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CORRECTION OF CHANGES IN LIPID METABOLISM AND REDOX SYSTEM IN PATIENTS WITH STEMI IN THE SETTING OF INSULIN RESISTANCE

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Abstract. Myocardial infarction (STEMI) remains one of the most important problems of modern Cardiology both in Ukraine and worldwide due to its recalcitrant indices of incidence, disability and mortality. The prevalence of metabolic syndrome (MS) and DM2 in Ukraine is quite high, accounting for 20-28% in the general population and over 50% in certain demographics. In persons with abdominal obesity, metabolic syndrome and DM2, there is a 30% total risk of developing MI in the next 8 years, and their mortality rate is double thatof persons without metabolic disorders. The unfavorable prognosis in such patients is attributed to insulin resistance as an additional risk factor for CAD progression and the development of ACS, which determines the need to develop methods for correction of these abnormal processes.

The aim of the research: to explore the efficacy of correcting the disorders of lipid profile and prooxidant/antioxidant system balance in patients with STEMI in a setting of insulin resistance and high risk of reperfusion complications by using dapagliflozin, a SGLT2 inhibitor.

The methods of the research. The basis of the work has been underlain by the analysis of a comprehensive assessment and surgical treatment (percutaneous coronary intervention) in 73 patients with STEMI in the setting of insulin resistance in MS and DM2. The parameters of lipid profile and the activity of the components in the prooxidant/antioxidant system were determined by spectrophotometric methods; the absorbancy was measured on a Biomat 5 spectrophotometer (United Kingdom).The diagnosis of ACS was verified according to ESC Guidelines in the presence of a typical anginal attack, ACS-specific ECG changes with time (reciprocal ST displacement) and the signs of necrosis-resorption syndrome.The diagnosis was subsequently confirmed by the results of urgent coronary angiography. The diagnosis of MS and type 2 DM was made according to the recommendations of the WHO Expert Committee (2013) and the updated ADA/EASD consensus (2018).

Results. In order to improve lipid profile and redox system balance in pre- and postoperative period, the patients were prescribed dapagliflozin at the dose of 10 mg/day, which allowed compensation of hyperglycemia, reduction of insulin resistance and stabilizing the activity of prooxidant/antioxidant system, preventing post-PCI reperfusion complications and stabilizing the clinical condition of comorbid patients in the postoperative period owing to a 40.4% reduction in the incidence of rhythm and conductivity disorders, and a 55.3% reduction in manifestations of acute heart failure. There has been a substantial reduction in free radical oxidation in the setting of dapagliflozin treatment, as suggested by a 1.3-fold reduction ($p<0.05$) in active products of thiobarbituric acid in the serum and a simultaneous restoration of functioning of enzymatic antioxidant systems, a 1.5-fold reduction ($p<0.05$) in the degree of superoxide dismutase blockage with an increased activity of catalase and ceruloplasmin.

Conclusions. The use of dapagliflozin in pre- and postoperative patients with STEMI in the setting of insulin resistance and high surgical risk contributes to improvement of lipid metabolism and a significant reduction in the activity of free radical oxidation with restoration of functioning of enzymatic antioxidant systems in the body, which allows for a significant reduction in the incidence of rhythm and conduction disorders and the manifestations of acute heart failure.

Keywords: acute coronary syndrome, metabolic syndrome, insulin resistance, prooxidant/antioxidant system, dapagliflozin.

Introduction. Myocardial infarction (STEMI) remains one of the most important problems of modern Cardiology both in Ukraine and worldwide due to its recalcitrant indices of incidence, disability and mortality [1, 2, 3]. According to the WHO, the annual mortality due to cardiovascular disease accounts for approximately 42-47% of all deaths [4]. Such negative medico-demographic trends have been attributed to widely spread risk factors of coronary atherosclerosis and concomitant comorbid conditions (hypertension, abdominal obesity and diabetes mellitus), which develop in a setting of insulin resistance, and cause activation of immune-mediated inflammation and the redox system, inhibition of the antioxidant host defenses, impairment of coagulation hemostasis and endothelial function, and lead to a rapid progression of CAD, development of acute coronary syndrome (ACS) and life-threatening complications [5,6].

The prevalence of metabolic syndrome (MS) and DM2 in Ukraine is quite high, accounting for 20-28% in the general population and over 50% in certain demographics [7, 8]. As reported by the International Diabetes Federation (IDF), people with obesity and DM2 have a 30% total risk of developing STEMI in the next 8 years [9]; of note, their CAD-associated mortality is 3 times higher and is double that of patients without metabolic disorders [10].

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In the recent years, the researchers have found insulin resistance and hyperglycemia to be the principal pathogenetic factors of MS and type 2 DM. These factors activate lipolysis, initiate lipid peroxidation (LPO) [11] and compromise nitric oxide synthesis. This, in turn, enhances endothelial dysfunction and contributes not only to an increase in atherogenic dyslipidemia and progression of atherosclerotic vascular damage, but also leads to an unstable and rupture-prone fibrous capsule of the atherosclerotic plaque and the development of myocardial infarction [12,13]. In addition, insulin resistance and hyperglycemia contribute to the development life-threatening complications, such as heart failure, electrical instability of myocardium and recurrent myocardial infarctions/strokes [14, 15, 16, 17, 18]. The above facts inform the approaches to the active study of roles played by the activity of free-radical lipid oxidation, non-specific low intensity vascular inflammation and endothelial dysfunction in the pathogenesis of this comorbidity, the development of its individual complications and development of ways to improve these abnormal processes with the aim of preparation to surgical interventions and prevention of perioperative and postoperative complications [19, 20,21].

There is a large literature representation of study findings concerning the activities of components of serum prooxidant/antioxidant system separately assessed in patients with acute coronary syndrome (STEMI), in patients with metabolic syndrome and in patients with type 2 diabetes mellitus. At the same time, there is insufficient research into the special characteristics of changes in lipid peroxidation in patients with critical myocardial ischemia (ACS) in the setting of these comorbid conditions. Also, there have been no studies of antioxidant efficacy and safety of a novel group of antihyperglycemic drugs (SGLT2 inhibitors) in patients with MS and DM2 when preparing them for revascularization procedures, which has become the focus of this study.

The aim of the research is to explore the efficacy of correcting the disorders of lipid profile and prooxidant/antioxidant system balance in patients with STEMI in a setting of insulin resistance and high risk of reperfusion complications by using dapagliflozin, a SGLT2 inhibitor.

Materials and methods. The basis for this research included the analysis of comprehensive assessment and combination treatment, which included surgical treatment (percutaneous coronary intervention with stenting of infarction-dependent coronary artery) and medical treatment (pharmacological support and improvement of the main abnormal manifestations of the disease according to the protocol) in 73 patients with ACS combined with type 2 diabetes mellitus. The study has enrolled patients aged 45 to 75 years; the mean age was 58.36±5.48 years, with predominance of males (83.5%). The diagnosis of ACS was verified according to ESC Guidelines [22] in the presence of a typical anginal attack, ACS-specific ECG changes with time (reciprocal ST displacement) and the signs of necrosis-resorption syndrome.The diagnosis was subsequently confirmed by the results of urgent coronary angiography. The diagnosis of MS and type 2 DM was made according to the recommendations of the WHO Expert Committee (2013) and the updated ADA/EASD consensus (2018) [23].

The test group included 47 patients who were receiving standard of care per-protocol treatment for ACS (STEMI) and additional dapagliflozin (Forxiga) 10 mg once a day for compensation of insulin resistance and hyperglycemia.

The control group included 26 patients who also had urgent balloon angioplasty and stenting of the infarction-dependent coronary artery.However, in addition to standard of care per-protocol treatment, the patients of this group received metformin at the dose of 1000±200 mg for compensation of diabetes.

Myocardial revascularization by PCI and primary coronary artery stenting in patients of the main and control groups was performed after (6.43 ± 1.32) and (6.34 ± 1.24) hours from the onset of anginal syndrome, respectively.

In addition to general clinical methods, instrumental methods and laboratory tests (complete blood count, MB fraction of creatine phosphokinase [CPK-MB] and troponin T), oxygen saturation of arterial blood [SpO_2], ECG in 12 standard leads, etc.), we were determining the main parameters of lipid metabolism and the activityof components of the prooxidant/antioxidant system by means of spectrophotometric methods (on a Biomat 5 spectrophotometer [United Kingdom]). The serum levels of active products of thiobarbituric acid (TBA-AP) were used as a criterion of the intensity of lipid peroxidation. Serum TBA-AP is an intensity marker of free radical processes as the end product of the peroxidation chain. The levels of TBA-AP were assessed using a color test with 2-thiobarbituric acid (TBA) in the presence of Fe^{3+} ions. We were adding 0.2 ml of 0.27% $FeCl_3$ solution to a test tube containing 0.05 ml of serum; 10 minutes later, the resulting mixture was diluted to 1.8 ml with a 0.2 M glycine buffer (at pH 3.6). After adding 1.55 ml of 0.8% TBA solution, we boiled the resulting mixture on a water bath for 15 min, then cooled it and added 1 ml of 20% trichloroacetic acid and 2 ml of chloroform. After adding trichloroacetic acid and chloroform, we stirred the resulting solution and centrifuged it for 15 min at 3000 rpm [24, 25].

The level of ceruloplasmin (CP) was determined using the modified Revin's method, which is based on oxidation of p-phenylenediamine (with the participation of CP with the reaction residues) by the sodium fluoride solution; the absorbancy was measured at 540 nm. The activity of superoxide dismutase (SOD) was determined in a model system of superoxide anion formation during the interaction between nicotinamide adenine dinucleotide and phenazine methosulfate. The ability of SOD to compete for superoxide anions was determined based on the degree of inhibition of nitro blue tetrazolium reduction to hydrazine tetrazolium.

The status of lipid metabolism was assessed by TC values and the values of TC fractions (HDL-C, LDL-C and TG). The serum levels of TC were determined with the Ilko method using the reagents produced by Felicit Diagnostics (Ukraine) [24, 25]. The assessments of HDL-C and TG levels were performed using the reagents produced by ELITech Diagnostics (France) and PLIVA-Lachema (Czech Republic). The fractions of LDL cholesterol were obtained from W. Friedwald's formula:

LDL-C = TC – (HDL-C + TG/2),

where: LDL-C is the low density lipoprotein cholesterol, mmol/l;

TC is the total cholesterol, mmol/l;

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HDL-C is the high density lipoprotein cholesterol, mmol/l;

TG is the triglycerides, mmol/l.

The level of glucose in the blood plasma was determined by the glucose oxidase method using the Bisens line automatic analyzer (Germany), insulin by the chemiluminescent method (analyzer Access 2, USA), and the level of glycatedhemoglobin (HbA1c) was also determined. The presence of insulin resistance (IR) was assessed by the level of the HOMA-IRindex, and the degree of its severity – by the value of the IR coefficient according to F.Caro. The criteria for the presence of IR were considered to be values of NOMA greater than 2.77, Caro's index less than 0.33, he higher the NOMA index and the lower the Caro's index, the lower the tissue sensitivity to insulin and the higher the IR.

The statistical analysis of study findings was performed using Statistica10.0 package of statistical software and Microsoft Excel-2013 spreadsheet software. Nonparametric statistical methods were used for data assessment, such as the Mann-Whitney U test to compare the results in two groups ($p<0.05$).

Results. The disorders of lipid metabolism are playing a no small part in CAD progression, while peroxide stress and activation of low-intensity inflammation are viewed as a trigger in CAD activation and the development of acute coronary syndrome or non-alcoholic fatty liver disease in patients with MS or DM2. In addition, dyslipidemia leads to worsening of oxidative processes, and impaired oxidation-reduction balance in the redox system has a negative impact on the both acute coronary syndrome (i.e. the incidence and the severity of complications) and the severity/clinical presentation of metabolic syndrome or diabetes complications (angio- and neuropathy, systemic multi-focal atherosclerosis, steatohepatosis, etc). Our research study has found substantial lipid profile abnormalities in patients of both study groups at baseline (i.e. before the start of the treatment). However, it must be mentioned that there was a significant increase in HDL-C levels and a reduction in both TG and LDL-C in patients of the dapagliflozin test group during their preparation to surgical procedure (PCI) and compensation of insulin resistance and hyperglycemia (Table 1).

The restored delivery of oxygen to ischemic tissues is considered a trigger of reperfusion syndrome in the concomitant disease under study. At the same time, there is an inconsistency between the amount of oxygen in the arterial blood and the capacity of re-oxygenated tissues to utilize that oxygen. Both of the aforementioned processes are closely associated with the oxygen transport function of the blood and the prooxidant-antioxidant balance. Comparison of study findings has shown an impairment of prooxidant-antioxidant balance at baseline (pre-treatment), which was seen as an increase in TBA-AP and reduced activity of antioxidant enzymatic systems such as catalase, superoxide dismutase and ceruloplasmin in patients of both study groups.

Table 1

Theparameters of lipid metabolism and the redox system activity in patients with STEMI in the setting of insulin resistance before and after a percutaneous coronary intervention (M±m)

Parameter		At hospitalization	After preoperative preparation	After PCI
TC, mmol/l	1	5.97 ± 0.15	5.84 ± 0.12	5.78 ±0.14
	2	5.88 ± 0.16	5.83 ± 0.22	4.28 ± 0.12**
TG, mmol/l	1	1.88 ± 0.10	1.75 ± 0.11*	1.72 ± 0.08
	2	1.81 ± 0.08	1.78 ± 0.04	1.98 ± 0.08**
HDL, mmol/l	1	1.06 ± 0.05	1.04 ± 0.02*	1.34 ± 0.03**
	2	1.12 ± 0.04	0.94 ± 0.04	0.68 ± 0.03**
LDL, mmol/l	1	4.12 ± 0.12	3.93 ± 0.13*	2.64 ± 0.12
	2	4.18 ± 0.11	3.91 ± 0.12*	4.13 ± 0.13**
TBA-AP, nmol/mg	1	74.7±2.4	60.2±3.63*	69.5±2.72**
	2	75.4±3,2	73.8±3.27	84.6±2.71**
Catalase, nmol/mg·sec	1	0.49±0.03	0.68±0.08*	0.89±0.08 **
	2	0.51±0.06	0.43±0.06	0.67±0.07**
SOD, IU/mgHb	1	0.96±0.14	0.64±0.22*	0.82±0.23
	2	0.95±0.14	0.86±0.21	0.92±0.24
CP, mg/ml	1	253.2±6.2	224.4±7.4*	264.5±7.3**
	2	254.2±6.4	259.7±7.2	277.4±8.1

Notes: 1,2 = test group and control group, respectively;
* = there is a significant difference between the values at hospital admission and after preoperative preparation;
** = there is a significant difference between the values after preoperative preparation and after PCI;
The underlined values are significantly different from the findings in the control group.

The substantial disorders of the functional activity of enzymatic antioxidant protection systems, which have been found in preoperative comorbid patients with ACS in the setting of insulin resistance, provided the rationale for correction of prooxidant-antioxidant balance during the preoperative period for prevention of perioperative reperfusion complications. To this end, dapagliflozin 10 mg/day was prescribed in the patients to compensate for hyperglycemia.

The use of the drug product made it possible to stabilize the parameters of carbohydrate metabolism and the activity of the prooxidant/antioxidant system at the time of surgical intervention in patients of the test group. In part, the activity of free radical oxidation has reduced in

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these patients during the above period, as suggested by a 1.3-fold reduction in serum TBA-AP ($p<0.05$). At the same time, there was a 1.5-fold reduction in SOD blockage ($p<0.05$), while there was a significant increase in the activity of catalase and ceruloplasmin. The improvement of protective antioxidant systems attained in patients of the test group has contributed to a significant reduction in the incidence of reperfusion syndrome; the incidence of rhythm and conduction disorders has decreased by 40.4%, and the manifestations of acute heart failure have decreased by 55.3%.

The activity of prooxidant/antioxidant system, which was reduced preoperatively, has significantly increased after myocardial revascularization was performed. In part, the serum levels of TBA-AP and catalase have increased 1.3-fold ($p<0.05$) and 1.9-fold ($p<0.001$), respectively, compared to the preoperative period. There were insignificant increases in serum levels of SOD and CP. The results of the study confirm that myocardial revascularization contributes to activation of prooxidant/antioxidant system and, primarily, to increased activity of free radical oxidation.

The findings of the study of prooxidant/antioxidant system activity in patients with preoperative preparation are substantially different from the results of the same study in patients with a standard PCI procedure. In part, patients of the test group (i.e. those with a targeted preoperative preparation) were found to have decreased glycemic levels, i.e. from 8.7±1.4 mmol/l to 6.2±0.8 mmol/l and a 11.94% lower activity of free radical oxidation after the surgical intervention ($p<0.05$) compared to the activity of free radical lipid oxidation in patients of the control group. At the same time, it must be mentioned that immediately after the surgical intervention (myocardial revascularization) both patients with special preoperative preparation and patients with standard preparation had increases in serum levels of atherogenic lipid fractions and in the activity of their free radical oxidation. Namely, there was a 1.3-fold increase in the test group and a 1.5-fold increase in control group, respectively ($p<0.05$) (fig.1). The study findings have substantiated the expediency of continuing the proposed sugar-lowering therapy with dapagliflozin into the postoperative period in order to stabilize the clinical condition of the patients and for further prevention of post-infarction complications.

The results of the antioxidant effect of a 10-day treatment course in patients with STEMI combined with insulin resistance and hyperglycemia are presented in Table 2.

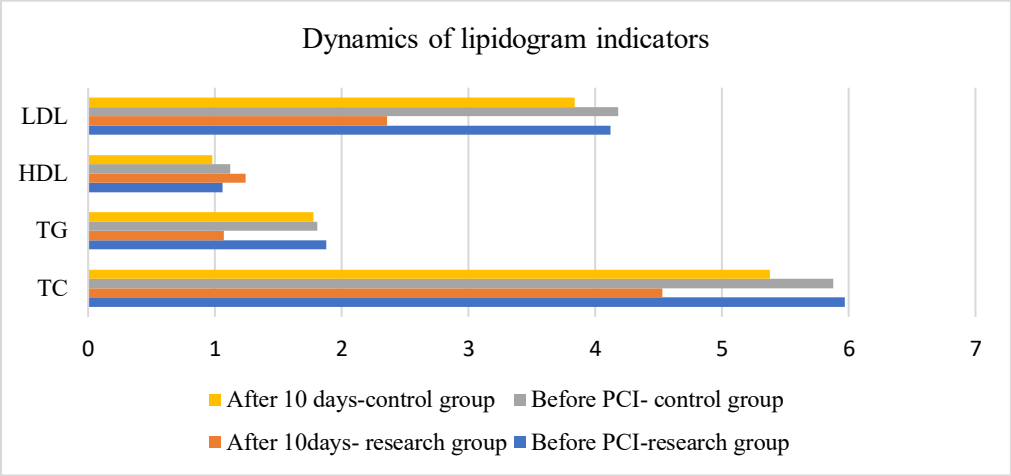

Fig. 1. Dynamics of lipidogram indicators in patients with STEMI against the background of insulin resistance and hyperglycemia under the influence of dapagliflozin therapy.

Table 2

The efficacy of correction of redox system activity with dapagliflozin in patients with STEMI in the setting of insulin resistance and hyperglycemia (M±m)

Parameter		Patients with STEMI combined with insulin resistance		
		Preoperatively	In 10 days post PCI	P
TBA-AP, nmol/mg	1	74.7 ± 2.4	57.6 ± 3.1*	<0.05
	2	75.4 ± 3.2	81.5 ± 2.55	>0.05
Catalase, nmol/mg·sec	1	0.49 ± 0.03	1.35 ± 0.16*	<0.05
	2	0.51 ± 0.06	0.68 ± 0.02	>0.05
SOD, IU/mgHb	1	0.96 ± 0.14	0.54 ± 0.16	<0.05
	2	0.95 ± 0.14	0.75 ± 0.14	>0.05
CP, mg/ml	1	253.2 ± 6.2	328.4 ± 8.4*	<0.05
	2	254.2 ± 6.4	256.5 ± 7.4	>0.05

Notes: * = there is a significant difference between the values in patients of the test group and the control group; P is the significance of the difference between the values before and after the surgical intervention (PCI).

Discussion. The results presented in this article support the efficacy of perioperative use of an SGLT2 inhibitor (dapagliflozin), which contributes not only to a significant reduction in glycemia, but also to improvement of atherogenic lipids (TC, LDL-C and TG), reduction of free radical oxidation and to an increase in the functional

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capacity of enzymatic antioxidant systems. Overall, this allows performing myocardial revascularization in a setting of hyperglycemia and insulin resistance.

In our opinion, the positive result of reduction in free radical oxidation and relative functional improvement of the prooxidant/antioxidant system in comorbid patients at high risk of ACS sequelae in a setting of MS/DM2 has been obtained owing to specific pharmacological properties of the study drug. One of the mechanisms behind the beneficial effect of dapagliflozin is its ability to reduce insulin resistance and the compensatory hyperinsulinemia and hyperglycemia, which cause redox system activation, endothelial dysfunction, non-specific inflammation, atherogenesis, DNA replication and irreversible left ventricular hypertrophy, hypertension and hypercoagulation [26, 27]. Thus, it is known that in 88% of the cases atherogenic dyslipidemia is attributable to insulin resistance and hyperinsulinemia [28]. In addition to that, as reported by an RCT with the use of inhibitors of type 2 sodium-dependent glucose transporter (SGLT2), these drugs were able to improve cardiovascular prognosis in patients with type 2 DM [29, 30] due to a 22% reduction in the incidence of primary endpoint (cardiovascular death, non-fatal MI, stroke) and a 35% reduction in heart failure-related hospital admissions [31]. In the DAPA-HF study, the use of dapagliflozin in patients with congestive heart failure (CHF) and reduced ejection fraction produced an 18% reduction in cardiovascular death risk and a 30% reduction in hospital admissions for CHF [32]. On the whole, the results of treatment with these drugs obtained in the perioperative period of ACS have confirmed their potential capacity not only to improve glycemic control but also to exert a positive influence on myocardial contractility in the early postoperative period [33,34]. In our opinion, it is owing to precisely these properties of dapagliflozin that the test group of comorbid patients could attain improvements of dyslipidemia and a dynamic equilibrium of the functional state of the redox system, which was associated with significant reductions in the incidence and severity of reperfusion arrhythmias (by 40.4%) and acute heart failure (by 55.3%).

Therefore, the proposed method of preventing reperfusion complications in comorbid patients with STEMI in the setting of insulin resistance and hyperglycemia who are at high surgical and postoperative risks using a course of treatment with dapagliflozin(an SGLT2 inhibitor) has demonstrated a sufficient clinical effect through a comprehensive pathogenetic influence on hyperglycemia, insulin resistance, atherogenic dyslipidemia, reduced inotropic function and oxidative stress present in these patients.

Conclusions. The use of dapagliflozin in pre- and postoperative (percutaneous coronary intervention) patients with STEMI in the setting of insulin resistance, hyperglycemia and high surgical risk contributes to improvement of lipid metabolism and a significant reduction in the activity of free radical oxidation with restoration of functioning of enzymatic antioxidant systems in the body, which allows to reduce the incidence of rhythm and conduction disorders by 40.4% and reduce the manifestations of acute heart failure by 55.3%.

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КОРЕКЦІЯ ЗМІН МЕТАБОЛІЗМУ ЛІПІДІВ ТАРЕДОКС-СИСТЕМИ У ХВОРИХ ЗІ STEMI НА ТЛІ ІНСУЛІНОРЕЗИСТЕНТНОСТІ

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Резюме. В осіб з абдомінальним ожирінням, метаболічним синдромом та ЦД2 сумарний ризик розвитку ІМ в найближчі 8 років становить 30%, а смертність у них удвічі вища, ніж у пацієнтів без метаболічних порушень.

Мета: вивчити ефективність корекції порушень ліпідограми та рівноваги прооксидантно-антиоксидантної системи у пацієнтів зі STEMI на тлі інсулінорезистентності та високим ризиком розвитку реперфузійних ускладнень шляхом застосування інгібітору SGLT2 – дапагліфлозину.

Методи. В основу роботи покладено аналіз комплексного обстеження та хірургічного лікування 73 хворих зі STEMI на тлі інсулінорезистентності при МС. Показники ліпідограми та активність складових прооксидантно-антиоксидантної системи визначали за допомогою спектрофотометричних методів, оптичну густину вимірювали на спектрофотометрі «Biomat 5» (Велика Британія).

Результати. З метою корекції ліпідограми та рівноваги в редокс-системі у перед- та післяопераційний періоди призначали дапагліфлозин у дозі 10 мг/добу, щодало можливість компенсувати гіперглікемію, знизити рівень інсулінорезистентності та стабілізувати активність прооксидантно-антиоксидантної системи, попередити розвиток реперфузійних ускладнень після ЧКВ. На фоні лікування дапагліфлозином суттєво знизилась активність вільнорадикального окиснення, про що свідчило зменшення в 1,3 рази ($p<0,05$) вмісту активних продуктів тіобарбітурової кислоти в сироватці крові.

Висновки. Застосування дапагліфлозину в перед- та післяопераційний періоди у хворих ziSTEMIна тлі інсулінорезистентності сприяє нормалізації ліпідного обміну та достовірному зниженню активності вільнорадикального окиснення з відновленням функціонування ферментних антиоксидантних систем організму.

Ключові слова: гострий коронарний синдром, метаболічний синдром, інсулінорезистентність, прооксидантно-антиоксидантна система, дапагліфлозин.

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