml, respectively) with significant ($p<0.05$) differences of DC indicators in patients of the 1st group (HTN with DM2T). Mass content of other peroxidation products – Malondialdehyd (MDA) in blood of patients showed the same changes as DC, namely, the values of MDA in patients of the 2nd group and 1st group were significantly ($p<0.05$) higher than in the control group. The highest MDA was determined in patients of the 1st group, being significantly ($p<0.05$) different from the 1st group from the control group

(30,0 ± 0,050 and 33,06±0,23 nmol/ml, respectively), confirming the progression of ED patients with comorbidity HTN and DM2T.

In addition, during the study it was recognized that increased levels of MDA and DC were correlated with increasing BMI, this was confirmed by the reliable differences ($p<0.05$) in their concentrations in normal weight and obesity.

With the aim of in-depth study of the role of IR in the expression of oxidative stress in the formation of DM2T, we compared the concentrations of MDA and DC in patients solely on HTN, but with or without IR. It is worth mentioning that if there are signs of IR, patients had sufficiently high levels of MDA (35,0 ± 0.2 and 33,0 ± 0.14 nmol/ml, respectively, $p<0.05$) and DC (27,13 ± 0,27 and 24.5± 0.2 nmol/ml, respectively, $p<0.05$), which was not identified in HTN patients without IR, which provided the opportunity to identify the important role IR plays in the onset and progression of ED, even before the specific signs of disorders of carbohydrate metabolism.

In the study, we evaluated changes of parameters of antioxidant protection in patients with HTN and concomitant DM2T that supports the balance regarding LPO. It was found that in patients exclusively with HTN with and without DM2T, the indicators of the antioxidant system superoxide dismutase (SOD) and catalase significantly ($p<0.05$) decreased compared with the control group. HTN patients with DM2T showed significantly ($p<0.001$) smaller indicators (41,9 ± 0,061 and 0.13 ± 0,032 u/mg Hb/min), patients only with HTN (of 46.01 ± 0.29 and 0,162 ± 0,018 u/mg Hb/ min, respectively), this can be attributed to the increased accumulation of peroxide.

It was also determined that patients with HTN with signs of IR had significantly ($p<0.05$) lower SOD and catalase, when compared with patients with HTN with no signs of IR, which once again demonstrated the presence of ED before the advent of DM2T in patients with HTN.

Estimating the correlation of the indicators of oxidative stress system with the structural and functional state of the heart and BMI (table 6), it should be noted that MDA and DC had weak direct correlation with the EDD and ESD direct correlation with BMI, a weak inverse correlation (only MDA) with EF; concerning the signs of ED – moderate strength inverse correlation with "E" and the weak inverse correlation with the "E/A" and E. MDA and DC were correlated with the data of structural-functional state of vessels: with TIM average force direct correlation.

We determined the correlation of MDA, DC, SOD and catalase with the morpho-functional state of the heart and blood vessels, according to the Association of an imbalance between the systems of oxidative stress, antioxidant protection with the development of remodeling of the heart and blood vessels.

Table 6

Correlation analysis of anthropometric, echocardiographic and system of indicators of oxidative stress, antioxidant defense

indicator	MDA	DC	Kat	SOD
BMI	r = 0,708, p<0,001	r = 0,689, p<0,001	r = -0,415, p<0,001	r = -0,578, p<0,001
SBP			r = -0,123, p<0,05	r = -0,242, p<0,001
DBP			r = -0,117, p<0,05	
EDD	r = 0,188, p<0,01	r = 0,199, p<0,05		
ESD	r = 0,195, p<0,01	r = 0,202, p<0,05		
EF	r = -0,144, p<0,05			
E	r = -0,265, p<0,001	r =-0,259, p<0,001	r = 0,153, p<0,01	r= 0,198, p<0,001
A			r = -0,131, p<0,01	r = -0,145, p<0,01
E/A	r = -0,171, p<0,01	r = -0,178, p<0,01	r = 0,125, p<0,05	r = 0,208, p<0,001
IMT	r = 0,367, p<0,001	r = 0,332, p<0,001	r = -0,415, p<0,001	r = -0,394, p<0,001

The next stage of the study was to investigate the impact of different pathogenetic mechanisms of IR on the development of comorbidity. To answer to this question violations by adipokine balance were assessed.

It is known that a larger number of patients with DM2T are overweight or obese, and the fact that some biologically active substances, which are synthesized by adipose tissue worsen the transmission of the insulin signal and promote the development of IR on the stage of prediabetes. Therefore, the next step of our study was to determine the relationship between imbalance of hormonal function of adipose tissue and signs of DM2T, as well as their influence on the course of HTN.

Carbohydrate metabolism and levels of adipokines (adiponectin and leptin) in the examined groups were evaluated, and it was found that all indicators significantly differed from the control group ($p<0.001$).

Comparing the data of patients with HTN and DM2T solely with patients with HTN have shown a reliable difference in levels of glucose, insulin, HOMA-IR also significantly lower concentrations of adiponectin (of 6.61 ± 0,080 and 8.1 ± 0,028 ng/ml, respectively, $p<0.001$) and significantly higher concentrations of leptin (16,61 ± 0.18 and of 12.91 ± 0,185 ng/ml, respectively, $p<0.001$) in the group of patients with comorbidity. The obtained values of the hormone leptin can be explained by the fact that it plays a leading role in the emergence of glucometabolic occurring disorders in patients with DM2T. Reducing of adiponectin levels in patients with comorbidity compared with patients with HTN can be regarded as the involvement of dysregulation of the secretion of hormone adiponectin in the development of DM2T.

Certain relations were revealed between levels of adipokines, carbohydrate metabolism and anthropometric indicators. It was established that in patients with HTN in the absence of DM2T, there were no significant differences in the levels of carbohydrate profile in subgroups with different weights. In both groups of patients the same time, the levels adipokines had the following trend: the concentration of leptin was significantly increased with increasing BMI ($p<0.001$), levels of adiponectin in patients only with HTN was significantly higher when defining obesity compared to patients with normal weight ($p<0.01$).

Patients exclusively with HTN with IR compared to patients without IR adiponectin had lower values, but these data did not show reliability. In relation to leptin, it was significantly higher in patients with HTN and IR (15,12 ± 0,36 vs 12,25 ± the 0.103 ng/ml, $p<0.05$), which suggests that this hormone helps to reduce the transmission of insulin signal to induce IR even before the emergence of DM2T.

Evaluating indices of contractile function of the heart in patients with comorbidity with normal weight (BMI 25-34. 9 kg/m^2) showed a significant decrease of EF (64,65±0,34% 63,12± 0,27%, respectively, ($p<0.05$) with increasing BMI.

We know that IR has a certain influence on the structural and functional parameters of the myocardium at the stage of IR, before the appearance of DM2T, therefore, we conducted an echo study in patients with HTN

before the development of carbohydrate disorders. It was found out that in the presence of IR patients with HTN showed characteristic increase in the following indicators: end-diastolic diameter (EDD) of the left ventricle ($p<0.05$) and TIVS ($p<0.05$), as well as LVMM ($p<0.05$) and LVMI ($p<0.001$), that was not observed in patients without disorders of carbohydrate metabolism. That provides the opportunity to confirm that IR on the background of HTN can contribute to the increase intensity of structural and functional abnormalities of the myocardium.

In modern literature, there are data on the effect of some proinflammatory markers in carbohydrate metabolism, the cardiovascular system, adipokines system and the severity of obesity. The next phase of the study appeared to determine the role of proinflammatory cytokines (IL-6 and TNF-α) in the development of comorbidities, the combination of DM2T with HTN. In the process of study a significant increase of these indicators in the group of HTN and DM was revealed when compared with the group of patients exclusively with HTN ($p<0.001$), and this, in turn, indicates polycomponent effects of these proinflammatory markers.

It was found that the concentration of TNF-α was significantly increased ($p<0.05$) with increasing of BMI. The same trend showed a different cytokine – IL-6 with increasing BMI with 118,21 ± 4.0 to 133,12 ± 4.1 ng/ml ($p<0.05$). The data demonstrate the influence of cytokines on the different stages of the development of IR.

The study showed that increasing BMI was associated with increase in blood insulin ($r=0,43$, $p<0.001$) and HOMA-IR ($r = 0,42$, $p<0,001$), expression of leptin ($r = 0,77$, $p<0,001$) and TNF-α ($r = 0,7$, $p<0,001$) and IL-6 ($r = 0,61$, $p<0.001$).

In the presence of concomitant pathology HTN and DM2T, proinflammatory cytokines play an important role in the development of ED, as well as in the formation of disorders of carbohydrate metabolism and the development of vascular remodeling. We noticed direct correlations between leptin and hyperinsulinemia ($r=0.24$, $p<0.001$) and HOMA-IR ($r=0.28$, $p<0.001$), confirming the involvement of the expression of leptin in the formation of the IR on the background of overweight or obesity.

Therefore, data of correlation analysis proved the relationship of carbohydrate metabolism disorders in patients with comorbidity indicators prooxidant and antioxidant systems. Indicators of morpho-functional state of vessels showed that with increasing activity indices of oxidative stress

and decreasing the activity of antioxidant protection indicators, the level of adiponectin is reduced which is demonstrated by the inverse correlation of adiponectin with MDA and DC ($r = -0.65$, $p<0.001$ and $r = -0,62$, $p<0.001$, respectively), at the same time, direct correlations with catalase and SOD ($r = 0.31$, $p<0.001$ and $r = 0,35$, $p<0.001$, respectively). Evaluating the correlation between increased leptin and the above-mentioned indicators prooxidant and antioxidant systems we have received some evidence about the direct correlation of the hormone leptin, MDA and DC ($r = 0,83$, $p<0.001$ and $r = 0.75$, $p<0.001$, respectively), as well as feedback from catalase and SOD ($r = -0.44$, $p<0.001$ and $r = -0,490$, $p<0.001$, respectively).

6. Conclusions

1. Prognostically unfavorable variants of hypertrophic remodeling of LV are determined in patients with HTN and DM2T – concentric (65,3 %) and eccentric (17,01 %) types of LV hypertrophy, whereas in HTN patients without comorbidities there are no statistically significant differences.

2. The progression of diastolic dysfunction is identified with combination HTN and DM2T, which is confirmed by indicators of blood flow in pseudonormal 14, 5 % of patients, higher values of E/A – integral indicator of diastolic function of the LV, while patients with exclusively HTN diastolic dysfunction is presented only by initial changes in the form of excited relaxation.

3. Specific feature of patients with concomitant HTN and DM2T in comparison with patients of HTN are higher values TIM, with increased carbohydrate metabolism (blood glucose index and HOMA-IR), confirming the aggressive vascular remodeling in this disease.

4. Pronounced activation of prooxidant system simultaneously with a depressed antioxidant defense system can be observed in patients with the combination of HTN and DM2T, as evidenced by significantly higher MDA and DC ($38,7 \pm 0,08$ nmol/ml and $40.0 \pm 0,050$ nmol/ml, respectively) while decreases of SOD and catalase ($41,9 \pm 0,061$ u/mg Hb min $0,162 \pm 0,018$ u/mg Hb min, respectively) compared with exclusively HTN ($p<0.001$).

5. In patients with HTNand DM2T, hyperleptinemia and hypoadiponectinemia were identified, the severity of which depends on the anthropometric indices (BMI). The effect of hyperleptinemia on the severity of IR with the growth of BMI is confirmed by the correlations between the increasing levels of leptin, insulin and increased HOMA-IR.

6. The role of proinflammatory cytokines TNF-α and IL-6 in the formation of ED, and disorders of carbohydrate metabolism in patients with HTN and DM2T was confirmed, increasing levels of which is associated with increases of TIM, index, HOMA-IR, fasting glucose and BMI.

This research optimized differentiated approaches to the diagnosis of patients with HTN and DM2T – based on the study of anthropometric, cardioghemodynamic, carbohydrate metabolism, proinflammatory markers, adipose tissue hormones and oxidative stress and antioxidant defense in the aspect of the development of comorbidity. It is promising for improving the diagnosis of metabolic disorders and as early as possible preventing cardiovascular complications and reducing mortality in the presence of comorbid pathology.

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