https://doi.org/10.38109/2225-1685-2019-2-64-75

ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

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CLINICAL AND INSTRUMENTAL ASSESSMENT OF MORPHO-FUNCTIONAL CONDITION OF THE HEART AND VASCULATURE IN COMORBIDITY OF ARTERIAL HYPERTENSION AND DIABETES MELLITUS TYPE 2

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SUMMARY

The aim of this study was to investigate the heart and common carotid arteries (CCA) morphological and functional condition and the lipid spectrum in patients with arterial hypertension (AH) and type 2 diabetes mellitus (DM-2).

Material and methods. The study included 144 patients with varying degrees of AH, 103 had AH without DM-2 (AH subgroup) and 41 patients with AH and DM-2 (AH+DM-2 subgroup). In all investigated patients the blood plasma lipid profile, echocardiographic examination of the heart and ultrasound Doppler examination of the CCA were carried out.

The results. Significant differences between the AH and AH+DM-2 subgroups were discovered, which confirmed the significant effect of DM-2 on various parameters of the cardiovascular system. The lipid profile in the above mentioned subgroups has not significant differences, but some separated indices (TG, VLDL) in the AH+DM-2 subgroup were comparatively higher and HDL level lower comparing to AH subgroup. Marked changes in echocardiographic parameters, such as lowering of left ventricle (LV) ejection fraction (EF), significant increase of interventricular septum and LV posterior wall thickness, high frequency of LV hypertrophy detection, diastolic dysfunction, diffuse hypokinesis and dilatation of the heart cavities in the AH+DM-2 subgroup were confirmed. A significant rise of CCA intima-media thickness also was found in the AH+DM-2 in comparison with AH subgroup, which proved the essential role of comorbidity of AH and DM-2 in the heart and vessels remodeling.

The conclusion. The results of the study confirm the role and significance of comorbidity of AH with DM-2 in the development of the cardiovascular system pathological changes.

Keywords: *Arterial hypertension, diabetes mellitus type 2, ultrasound dopplerography, common carotid arteries, lipid exchange.*

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For citation: Бабаева Н.З. Клинико-инструментальная оценка морфо-функционального состояния сердца и сосудов при коморбидности АГ И СД-2. Евразийский кардиологический журнал. 2019, Май 25; 2: 64-68 [Trans. into Eng. ed.: Babayeva N.Z. Clinical and instrumental assessment of morpho-functional condition of the heart and vasculature in comorbidity of arterial hypertension and diabetes mellitus type 2. Eurasian heart journal. 2018, May 25; 2:70-75]

INTRODUCTION

In prevalence, severity of complications, psychological and material damage, arterial hypertension (arterial hypertonia) is one of the main medical and social problems as it is associated with a strong increase in the risk of cardiovascular diseases [1, 2]. AH increases the risk of a range of cardiovascular diseases [3], including stroke, coronary heart disease, heart failure, atrial fibrillation, and peripheral vascular disease [4].

Diabetes mellitus (DM) in patients with arterial hypertension (AH) is significant along with associated clinical conditions and causes a very high risk of cardiovascular complications [5].

Arterial hypertension is present in more than 60% of patients with type 2 diabetes mellitus [6]. This is directly related to: (1) increased activity of the renin-angiotensin-aldosterone system; (2) hyperinsulinemia associated with increased renal sodium reabsorption; and (3) elevated sympathetic tonicity [7]. Aging, obesity and the onset of kidney disease also contribute to an increase in the prevalence of hypertension. Hypertension and DM are additive risk factors for CVD development.

The main target organs in hypertension are the heart and blood vessels. The most frequent cardiac changes in hypertension are left ventricular hypertrophy (LVH) and LV diastolic dysfunction [8]. At the same time, the contribution of comorbidity, in particular, type 2 diabetes mellitus, to the remodeling of the heart and blood vessels in patients with arterial hypertension is not well understood. Meanwhile, type 2 DM can lead to structural and functional changes in the heart and blood vessels even in the absence of hypertension [9].

In the light of the above, the study of changes in the morpho-functional condition of the heart and blood vessels in the comorbidity of these pathologies remains an unsolved problem.

MATERIAL AND METHODS.

The study included 144 patients with varying degrees of hypertension, 103 of them had isolated hypertension of various degrees, 41 patients were diagnosed with type 2 DM along with hypertension. Thus, two compared subgroups were identified: AH and AH + DM2. All patients underwent an echocardiographic study of the heart, a duplex ultrasound study of the carotid arteries and an assessment of lipid profile parameters. Among the total number of patients, 15 of them received lipid-lowering therapy, in particular, statins, but 2 months before the study, this group stopped taking the drugs.

The lipid profile parameters were determined in the biochemical analyzer Multi+ (Poland) using Human (Germany) and Erba (European Union) reagents. The levels of total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL) were measured. The level of low-density lipoprotein (LDL) concentration was calculated using the Friedewald formula if the TG concentration level was below 400 mg/dL: LDL = TC-HDL-TG /5. Values of very low-density lipoproteins were calculated by the formula: VLDL = TC-HDL. The atherogenic coefficient (CA) was calculated by the formula: CA = TC-HDL/HDL. The norm of lipid profile values is: TC <5.2 mmol/l; TG <1.7 mmol/l; HDL >1.1 mmol/l; LDL <2.6 mmol/l; VLDL <0.6 mmol/l; CA <3.0.

Transthoracic polypositional echocardiography was performed on the ultrasonic device manufactured by Hong Kong using a 2.5 MHz linear transducer according to the generally accepted method in M and B modes during which interventricular septum thickness (IVS thickness) was measured (normal 6-9 mm), left ventricle posterior wall thickness (LVPW thickness) (normal 6-9 mm) during systole and diastole, ejection fraction (EF) of the left ventricle (LV) (normal > 55%). Evaluation of the transmitral flow was made in a pulsed Doppler mode in 4-chamber position in the area of the LV apex. LV diastolic function was assessed by E and A peaks of maximum blood flow velocity, E/A ratio as well as LV isovolumic relaxation time (LV IVRT). LV IVRT more than 100 ms and E/A below 1.0 were considered signs of diastolic dysfunction. The presence of LVH was confirmed with an increase in IVS and LVPW thickness > 1.2 cm and/or an increase in the LVMM index > 125 g/m^2 [10].

Duplex ultrasound scanning of the carotid arteries (CA) was performed using a standard method on an ultrasound machine (Hong Kong) using a 7.5 MHz linear transducer. The structural and morphological indices of the right and left CCA including the interadventitial diameter (IAD), the intima-media complex thickness (IMCT) (normal <0.9 mm) with calculation of IMCT /IAD ratio (normal <0.013) were measured. Atherosclerotic plaque was diagnosed by duplex scanning as a distinct formation that is 50% or more than the intima-media complex thickness in the neighboring part of the artery, i.e., a structure that protrudes into the artery lumen by 1.5 mm or more [11]. Stenoses of varying degrees were also determined according to the NASCET classification (0-40% mild stenosis, 50-60% moderate stenosis, ≥70% high stenosis) [12, 13], vascular tortuosity and varicose veins (v. jugularis). Along with this, blood flow velocity parameters (maximum systolic and diastolic speeds (MaxSS, MaxDS), mean speed (Tamax), pulsation index (PI) and resistance index (RI)) were measured.

Statistical data processing was performed using Microsoft Word Excel 2013 and Statistica SPSS 2013. Standard descriptive statistical methods (calculation of averages, standard deviations, standard errors, etc.) and non-parametric significance criteria (χ2, Mann-Whitney test) were used.

RESULTS

The average age in the AH group was 54.1±1.1 (27-77) (CI 95% 51.8-56.3) and the patients in this subgroup were significantly younger than in the AH + DM2 subgroup 59.7±1.6 (40-80) (CI 95% 56.6-62.9) (p = 0.014). When measuring blood pressure, the following indicators were noted: the level of SBP was 168.0±1.7 mm Hg in the AH subgroup and 171.2±3.2 mm Hg in the AH + DM2 subgroup (F = 0.890; p = 0.347); DBP level was 102.0±0.9 mm Hg in the AH subgroup , 103.8±1.6 mm Hg in the subgroup AH + DM2 (F = 0.932; p = 0.336); mean BP level was 124.0±1.1 mm Hg in the AH subgroup, 126.3±2.0 mm Hg in the subgroup AH + DM2 (F = 0.992; p = 0.321). Differences in these values between subgroups were statistically insignificant.

The study of lipid spectrum indices revealed certain differences between the AH and AH+DM2 subgroups (Table 1).

The higher mean value of total cholesterol in the AH subgroup compared to AH + DM2 subgroup did not reach statistical significance (p = 0.313), total cholesterol values were higher than normal in the AH subgroup in 54 of 103 patients (52.4%) and in the AH + DM2 subgroup in 19 of 41 patients (46.3%).

The mean TG value was slightly higher but insignificantly (p = 0.325) in the AH + DM2 subgroup. In the AH subgroup, 37 of 103 patients (35.9%) and in the AH + DM2 group, 18 of 41 patients (43.9%) had TG values above normal.

The mean value of HDL was below normal in both subgroups while it was insignificantly lower in the AH + DM2 subgroup compared to the AH subgroup (p = 0.898). 57 of 103 patients (55.3%) and 22 of 41 patients (53.7%) had HDL values below normal in the AH subgroup and in the AH + DM2 subgroup respectively.

The mean value of LDL was above normal in the AH subgroup being at the upper limit of normal in the AH + DM2 subgroup (the differences between the subgroups did not reach statistical significance (p = 0.056)). In 67 of 103 patients (65.0%) and 20 of 41 patients (48.8%), LDL values were higher than normal in the AH subgroup and in the AH + DM2 subgroup respectively.

The mean values of VLDL, not differing significantly (p = 0.325), were higher than normal in both subgroups with some

Table 1. Comparison of lipid spectrum in AH and AH+DM2 subgroups

Parameters	AH subgroup	AH + DM2 subgroup	Statistical significance
TC (M±m, mmol/l)	5,54±0,12	5,31±0,18	p=0,313
TG (M±m, mmol/l)	1,70±0,07	1,99±0,23	p=0,325
HDL (M±m, mmol/l)	1,08±0,03	1,04±0,03	p=0,898
LDL (M±m, mmol/l)	3,69±0,09*	3,36±0,15*	p=0,056*
VLDL (M±m, mmol/l)	0,77±0,03	0,90±0,11	p=0,325
CA (M+ m)	4,32±0,13	4,21±0,29	p=0,794

predominance in the AH + DM2 subgroup. 75 of 103 patients (72.8%) and 31 of 41 patients (75.6%) had a high VLDL level in the AH subgroup and in the AH + DM2 subgroup respectively.

The mean values of atherogenic index were elevated above the normal values in both subgroups. Elevated values of atherogenic index were detected in 90 of 103 patients (87.4%) in the AH subgroup and in 34 of 41 patients (82.9%) in the AH + DM2 subgroup. Differences between subgroups did not reach statistical significance (p = 0.794).

Along with the above, various echocardiographic changes in the heart were also observed in the compared subgroups. Various pathological echocardiographic changes were detected in 72 of 103 patients in the AH subgroup (69.9%). In the subgroup AH + DM2, changes were noted in 40 of 41 patients (97.6%). Thus, in the AH + DM2 subgroup, pathological echocardiographic changes were detected to a significantly greater extent ($\chi 2$ = 12.980; p<0.0001) indicating an additional pathogenic effect of DM2 on the structural-functional condition of the heart.

The incidence of IHD between subgroups was not significantly different as stable angina in the AH subgroup was found in 23 patients (22.3%) and in 11 patients (12.2%) in the AH + DM2 group ($\chi 2$ = 4.174; p = 0.243); postinfarction cardiosclerosis – in 9 patients (8.7%) in the AH subgroup and in 4 patients (9.8%) in the AH + DM2 subgroup ($\chi 2$ = 0.037; p = 0.847); atherosclerotic cardiosclerosis – in 30 patients (29.1%) in the AH subgroup and in 12 patients (29.3%) in the AH + DM2 subgroup ($\chi 2$ = 0.001; p = 0.986).

Data on the frequency of various pathological echocardiographic changes in the compared subgroups are presented below (Table 2):

As the table shows, there was a clear tendency to increased frequency in some echocardiographic signs indicating cardiac pathology in the AH + DM2 subgroup; at the same time, in a number of parameters (the frequency of LVH, dilatation of the cardiac cavities, development of diastolic dysfunction and diffuse hypokinesis), differences with the AH subgroup were significant. Relatively more often, but unreliably, local hypokinesis and akinesis were also detected in the AH + DM2 subgroup.

The mean value of EF was 56.5±0.6% (with variance of 36-71%) and 53.1±1.1% in the AH subgroup and in the AH + DM2 subgroup, respectively, (36-66%), the difference between subgroups was significant (p = 0.012).

A similar picture was observed in relation to the mean values of IVS and LVPW thickness, which were significantly higher in the AH + DM2 subgroup: 12.2±0.2 (9.8-15) mm and 11.5±0.2 (7-15) mm (p = 0.027); 11.4±0.2 (9-15) mm and 10.7±0.1 (7-15) mm (p = 0.004), respectively.

The results of the CCA ultrasound scan also showed the presence of certain differences between the compared subgroups (Table 3).

According to the results of this study, the mean value of IAD in the right CCA was higher in the AH group compared to the AH + DM2 subgroup but the difference was not statistically significant (p = 0.363). In the right CCA, the mean IMCT value was higher in the AH + DM2 subgroup compared to the AH group but no significance was found (p = 0.253). The ratio IMCT /IAD in the right CCA was higher in the AH + DM2 subgroup compared to the AH subgroup but the difference was not statistically significant (p = 0.115).

In the left CCA, the mean values of IAD and IMCT /IAD ratios were not significantly higher in the AH subgroup compared to the AH + DM2 group (p = 0.415 and p = 0.591). The mean values of IMCT in the right CCA in the AH + DM2 and AH subgroups were not significantly different.

The speed values as well as the pulsation and resistant indices of the vascular bed did not differ significantly in the compared subgroups.

When analyzing the frequency of various pathological changes in the CCA, significant differences were found between the compared subgroups (Table 4).

As the table shows, a comparative predominance of some pathological signs was noted during ultrasound examination of the CCA in the AH + DM2 subgroup. Thus, an increase in IMCT was significantly more frequently detected in the AH + DM2 subgroup (p = 0.012). AP and stenosis were also detected inconsistently more frequently in the AH + DM2 subgroup (p = 0.710 and p = 0.525, respectively).

When considering the frequency of stenosis of varying degrees, the following differences between subgroups were noted: Grade I stenosis was observed in 11 of 103 patients (10.7%) in the AH

Table 2. The frequency of various pathological echocardiographic changes in the AH and AH + DM2 subgroups

Echocardiographic sign	AH subgroup (n = 103)	Subgroup AH + DM2 (n = 41)	Statistical significance
Left ventricular hypertrophy (LVH)	50 (48,5%±4,9)	33 (80,5%±6,2)	$\chi 2$=12,256; p<0,0001
Diastolic dysfunction of all types	53 (51,5%±4,9)	32 (78,0%±6,5)	$\chi 2$=8,575; p=0,003
Diffuse hypokinesis	7 (6,8%±2,5)	9 (22,0%±6,5)	$\chi 2$=6,820; p=0,009
Local hypokinesis of different LV segments	23 (22,3%±4,1)	12 (29,3%±7,1)	$\chi 2$=0,767; p=0,381
Dilatation of the heart cavities	2 (1,9%±1,4)	4 (9,8%±4,6)	$\chi 2$=4,485; 0,034
Akinesis of various LV segments	5 (4,9%±2,1)	5 (12,2%±5,1)	$\chi 2$=2,445; p=0,118

Table 3. The results of some quantitative indicators of the ultrasound examination of the CCA in AH and AH + DM2 subgroups

	AH Subgroup		AH + DM2 Subgroup	
CCA interadventitial diameter (mm) (IAD)	Right CCA	Left CCA	Right CCA	Left CCA
	7,78±0,10	7,64±0,10	7,58±0,16	7,46±0,14
Intima-Media Complex Thickness (mm) (IMCT)	1,09±0,02	1,12±0,02	1,13±0,03	1,11±0,03
Ratio of IMCT /IAD	0,142±0,004	0,147±0,003	0,152±0,006	0,151±0,005

Table 4. The frequency of pathological changes in AH and AH + DM2 subgroups

Ultrasound signs	AH subgroup (n = 103)	AH + DM2 subgroup (n = 41)	Statistical significance
Increased IMCT (calcification)	76 (73,8%)	38 (92,7%)	$\chi2$=6,349; p=0,012
Atherosclerotic plaques (ASP)	27 (26,2%)	12 (29,3%)	$\chi2$=0,139; p=0,710
Stenosis	26 (25,3%)	12 (29,3%)	$\chi2$=2,225; p=0,527
Vascular tortuosity	10 (9,7%)	2 (4,9%)	$\chi2$=0,896; p=0,344
Varicose veins (v.jugularis)	30 (29,1%)	9 (22,0%)	$\chi2$=0,764; p=0,382

subgroup, 7 of 41 patients (17.1%) in the AH + DM2 subgroup; Grade II stenosis was observed in 12 of 103 patients (11.7%) in the AH subgroup, in 5 of 41 patients (12.2%) in the AH + DM2 subgroup; Grade III stenosis was observed in 3 of 103 patients (2.9%) in the AH subgroup and it was not detected AH + DM2 subgroup at all.

Despite the fact that the frequency of tortuosity and varicose veins was definitely higher in the AH subgroup, this difference between the subgroups did not reach statistical significance (p> 0.05).

DISCUSSION

The results of the study showed significant differences between the AH and AH + DM2 subgroups confirming the significant effect of type 2 diabetes mellitus on the deterioration in various parameters reflecting the morpho-functional state of the cardiovascular system, which led to a conclusion on the aggravating effect of type 2 diabetes mellitus on the AH course. Marked pathological change in echocardiographic parameters such as reduced LVEF, significant thickening of IVS and LVPW, high incidence of LVH, diastolic dysfunction, diffuse hypokinesis and dilatation of the heart cavities in the AH + DM2 subgroup prove the additional damaging type 2 diabetes mellitus impact on the cardiomyocytes strictly and the functional state of the heart as a whole.

It is well known that type 2 diabetes mellitus 2 affects various body systems (including cardiovascular) and patients with type 2 diabetes mellitus have a higher risk of cardiovascular morbidity and mortality compared to those without this pathology [14]. The main danger of DM-2 is the development of macrovascular complications and, accordingly, cardiovascular accidents, due to the accelerated rate of progression of atherosclerosis, caused by the corresponding metabolic abnormalities. The process of a therogenesis begins with endothelial cell dysfunction, in which various pathological factors (dyslipidemia, hypertension, diabetes, smoking, etc.) are given an increased ability to lead to a deficiency in the synthesis of nitric oxide (NO), prostacyclin and, most importantly in DM-2, to cause oxidative stress [15, 16], which plays the most important role in atherogenesis due to the rapid oxidation of LDL, enhancing their atherogenic properties [17, 18]. Thus, DM2 leads to the development of cardiovascular diseases due to the complex combination of various factors that play an important role in the accelerated formation of atherosclerosis, ranging from endothelial dysfunction to the development of clinical manifestations [19].

The blood lipid profile in the compared subgroups did not differ significantly, but there was a comparative increase in the level of TG, LDL, VLDL and a decrease in HDL in the AH + DM2 subgroup.

Large-scale clinical studies have demonstrated an association between dyslipidemia and cardiovascular risk in type 2 diabetes, which is associated, at least in part, with increased levels in TG, LDL and low HDL levels [20, 21]. Since the development of atherogenic dyslipidemia precedes the appearance of obvious glycemia and clinical diagnosis of diabetes, early effective treatment is recommended to reduce the risk of premature cardiovascular diseases.

Almost all the patients included in this study showed an increase in IMCT confirming the presence of an atherosclerotic process in the example of the carotid arteries of the patients studied. The average value of IMCT was significantly higher in the AH + DM-2 subgroup compared with the AH subgroup, which indicated the more frequent atherosclerotic vascular damage in this subgroup of patients.

The CCA IMCT indicator is often used to assess the degree of vascular remodeling, since this indicator reliably indicates the onset of the atherosclerotic process in the blood vessel walls in its early subclinical stages. It has been proven that IMCT exceeds all lipid spectrum parameters in sensitivity and specificity as a marker of atherosclerosis [22]. Increased IMCT is also associated with a higher incidence of cardiovascular disease.

In a number of studies, it was found that in patients with DM-2, T, along with traditional factors (AH, dyslipidemia, smoking, and others), such factors as hyperglycemia, hyperinsulinemia and insulin resistance have an additional pathogenic effect on the IMCT [23, 24].

CONCLUSION

The results of the study confirm the role and significance of DM-2 in exacerbating the pathological changes in the heart and blood vessels in comorbidity with hypertension. In patients with hypertension, when combined with type 2 diabetes mellitus, more pronounced echocardiographic signs of heart disease and atherosclerotic changes in the CCA are observed as compared to patients with hypertension without carbohydrate metabolic disorders.

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