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ORIGINAL ARTICLE
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ASSOCIATIONS OF IRS-1 POLYMORPHISM WITH VARIOUS COMPONENTS OF THE METABOLIC SYNDROME IN HYPERTENSIVE PATIENTS

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ABSTRACT

Introduction: The metabolic syndrome is one of the most discussed cross-disciplinary problems of modern medicine. Now there are various definitions and criteria of diagnostics of metabolic syndrome. The abdominal obesity is considered the main component of the metabolic syndrome, as a reflection of visceral obesity which degree is offered to be estimated on an indirect indicator – a waist circumference. Alongside with abdominal obesity, a number of classifications distinguish insulin resistance (IR) as a diagnostic criterion of metabolic syndrome. It is proved that IR is one of the pathophysiological mechanisms influencing the development and the course of arterial hypertension (AH), type 2 DM and obesity. There are two components in the development of IR: genetic (hereditary) and acquired. In spite of the fact that IR has the accurate genetic predisposition, exact genetic disorders of its appearance have not been identified yet, thus demonstrating its polygenic nature.

The aim: To establish possible associations of the insulin receptor substrate-1 (IRS-1) gene polymorphism with the severity of the metabolic syndrome components in patients with arterial hypertension (AH).

Materials and methods: 187 patients with AH aged 45-55 years and 30 healthy individuals. Methods: anthropometry, reactive hyperemia, color Doppler mapping, biochemical blood analysis, HOMA-insulin resistance (IR), glucose tolerance test, enzyme immunoassay, molecular genetic method.

Results: Among hypertensive patients, 103 had abdominal obesity, 43 - type 2 diabetes, 131 - increased blood triglycerides, 19 - decreased high density lipoproteins, 59 - prediabetes (33 - fasting hyperglycemia and 26 - impaired glucose tolerance), 126 had IR. At the same time, hypertensive patients had the following distribution of IRS-1 genotypes: Gly/Gly - 47.9%, Gly/Arg - 42.2% and Arg/Arg - 10.7%, whereas in healthy individuals the distribution of genotypes was significantly different: Gly/Gly - 86.8% ($p<0.01$), Gly/ Arg - 9.9% ($p<0.01$) and Arg/Arg - 3.3% ($p<0.05$). Hypertensive patients with Arg/Arg and Gly/Arg genotypes had significantly higher HOMA-IR ($p<0.01$), glucose, insulin and triglycerides levels ($p<0.05$), than in Gly/Gly genotype. At the same time, body mass index, waist circumference, blood pressure, adiponectin, HDL, interleukin-6, C-reactive protein, degree of endothelium-dependent vasodilation, as well as the frequency of occurrence of impaired glucose tolerance did not significantly differ in IRS-1 genotypes.

Conclusions: in hypertensive patients, the genetic polymorphism of IRS-1 gene is associated with such components of the metabolic syndrome as hypertriglyceridemia and fasting hyperglycemia; it is not associated with proinflammatory state, endothelial dysfunction, dysglycemia, an increase in waist circumference and decrease in HDL.

KEY WORDS: metabolic syndrome, insulin receptor substrate-1 gene, arterial hypertension, genetic polymorphism

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INTRODUCTION

The metabolic syndrome is one of the most discussed cross-disciplinary problems of modern medicine. Initially the term "metabolic syndrome" was offered for the persons having the increased risk of cardiovascular diseases devel-opment and type 2 diabetes mellitus (DM) [1–3]. Then this term was complemented with new criteria.

Now there are various definitions and criteria of diagnostics of metabolic syndrome (World Health Organization; European Group for the Study of Insulin Resistance; National Cholesterol Education Program-Adult Treatment Panel III; American Association of Clinical Endocrinologists; International Diabetes Federation; International Atherosclerosis Society, International Association for the Study of Obesity [4–8]. Irrespective of one or another definition, criteria of diagnostics of metabolic syndrome is existence of at least three of its components (various combination of obesity, the increased arterial blood pressure (BP), increases of the low density lipoproteins (LDL), triglycerides, decrease of the high density lipoproteins (HDL) and violations of carbohydrate metabolism).

The abdominal obesity is considered the main component of the metabolic syndrome, as a reflection of visceral obesity which degree is offered to be estimated on an indirect indicator – a waist circumference [9–14]. Alongside with abdominal obesity, a number of classifications distinguish insulin resistance (IR) as a diagnostic criterion of metabolic syndrome.

It is proved that IR is one of the pathophysiological mechanisms influencing the development and the course of arterial hypertension (AH), type 2 DM and obesity [6, 15, 16].

There are two components in the development of IR: genetic (hereditary) and acquired. In spite of the fact that IR has the accurate genetic predisposition, exact genetic disorders of its appearance have not been identified yet, thus demonstrating its polygenic nature.

At the present stage, it is known that the sensitivity of peripheral tissues to insulin is defined also by the existence of specific receptors, which mediate the stimulating influ-ence of insulin on glucose utilization with the participation of glucose conveyors and start the whole range of cellular reactions [15, 17]. Receptor level of IR formation is one of three levels of disorders and consists of the reduction of the number of insulin receptors, abnormal shapes of receptors to insulin and substrate of an insulin receptor (IRS) of type 1 and also the disorder in affinity of insulin receptors [15–18]. At the present stage, there are known 4 main IRS among which IRS-1 and IRS-2 are leading because of their mediation the majority of biological effects of insulin.

Despite the considerable achievements in genome researches, the majority of the genetic factors contributing to the development and progressing of various components of the metabolic syndrome remain uncertain. The existence of contradictory views of a contribution of polymorphism Gly972Arg of IRS-1 gene to the formation of IR in various populations [18–26] caused carrying out this research in the Ukrainian population of patients.

THE AIM

The aim of the research: establishment of possible asso-ciations of polymorphism of IRS-1 gene with the expres-siveness of various components of the metabolic syndrome in patients with AH.

MATERIALS AND METHODS

We examined 187 patients aged 45-55 years with AH stage II grade 2 (the main group) and 30 healthy individuals (the control group). Patients of the main group (92 men and 95 women) had a history of hypertension for less than 5 years, medicated with antihypertensive drugs non-systemically and/or did not reach target BP levels when prescribing drug therapy.

In this study, using standard biochemical methods on the patients, we defined venous blood glucose concentration, and insulin levels. IR was determined using the homeo-stasis model assessment index (HOMA-IR). In patients without previously established DM, a glucose tolerance test was conducted. For studying endothelial function, the degree of endothelium-dependent vasodilation (EDVD) in reactive hyperemia was determined in all patients. Investigations were carried out using a broadband linear transducer 5-12 MHz Doppler color mapping with three readings being taken arteries at 15-min intervals between samples on the left and right brachial arteries, according to the method of Celermajer D.S. (in the modification of the method by Ivanova O.V.) [27, 28]. Normally, the maximum vasodilation of the brachial artery should exceed 10% of the original diameter. Simultaneously, we measured the intima media thickness (IMT) of the carotid artery (CA, 2 cm proximal to the bifurcation of the common CA). Determining the pulse wave velocity (PWV) of the abdominal aortic (AA, on the left subclavian artery to the femoral artery) was performed using a phased transducer with a frequency of 2-4 MHz.

Levels of interleukin-6 (IL-6), C-reactive protein (CRP) and adiponectin in blood were determined during enzyme immunoassay. The rs1801278 polymorphism of the IRS-1 gene was assessed by the molecular genetic method. Three genotypes of the IRS-1 gene (Gly/Gly, Gly/Arg and Arg/Arg) were identified. Processing of statistical data was per-formed using the software package “Statistics”. The values are presented as the average value of parameters (M) and standard error (m).

The study protocol was approved by the Ethics Commit-tee. All participants were informed about the aim of the study and signed a written consent form.

RESULTS

It was established that among 187 examined persons with AH the main components of the metabolic syndrome were present at such percentage: 55.1% had abdominal obesity, 33% – fasting hyperglycemia (≥ 5.6 mmol/l), 22.9% – diag-nosed earlier (established less than 2 years ago) type 2 DM, 70.1% had increased blood triglycerides (≥ 1.7 mmol/l), and 10.2% – decrease in HDL <1.03 mmol/l in men and <1.29 mmol/l in women). IR estimated by the index of HOMA is established in 67.8% of patients (table 1).

Dysglycemia (impaired glucose tolerance) as an addi-tional criteria of the metabolic syndrome was noted in 13.9% of patients, the endothelial dysfunction (estimated on such indicators as EDVD according to test with reactive hyperemia, PWV and IMT) – in 72.7%, and the pro-in-flammatory state (diagnosed according to the content of the CRP, IL-6 and adiponectin) – in 65.8% of patients (table I).

At the same time patients with AH had the following distribution of IRS-1 genotypes (table II): Gly/Gly – 47.9%, Gly/Arg – 42.2% and Arg/Arg – 10.7% whereas in control group there were reliable differences in genotypes distribu-tion: Gly/Gly – 86.8% ($p<0.01$), Gly/Arg – 9.9% ($p<0.01$) and Arg/Arg – 3.3% ($p<0.05$).

Thus, the frequency of occurrence of various options of genotypes IRS-1 gene authentically differed at almost healthy patients and in hypertensive patients with various components of the metabolic syndrome. At the following stage, associations

Table I. Presence of the metabolic syndrome components at hypertensive patients

Components of the metabolic syndrome	Hypertensive patients with different components of the metabolic syndrome	
	n	%
Abdominal obesity	103	55.1
Triglycerides ≥ 1.7 mmol/l	131	70.1
HDL <1.03 mmol/l at men and <1.29 mmol/l at women	19	10.2
Fasting hyperlycemia ≥ 5.6 mmol/l	33	17.6
Earlier diagnosed type 2 DM	43	22.9
IR (↑HOMA- IR)	126	67.4
Impaired glucose tolerance (dysglycemia)	26	13.9
Endothelial dysfunction (↓EDVD, ↑ PWV, ↑IMT)	136	72.7
Pro-inflammatory condition (↑CRP, ↑IL-6, ↓adiponectin)	125	65.8

Table II. Distribution of IRS-1 genotypes in the main and control groups

Genotypes	Main group, n=187		Control group, n=30		Reliability of a difference between groups
	n	%	n	%	
Gly/Gly	88	47,9	26	86.8	p<0.01
Gly/Arg	79	42,2	3	9.9	p<0.01
Arg/Arg	20	10,7	1	3.3	p<0.05

of polymorphism of IRS-1 gene with anthropometrical, metabolic and hemodynamic indicators in hypertensive patients were estimated. It was established that patients of the main group with Arg/Arg and Gly/Arg genotypes had significantly higher levels of glucose ($p<0.05$), insulin ($p<0.05$), HOMA-IR ($p<0.01$), triglycerides ($p<0.05$), than patients with Gly/Gly genotype. Although BMI, waist circumference, BP levels, adiponectin, LDL, IL-6, CRP, EDVD degree and also frequency of occurrence of the impaired glucose tolerance significantly did not differ in various IRS-1 genotypes (table III).

Considering the fact that genotypes of Arg/Arg and Gly/Arg significantly differed from Gly/Gly genotype in lager expressiveness of metabolic disorders, and among themselves – only HOMA-IR, at a further stage genotypes of Arg/Arg and Gly/Arg were united in one group – with (Gly/Arg + Arg/Arg) genotypes (table IV).

DISCUSSION

The features of distribution of genotypes of IRS-1 gene established in our research at hypertensive patients in the presence of different components of the metabolic syn-drome, confirm results of a number of researches according to which Gly972Arg the polymorphism of the specified gene is associated with development of IR in the European and Mexican populations [16–20].

In spite of the fact that according to some authors [17] Gly972Arg the polymorphism is associated with BMI, in this research there was not established the reliable distinctions of BMI in various IRS-1 genotypes in patients with AH.

The data obtained in our research, coincide with results of a number of researchers according to which existence of Gly/Arg and Arg/Arg genotypes was associated with higher levels of atherogenous lipoproteins [17–19].

Reliable distinctions of levels of insulin, glucose and HOMA-IR in various IRS-1 genotypes are confirmation of Gly972Arg polymorphism association with development and progressing of receptor level of IR in hypertensive patients. At the same time, the most expressed IR is char-acteristic of hypertensive patients with homozygous Arg/ Arg genotype of IRS-1.

In spite of the fact that endothelial dysfunction is one of links between IR and cardiovascular diseases and also is considered as additional criterion of the metabolic syndrome, in our research the analysis of a structurally functional condition of vessels in various IRS-1 genotypes did not show reliable distinctions of indicators depending on IRS-1 polymorphism.

It should be noted that one more component of the met-abolic syndrome – the pro-inflammatory condition that is estimated on the CRP, IL-6 and adiponectin levels, also did not show reliable distinctions in different IRS-1 genotypes.

Thus, results of our research showed that in hypertensive patients, Gly972Arg polymorphism of IRS-1 gene is associated only with separate components of the metabolic syndrome.

CONCLUSIONS

In hypertensive patients, the polymorphism of IRS-1 gene is associated with such components of metabolic syndrome as hypertriglyceridemia and fasting hyperglycemia; the

Table III. Comparative assessment of indicators in hypertensive patients depending on IRS-1 polymorphism

Indicators	Hypertensive patients, n=187		
	Genotype		
	Gly/Gly, n=88	Gly/Arg, n=79	Arg/Arg, n=20
SBP, mm Hg	168.7 ± 0.41	169.4 ± 0.43	169.9 ± 0.62
DBP, mm Hg	99.8 ± 0.24	100.5 ± 0.28	101.1 ± 0.34
BMI, kg/m$_2$	29.8 ± 0.39	31.1 ± 0.35	30.7 ± 0.44
Waist circumference, cm	94.5 ± 2.46	96.3 ± 3.57	97.1 ± 4.04
IMT, mm	0.85 ± 0.008	0.87 ± 0.012	0.86 ± 0.009
PWV AA, m/s	8.46 ± 0.12	8.49 ± 0.15	8.47 ± 0.12
EDVD, %	7.71 ± 0.07	7.57 ± 0.08	7.49 ± 0.14
Cholesterol, mmol/l	5.97 ± 0.05	6.12 ± 0.04	6.07 ± 0.05
Triglycerides, mmol/l	1.82 ± 0.04	2.12 ± 0.05*	2.18 ± 0.06**
LDL, mmol/l	4.49 ± 0.05	4.89 ± 0.04*	4.94 ± 0.08**
HDL, mmol/l	1.14 ± 0.01	1.08 ± 0.01	1.05 ± 0.02
Blood glucose, mmol/l	5.65 ± 0.02	6.43 ± 0.03*	6.51 ± 0.04**
Insulin, mcU/ml	16.8 ± 0.48	22.1 ± 0.52*	23.8 ± 0.43**
HOMA-IR	3.96 ± 0.11	5.21 ± 0.08*	6.05 ± 0.09**º
Adiponectin, ng/ml	7.82 ± 0.03	7.54 ± 0.02	7.65 ± 0.03
IL-6, ng/ml	139.6 ± 4.12	145.9 ± 5.31	148.7 ± 4.99
CRP, mg/dl	6.3±0.22	6.7±0.25	6.6±0.34
Distribution of patients with impaired glucose tolerance, %	46.2	38.5	15.3

Note: * – statistically significant difference between genotypes of Gly/Gly and Gly/Arg; ** – statistically significant difference between genotypes of Gly/Gly and Arg/Arg; º – statistically significant difference between genotypes of Gly/Arg and Arg/Arg.

Table IV. Comparative assessment of indicators at Gly/Gly and Gly/Arg + Arg/Arg genotypes IRS-1 in patients with AH

Indicators	Hypertensive patients, n=187	
	Genotype	
	Gly/Gly, n=88	Gly/Arg + Arg/Arg, n=99
SBP, mm Hg	168.7 ± 0.41	169.6 ± 0.45
DBP, mm Hg	99.8 ± 0.24	100.9 ± 0.31
BMI, kg/m$_2$	29.8 ± 0.39	30.0 ± 0.32
Waist circumference, cm	94.5 ± 2.46	96.8 ± 3.29
IMT, mm	0.85 ± 0.008	0.87 ± 0.011
PWV AA, m/s	8.46 ± 0.12	8.48 ± 0.14
EDVD, %	7.71 ± 0.07	7.55 ± 0.09
Cholesterol, mmol/l	5.97 ± 0.05	6.09 ± 0.05
Triglycerides, mmol/l	1.82 ± 0.04	2.14 ± 0.05*
LDL, mmol/l	4.49 ± 0.05	4.91 ± 0.05*
HDL, mmol/l	1.14 ± 0.01	1.07 ± 0.02
Blood glucose, mmol/l	5.65 ± 0.02	6.46 ± 0.03*
Insulin, mcU/ml	16.8 ± 0.48	22.9 ± 0.44*
HOMA-IR	3.96 ± 0.11	5.42 ± 0.07*
Adiponectin, ng/ml	7.82 ± 0.03	7.57 ± 0.03
IL-6, ng/ml	139.6 ± 4.12	146.9 ± 6.13
CRP, mg/dl	6.3±0.22	6.7±0.27
Distribution of patients with impaired glucose tolerance, %	46.2	53.8

Note: * – statistically significant difference between genotypes of Gly/Gly and Gly/Arg +Arg/Arg.

specified polymorphism is not associated with pro-inflammatory state, endothelial dysfunction, dysglycemia, increase in waist circumference and decrease in HDL.

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