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ORIGINAL RESEARCH

Predictors of the progression of metabolic disorders and insulin resistance in patients with arterial hypertension and diabetes mellitus type 2

Predictores de la progresión de los trastornos metabólicos y la resistencia a la insulina en pacientes con hipertensión arterial y diabetes mellitus tipo 2

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Key words:
Arterial hypertension, diabetes mellitus type 2, metabolic disorders, insulin resistance, adipocytokines.

Palabras clave:
Hipertensión arterial, diabetes mellitus tipo 2, trastornos metabólicos, resistencia a la insulina, adipocitoquinas.

ABSTRACT

The mechanisms of the metabolic disorders progression were analyzed in patients with concomitant course of arterial hypertension and diabetes mellitus type 2, of which the most significant are the insulin resistance state, disorders of carbohydrate metabolism, development of atherogenic dyslipidemia and systemic inflammation in correlation with the imbalance of adipocytokines, which contributes to high cardiovascular risk.

RESUMEN

Se analizaron los mecanismos de progresión de los trastornos metabólicos en pacientes con hipertensión arterial y diabetes mellitus tipo 2, de los cuales los más significativos son el estado de resistencia a la insulina, los trastornos del metabolismo de los carbohidratos, el desarrollo de dislipidemia aterogénica y la inflamación sistémica en correlación con el desequilibrio de las adipocitoquinas, lo que contribuye al alto riesgo cardiovascular.

Arterial hypertension (AH) and diabetes mellitus (DM) type 2 are the components of the metabolic syndrome that contribute to the early development of target organs damage and consequently, cardiovascular accidents.[1,2]

The identification of insulin resistance (IR) effect on the incidence of cardiovascular events development in DM type 2.

Studies of the last years established that high insulin level in the blood serum can accelerate the development of atherosclerotic processes.[3,4]

IR is considered not only as the main link in the development of DM type 2 and its complications, but also a component which participate in the pathogenesis of atherosclerosis, hypertension and other diseases.[5,6]

The evidence from epidemiological studies indicate that approximately 80-90% of patients with DM type 2 are overweight or obese. Thus, the presence of I degree obesity is 2 times increase the risk of developing DM type 2, II degree-5 times, III degrees - more than 10 times. A particular role is played by fat distribution.[7,8] Established that visceral fat accumulation is associated with impaired glucose tolerance and IR regardless of body weight.[9,10]

Adipose tissue is an endocrine organ that is the site of synthesis of a large number of hormones and bioactive peptides.[11] There is evidence that some substances synthesized by adipose tissue can impair insulin signal transduction and cause IR in early stages on the stage of pre-diabetes.[12,13]

Recent studies have confirmed that the obesity progression may be caused by decrease in the secretion of zinc α2-glycoprotein (ZAG).[14-16] ZAG is a newly identified adipokines.

Recent studies show that ZAG levels in blood serum and adipose tissue in obese

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patients is significantly lower towards patients with normal body weight.[17,18] ZAG levels are negatively correlated with body weight.[19] The experimental research ZAG infusion caused a steep body mass decline in mice.[20] Single cases study identified that patients with AH had decreased ZAG levels.[21] These results show that ZAG is a new adipokines which is associated with the metabolic syndrome and its components. Thus the study of ZAG influence on the pathogenetic mechanisms of metabolic disorders progression in patients with AH and DM type 2, is an urgent problem.

Aim

To study the influence of hormonal factors on the progression of metabolic disorders in patients with hypertension and type 2 diabetes.

MATERIAL AND METHODS

The study involved 110 patients with AH and DM type 2: the 1st group consisted of 57 patients with AH, 2nd group - 53 patients with concomitant AH and DM type 2. The control group (n = 20) was the most comparable in age and sex to the patients surveyed. The average age of patients was 54.5 ± 4.5 years. Clinical examination of patients included an analysis of complaints, collection of medical anamnesis, physical monitoring and an evaluation of anthropometric indicators.

Diagnosis of hypertension 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). To study the anthropometric characteristics of the course of AH and DM type 2, patients were grouped according to Body Mass Index (BMI). The diagnosis of DM type 2 were carried out according to the criteria of the International Diabetes Federation (IDF, 2015). The criteria for inclusion into study was subcompensated diabetes: Impaired fasting glycaemia (IFG) not exceeding 8.5 mmol/L, postprandial hyperglycemia not exceeding 11 mmol/L and HbA1c level not higher than 9%.

Lipid spectrum Indicators of blood serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein - (HDL), low-density lipoprotein (LDL) was determined by an enzymatic colorimetric method using sets «Human» (Germany).

Insulin levels in blood serum were determined by enzyme-linked immunosorbent assay ELISA, «DRG» sets, (USA). Assessment of insulin resistance level was performed using HOMA (homeostasis model assessment) - homeostasis model assessment to insulin resistance by calculating the index (HOMA-IR) by the formula: HOMA-IR = insulin mcU/mL, glucose, mmol/L/22.5. The concentration of glucose in fasting blood serum (FBS) was determined by glucose oxidation method, also was determined glucose tolerance.

The content of tumor necrosis factor- α (TNF- α) in the blood serum were determined by enzyme immunoassay using sets of «Protein contour» (St. Petersburg).

ZAG level was determined by ELISA using «Bio Vendor» reagent kit (Czech Republic). The content of C - reactive protein (CRP) was analyzed by using ELISA with «DRG» set of reagent (USA).

The statistical processing of the results the research carried out by means of the software package Statistica - 6.0 using Student's t-test and nonparametric statistical methods.

RESULTS AND DISCUSSION

The analysis of the trophological status identified characteristics for both groups. Patients with BMI in the range 18.5-24.9 kg/m^2 (6 patients) identified in the group with progression of isolated AH. However, III degree of obesity (BMI exceed 40.0 kg/m^2) was observed in two patients with AH and in 5 patients with concomitant AH and DM type 2. The predominant majority of patients with isolated and combined course of the disease (67.1% and 54.2%, respectively) had a BMI in the range 30-34.9 kg/m^2. Thus, in patients with AH and BMI 30-34.9 kg/m^2 prevail men (71.2%), and with a BMI 35-39.9 kg/m^2 and more-women (74.5%).

Indicators of the lipid levels in patients with comorbid hypertension and DM type

2, characterized by the progression of an atherogenic dyslipidemia *(Table I)*. The triglyceride levels in blood serum of patients with AH and DM type 2 is 1.4 times ($p < 0.05$) higher than in patients of the 1st group and 2.3 times higher- indicators of the control group ($p < 0.05$). Reducing HDL levels in patients with AH and DM type 2 was observed significantly more frequently than in the control group (55.4% and 22.4%, respectively; $p < 0.05$). In patients with comorbidities BMI 30-34.9 kg/m2 had lower HDL levels compared with the value of this indicator in the comparison group ($p < 0.05$). Progression of lipid disorders in patients with concomitant course of the disease depending on BMI: maximum values of TC and TG were observed with BMI 35-40 kg/m2 ($p = 0.240$, $p = 0.064$, respectively), and the concentration of HDL in blood serum had the lowest value.

The concomitant and DM type 2 caused to increase in the ratio of an atherogenic index (AI) in 2.3 times in comparison with the control and 1.2 times with the comparison group, indicating the progression of atherosclerotic lesions in blood vessels.

Analysis of the insulin resistance (IR) indicators in patients of both groups testified that the maximum values of HOMA-IR index, insulin and C-peptide were patients in the 2nd group in comparison with indicators of the 1st group and the control ($p = 0.000$; $p = 0.007$; $p = 0.005$, respectively) *(Table II)*, indicating that the progression of IR in hyperinsulinemia conditions associated with the presence of DM type 2.

HOMA-IR index exceeded the control indicators by 2.1 times in the group of patients with isolated course of disease and 2.4 times was significantly higher in patients with concomitant AH and DM type 2 ($p = 0.005$) *(Table II)*.

Identified statistically significant relationship between glucose levels ($r = 0.54$; $p = 0.04$), BMI ($r = 0.54$; $p = 0.0056$) and the level of TC ($r = 0.60$; $p = 0.052$) confirms the hypothesis that IR influence on the development of dyslipidemia and associated with inflammation in patients with concomitant AH and DM type 2.

Impaired glucose tolerance (IGT) in patients with AH was observed in 9.6% of cases ($p < 0.05$), whereas patients of 2nd group in 97.5% ($p < 0.05$). A significant increase of HbA1c observed in patients of 2nd group compared to control ($p < 0.05$) confirms the negative impact of excess weight on carbohydrate metabolism and unsatisfactory compensation of carbohydrate metabolism, which increases the metabolic disorders and

Table I. Characteristics of the lipid spectrum in examined patients (M ± SD).

	Control group n = 20	AH n = 57	AH + DM n = 53	
Indicators	1	2	3	p
Total cholesterol mmol/L	5.3 ± 2.2	5.5 ± 2.3	5.8 ± 2.8	$p_{1-2} = 0.46$ $p_{1-3} = 0.32$ $p_{2-3} = 0.72$
HDL, mmol/L	1.3 ± 0.6	1.2 ± 0.7	0.7 ± 0.42	$p_{1-2} = 0.53$ $p_{1-3} = 0.003$ $p_{2-3} = 0.009$
TG, mmol/L	1.8 ± 0.8	1.7 ± 1.1	2.9 ± 1.2	$p_{1-2} = 0.73$ $p_{1-3} = 0.002$ $p_{2-3} = 0.0002$
LDL, mmol/L	3.2 ± 1.54	3.64 ± 1.6	4.07 ± 3.0	$p_{1-2} = 0.27$ $p_{1-3} = 0.054$ $p_{2-3} = 0.34$

cause the atherosclerotic vascular lesion *(Table III)*, patients of the 1st group 1 (7.4%) has been observed a significant increase in FBG levels compared to the control group ($p < 0.05$), which is explained by the presence of abdominal obesity, because excess body weight is one of the cause for IR progression, the maximum value of this indicator has been reached in patients with concomitant AH and DM type 2 ($p < 0.05$).

Analysis of changes in the blood serum concentration of ZAG in patients with isolated and concomitant course of disease set the reduction of ZAG level in patients in both groups comparatively to the control, indices lowest ZAG level observed in patients with concomitant course of AH and DM type ($p < 0.05$), and negatively correlated with the index HOMA-IR ($r = -0.52$; $p < 0.05$), the concentration of TG ($r = -0.54$; $p < 0.05$), the level of glucose ($r = -0,48$; $p < 0.05$), BMI ($r = -0.48$; $p < 0.05$) and HbA1c ($r = -0.57$; $p < 0.01$), which proves its participation in the progression and formation of IR and its impact on carbohydrate and lipid metabolism.

In both groups, there was observed a significant increase of TNF-α in blood serum comparatively to the control group ($p < 0.05$). The largest increase in 2.5 times ($p < 0.001$) was observed in concomitant course of AH and DM type 2.

CRP levels in blood serum exceed the reference values in both groups of surveyed

Table II. The characteristics of insulin resistance in patients surveyed (M ± SD).

	Control group n = 20	AH n = 57	AH+DM n = 53	
Indicators	1	2	3	p
HOMA-IR	1.64 ± 0.52	4.47 ± 2.5	5.43 ± 3.2	$p_{1-2} = 0.00001$ $p_{1-3} = 0.00002$ $p_{2-3} = 0.15$
Insulin, mcU/mL	5.56 ± 2.2	10.7 ± 5.6	13.6 ± 7.2	$p_{1-2} = 0.0004$ $p_{1-3} = 0.0002$ $p_{2-3} = 0.049$

Table III. The characteristics for carbohydrate metabolism in patients surveyed (M ± SD).

	Control n = 20	AH n = 57	AH + DM n = 53	
Indicators	1	2	3	p
Glucose (mmol/L)	4.24 ± 2.34	6.26 ± 3.72	7.76 ± 3.91	$p_{1-2} = 0.034$ $p_{1-3} = 0.0003$ $p_{2-3} = 0.074$
HbA1c (%)	4.4 ± 2.3	6.3 ± 3.51	8.4 ± 4.16	$p_{1-2} = 0.0976$ $p_{1-3} = 0.0002$ $p_{2-3} = 0.0056$
GTT, mmol/L	5.14 ± 3.6	10.32 ± 4.91	13.6 ± 7.21	$p_{1-2} = 0.0002$ $p_{1-3} = 0.0000$ $p_{2-3} = 0.01$

Table IV. The indicators for inflammation markers and glycoprotein in patients with concomitant course of disease (M ± SD).

	Control group n = 20	BMI = 25.0-29.9 kg/m^2; n = 30	BMI = 30.0-34.9 kg/m^2; n = 15	BMI = 35.0-39.5 kg/m^2; n = 8	
Indicators	1	2	3	4	p
Zinc-alpha 2-glycoprotein mg/mL	78.2 ± 39.2	64.5 ± 31.1	52.0 ± 25.1 p_{2-3} = 0.26	46.2 ± 21.3 p_{2-4} = 0.06 p_{3-4} = 0.21	p_{1-2} = 0.44 p_{1-3} = 0.075 p_{1-4} = 0.053
TNF-α, pg/mL	5.22 ± 3.2	7.6 ± 3.64	10.3 ± 4.91 p_{2-3} = 0.087	14.3 ± 6.68 p_{2-4} = 0.006 p_{3-4} = 0.14	p_{1-2} = 0.02 p_{1-3} = 0.0008 p_{1-4} = 0.0001
CRP, mg/L	3.82 ± 1.81	4.5 ± 1.91	7.8 ± 3.84 p_{2-3} = 0.004	11.3 ± 6.3 p_{2-4} = 0.0004 p_{3-4} = 0.12	p_{1-2} = 0.26 p_{1-3} = 0.0002 p_{1-4} = 0.0001

patients ($p < 0.05$). The greatest increase for CRP indicators (in 2.2 times) was observed in patients with comorbidity ($p < 0.05$) and correlated with BMI ($r = 0.45$; $p < 0.001$), FBG level ($r = 0.46$; $p < 0.001$) and TG levels ($r = 0.39$; $p < 0.04$), index of HOMA-IR ($r = 0.48$; $p < 0.001$).

It was found that ZAG level decreased in a linear regression of BMI in patients with concomitant course of disease, which may be considered as a marker for progression of metabolic disorders in patients with comorbid AH and DM type 2 *(Table IV)*.

With an increasing BMI index was registered a significant increase in TNF-a and CRP ($p < 0.05$), which is associated with the activation of systemic inflammation.

CONCLUSION

The mechanisms of metabolic disorders formation were analyzed in patients with concomitant course of AH and DM type 2, which are characterized by the progression of IR and the development of atherogenic dyslipidemia (reduced HDL, increasing LDL and TG), the increase in systemic inflammation markers and most observed in patients with overweight and obesity.

In patients with AH and DM type 2 occurs the decrease of ZAG indicators in blood serum, which is most observed in patients with obesity, making it possible to recognize the adipokine as a new marker for progression of metabolic disorders in these patients.

Thus, a comprehensive diagnosis of hypertension with concomitant AH and DM type 2 based on the definition for indicators of hormonal and metabolic disorders, will contribute to the individualization of preventive and therapeutic measures, and as a result to establish control of atherosclerosis progression and reduction in cardiovascular risk.

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