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Clinical evaluation of the insulin resistance syndrome in hypertensive patients with normal body weight

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Abstract

Objective. To evaluate the effect of insulin resistance on arterial hypertension and target organ damage in patients with normal body weight. **Design and methods.** The study involved 95 patients with arterial hypertension 1–2 degree (essential hypertension stage I–II) with normal body weight (body mass index 18.5–24.9 kg/m^2) aged 30–50 years. The examination included fasting blood glucose, immunoreactive insulin, the index of insulin resistance — QUICKI factor, as well as lipids, serum uric acid and microalbuminuria. In addition, patients underwent ambulatory blood pressure monitoring, duplex scanning of neck vessels, echocardiography, endothelial function assessment. **Results.** The rate of insulin resistance-hyperinsulinaemia syndrome was 36% in the studied group of hypertensive patients with normal body weight. Hypertensive patients with insulin resistance had higher average daily systolic blood pressure, higher rate and more severe target organ damage (left ventricular hypertrophy, endothelial dysfunction, intima media thickness). Among metabolic disorders, dyslipidemia was predominant, in particular, hypertriglyceridemia, as well as increased total cholesterol and LDL-cholesterol, and decrease in HDL-cholesterol. **Conclusions.** Insulin resistance and hyperinsulinaemia syndrome is registered in 36% of hypertensive patients with normal body weight. They are characterized by high rate of hypertension and more severe target organ damage, and metabolic disorders (mainly hypertriglyceridemia).

Key words: hypertension, insulin resistance, hyperinsulinaemia, metabolic syndrome, insulin

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Клиническая оценка гемодинамических и метаболических нарушений, развивающихся при инсулинорезистентности у больных артериальной гипертензией с нормальной массой тела

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Резюме

Цель исследования — изучить влияние инсулинорезистентности (ИР) на характер течения артериальной гипертензии, ассоциированные метаболические расстройства и степень поражения органов-мишеней у больных с нормальной массой тела. **Материалы и методы.** Обследовано 95 больных артериальной гипертензией 1–2-й степени (гипертонической болезнью I–II стадии) с нормальной массой тела (индекс массы тела: ИМТ = 18,5–24,9 кг/м²) в возрасте 30–50 лет. В программу обследования входило определение уровня глюкозы крови натощак, иммунореактивного инсулина, показателя инсулинорезистентности — величины коэффициента QUICKI, показателей липидограммы, уровня мочевой кислоты крови и тест на наличие микроальбуминурии (МАУ). Включенным в исследование пациентам, помимо офисного артериального давления, проводили суточное мониторирование артериального давления, дуплексное сканирование сосудов шеи, эхокардиографическое исследование и оценивали эндотелиальную функцию. **Результаты.** Частота регистрации синдрома инсулинорезистентности-гиперинсулинемии (ИР-ГИ) в исследуемой группе пациентов с артериальной гипертензией (АГ) с нормальной массой тела составила 36 %. При наличии ИР у пациентов с АГ отмечены более высокие значения среднесуточного систолического артериального давления (САД) по данным суточного мониторирования артериального давления (СМАД), бóльшая частота регистрации и степень выраженности органных изменений — гипертрофия левого желудочка (ГЛЖ), показателей дисфункции эндотелия (ДЭ), гиперплазии комплекса интима-медиа (КИМ). Из метаболических нарушений отмечены чаще встречающиеся изменения липидного профиля — прежде всего повышение уровня триглицеридов (ТГ), а также увеличение холестерина (ХС) и липопротеинов низкой плотности (ЛПНП), снижение липопротеинов высокой плотности (ЛПВП). **Выводы.** В исследуемой группе пациентов с АГ и нормальной массой тела синдром ИР-ГИ зарегистрирован в 36 % случаев. В этой группе больных АГ отмечены бóльшая степень АГ, чаще встречающиеся и более выраженные поражения органов мишеней, а также метаболические расстройства — прежде всего повышение уровня ТГ.

Ключевые слова: артериальная гипертензия, инсулинорезистентность, гиперинсулинемия, метаболический синдром, инсулин

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Introduction

Insulin resistance (IR) is one of the most common, but less examined risk factors of cardiovascular complications promoting numerous hemodynamic and metabolic disorders.

Insulin resistance — a primary, selective and specific disorder of insulin biological action which is accompanied with the decrease of glucose consumption by tissues (skeletal muscles, adipose tissue and liver) and results in chronic compensatory hyperinsulinemia (HI) [1].

The mechanisms of evolving IR-HI and development of associated cardiovascular disorders are most well-studies in android-type obesity — "metabolic syndrome" [2–4]. It is established that evolving arterial hypertension (AH) in metabolic syndrome is the consequence of insulin resistance — hyperinsulinemia. However IR and AH may have reverse causalities, i.e. hypertensive patients with normal body weight having hemodynamic changes may develop secondary IR-HI which promotes further progression of metabolic disorders. The frequency of IR reporting in AH in patients with a normal body weight varies, according to various authors, from 30% to 40% [5, 6]. However, in general, the assessment of IR-HI in hypertensive patients without concomitant obesity and progression of cardiovascular disorders remains unspecified.

The study aim — to examine IR effect on the nature of arterial hypertension, associated metabolic disorders and degree of damage of target organs in patients with normal body weight.

Materials and methods

95 patients with arterial hypertension of 1–2 degree (essential hypertension of stage I–II) with a normal body weight with any significant concomitant pathology which had been randomly chosen were examined at the outpatient visit. Inclusion criteria: patients with arterial hypertension of 1–2 degree (essential hypertension of stage I–II), body mass index (BMI) 18.5–24.9 kg/m^2, aged 30–50 years, informed voluntary patient's consent for participation in the study. Exclusion criteria: obesity/excessive body weight, essential hypertension of degree III, diabetes mellitus, study withdrawal. The examination program included the determination of fasting glucose level (G) in venous blood and immunoreactive insulin (I) to determine IR value —QUICKI factor value. QUICKI factor = 1/(log (I))+log (18*G). IR was diagnosed with QUICKI < 0.32. Cholesterol (CL), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), blood triglycerides (TG), uric acid levels were determined in all patients. To identify changes in renal function, the semi-quantitative test for microalbuminuria (MAU) was made

Figure. Proportion of patients with insulin resistance in the examined group of hypertensive patients with a normal body weight

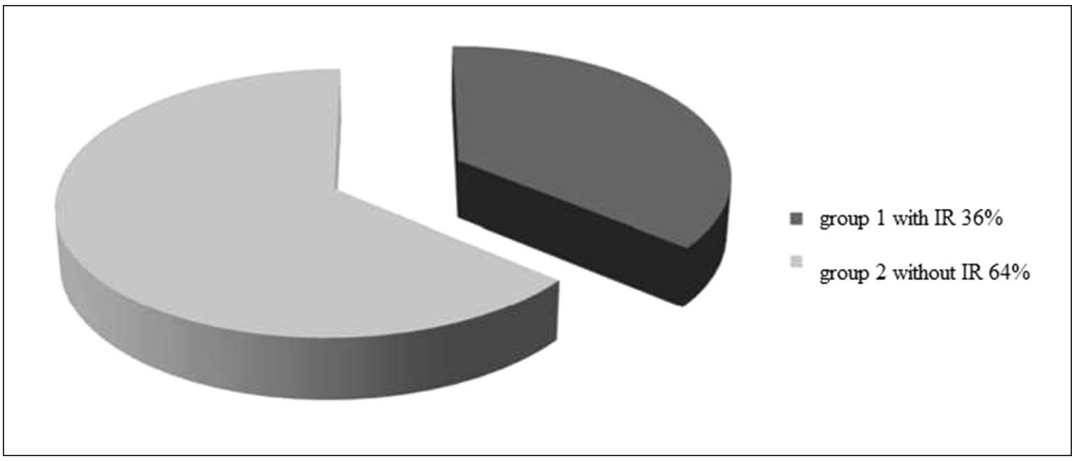

Table 1

CLINICAL CHARACTERISTICS OF THE STUDY GROUPS OF HYPERTENSIVE PATIENTS

Age, years	With IR n= 34	Without IR n = 61	p
	41.3 ± 0.91	41.6 ± 0.68	p > 0.05
Sex (f/m), n	15/19	32/29	p > 0.05
AH history, years	4.73 ± 0.33	5.08 ± 0.28	p > 0.05
SBP, mm Hg	145.2 ± 2.6	143.0 ± 1.3	p > 0.05
DBP, mm Hg	87.2 ± 1.0	88.9 ± 0.7	p > 0.05

Table 2

LEVELS OF OFFICE BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH A NORMAL BODY WEIGHT

Parameters	M ± m		p
	with IR (n = 34)	without IR (n = 61)	
САДсс, мм рт. ст.	152.4 ± 2.1	146.4 ± 1.9	p < 0.05*
САДсд, мм рт. ст.	155.1 ± 1.3	152.3 ± 1.9	p > 0.05
САДсн, мм рт. ст.	133.3 ± 1.0	135.8 ± 1.3	p > 0.05
ДАДсс, мм рт. ст.	83.3 ± 1.6	86.5 ± 1.1	p > 0.05
ДАДсд, мм рт. ст.	92.6 ± 1.7	89.7 ± 1.9	p > 0.05
ДАДсн, мм рт. ст.	77.3 ± 1.9	74.5 ± 1.3	p > 0.05
ИВ АД днем, %	53.4 ± 12.3	56.7 ± 17.2	p > 0.05
ИВ АД ночью, %	46.3 ± 11.2	48.4 ± 15.9	p > 0.05
ИВ АД за сутки, % (blood pressure load)	58.5 ± 15.4	51.2 ± 10.7	p < 0.05*
Суточный ритм АД типа dipper, %	65	70	p > 0.05
Суточный ритм АД типа non-dipper, %	35	29	p < 0.05*

Note: he table presents the mean arythmetic values in each of the group, the value of Student's t-test and p-value corresponsing to the test which characterizes the degree of statistical significance in differences of the two means; SBP — systolic blood pressure; DBP — diastolic blood pressure; * — significance of differences between the study groups of patients..

using the first morning urine portion (30–300 mg/day). Moreover, the patients enrolled to the study, along with office blood pressure (BP), had 24-hour blood pressure monitoring (BPM), duplex scanning of neck vessels to reveal structural changes of major vessels (carotid arteries) which were diagnosed based on ultrasonic data on thickness of the intima-media complex (IMC > 0.9 mm) or presence of an atherosclerotic plaque. The structural and functional cardiac changes were assessed with echocardiographic examination (ECHO-CG) in M-, V-modes and Doppler modes using the generally accepted Feigenbaum A. method (1986). The left ventricular myocardial mass (LVMM) was calculated by the R. Devereux formula (1977). LVMM index (LVMMI) was calculated based on the ratio of LVMM to a body surface area. The left ventricular hypertrophy (LVH) was diagnosed with LVMMI values above 110 g/m^2. The endothelial function was analyzed based on determination of endothelium-dependent vasodilatation during the test in reactive hyperemia on apparatus Endo-PAT 2000 (ITAMAR, Israel). As normal values, reactive hyperemia index (RHI) > 1.67 was accepted. The statistical analysis of the results was made using with program Statistica 6.0. Excel for Windows (Microsoft, USA, 2000). The examination results were presented as M ± SD (mean value of the tested parameter ± standard deviation). The statistical

significance of group differences was assessed using t-Student's test. Considering low degree of arterial hypertension (essential hypertension of 1–2 degree), the current therapy was withdrawn in the patients 2 days prior the study with careful control of BP level and compliance of recommendations on non-drug anti-hypertensive therapy (as rule, angiotensin-converting enzyme inhibitors, iACE). If necessary, capoten 25 mg once was administered.

Results

Hypertensive patients in the study were divided to 2 groups per QUICKI: group 1–34 subjects with IR, group 2–61 subjects without IR. Therefore the rate of IR reporting in the examined patients with hypertension and normal body weight was 36 % (Fig.). The compared groups did not differ per the age composition, AH history and degree (Tab. 1).

The office BP levels in groups 1 and 2 were comparable: systolic BP (SBP) in group 1 was 145.2 ± 2.6 mm Hg, in group 2–143.0 ± 1.3 mm Hg ($p > 0.05$); the level of diastolic BP (DBP) — 87.2 ± 1.0 and 88.9 ± 0.7 mm Hg, respectively ($p > 0.05$). The 24-hour BP monitoring established the absence of significant differences between the analyzed values of average daytime, average night SBP, DBP in both groups (Tab. 2). Therefore average daytime SBP in group 1 was 155.1 ± 1.3 mm Hg, in group 2 — 152.3 ± 1.9 mm Hg ($p > 0.05$), average daytime DBP in group 1 — 92.6 ± 1.7 mm Hg, in group 2 — 89.7 ± 1.9 mm Hg ($p > 0.05$), average night SBP in group 1 — 133.3 ± 1.0 mm Hg, in group 2–135.8 ± 1.3 mm Hg ($p > 0.05$), average night DBP in group 1 — 77.3 ± 1.9 mm Hg, in group 2 — 74.5 ± 1.3 mm Hg ($p > 0.05$). However the value of average daily SBP in patients with IR (group 1) was higher than in the control group — in patients without IR (group 2): 152.4 ± 2.1 and 146.4 ± 1.9 mm Hg, respectively ($p < 0.05$). The differences may be explained by the fact that daily blood pressure load (BPL) in group 1 was higher than in group 2 and amounted to 58.5 ± 15.4 %, and 51.2 ± 10.7 %, respectively ($p < 0.05$). Daytime blood pressure load in group 1 — 53.4 ± 12.3 %, in group 2 — 56.7 ± 17.2 % ($p > 0.05$).

Night blood pressure load in group 1 — 46.3 ± 11.2 %, in group 2 — 48.4 ± 15.9 % ($p > 0.05$). The normal BP decrease in night hours (dipper) was observed in 22 subjects (65 %) of group 1 and 43 subjects (70 %) of group 2 ($p > 0.05$). The changes of non-dipper daily BP rhythms were observed in 12 subjects (35 %) of group 1 and in 18 subjects (29 %) of group 2 ($p < 0.05$). The more significant changes in LVH values in patients with IR-associated AH are more likely to be related with the higher AH degree (Tabl. 3). So the rate of LVH reporting, based on the left ventricular myocardial mass index (LVMMI) per ECHO-CG, in group 1 and 2 was observed in 27 and 47 patients and amounted to 82 % and 77 %, respectively ($p < 0.05$). LVMMI in patients of group 1 was 124.0 ± 1.70 g/m², group 2 — 120.59 ± 1.23 g/m² ($p < 0.05$).

The carotid doppler ultrasound examination in the study patients established the higher frequency of reporting and intensity of IMC changes in the patients of group 1. So the manifestation of carotid wall hyperplasia (IMC > 0.9 mm) was observed in 21 subjects (62 %) of group 1 and 33 subjects (55 %) — of group 2 ($p < 0.05$). Atherosclerotic plaques were detected in 8 subjects (24 %) in group 1 and in 9 subjects (15 %) — in group 2 ($p < 0.05$).

The most marked vascular wall changes in the hypertensive patients with IR were also detected in the assessment of endothelial function. The presence of endothelial dysfunction was established in 29 subjects (85 %) of group 1 and 48 subjects (78 %) — of group 2 ($p < 0.05$).

One of the manifestations of the endothelial dysfunction — microalbuminuria was observed in 19 (56 %) patients of group 1 and 20 (33 %) patients of group 2 ($p < 0.05$).

The analysis of metabolic disorders in patients with IR-associated AH also revealed certain particularities (Tabl. 4). They were mainly related to carbohydrate metabolism disorders. So the blood level of fasting glucose (G) in group 1 was 5.4 ± 0.06 mmol/l, in group 2–5.19 ± 0.05 mmol/l ($p < 0.05$), postprandial G value in group 1 was 7.58 ± 0.23 mmol/l, in group 2–6.5 ± 0.1 mmol/l ($p < 0.001$). The patients of group 1 had the higher immunoreactive insulin value, respectively, which amounted to 15.88 ± 0.30 μU/ml, in group 2–9.06 ± 0.35 μU/ml ($p < 0.001$). The impaired glucose tolerance tests were observed in 44 % (15 subjects) of cases in patients of group 1 and in 27 % (17 subjects) of cases — in hypertensive patients of group 2 ($p < 0.05$). The serum lipid abnormalities were mainly related to frequency of the change detection. Hypertriglyceridemia (HTG) in the group of patients with IR was observed most frequently in 29 patients (85 %); the dyslipidemia variant was observed in 67 % of cases ($p < 0.001$) in the group of patients without IR. There were 25 patients with hypercholesteremia in group 1 (73.5 %), in group 2–40 patients (65 %), ($p < 0.05$). The increased LDL level was observed in 30 subjects of group 1 (88 %) and 50

Table 3

FREQUENCY OF REPORTING AND DEGREE OF THE LEFT VENTRICULAR HYPERTROPHY IN THE STUDY HYPERTENSIVE PATIENTS

Rate of LVH reporting, %	with IR (group 1)	without IR (group 2)	p
	82	77	$p < 0.05$
LVMMI, g/m²	124.0 ± 1.70	120.59 ± 1.23	$p < 0.05$

Note: the table presents the mean arithmetic values in each of the group, the value of Student's t-test and p value corresponding to the test which characterizes the degree of statistical significance in differences of the two means; LVMMI — left ventricular myocardial mass.

Таблица 4

METABOLIC VALUES IN THE STUDY GROUPS OF HYPERTENSIVE PATIENTS

Parameters	M ± m		p
	with IR (n = 34)	without (n = 61)	
Glucose, mmol/l	5.4 ± 0.06	5.19 ± 0.05	$p < 0.05$*
Insulin, μU/ml	15.88 ± 0.3	9.06 ± 0.35	$p < 0.001$*
Cholesterol, mmol/l	5.63 ± 0.21	5.51 ± 0.13	$p > 0.05$
HDL, mmol/l	1.32 ± 0.23	1.24 ± 0.27	$p > 0.05$
LDL, mmol/l	3.9 ± 0.15	3.6 ± 0.17	$p > 0.05$
Triglycerides, mmol/l	2.23 ± 0.15	2.01 ± 0.23	$p > 0.05$
Uric acid, μmol/l	357 ± 24	335 ± 21	$p > 0.05$

Note: the table presents the mean arithmetic values in each of the group, the value of Student's t-test and p value corresponding to the test which characterizes the degree of statistical significance in differences of the two means. HDL — high-density lipoproteins; low — low-density lipoproteins;* — significance of differences between the study groups of patients.

(81 %) — of group 2 ($p < 0.05$). HDL decrease was revealed in two patients of group 2 (3.27 %). However, the mean values of CL, LDL, HDL, TG levels in both groups were comparable — their differences did not reach the level of statistical significance. CL level in group 1 was 5.63 ± 0.11 mmol/l, in group 2 — 5.51 ± 0.07 mmol/l ($p > 0.05$); HDL 3.9 ± 0.1 and 3.6 ± 0.07 mmol/l, respectively ($p > 0.05$). HDL level in group 1 was 1.32 ± 0.006 mmol/l, in group 2 — 1.24 ± 0.01 mmol/l ($p > 0.05$), TG level — 2.23 ± 0.07 and 2.01 ± 0.07 mmol/l, respectively ($p > 0.05$).

There were no significant changes in purine metabolism in both study groups of patients. Uric acid level in group 1 was 357 ± 24 μmol/l, in group 2 — 335 ± 21 μmol/l ($p > 0.05$).

Discussion

IR-HI syndrome is usually considered as associated with the metabolic cardiovascular syndrome. However, nowadays it is established that IR is a common complex of symptoms in the clinical practice and, according to several authors [7–10], it occurs in 20–25 % of apparently healthy subjects without obesity. So the large-scale population study by Bruneck [6] has shown that IR occurs in 58 % of hypertensive patients both with a normal and excessive body weight. In our study, hypertensive patients with normal body weight had IR syndrome in 36 % of cases. It is supposed that damage of non-oxidative pathway of glucose consumption driven by insulin underlies IR, and skeletal muscles are mainly damaged [11–13]. It is established that insulin sensitivity

of peripheral tissues is closely related to genetically influenced particularities of skeletal muscle morphology. In AH, the number of slowly contracting muscle fibers is significantly decreased which results in a considerable depletion of vascular stream leading to decrease of volumetric blood flow, increase of a total peripheral vascular resistance, increase of glucose diffusion pathway to cells, i.e. IR develops in such cases secondarily to AH. However, according to some authors, IR is fundamental in AH formation which is often its first clinical manifestation. The main mechanisms resulting in BP increase in IR-HI are hypervolemia which is associated with the increased sodium reabsorption in proximal tubules and results in the increase of cardiac output, as well activation of sympathetic nervous system that leads to the increase of cardiac output and results in peripheral vascular spasm and increase of total vascular peripheral resistance [14, 15]. Therefore pathogenetic AH and IR-HI mechanisms are closely interrelated and, as a rule, enhance each other [16]. The obtained data on a more significant increase of an average daily BP in hypertensive patients with IR-HI are likely to be explained with the factor. The results of the comparative analysis of the damage degree of target organs in hypertensive patients with IR enrolled to the study are also explained by the increased hypertensive effect. The larger rate was observed by us — rate and degree of LVH in patients of the group.

The analysis of vascular wall changes, according of carotid ultrasound testing in hypertensive patients with IR, showed higher prevalence of vascular hyperplasia manifestations — thickening of IMC (> 0.9 mm). The changes may be related to endothelial dysfunction developing in IR — a subclinical early marker of atherosclerotic damage of a vascular wall. It is established that ED is a consequence of an impaired nitrogen oxide — a potent vasodilator, the main synthesis product of the vascular endothelium as the endocrine organ of the cardiovascular system [17]. Along with the decrease of secretion of such potent vasodilators such as prostacycline and nitrogen oxide, in the settings of IR-HI under insulin exposure, the endothelium has the increased release of vasoconstrictor biologically substances — endothelin, tromboxane A2 and the decreased secretion of such potent vasodilators such as prostacycline and nitrogen oxide which results in the increase of vascular tone and delayed vasodilation [18, 19],— i.e. endothelial dysfunction develops.

In the study, the larger frequency of ED associated with IR-HI is reported in comparison with the control group: in 29 subjects in group with IR (85%) and 48 subjects in the group without IR (78%), respectively ($p < 0.05$). One of the ED manifestations is MAU — the early parameters of renal impairment due to developing angiopathy. The most significant MAU values was observed more frequently in hypertensive patients with normal body weight and IR than in the control group — in hypertensive patients without IR.

Along with AH and other hemodynamic disorders, IR-HI promotes development of a complex of metabolic disorders — disorders of carbohydrate, lipid, purine and other metabolism types.

It is established that IR-HI syndrome is one of the main factors which results in 2 type diabetes mellitus (DM) especially in the subjects with genetic predisposition. The method of IR determination with QUICKI factor itself is based on the identification of subjects with carbohydrate metabolism disorders. The hypertensive patients with IR examined by us had the increased glucose levels which are determined in fasting conditions and in the glucose tolerance test, as well higher levels of immunoreactive insulin. It should be noted that the increase of absolute values of the parameters does not indicate the development of IR syndrome. QUICKI factor considers the changes of an optimum glucose/insulin ratio which when impaired results in IR.

Along with carbohydrate metabolism disorders, IR-HI results consistently in atherogenic dyslipidemias, in particular hypertriglyceridemia, increase of very low-density lipoprotein cholesterol concentration (VLDL) and HDL decrease. In our work, we noted the larger frequency of dyslipidemia reporting in the group of IR patients [20]. To a greater extent, it was related to the number of patients with hypertriglyceridemia in which the difference between the groups achieved the higher significance level. The changes develop due to the fact that specific effects on lipid synthesis and transport exposed by insulin are typical for insulin. In IR-HI, the blood concentration of free fatty acid being the main precursors of triglyceride synthesis is increased which results in hyperlipidemia typical for IR — hypertriglyceridemia.

Therefore IR-HI syndrome plays an important role in pathogenesis of dyslipidemias which are the proven risk factors of coronary artery disease and other atherosclerotic diseases.

Conclusions

1. The rate of IR reporting in the study patients with AH and normal body weight was 36%.

2. According to the data of 24-hour blood pressure monitoring, the degree of AH in the group of patients with IR was significantly higher in comparison with the group of hypertensive patients without IR.

3. Concentric LVH remodeling in hypertensive patients with AR was observed 1.5 times more often than in the group of patients without IR.

4. Common changes of arterial vessels and kidneys in hypertensive patients with normal body weight and IR were ED and MAU: they occurred in 85% and 56% of cases which significantly exceeded the value of the parameters in hypertensive patients without IR (78% and 33%, respectively).

5. The most marked metabolic disorders in hypertensive patients with normal body weight and IR were related to carbohydrate metabolism. The impaired glucose tolerance tests were detected in 44% of patients of the group and 27% of hypertensive patients without IR.

6. The lipid profile change as hypertriglyceridemia was observed in hypertensive patients with IR in 85% of cases which significantly exceeded the rate of HTGin hypertensive patients without IR — 67%.

Conflict of interest

The authors declare no conflict of interest.

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