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Abstract

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DETERMINANTS OF FORMATION OF TRUE RESISTANCE TO ANTIHYPERTENSIVE TREATMENT IN PATIENTS WITH ARTERIAL HYPERTENSION WITH CONCOMITANT OBESITY

The aim of the research: identify combinations of genetic and neurohumoral factors that influence the development of true resistance to antihypertensive therapy (AHT) in patients with concomitant obesity (OB).

Materials and Methods. The study included 200 patients aged 45–55 with uncontrolled hypertension and obesity. Treatment was prescribed in accordance with the European Guidelines 2018. Thiazide-like diuretics were additionally prescribed to those patients who did not reach the target blood pressure (BP) level after 3 months of dual therapy. Resistant hypertension was diagnosed in 48 patients who had an uncontrolled course of hypertension at the optimal doses of three antihypertensive drugs during the next month of their reception, while true resistance was found in 21 patients. The effectiveness of comprehensive treatment was evaluated after 6 months.

Results. The application of the logistic regression method at the stage of initial examination of patients showed that the early predictors of the formation of truly resistant hypertension in obese patients are CIMT, HOMA index and genetic polymorphism IRS-1.

After treatment, the model of truly resistant hypertension in patients with obesity included indicators that influenced its formation at the pre-treatment stage, as well as the new ones: adiponectin, waist circumference and genetic polymorphism ADIPOQ.

Conclusions. Genetic markers, insulin resistance, and vascular wall status play a leading role in the development of true resistance to AHT in obese patients. It is established that the main determinants of the formation of true resistance to AHT in patients with this comorbidity are IRS-1 polymorphism, HOMA index and CIMT.

Key words: resistant hypertension, antihypertensive therapy, obesity, genetic polymorphism, logistic regression.

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Резюме

ДЕТЕРМІНАНТИ ФОРМУВАННЯ ІСТИННОЇ РЕЗИСТЕНТНОСТІ ДО АНТИГІПЕРТЕНЗИВНОЇ ТЕРАПІЇ У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ ІЗ СУПУТНІМ ОЖИРІННЯМ

Мета дослідження: виявити комбінації генетичних і нейрогуморальних чинників, що впливають на розвиток істинної резистентності до антигіпертензивної терапії (АГТ) у пацієнтів з супутнім ожирінням (ОЖ).

Матеріали і методи. У дослідження включено 200 пацієнтів у віці 45–55 років із неконтрольованою АГ та ОЖ. Лікування призначали відповідно до Європейських настанов 2018 року. Тим хворим, які не досягли цільового рівня артеріального тиску (АТ) через 3 місяці на подвійний терапії, додатково призначали тіазидоподібний діуретик. Резистентну АГ діагностували у 48 пацієнтів, які мали неконтрольований перебіг АГ на оптимальних дозах трьох гіпотензивних препаратів протягом наступного місяця їх прийому, водночас істинна резистентність виявлена у 21 хворого. Ефективність комплексного лікування оцінювали через 6 місяців.

Результати: Застосування методу логістичної регресії на етапі первинного обстеження пацієнтів продемонструвало, що ранніми предикторами формування істинно резистентної АГ у пацієнтів з ожирінням є показники ТІМ ЗСА, індексу HOMA й генетичний поліморфізм IRS-1.

Після проведеного лікування в модель істинно резистентної АГ у хворих з ОЖ входили як індикатори, що впливали на її формування на етапі до лікування, а також нові індикатори: адипонектин, показник окружності талії (ОТ) та генетичний поліморфізм ADIPOQ.

Висновки. Генетичні маркери, інсулінорезистентність та стан судинної стінки відіграють провідну роль в розвитку істинної резистентності до АГТ у пацієнтів із ожирінням. Встановлено, що основними детермінантами формування істинної резистентності до АГТ у хворих із цією коморбідністю є поліморфізм IRS-1, індекс HOMA та ТІМ ЗСА.

Ключові слова: резистентна гіпертензія; антигіпертензивна терапія, ожиріння, генетичний поліморфізм, логістична регресія.

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Introduction/Вступ

According to the epidemiological studies, the definition of "non-infectious" epidemics can be applied to both hypertension (AH) and obesity (OB). AH takes an important place among diseases with significant social consequences increasing disability and mortality [1]. At the same time, according to the World Health Organization in 2018, obesity is one of the independent risk factors for the development of cardiovascular pathology

and a frequent comorbid condition in patients with hypertension [2]. The simultaneous presence of hypertension and obesity in patients is associated with the earlier development of cardiovascular catastrophes, as well as an increase in the number of cases of treatment-resistant hypertension [3]. The prognosis in patients with resistant hypertension is particularly unfavorable. The risk of developing cardiovascular complications in the form of stroke, myocardial infarction, heart failure, end-stage renal disease is many times greater than in the absence of resistance to treatment in patients [4–6]. Multifactorial diseases (MFDs) are pathogenetically dependent on the interaction of exogenous, endogenous and epigenetic factors. Regardless of the cause that triggers the pathological process, its manifestations, taking into account the individual characteristics of each person's genotype, are always unique. The study of any MFD, assessment of hereditary risk factors, and construction of appropriate models require consideration of all these components [7–9]. To date, there are many questions about the contribution of molecular genetic and neurohumoral factors in the pathogenesis of cardiovascular remodeling, methods for early diagnosis of non-resistant and resistant hypertension in patients with metabolic syndrome are in the process of developing [10–13].

Aim of the research. Identify combinations of genetic and neurohumoral factors that influence the development of true resistance to antihypertensive therapy (AHT) in patients with concomitant obesity (OB).

Materials and Methods.

We examined 200 stage II hypertensive patients with class I–II obesity aged 45–55, who provided informed written consent to participate in the study.

Patients underwent a comprehensive general clinical examination with assessment of anthropometric parameters, office blood pressure was measured according to the generally accepted method, and home blood pressure monitoring was performed to exclude white coat hypertension. In the absence of both office control and blood pressure control at home, "uncontrolled persistent hypertension" was diagnosed.

The degree of carbohydrate metabolism disorders was assessed by determining fasting glucose, glycosylated hemoglobin (HbA1c) and performing an oral glucose tolerance test. Serum insulin concentration was determined using Insulin ELISA kits («DRG Diagnostics», Germany). The HOMA index was calculated by the formula:

HOMA-IR = blood glucose (mmol/L) × blood insulin (μU/mL) / 22.5

HOMA-IR values of 2.77 or more were regarded as the insulin resistance (IR) presence.

The functional state of adipose tissue was assessed by leptin and adiponectin parameters, the state of proinflammatory activity was assessed by the levels of interleukin-6 (IL-6) and C-reactive protein (CRP), the activity of RAAS was assessed by the content of aldosterone and plasma renin activity. The intensity of lipid peroxidation was evaluated by indicators of prooxidant activity – levels of malonic dialdehyde and diene conjugates, antioxidant capacity - by the indicator of general antioxidant protection.

Genomic DNA was extracted from peripheral blood leukocytes using "DNA express blood" kit. Identification of the G276T polymorphism of the ADIPOQ gene and the G972R polymorphism of the IRS-1 gene was performed by the polymerase chain reaction followed by restriction analysis using sequences of specific primers (direct – 5'GGCCTCTTTCATCACAGACC-3' and reverse – 5'AGATGCAGCAAAGCCAAAGT-3' for identification of G972T polymorphism; for identification of G972T polymorphism – direct – 5'AGTCTGGCTACTTGTCTGGC-3, reverse – 5'ATGAGTTGTCCCCGTCAGA-3'). The BsmI enzyme was used to cleave the polymerase chain reaction products at genotyping the G276T polymorphism of the ADIPOQ gene, and the amplification products were incubated with AluI restriction enzyme when genotyping the G972R gene of the IRS-1 gene. The hydrolysis products were isolated in 3% agarose gel and visualized. Three genotypes of the IRS-1 gene (G/G, G/R and R/R) and three genotypes of the ADIPOQ gene (G/G, G/T, T/T) were identified.

Morphofunctional properties of the heart and blood vessels were evaluated on an ultrasound scanner "IMAGIC Agile" (manufactured by "Kontron Medical", France). Ultrasound scanning of the arteries was performed according to the standard method with a linear broadband sensor 5-12 MHz in duplex mode with color mapping. The pulse wave velocity in the carotid artery (cPWV) and the abdominal aorta (aPWV) was determined using the W-track method. The degree of endothelium-dependent vasodilation (EDVD) was determined in a sample with reactive hyperemia according to the method of D. S. Celermajer in the modification of O. V. Ivanova [14].

Statistical methods were used for mathematical data processing: variation statistics, factor analysis, correlation analysis, ROC-analysis, logistic regression method.

Research results and their discussion.

According to the European guidelines for the management of patients with hypertension in 2018, drug treatment of patients starts with the double AHT prescription. Patients received a combination of angiotensin-converting enzyme (ACE) inhibitor perindopril and calcium channel blocker (CCB) amlodipine. The primary target blood pressure levels were < 140/90 mm Hg. As a non-drug treatment, patients with hypertension with concomitant obesity were prescribed diet therapy aimed at correcting body weight and reducing blood pressure to target values. Patients were also advised to increase physical activity, mainly by walking at a fast or moderately fast pace for at least 45 minutes per day.

After 3 months from the beginning of the prescribed therapy, the patients' achievement of the target blood pressure values was assessed with double AHT. Patients who achieved BP targets continued to receive prescribed therapy. The rest were prescribed a third antihypertensive drug, the thiazide-like diuretic indapamide. At this stage, a fixed combination of perindopril arginine, amlodipine, and indapamide (Triplixam) was recommended to improve adherence to treatment, and a diagnostic test was performed to rule out secondary hypertension. If after 1 month treatment patients did not reach the target blood pressure levels with the use of optimal daily doses of three antihypertensive drugs, they were considered as patients with resistant hypertension and were additionally prescribed aldosterone antagonist - spironolactone. Physical activity considered sufficient in case of the increase of the average intensity of aerobic exercise not least than 300 minutes per week, and patients who did not adhere to it – patients with reduced physical activity.

According to ESC/ESH criteria, 21 patients were diagnosed true resistance to AHT. The use of logistic regression in such patients at the stage of the initial examination showed that the model of true resistance included indicators: CIMT (regression coefficient (CR) 7.06), genetic polymorphism IRS-1 (CR 2.90) and HOMA index (CR 1.62) ($p < 0.05$ for all indicators). The influence of these indicators on the formation of true resistance was confirmed by the odds ratio (OR) and 95% confidence intervals (CI) and the area under the ROC curve (0, 953). For HOMA-IR: OR – 5.03; 95% CI – 2.50–10.11; for IRS-1: OR – 18.15; 95% CI – 4.46–73.91; for CIMT: OR – 1161.53; 95% CI – 1.5386–25047.42.

Given the above data, the model of true resistance hypertension to AHT in patients with concomitant obesity in the pre-treatment phase is as follows:

$y = \exp (b_0 + 1.62x_1 + 2.90x_2 + 7.06x_3)/[1+ \exp (b_0 + 1.62x_1 + 2.90x_2 + 7.06x_3)]$,

where $b_0 = -19.64$ – constant; x_1– HOMA-IR; x_2 – polymorphism IRS-1; x_3 – CIMT.

After treatment, the model of true resistance included some of the indicators that impact the pre-treatment phase (CIMT (CR 11.08). HOMA index (CR 1.06)), as well as new indicators (adiponectin (CR (–2.08)), waist circumference (CR 0,13) and ADIPOQ polymorphism (CR 2,34), ($p < 0.05$ for all indicators)).

The effect of these indicators on the formation of true resistance to AHT in patients with obesity, assessed by logistic regression at the after treatment stage confirmed by the odds ratio and 95% confidence intervals, as well as the area under the ROC curve (0.960). For adiponectin: OR – 7.98; 95% CI – 2.36–27.01; for HOMA-IR: OR – 2.89; 95% CI – 0.97–8.60; for waist circumference: OR– 1.14; 95% CI – 1.02–1.27; for CIMT: OR – 65058.06; 95% CI – 20.81–2033729.38; for ADIPOQ polymorphism: OR –10.40; 95% CI – 1.14–95.02.

Thus, the model of true resistance hypertension in patients with concomitant obesity:

$y = \exp (b_0 – 2.08x_1 + 1.06x_2 + 0.13x_3 + 11.08x_4 + 2.34x_5)/[1+ \exp (b_0 –$

$–2.08x_1 + 1.06x_2 + 0.13x_3 + 11.08x_4 + 2.34x_5)]$,

where $b_0 = -49.94$ – constant; x_1 – adiponectin; x_2 – HOMA-IR; x_3 – waist circumference; x_4 – CIMT; x_5 – genetic polymorphism ADIPOQ.

The results of the study bring some clarity to the understanding of the features of the differentiated integration of molecular genetic, neurohumoral, and environmental factors involved in the formation of resistant hypertension (RAH) in patients with concomitant obesity. We have defined the leading role of genetic markers, insulin resistance and vascular wall condition in the development of true resistance to AHT and proved the feasibility of studying polymorphisms ADIPOQ and IRS-1, HOMA-IR and CIMT as markers of RAH. It is important despite significant advances in genetic research, there is still insufficient data on the contribution of molecular genetic factors in

cardiovascular remodeling in patients with hypertension, there are quite conflicting views on the role of gene expression and genetic polymorphism in development and course of diseases in different populations of patients [13]. Our proposed methods of mathematical modeling are quite promising in terms of predicting the development of RAH in patients with obesity, and their use expands opportunities for physicians to individualize a comprehensive therapeutic approach at the stage of treatment.

According to a number of studies, resistance to AHT is associated with almost a threefold increase in the risk of cardiovascular events [4, 6, 15], and its prevalence varies depending on the selected criteria and characteristics of patients. Given the use of European criteria in 2018, the prevalence of RAH in adults reaches 13% [4, 16]. The prognosis in these patients is much worse than in the general population of patients with hypertension [6, 15]. This justifies the need for a further comprehensive and balanced approach both to search for new markers of the disease and to assess their suitability for accurate risk prediction.

Conclusions/Висновки

Genetic markers, insulin resistance, and vascular wall status play a leading role in the development of true resistance to AHT in obese patients. The IRS-1 polymorphism, HOMA index, and CIMT have been defined to be the main determinants of the formation of true resistance to AHT in patients with this comorbidity.

Prospects for future research/Перспективи подальших досліджень

Search for new markers of resistant hypertension and assess their suitability for accurate risk prediction.

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Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

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