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SPECIAL CHARACTERISTICS OF THE COURSE OF MYOCARDIAL INFARCTION IN PATIENTS WITH INSULIN RESISTANCE AND CARBOHYDRATE METABOLISM DISORDERS

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Abstract There is limited research concerning the role of insulin resistance and hyperglycemia in the development of myocardial infarction (MI) and its complications.The aim of the study. To investigate the correlations between the changes of insulin resistance and carbohydrate metabolism parameters and individual life-threatening complications of myocardial infarction.
Materials and methods. The study enrolled 67 male patients with acute myocardial infarction with ST segment elevation, who have been divided into the following two groups: Group 1 (*n* =35) included the patients who had no carbohydrate metabolism disorders (CMD) prior to the development of MI (the HbA1c levels in these patients did not exceed 6.0%) and Group 2 (n = 32), which consisted of patients receiving oral sugar-lowering drugs for type 2 diabetes (the HbA1c levels in these patients exceeded 6.0%).
In addition to assessment of hematology parameters and the levels of cardiac troponin I and T and MB fraction of creatine phosphokinase (CPK-MB), ECG and echocardiography monitoring, calculation of the incidence and hemodynamic severity of coronary artery damage based on the results of coronary angiography, the authors have been documenting the following MI complications: rhythm and conductivity disorders, recurrent MI at the hospital stage, early postinfarction angina, acute left ventricular aneurysm and acute heart failure (the class was determined using a Killip scale).
In order to evaluate the status of carbohydrate metabolism in CMD-free patients, the authors performed standard oral glucose tolerance tests (OGTT), assessed fasting and postprandial glycemic levels, determined immunoreactive insulin (IRI) levels under fasting conditions and 2 hours after a carbohydrate challenge and assessed the HOMA–IR index.
Results. The majority of patients with MI combined with metabolic syndrome were found to have insulin resistance and a significantly higher incidence of carbohydrate metabolism disorders; high values of HOMA index were diagnosed in 88.0% of study patients.

Decompensation of carbohydrate metabolism was found to disrupt metabolic and energy processes in the myocardium and contribute to development of such life-threatening complications of MI as rhythm and conductivity disorders, recurrent MI, early postinfarction angina, LV aneurysm and acute heart failure. The above inference is confirmed by the presence of a direct correlation between the parameters of carbohydrate metabolism compensation and the incidence of arrhythmias, early postinfarction angina and the degree of heart failure ($p < 0.05$).

Conclusion. The presence of insulin resistance and decompensation of carbohydrate metabolism in patients with myocardial infarction with comorbid metabolic syndrome is an independent predictor of worse functional status and may trigger such life-threatening complications as rhythm and conductivity disorders, acute heart failure and progressive coronary disease.

Key words: *myocardial infarction, insulin resistance, HOMA index, hyperglycemia.*

Introduction

Myocardial infarction (MI) takes the lead among causes of death due to cardiovascular disease (27%) and is the main cause of associated disability [1, 2]. The situation is largely determined by the prevalence of such risk factors of MI as hypertension, smoking, obesity, dyslipidemia and diabetes [3, 5]. The hyperglycemic syndrome in patients with MI has also been found to be an unfavorable predictor, which contributes to the development of heart failure, aggravates the stenosis of the "infarction-dependent" coronary artery and increases the risk of repeated MIs [4, 6, 11]. However the role of insulin resistance (IR) in the development of other life-threatening MI complications in patients with impaired and normal carbohydrate metabolism has not been sufficiently explored. At present, IR is not an officially recognized risk factor of MI or a predictor of complicated postinfarction period, while some researchers [7, 8] recognize insulin resistance as a leading factor in the mechanism behind the development of MI and some of its complications. There are data that IR in general and diabetic populations is associated with cardiovascular risk factors including hyperglycemia, dyslipoproteinemia, arterial hypertension, obesity, thrombosis, and smoking [19,20,21,22]. Additionally, it was established that the course of MI as a separate disease is accompanied by IR development and that the pathogenetic mechanisms are unclear [22].

The aim of the study was to investigate the correlations between the changes of insulin resistance and carbohydrate metabolism parameters and individual life-threatening complications of myocardial infarction.

Methods

The study enrolled 67 male patients with acute myocardial infarction with ST segment elevation. The age of study subjects was 57.54±8.02 years. All patients were receiving standard of care treatment according to the protocols of the MoH of Ukraine [10].

On admission to the hospital, the patients were tested for glycated hemoglobin (HbA1c). The patients were divided into the following two groups: Group 1 (n =35) included the patients who had no carbohydrate metabolism disorders (CMD) prior to the development of MI (the HbA1c levels in these patients did not exceed 6.0%) and Group 2 (n = 32), which consisted of patients receiving oral sugar-lowering drugs for type 2 diabetes (the HbA1c levels in these patients exceeded 6.0%) [9].

The diagnosis of acute MI was verified according to ESC Guidelines [2] in the presence of a typical anginal attack, MI-specific ECG changes with time (reciprocal displacement of the ST segment) and the signs of resorption-necrosis syndrome. The diagnosis was confirmed by means of laboratory and instrumental tests. The investigational parameters included hematology indices and the levels of cardiac troponin I/T and MB fraction of creatine phosphokinase (CPK-MB) obtained using a Cobas integra 400 plus automatic biochemical analyzer by Roche (Switzerland). Quantitative determination of troponin T was performed using an electrochemiluminescent biochemical analyzer Elecsys 2010 by Roche/Hitachi (Switzerland).

The following MI complications were documented: rhythm and conductivity disorders, recurrent MI at the hospital stage, early postinfarction angina, acute left

ventricular aneurysm and acute heart failure (the class was determined using a Killip scale). The incidence and the hemodynamic severity of coronary artery damage was assessed in all patients based on the results of coronary angiography (using the Gensini scale).

In order to assess the status of carbohydrate metabolism in CMD-free patients, a standard oral glucose tolerance test (OGTT) was performed. The normal limit was accepted as a fasting glycemia of <5.6 mmol/L and postprandial glycemia in 2 hours of <7.8 mmol/L. In patients with CMD, a single glycemic test was performed under fasting conditions and 2 hours after breakfast using a ONE TOUCH Ultra Easy blood glucose monitor. The assessment of blood glucose levels was performed on Day 7–12 after the onset of MI [12]. Carbohydrate metabolism was considered compensated when glycemia was <6.5 mmol/L under fasting conditions and <8.0 mmol/L 2 hours after breakfast, with HbA1c<7.0%. During the OGTT, i.e. the test of fasting and postprandial glycemia, the levels of immunoreactive insulin (IRI) were assessed under fasting conditions and in 2 hours after carbohydrate challenge with 75 g of glucose (breakfast); this test also included an assessment of the HOMA–IR index. Normal baseline IRI values were considered to be <89.6 pmol/L; the IRI in 2 hours after the carbohydrate challenge was expected to be <204.4 pmol/L. The presence of IR was confirmed by a HOMA index of over 2.77.

Statistical analysis of the results obtained was performed using "Statistica 10.0" statistical software package and "Microsoft Excel-2013" software. Mean values were presented as a median and a quartile deviation. The Mann–Whitney U test was used in analysis of quantitative parameters. Comparisons across the three groups were performed using the Kruskal–Wallis test. The presence of relationship between the parameters was assessed using the Spearman rank-order correlation method. The critical significance level when checking statistical hypotheses was taken equal to 0.05.

Results

The majority of the patients assessed (87.5%) had a complicated course of MI. The structure and the incidence of complications in the acute period of the disease are summarized in Table 1. That being said, it must be mentioned that complications were more frequent in Group 2 (91.3%) than in Group 1 (79.5%, p <0.001). Thus, in Group 2, the diagnosis of early postinfarction angina was 2.6 times more frequent (p=0.04), LV aneurysm was 4.3 times more frequent (p=0.05), and AHF of functional class II-III was 1.6 times more frequent than in patients of Group 1.

One of the causes of a more severe clinical course and worse prognosis of MI in patients with DM may include more pronounced coronary circulation disorders. Thus, the incidence of hemodynamically significant (stenosis of more than 50%) multivascular lesions of coronary vessels was 90.6% in Group 2 and 71.4% in Group 1 (p =0.005), which coincides with the literature [13,14].

The severity of coronary blood flow impairment in both groups has been analyzed in relation to IR and carbohydrate metabolism status according to the previously assessed IRI, HOMA index, blood glucose levels and HbA1c. The results of the IRI assessment suggested a significant incidence of hyperinsulinemia in MI,

especially among patients with diabetes (91%), to a lesser degree among the patients with normal HbA1c values (77.6%; p =0.0001). That being said, the IRI values in Group 2 were higher under fasting conditions (p=0.047) and lower after the challenge (p=0.004) compared to Group 1, which may suggest reduced functional reserves of beta cells in people with diabetes.

More than 2/3 of study patients with MI had high HOMA values: 78.5% in Group 1 vs. 88% in Group 2 (p < 0.001). This finding suggests an important role of IR in the development of MI. However, the values of the HOMA index in Group 2 were higher than in Group 1 (p < 0.001) (see Table 2).

The impact of IR on the severity of coronary blood flow impairment in patients with MI was evaluated by correlation analysis, which allowed establishing the presence of a direct (medium strength) relationship between the number of affected coronary vessels and fasting IRI levels (r=0.347, p=0.001), as well as the HOMA index (r=0.343, p=0.003). The data obtained explained the higher incidence (86%) of hemodynamically significant multivascular lesions of coronary vessels in IR compared to subjects with preserved insulin sensitivity (41.6%; p<0.001).

It should be noted that in the presence of IR, the incidence of multivascular coronary artery damage was not different between the patients with (86%) and without carbohydrate metabolism disorders (85.7%; p=0.152). The data obtained suggest that IR may appear long before the onset of DM and lead to hemodynamically significant disorders of coronary circulation and MIs with severe, often fatal complications due to which patients fail to live to eventually develop DM. IR-associated carbohydrate metabolism disorders may substantially increase the severity and complicate the course of ischemic heart disease.

According to this study, most patients of either Group 1 or Group 2 develop clinically significant changes of carbohydrate metabolism in the acute and chronic periods of MI regardless of baseline glycemia parameters. Thus, decompensation of DM was observed in 85% of patients in Group 2: the HbA1c level was 8.8% (7.4–10.9), fasting glycemia was 9.4 mmol/L and glycemia 2 hours after breakfast was 12.6 mmol/L. In Group 1, the development of MI was accompanied by impaired fasting glycemia (IFG) in 6.25% of cases, impaired glucose tolerance (IGT) in 26.7% of cases and new onset diabetes mellitus (NODM) in 18.7% of cases. These disorders were most frequently reported among patients with IR (p=0.0006): IFG in 6.9%, IGT in 27.5%, and DM in 21.5%. In the IR-free patient cohort, the above disorders were significantly less frequent: IFG in 4.1%, IGT in 25% (p=0.023), and DM in 8.3% (p = 0.043).

Overall, the results of the study suggested an adverse impact of carbohydrate metabolism disorders on the severity of MI course and on prognosis in patients with MI. Thus, compared to the patients with normal carbohydrate metabolism, the CMD in patients of Group 1 were significantly more frequently accompanied by heart rhythm disorders (p=0.042), MI recurrence (p=0.055), early postinfarction angina (p=0.031) and Killip II acute heart failure (p=0.051) (see Table 3).

The analysis of MI complications in patients with various degrees of carbohydrate metabolism compensation is summarized in Table 4. In high values of glycemia in patients of Group 2, the course of MI was more frequently

complicated by rhythm and conductivity disorders (p=0.028), early postinfarction angina (p=0.011) and Killip II-III (p=0.030) heart failure than in patients with compensated DM. Correlation analysis has established a direct relationship between the level of compensation of carbohydrate metabolism and the incidence of rhythm disorders (r=0.357, p=0.002), early postinfarction angina (r=0.364, p=0.002) and the degree of heart failure (r=0.349, p=0.017).

In general, we can conclude that decompensation of carbohydrate metabolism disrupts metabolic and energy processes in the myocardium and contributes to development of such life-threatening complications of MI as rhythm and conductivity disorders, recurrent MI, early postinfarction angina, LV aneurysm and acute heart failure. The above inference is confirmed by the presence of a direct correlation between the parameters of carbohydrate metabolism compensation and the incidence of arrhythmias, early postinfarction angina and the degree of heart failure ($p < 0.05$).

The researchers explain the found relationship by the fact that increased glucose levels in the blood and insulin resistance of cardiomyocytes in a setting of myocardial ischemia (hypoxia) is accompanied by a transition to anaerobic glycolysis, accumulation of lactic acid and an increased concentration of free fatty acids, which, in turn, deepens the ischemia and leads to electrolyte and energy disorders and reduced ventricular contractility [15]. Hyperglycemia is also enhancing the endothelial inflammatory response by activating the expression of intercellular interaction molecules, which increases platelet adhesion and platelet aggregation, causing further endothelial damage and microvascular dysfunction [17,18]. In addition to that, the increased level of glucose in the blood reduces ischemic preconditioning of myocardial cells, making them even more vulnerable to ischemia [16]. The study findings suggest an important role of carbohydrate metabolism in the processes of energy supply of the functional state of the myocardium, and impaired carbohydrate metabolism in patients with MI combined with MS and insulin resistance may act as a trigger for development of such life-threatening complications as rhythm and conductivity disorders, acute heart failure and progressive coronary disease.

The established pathogenetic features of the comorbid condition under study and the predicted development of life-threatening MI complications provide a rationale for a more thorough clinical and laboratory control and an individual approach to therapeutic interventions in this patient population.

Conclusions

1. The majority of patients with MI combined with metabolic syndrome were found to have insulin resistance and a significantly higher incidence of carbohydrate metabolism disorders; high values of HOMA index were diagnosed in 88.0% of study patients.
2. The presence of insulin resistance and decompensation of carbohydrate metabolism in patients with myocardial infarction with comorbid metabolic syndrome is an independent predictor of worse functional status and may trigger such life-threatening complications as rhythm and conductivity disorders, acute heart failure and progressive coronary disease.

3. In a setting of myocardial infarction in patients with insulin resistance, hemodynamically significant multivascular coronary artery damage are diagnosed significantly more often (in 86.0%) than in absence of insulin resistance (in 41.6%; p<0.001). A direct correlation was found between the number of the involved coronary arteries and fasting IRI levels (r=0.347), as well as the HOMA index (r=0.343).

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Table 1. The structure and the incidence of complications in the acute period of myocardial infarction in patients with carbohydrate metabolism disorders.

Complications	Patient group 1 (n = 35)	Patient group 2 (n = 32)	P_{1-2}
Rhythm and conductivity disorders	19 (54.3%)	20 (62.5%)	< 0.05
MI recurrence	3 (8.6%)	3 (9.4%)	> 0.05
Early postinfarction angina	6 (17.1%)	14 (43.8%)	< 0.05
LV aneurysm	1 (2.9%)	4 (12.5%)	< 0.05
AHF, Killip I	26 (74.3%)	19 (59.4%)	> 0.05
AHF, Killip II	7 (20 %)	9 (28.1%)	< 0.05
AHF, Killip III	2 (5.7%)	4 (12.5%)	< 0.05

Table 2. The parameters of insulin resistance in MI patients with carbohydrate metabolism disorders.

Parameter	Group 1 (n = 35)	Group 2 (n = 32)	P_{1-2}
IRI_1, pmol/L	113.4 (86.1 – 179.3)	131.2 (57.4 – 308.5)	< 0.05
IRI_2, pmol/L	388.4 (179.3 – 602.7)	247.1 (121.9 – 502.2)	< 0.05
HOMA	3.8 (3.0 – 6.7)	8.3 (3.3 – 17.8)	< 0.05

Notes. IRI_1 = the fasting value, IRI_2 = the value 2 hours after the carbohydrate challenge.

Table 3. The incidence of MI complications in study patients depending on the parameters of carbohydrate metabolism.

Complications	CMD-free patients (n =16)	Patients with CMD (n = 19)	P
Rhythm and conductivity disorders	10 (62.5%)	15 (78.4%)	< 0.05
MI recurrence	1 (6.2%)	3 (15.8%)	< 0.05
Early postinfarction angina	2 (12.5%)	4 (21.1%)	< 0.05
LV aneurysm	1 (6.2%)	3 (15.8%)	< 0.05
AHF, Killip I	12 (75.0%)	11 (57.9%)	> 0.05
AHF, Killip II	3 (18.8%)	5 (26.3%)	< 0.05
AHF, Killip III	1 (6.2%)	3 (15.8%)	< 0.05

Table 4. The analysis of MI complications in patients with various degrees of carbohydrate metabolism compensation

Complications	Patients with carbohydrate metabolism compensation (n = 12)	Patients with carbohydrate metabolism decompensation (n = 20)	P
Rhythm and conductivity disorders	8 (67%)	17 (85%)	< 0.05
MI recurrence	0 %	5 (25%)	< 0.05
Early postinfarction angina	2 (16.7%)	11 (55%)	< 0.05
LV aneurysm	3 (25%)	9 (45%)	< 0.05
AHF, Killip I	9 (75%)	6 (30%)	> 0.05
AHF, Killip II	1 (8.3%)	12 (60%)	< 0.05
AHF, Killip III	0%	2 (10%)	< 0.05