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Abstract

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DEPENDENCE OF THE ACTIVITY OF THE SYSTEM OF OXIDATIVE STRESS – ANTIOXIDANT PROTECTION ON INSULIN RESISTANCE IN PATIENTS WITH ESSENTIAL HYPERTENSION AND OBESITY

Relevance. The activation of free radical oxidative processes and the development of oxidative stress is one of the most important pathogenetic mechanisms of cardiovascular diseases. Active forms of oxygen can change cellular infiltration of vessels and endothelial function, having an impact on a functional condition of the adhesive molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. Under condition of insulin resistance (IR), the balance in the system of oxidative stress – antioxidant protection is disturbed, the result of which is insufficient resistance to the damaging effect of the LPO products.

The aim of the study was to assess the dependence of the activity of the system of oxidative stress – antioxidant protection on insulin resistance (IR) in patients with comorbidity of arterial hypertension and obesity.

We examined 200 patients with hypertension and class I–II obesity. The patients were divided into two groups depending on IR: the first group included 80 patients without IR and the second group – 120 patients with IR.

As the result of the study, it was established that the presence of IR affects the activity of the system of oxidative stress – antioxidant protection in comorbidity of hypertension and obesity. In the presence of IR, patients with hypertension and concomitant obesity have significantly higher levels of indicators of the system of oxidative stress (malondialdehyde (MDA) and diene conjugates (DC)) compared with patients without IR. In patients with comorbidity of hypertension and obesity, HOMA-IR directly correlated with the indicators of the oxidative stress system (MDA and DC) and inversely correlated with the indicator of total antioxidant protection. In hypertensive patients with obesity and no IR, an increase in HOMA-IR was associated with a decrease in total antioxidant protection, and in patients with IR, an increase in HOMA-IR was associated with an increase in MDA and DC, as well as a decrease in total antioxidant protection.

Keywords: insulin resistance, oxidative stress, antioxidant protection, hypertension, obesity.

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Резюме

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ЗАЛЕЖНІСТЬ АКТИВНОСТІ СИСТЕМИ ОКСИДАТИВНОГО СТРЕСУ – АНТИОКСИДАНТНОГО ЗАХИСТУ ВІД НАЯВНОСТІ ІНСУЛІНОРЕЗИСТЕНТНОСТІ У ПАЦІЄНТІВ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ТА ОЖИРІННЯМ

Мета роботи полягала в оцінюванні залежності активності системи оксидативного стресу – антиоксидантного захисту від наявності інсулінорезистентності (ІР) у пацієнтів із коморбідністю артеріальної гіпертензії та ожиріння.

Обстежено 200 пацієнтів із гіпертонічною хворобою (ГХ) та ожирінням I–II ступенів. Пацієнти були поділені на дві групи залежно від наявності у них ІР: до першої групи ввійшло 80 пацієнтів без ІР, до другої – 120 пацієнтів з ІР.

У результаті проведеного дослідження встановлено, що наявність ІР впливає на активність системи оксидативного стресу – антиоксидантного захисту при коморбідності ГХ та ожиріння. За наявності ІР пацієнти з ГХ і супутнім ожирінням мають достовірно вищі рівні показників системи оксидативного стресу (малонового діальдегіду (МДА) та дієнових кон'югатів (ДК)) порівняно з пацієнтами без ІР. У пацієнтів із коморбідністю ГХ та ожиріння HOMA-IR прямо корелює з показниками системи оксидативного стресу (МДА і ДК) і зворотно корелює з показником загального антиоксидантного захисту. У гіпертензивних пацієнтів з ожирінням в умовах відсутності ІР збільшення HOMA-IR асоціюється зі зниженням загального антиоксидантного захисту, а в пацієнтів з ІР – зі збільшенням МДА і ДК, а також зниженням загального антиоксидантного захисту.

Ключові слова: інсулінорезистентність, оксидативний стрес, антиоксидантний захист, гіпертонічна хвороба, ожиріння.

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Introduction

The results of recent studies have shown that the activation of free radical oxidative processes and the development of oxidative stress is one of the most important pathogenetic mechanisms of cardiovascular diseases [1, 3, 5, 14]. Increased production of free radicals contributes to the development of endothelial dysfunction (ED) with a violation of the ratio of the influence of vasoactive substances and factors with a predominance of vasoconstrictor effects [2, 8, 12, 13]. The activity of free radical oxidative processes is estimated by the content of lipid peroxidation products (LPO) – diene conjugates (DC), malondialdehyde (MDA) and Schiff bases in blood serum. The effectiveness of antioxidant protection is evaluated by changes in the activity of superoxide dismutase, which binds reactive oxygen species with formation of hydrogen peroxide, glutathione peroxidase, which reduces lipid hydroperoxides, glutathione reductase, which restores glutathione by oxidation of NADPH, catalase, which destructs peroxide into lipid hydroperoxides, as well as by the overall antioxidant activity [1, 4, 5, 9].

In general, LPO is a process in which oxidants, such as free radicals, attack lipids, primarily polyunsaturated fatty acids (PUFA), as a result of which hydrogen is cleaved from carbon, and released oxygen forms peroxide radicals and hydroperoxides. The main substrates for LPO are PUFA. In general, LPO consists of three stages: initiation, propagation and termination resulting in the formation of a wide range of oxidation products. In healthy individuals, the activity of the LPO system is opposed by the system of antioxidant protection, but in insulin-resistant (IR) states, the balance in the system of oxidative stress -– antioxidant protection is disturbed, the result of which is insufficient resistance to the damaging effect of the LPO products [3, 4, 6, 9].

It has been established that IR and ED are closely associated conditions, since IR is considered an independent risk factor for dyslipidemia, systemic inflammation, and oxidative

stress, and ED is the link between IR and cardiovascular disease [7, 8, 11, 15-17].

At the same time, hypotheses regarding the primacy of the origin and relationships of IR and ED are quite contradictory, which leads to further study of these states.

Thus, the **aim of the study** was to assess the dependence of the activity of the system of oxidative stress – antioxidant protection from the presence of IR in patients with comorbidity AH and obesity.

Clinical characteristics of patients and research methods. 200 patients with essential hypertension (EH) and class I–II obesity, who gave informed written consent to participate in the study and met the inclusion criteria, were examined. Patients were divided into two groups depending on IR presence: the first group included 80 patients without IR, the second – 120 patients with IR.

Criteria for inclusion in the study: stage II, grade 2 EH; class I obesity (BMI – 30–34.9 kg/m^2), class II obesity (BMI – 35–39.9 kg/m^2), abdominal obesity (according to IDF criteria, 2005): waist circumference > 94 cm for men and > 80 cm for women; chronic heart failure (CHF) I – II functional classes (FC); preserved ejection fraction (EF) of the left ventricle (LV); normal glomerular filtration rate (GFR), normokreatininaemia, absence of proteinuria (only microalbuminuria is allowed); age of patients – 45-55 years.

Criteria for exclusion from the study: the presence of comorbidities in patients with EH (acute coronary syndrome, post-infarction cardiosclerosis, severe rhythm and conduction disorders, rheumatic heart disease, systemic connective tissue diseases, oncological diseases, symptomatic arterial hypertension (AH), thyroid diseases, acute inflammatory processes); stage III, grade 3 EH; class III obesity; type 1 and type 2 diabetes; III–IV FC CHF; moderately reduced and reduced LV EF; reduced GFR, the presence of proteinuria; age of patients less than 45 and more than 55 years; refusal of patients to participate in the study.

IR was calculated using the HOMA model:

HOMA-IR = blood glucose (mmol/l) × blood insulin (μAU/l) /22.5.

HOMA-IR value 2.77 and greater was considered as IR presence.

The concentration of insulin in the blood serum was determined using "Insulin ELISA" ("DRG Diagnostics", Germany) sets using solid-phase radioimmunological analysis.

The condition of the prooxidant system was assessed by the levels of molecular products of LPO – DC and MDA, and the condition of the antioxidant protection system – by the overall antioxidant activity (during spectrophotometry).

The results were processed by methods of variation statistics using the "STATISTICA" software. The data are presented as M ± σ, where M is the average value; σ is the standard deviation. During the significance analysis of the differences between the two groups in the severity of the index, expressed by a number, the Student's t-test was used. To estimate the degree of connectivity or synchronicity in the changes of indicators, the R – coefficient of linear correlation (Pearson product-moment correlation) was calculated.

Results and discussion

The results of the study showed that the activity of the system of oxidative stress in hypertensive patients with obesity in the presence of IR was more pronounced than in patients without IR (Table 1). Thus, patients with IR had significantly ($p = 0.000$) higher levels of DC ((33.444 ± 3.142) nmol/ml) than patients with EH without IR ((29.591 ± 2.094) nmol/ml). Similar differences were observed in MDA levels: (36.924 ± 2.860) nmol/ml with IR and (33.729 ± 3.447) nmol/ml without IR, which significantly ($p = 0.000$) distinguished the groups from each other. The established features are a confirmation of the important role of IR in the occurrence and progression of endothelial dysfunction. Thus, in the presence of IR endothelial dysfunction occurs long before the appearance of obvious disorders of carbohydrate metabolism. Considering the results and the presence of conflicting hypotheses of the relationship of IR and ED, IR can be considered, on the one hand, as a factor in the development of endothelial dysfunction, and on the other – as a consequence [1, 3, 5, 10].

As for the indicator of activity of the antioxidant protection system (total antioxidant protection), during the study there was no significant difference in its levels in the presence and absence of IR ($p = 0.149$). It can be assumed that these features are associated with the fact that the system of oxidative stress is more sensitive to IR than the system of antioxidant protection.

Table 1 – Indicators of the system of oxidative stress – antioxidant protection in patients in the presence and absence of IR

Indicators	Patients with EH and obesity, n = 200		
	IR absent, n = 80	IR present,n = 120	p
MDA, nmol/ml	33.729 ± 3.447	36.924 ± 2.860	0.000
DC, nmol/ml	29.591 ± 2.094	33.444 ± 3.142	0.000
Total antioxidant protection, mmol/l	1.068 ± 0.068	1.054 ± 0.064	0.149

The next stage of the study was to assess the degree of coherence and synchronicity in the changes of indicators by conducting a correlation analysis with the calculation of the coefficient of linear correlation (r) (Pearson product-moment correlation).

As a result of the correlation analysis in patients with comorbidity EH and obesity, the relationship of indicators of the system of oxidative stress – antioxidant protection and HOMA-IR was established (Table 2–4).

Table 2 – Correlation analysis of indicators of the system of oxidative stress – antioxidant protection with HOMA-IR in the General group of patients with EH and obesity

Indicators	Patients with EH and obesity, n = 200	
	r	p
MDA	0.457	0.000
DC	0.608	0.000
Total antioxidant protection	–0.250	0.000

In particular, it was found that in the General group of patients with EH and concomitant obesity (without division into groups based on the absence of IR) indicators of oxidative stress system (MDA and DC) had direct correlations with HOMA-IR ($r = 0.457$, $p = 0.000$ and $r = 0.608$, $p = 0.000$, respectively), the indicator of total antioxidant protection had inverse correlations with HOMA-IR ($r = –0.250$, $p = 0.000$) (Table 2).

Table 3 – Correlation analysis of indicators of the system of oxidative stress – antioxidant protection with HOMA-IR in the group of patients without IR

Indicators	Patients with EH and obesity, n = 80	
	r	p
MDA	0.042	0.710
DC	0.006	0.961
Total antioxidant protection	–0.409	0.000

The division of patients into groups according to IR showed that the presence of IR affects the association of HOMA-IR with indicators of the system of oxidative stress – antioxidant protection. In patients without IR, HOMA-IR was associated with a decrease in overall antioxidant protection, which was confirmed by the presence of an inverse correlation ($r = 0.409$, $p = 0.000$) (Table 3).

Table 4 – Correlation analysis of indicators of the system of oxidative stress – antioxidant protection with HOMA-IR in the group of patients with IR

Indicators	Patients with EH and obesity, n = 120	
	r	p
MDA	0.219	0.016
DC	0.353	0.000
Total antioxidant protection	–0.314	0.000

It should be noted that in the presence of IR increase of HOMA-IR was also accompanied by a decrease in the activity of the total antioxidant protection, as evidenced by the inverse correlation with HOMA-IR (r = –0.314, p = 0.000) (Table 4). However, in patients with comorbidity EH and obesity in the presence of IR, the increase of HOMA-IR was associated with an increase in oxidative stress system indicators (MDA and DC), which was confirmed by the presence of their direct correlations with HOMA-IR (r = 0.219, p = 0.016 and r = 0.353, p = 0.000, respectively).

Conclusions

The presence of IR affects the activity of the system of oxidative stress – antioxidant protection in comorbidity EH and obesity.

In the presence of IR, patients with EH and concomitant obesity have significantly higher levels of the oxidative stress system indicators (MDA and DC) compared to patients without IR.

In patients with comorbidity EH and obesity HOMA-IR directly correlates with oxidative stress system indicators (MDA and DC) and inversely correlates with the indicator of total antioxidant protection.

In hypertensive patients with obesity in the absence of IR, increased HOMA-IR is associated with reduced total antioxidant protection and in patients with IR – with an increase of MDA and DC, as well as a decline in overall antioxidant protection.

Prospects for further research

Prospects for further research are to assess the effect of IR on haemodynamic and metabolic parameters of patients with EH and concomitant obesity.

Conflict of interest

The authors declare no conflict of interest.

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