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THE INFLUENCE OF METABOLIC DISORDERS ON THE PROCESS OF CARDIAC HEMODYNAMICS AND REMODELING OF THE VASCULAR WALL IN PATIENTS WITH HYPERTENSION AND TYPE 2 DIABETES

ABSTRACT

Aim - The article deals with the study of the influence of metabolic disorders on the progression of structural and functional changes in the myocardium and blood vessels in patients with hypertension and type 2 diabetes mellitus.

Key words: arterial hypertension, type 2 diabetes mellitus, insulin resistance, vascular remodeling, cardiac hemodynamics.

INTRODUCTION

Despite the appreciable achievement in the arterial hypertension (AH) prevention and treatment, the disease remains to be one of the most urgent problems of cardiology [1]. The most commonly AH occurs in comorbidity

with pre-diabetes and type 2 diabetes mellitus (DM) that is significantly increasing the risk of cardiovascular complications.

Chronic hyperglycemia in AH patients with glucose metabolism disorders and type 2 DM significantly contributes to the formation and progression of cardiovascular disease [2]. Carbohydrate metabolism disorders significantly increase risk of acute cardiovascular events, such as myocardial infarction [3]. A meta-analysis of large prospective studies that totally included 450.000 patients has demonstrated that the risk of coronary death in patients with diabetes occurs 2–3 times more often [4]. This is due to the fact that, on the one hand, chronic hyperglycemia directly promotes myocardial lesions, on the other, it increases the negative effect of other risk factors for cardiovascular pathology progressing [5]. It has been noted that the degree of impairment of myocardial diastolic properties directly depends on the level of glycated hemoglobin, that represens the degree of myocardium proteins glycation [6] and deposition of collagen in the myocardium with its fibrosis [7]. Furthermore, it is known that patients with carbohydrate metabolism disorders have higher left ventricular mass even in the absence of AH and heart diseases [8].

Thus, the study of the influence of metabolic disorders in the development of cardiovascular remodeling in patients with hypertension and diabetes is a relevant

Aim — to study the effect of metabolic disorders in the progression of structural and functional changes in the myocardium and blood vessels in patients with AH and type 2 DM.

MATERIALS AND METHODS

Eighty–five patients with hypertension stage II, 2nd degree (45 men and 40 women). The patients have been distributed into following groups: 1st group (n=26) included patients with arterial hypertension, without carbohydrate metabolism disorders; 2nd group (n=30) – patients with arterial hypertension and pre-diabetes; 3rd group (n=29) – patients with concomitant course of AH and

type 2 DM. The control group (n=20) has been comparable by age and sex to each of groups of surveyed patients. All surveyed patients signed an informed consent agreement to participate in the research.

The exclusion criteria have been such severe somatic diseases as kidney, liver, heart, and respiratory failure, anamnestic evidences of stroke, myocardial infarction, oncological diseases, decompensated type 2 DM course according to WHO criteria, female patients previously diagnosed with type 2 DM macrovascular complications , thyroid function disorders, primary familial hypercholesterolemia, secondary hypertensions, and pregnancy.

Arterial hypertension diagnostics was performed according to the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC, 2013), as well as Ukrainian Association of Cardiology on prevention and treatment of hypertension (2013). Anthropometric measurements included the calculation of body mass index (BMI) and the degree of obesity according to the IDF criteria (2015). Type 2 DM was diagnosed according to the general recommendations of the European Association for the Study of Diabetes (EASD, 2013).

Glycated hemoglobin levels (HbA1c) in whole blood was performed using the test-system of company "Reagent" (Ukraine). Insulin resistance index (HOMA-IR) was calculated by the formula: HOMA-IR = insulin (fasting insulin, mcU/ml) × fasting glucose (mmol/l) / 22.5. At HOMA-IR>2.77 patients were considered as having insulin resistance. C-reactive protein (CRP) levels were identified by enzyme-linked immunosorbent assay (ELISA) using «DRG» reagent kit (USA).

The concentrations of fasting blood glucose (FBG) and insulin in blood serum were identified using ELISA with "DRG" kit (USA). In order to determine glucose tolerance we have performed an oral glucose tolerance test.

Structural-functional cardiac parameters were determined by echocardiography using the diagnostic system «Philips IU» (USA) in B and M

modes by standarg technique according to the general recommendations of the American Society of Echocardiography (2015) with the determination of the interventricular septal wall thickness (IVST), left ventricular posterior wall (LVPWd) end-diastolic dimension, end-systolic dimension (ESD), end-diastolic dimension (EDD), left ventricle ejection fraction (LVEF); end-systolic volume (ESV), end-diastolic volume (EDV); analysis of the left ventricular diastolic function (DFLV) has been conducted during the registration of transtricuspid diastolic flow in the pulsed-wave Doppler mode; LV myocardial mass (LVMM) was calculated using the formula of Devereux R. B. (1986), index of LVMM (LVMMI) was determined as the ratio of LVMM to body surface area by Brown D. W. (2000).

To assess the structural-functional state of the vessels we performed ultrasound scanning of common carotid arteries with measurement of the intima-media complex thickness of the common carotid artery (IMT CCA) using an ultrasound diagnostic system "Phillips IU" with linear sensor at the frequency of at least 7 MHz in B-mode.

As soon as the distribution of values has been reviled to be normal, statistical processing of obtained results was performed by parametric methods (with evaluation of mean, its standard error or standard deviation; Student t-test for independent samples by groups, Pearson correlation) using Statsoft Statistica 8.0 software package. The threshold of p-value of 0.05 has been chosen; in case of multiple comparison a Bonferroni correction was made.

RESULTS AND DISCUSSION. The results of trophological status analysis discovered characteristic features in the surveyed groups. Patients with a BMI in the range of 18.5–24.9 kg/m^2 (n=5) were identified in the group with AH isolated course. However third-degree obesity (BMI>40.0 kg/m^2) was observed in one patient with AH, in three patients with AH and pre-diabetes, and in 5 patients with concomitant AH and type 2 DM. The predominant majority of patients with isolated and concomitant course of the disease in the

2nd and 3rd groups (64.2%,54.3%, and 51.3% respectively) had a BMI in the range of 30–34.9 kg/m2. At the same time, in patients with type 2 DM and BMI within 30.0–34.9 kg/m^2 men were predominate (67.3%), and with BMI within 35.0–39.9 kg/m^2 and more – women (74.5%).

FBG levels were significantly higher in patients with concomitant course of AH and type 2 DM compared with patients in 1st group, 2nd group, and the control group ($p<0.05$).

In patients of the examined groups we have determined the maximal values of HOMA-IR, insulin and C-peptide in patients of the 3rd group comparing to respective indices of the 1st and 2nd groups (table 1), that indicates the progression of insulin resistance (IR) under hyperinsulinemia associated with the presence of type 2 diabetes. HOMA-IR exceeded control indices by 2.1 times in the group of patients with AH, 2.4 times in patients with AH and pre-diabetes, and by 2.7 times significantly higher in patients with concomitant AH and type 2 DM.

Table 1

Carbohydrate metabolism and IR indices in surveyed groups of patients (M±SD)

Indices	Control group n=20	AH n=26	AH+pre-diabetes n =30	AH+ type 2 DM n=29	p
	1	2	3	4	
HOMA-IR	1.64±0.54	4.42±2.72	3.44±2.72	5.44±3.12	p_{1-2} =0.00001 p_{1-3} =0.00001 p_{2-3} =0.15
Insulin mcU/ml	5.45±2.1	10.8±5.4	11.6±5.2	13.6±7.3	p_{1-2} =0.0004 p_{1-3} =0.0002 p_{2-3} =0.047

CRP, ng/ml	0.46±0.23	0.95±0.51	1.02±0.42	1.22±0.72	p_{1-2} =0.0003 p_{1-3} =0.0001 p_{2-3} =0.064
Glucose, mmole/l	4.23±0.14	6.56±1.14	7.62± 3.84	8.24±1.26	p_{1-2} =0.00002 p_{1-3} =0.00003 p_{2-3} =0.16
HbA1c (%)	4.62±0.04	6.53±0.03	7.2±0.3	9.3±0.4	p_{1-2} =0.0006 p_{1-3} =0.0004 p_{2-3} =0.031
GTT mmole/L	5.14±0.02	6.18±0.04	11.36±0.42	14.3±2.1	p_{1-2} =0.0004 p_{1-3} =0.0003 p_{2-3} =0.052

In the 2nd and 3rd groups of patients we revealed a positive correlation between the insulin levels in the peripheral blood and LVH ($r=0.44$; $p<0.01$ and $r=0.42$; $p<0.01$ respectively) and IMT CCA ($r=0.36$; $p<0.05$ and $r=0.38$; $p<0.05$ respectively). These data suggest that hyperinsulinemia is an important component for the development and progression of AH and contributes to the development of myocardial hypertrophy and smooth muscle elements of peripheral vessels.

Examination of IMT CCA showed mean values in patients with AH (0.85± 0.05 mm, $p<0.05$) in comparison with the 2nd, 3rd and control group, and in patients with AH and pre-diabetes this index was 0.9±0.05 mm ($p<0.05$). In patients with AH and type 2 diabetes IMT CCA was 0.95±0.07 mm ($p<0.05$). IMT CCA indices in 2nd and 3rd groups presented reverse correlation with HOMA-IR ($r=0.36$, $p <0.001$).

We observed an increase of IMT CCA ≥0.9 mm in patients with AH in 46.8% of cases, 52.7% in patients with AH and pre-diabetes, and 59.2% in patients with concomitant course of disease, due to the severity of atherosclerotic processes that are affected by insulin resistance index (glucose

and hyperinsulinemia), which indicates the influence of carbohydrate metabolism disorders on the progression of vascular remodeling.

Indices of IMT CCA were associated with age (p=0.032), BMI (p=0.044), waist measurements (p=0.046), and HOMA-IR (p=0.044). Patients from 2nd group in 12.3% of cases, patients from 3rd group in 38.7% were marked as having atherosclerotic plaques with a degree of stenosis <10%, which requires further monitoring, because it is a trigger factor for the development of cardiovascular complications.

These results are concordant with the Insulin Resistance Atherosclerosis Study (IRAS) which revealed a clear direct dependence between the degree of insulin resistance and the carotid artery wall thickness both in people without diabetes, and in patients with type 2 DM. Each unit of insulin resistance IMT increased by 30 mcm [9]. Similar results were obtained during analyzing the results of 11 studies, which involved 1578 patients with type 2 diabetes, including 132 patients with pre-diabetes, who developed IMT CCA index during the treatment [10]. It was found that patients with type 2 diabetes without treatment having average content of HbA1c=7.86% had IMT CCA increasing by 0.034 mm per year [11]. This revealed significant dependence between HbA1c level and the rate of IMT CCA increase [12].

Left ventricular hypertrophy (LVH) was diagnosed in 92.3% of patients from 3rd group, 75.8% of patients from 2nd group, and 55.4% of patients from 1st group compared to the controls (p<0.05). Patients with AH and type 2 diabetes are characterized by an increase of average LVMM (p<0.05) and LVMMI values (p<0.05) compared with patients in 1st group, 2nd group 2, and the controls. Indices of Doppler echography intracardiac hemodynamics in patients with AH were characterized by a decrease in the early and late diastolic filling rate of LV (table 2). However, under the concomitant course of the disease in the 2nd and 3rd groups, these indexes were significantly reduced comparing to the 1st group of patients and controls (p<0.05). Similar patterns

were observed in the ratio of the early and late diastolic filling velocities (E/AL) LV.

Table 2

Hemodynamic parameters in surveyed groups of patients

Indexes	Control n=20	AH n=26	AH+ pre-diabetes n =30	AH+DM type 2 n=29
SBP, mm Hg..	125.5±4.2	156.5±3.4*	175.8±4.6*/**	185.4±4.8***
DBP, mm Hg	82.7±5.5	91.3±5.2*	98.3±8.1*/**	106.1±9.1***
LASF, sm	2.74±0.08	2.84±0.06	3.23±0.03*/**	3.64±0.07***
EDV, sm^3	129.23±1.12	133.26±1.14	141.8±1.14*/**	146.30±1.14**
ESV, sm^3	47.2±0.2	48.3±0.3	62.4±0.6*/**	76.4±0.4***
EDD, sm^3	4.64±0.04	5.14±0.04*	5.33±0.04*/**	5.54±0.06**
ESD LV, sm	4.14±0.02	4.16±0.06	3.57±0.03*	3.94±0.02**
Stroke volume (SV), sm^3	75.52±1.26	83.93±1.36	92.14±0.74*/**	98.24±0.74**
Ejection fraction (EF), %	65.44±0.82	66.84±0.72	52.94±0.42*	54.82±0.42**
Myocardium Mass Index LV, g/m^2	81.64±0.02	98.66±0.03	116.44±1.42*/**	146.42±1.34**/***

* - $p<0.05$ - significant differences comparatively to the control group;

** - $p<0.05$ - significant differences comparatively to the AH patients

*** - $p<0.05$ - significant differences comparatively to the patients with AH and pre-diabetes

Also, the maximum ESD LV and EDD LV values were registered in patients of 3rd group in comparison with respective indices of the 1st and the

control group ($p<0.05$) and increasing pattern of these indicators in the 2nd group. The same situation was observed as to ESV LV and EDV LV ($p<0.05$). Patients in 2nd and 3rd groups with concomitant disease course had a significant increase of MMI in comparison with the 1st group ($p<0.05$), which is the evidence that more severe changes of diastole can be observed in patients with concomitant AH and pre-diabetes or type 2 diabetes.

Thus, patients of the 2nd group with the concomitant course of AH presented structural-functional and intraventricular hemodynamic changes, which were most expressed in the 3rd group and appeared as a diastolic dysfunction, due to diastolic LV myocardium relaxation dysfunction.

As to the mechanisms of LVH in AH patients with type 2 diabetes, we should mentioned a complex of metabolic disorders which are typical for type 2 diabetes [13]. Those disorders primary include expressed IR and hyperinsulinemia. Indeed, IR and hyperinsulinemia are the trigger factors that cause a series of hormonal, neurohumoral and metabolic processes being the basis of early LVH in concomitant AH and type 2 diabetes [14]. This is an activation of the sympathetic-adrenal system, a powerful stimulus for renin and angiotensin II excretion with a consequent increase of aldosterone production and transformation of hyperkinetic, hyper-renin variant of hypertension. Powerful hypertrophic and proliferative processes in myocardium are triggered, accompanied by the processes of volume overload of the heart, which leads to LVH in patients with AH and type 2 diabetes [15]. The most important proliferative and hypertrophic factors that are included in the processes of myocardial hypertrophy, are series of cytokines and other growth factors [16].

Conclusions.

It has been found that the combined course of AH and pre-diabetes is accompanied by disorders of carbohydrate and lipid metabolism, which are most pronounced in patients with AH and type 2 DM.

It is proved that chronic hyperglycemia and insulin resistance contribute to the progression of cardiovascular remodeling and hemodynamic disorders which greatly increases the cardiovascular risk in patients with AH and type 2 DM.

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