



STUDY OF THE PROGNOSTIC VALUE OF EARLY DISORDERS OF CARBOHYDRATE METABOLISM IN CASE OF MYOCARDIAL INFARCTION

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Abstract

For many years, acute myocardial infarction has been one of the urgent problems of cardiology. Myocardial infarction is the leading cause of death and disability from cardiovascular diseases in the population by 27%. Hyperglycemia is known to be one of the most important risk factors for an unfavorable prognosis of myocardial infarction. Despite studying the value of hyperglycemia in patients with acute coronary syndrome in the early stages of the disease, as well as information about the simplicity and accessibility of this parameter, the most common risk of myocardial infarction stratification is not taken into account in stratification scales. To date, there is no consensus on the role of hyperglycemia in the prevention of adverse consequences of myocardial infarction in the hospital period, so it requires further study.

6438

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Introduction

It has been established that patients with type 2 diabetes mellitus (DM) are at a high risk of developing cardiovascular complications, which can be compared with those in patients without diabetes who have had acute myocardial infarction (AMI). Recently, much attention has been paid to the state and early stages of carbohydrate metabolism disorders in patients with acute coronary syndrome (ACS), regardless of the presence or absence of diabetes mellitus in the anamnesis. The great interest in early disorders of carbohydrate metabolism in patients with ACS is associated with their unfavorable prognostic significance in relation to cardiovascular outcomes, comparable to that in patients with type 2 diabetes mellitus (DM) (Stranders I, 2004; Kosiborod M, 2005; Goyal A, 2006). It was noted that the level of glycemia at admission in patients with AMI is associated with an increased risk of cardiovascular events and death not only during hospitalization, but also during subsequent long-term follow-up of this category of patients (Bartnik M, 2004). An increase in the frequency of cardiovascular complications is observed at all stages of carbohydrate metabolism disorders, which led to the emergence of the concept of cardiometabolic risk, which is presumably associated with dysglycemia. In this regard, the study of the prognostic value of early carbohydrate metabolism disorders in relation to early and long-term cardiovascular complications is of particular interest.

Objective: to study the prognostic value of early disorders of carbohydrate metabolism in myocardial infarction.

Results and discussion

In 2015, noncommunicable diseases (NCDs) accounted for 79% of all deaths in Uzbekistan, which is higher than the NCD-related mortality rate (71%) at the global level. According to the latest data from 2015, the probability of premature death (under the age of 70) from the four main groups of NCDs (cardiovascular diseases (CVD), diabetes, chronic respiratory diseases or cancer) for an Uzbek citizen is higher

than 1 in 4 (26.9%), with a much higher probability for men (32.9%) than for women (21.4%) (WHO, 2017a). This fact offers a good opportunity to make progress towards achieving the United Nations Sustainable Development Goals, which aim to reduce premature deaths from NCDs by one third by 2030 [1]. According to the WHO technical report, pre-diabetes or early carbohydrate metabolism disorders include HTH and impaired fasting glycemia (NGN). According to epidemiological studies in the world, 314 million people have "prediabetes" (8-14% of the adult population), in 20 years their number will increase by 1.5 times and will amount to about 500 million. In 2007, a Russian national multicenter epidemiological study was launched (7 large cities, a total of 10,000 respondents selected randomly) to identify 20 risk factors (RF), including the determination of fasting blood glucose levels and 2 hours after taking 75 g of glucose. According to the results of the first completed study in Cheboksary in 8.3% of respondents (1800 people aged 30-69 years) hyperglycemia was detected, of which 4.5% were found to have HTG. In most adult populations, NTG is twice as common as NGN. According to European experts, the prevalence of NTG ranges from 10 to 25%. It has also been shown that the prevalence of DM and HTG diagnosed on the basis of postprandial hyperglycemia (PG) is higher in women than in men. However, the incidence of type 2 diabetes and fasting hyperglycemia is higher in men than in women [1,2,5,2,5].

According to British scientists, only 39% of patients suffering from hypertension have normal glucose tolerance, while 10% have NGN, and 22% have HTH. The number of people with newly diagnosed type 2 diabetes is twice as high as that diagnosed with type 2 diabetes [3,4,6]. The number of people with diabetes worldwide has more than doubled over the past 10 years and reached 425 million people by 2017. According to the International Diabetes Federation, the number of patients with diabetes will reach 592 million by 2035 and 642 million by 2040 [7]. Due to the rapid increase in the incidence of diabetes, a UN political declaration was adopted in 2011, addressing national health



systems. It called for the creation of multidisciplinary strategies for the prevention and control of noncommunicable diseases, with special attention paid to the problem of DM as one of the leading causes of disability and mortality in the population. In the Russian Federation, according to the Federal Register of Diabetes Mellitus, the number of patients with diabetes in January 2017 is 4.35 million people (3% of the population), of which 4 million (92%) are type 2 diabetes mellitus (DM2). Prevalence and mortality from DM 2 per 100 thousand population is 2637.17 and 60.29 people, respectively [8,10]. However, these indicators only take into account patients who are under dispensary supervision. The estimated number of patients with DM2, according to the large Russian epidemiological study NATION, should be at least 8-9 million [9]. Among the causes of death of patients with SD in the Russian Federation, the leading positions are occupied by cardiovascular diseases (CVD). There is a direct relationship between the duration of DM and CVD. On the other hand, patients with CVD are at risk for developing DM 2. In fact, the problem of late diagnosis and late initiation of DM therapy in adults is a problem of insufficient cardiovascular prevention. The most dangerous consequences of the global epidemic of DM are its systemic vascular complications - nephropathy, retinopathy, damage to the main vessels of the heart, brain, and peripheral vessels of the lower extremities. In the structure of causes of death of patients with DM2 in 2016, the first places are occupied by chronic cardiovascular insufficiency (29.8%), cerebral circulatory disorders (12.2%), myocardial infarction (5.1%), acute cardiovascular events (2.4%) [11,12]. Epidemiology of diabetes and cardiovascular diseases in the Russian Federation, the high incidence of cardiovascular complications in patients with diabetes mellitus (DM) is one of the most important problems not only in Russia, but also in the world health care. Expenses for the treatment of DM and its complications in the Russian Federation in 2017, US \$ 327 billion was accounted for, of which 71% was due to complications associated with atherosclerosis [13,14]. According to the FORESIGHT-DM2 study,

the PΦ cost of DM2 treatment in the Russian Federation is more than 7 thousand rubles. \$1 per patient per year, and 53.5% of this amount is GDP losses due to disability of patients, 37.7% - direct medical costs, of which 57% is accounted for by the treatment of complications of diabetes and concomitant diseases, and the share of anti-hyperglycemic therapy - only 10% [15]. Unfortunately, it is not yet possible to significantly reduce the mortality rate from CHD in patients with DM in any country of the world. Sudden death in DM is 50% more common in men and 300% more common in women than in people of the same sex and age without diabetes [16,17,18]. In the Russian Federation, among all CVD cases, coronary heart disease (CHD) remains the most common cause of adult visits to medical institutions (28% of cases) [19]. With age, the prevalence of CHD and its most common form, angina pectoris, in the general population increases, and gender differences in frequency are leveled [20]. In addition to population risk factors for CHD (hyperlipidemia, inactivity, obesity, arterial hypertension, burdened heredity due to CVD and smoking), patients with Diabetes also have specific factors, such as hyperglycemia, insulin resistance, microalbuminuria, and impaired hemostasis. The prevalence of CHD among patients with DM2 is 2-4 times higher than the average in the population and is about 70-80%. According to a large INTERHEART study, DM is one of the three most important risk factors for AMI in middle-aged men (after lipid metabolism disorders and smoking), which is more significant than arterial hypertension (AH) [21,22,24]. By the age of 50, almost half of patients with diabetes have at least one of the following complications of CHD: unstable angina, MI, life-threatening cardiac arrhythmias, and rapid development of chronic heart failure (CHF) [23]. According to the PROGNOSIS-CHD registry, during 7.3 years of follow-up, 504 patients with a confirmed diagnosis of CHD had a relative risk of developing a primary endpoint (all-cause deaths, fatal and non-fatal cardiovascular events) in the presence of DM increased 1.7 times, and in the presence of a combination of DM and arterial hypertension - 2.4 times [25]



DM is an independent risk factor for cardiovascular diseases in both men and women. This was established in such classic studies as the Framingham Study, MRFIT, and the Paris Prospective Study. The risk of cardiovascular complications and mortality in DM is 2-5 times higher than in the population, even in the absence of classical risk factors such as arterial hypertension (AH), hyperlipidemia, and smoking. The increase in the number of adverse cardiovascular outcomes associated with DM is explained by the accumulation of other risk factors, the development of myocardial damage (diabetic cardiomyopathy), and macro- and microvascular complications of diabetes. DM significantly increases cardiovascular morbidity: the relative risk of CHD increases 2-fold, coronary death - 2.31-fold, nonfatal MI - 1.82-fold, and ischemic stroke - 2.27-fold [23]. All this indicates the presence of specific, associated with DM is a risk factor that requires in-depth study and adequate correction. Hyperglycemia is the main risk factor for the development of cardiovascular complications in patients with type 2 diabetes. The results of numerous studies have shown that a decrease in the level of glycated hemoglobin (HbA1c) is accompanied by a decrease in the risk of specific vascular complications of diabetes. An improvement in glycemic control was shown when switching from traditional to intensive insulin therapy, which was accompanied by a reduction in the risk of developing and progressing vascular complications [24]. The EDIC (The Epidemiology of Diabetes Interventions and Complications Research Study), which was a continuation of the DCCT study, demonstrated that 4 years after all patients were transferred to an intensive insulin therapy regimen, while achieving the same glycemic control in both groups of adolescents, the risk of retinopathy progression remained lower in the group that initially received intensive treatment [22-5]. This phenomenon is called "positive metabolic memory". The results of this study showed that it is important not only to ensure that glucose levels are reduced to target levels, but also to prevent cardiovascular risk factors in patients with type 2 diabetes and to prevent

hypoglycemia, as well as significant fluctuations in blood glucose levels, since all these conditions initiate oxidative stress, chronic inflammation, endothelial dysfunction in the vessels and play an important role in the development of role in the development of diabetic complications [21, 22]. Large clinical trial of UKPDS (U. K. Prospective Diabetes Study) allowed us to determine the most significant risk factors for CHD and its complications in patients with type 2 diabetes. These include (in descending order of importance): increased LDL cholesterol, hypertension, smoking, low HDL cholesterol, increased HbA1c [17]. So, reducing the level of HbA1c approximately at 1% in patients with DM2 resulted in a 14% reduction in the incidence of MI, and a 21% reduction in overall mortality. On the contrary, a 1% increase in this indicator contributed to an 18% increase in cardiovascular morbidity [18]. However, с тем исследованием, the ACCORD, ADVANCE, and VADT studies, which included high- and very high-risk cardiovascular patients with long-term DM2, did not demonstrate the benefits of strict glycemic control in relation to the risk of CVD in this category of patients. This approach may even have worsened the prognosis of these patients, which determined in the консенсусе ADA/EASD consensus (2012) the need to establish individual glycemic targets in patients with DM2, especially those receiving drugs that can increase the frequency of hypoglycemia (MSM, insulin).

The Cooperative Cardiovascular Project study presented above Project analyzed the prognosis of patients with MI with and without DM, depending on their blood glucose levels. It was noted that the 30-day mortality rate of patients with diabetes with a glycemia of more than 13 mmol / l was 15% lower than in the group of patients with severe hyperglycemia at admission, but without previously established diabetes. In addition, multivariate analysis revealed that the mortality rate for patients without previously diagnosed DM increased for almost all values of hyperglycemia, while in the group of patients with established DM-only at values of 13 mmol / l and higher. No intergroup differences in one-year mortality rates were found [10]. The values of glycemia at admission were identified as an



independent predictor of death in patients with ACS based on the results of a study conducted by Dutch scientists. An increase in blood sugar concentrations of 1 mmol/l (at baseline values above 9 mmol/L) has been shown to increase the risk of death by 10%. At the same time, the 30-day mortality rates among DM patients and non-diabetic patients were 16% and 5%, respectively [12]. The effect of DM on the long-term prognosis of patients with MI was studied in another prospective study. The data of about 2000 patients hospitalized with ACS were studied, of which 1 / 5 had previously established DM. The results showed that 320 (17%) patients died during the medium-term follow-up period (3.7 years), while the presence of concomitant diabetes contributed to a significant increase in the risk of death. The prognostic significance of DM did not depend on smoking, age, thrombolysis, or the type of hypoglycemic therapy, but the risk of death associated with diabetes was significantly higher in women [13]. Pathogenesis of acute ischemic events in DM patients The pathogenetic mechanisms of CHD development and progression in DM are diverse. The main generally accepted factors are changes in the vascular wall as a result of metabolic shifts (hyperglycemia and dyslipidemia) - endothelial dysfunction, as well as systemic inflammation and hypercoagulation. These changes occur not only in the area of the affected artery in ACS, but also in the entire myocardium, causing a smaller coronary reserve due to a combination of microangiopathy and multi-vascular lesions of the distal coronary bed that reduce collateral blood flow in T2DM [12]. DM also contributes to the progression of left ventricular (LV) systolic dysfunction. Heart failure in CHD and DM occurs not only in connection with atherosclerosis of the coronary arteries and the development of fibrosis, but also due to the development of a specific myocardial lesion, the so-called "diabetic" cardiomyopathy. At the same time, this cardiomyopathy is characterized by a violation of both diastolic and systolic LV myocardial function [1-5]. The damaging effect of hyperglycemia on endothelial function, the development of collateral blood circulation, as well as an increase in microvascular dysfunction has been proven in

experimental studies. In addition, acute hyperglycemia can potentiate coagulation mechanisms, which may result in an increased risk of atherothrombosis. A group of American researchers on the culture of umbilical vein cells experimentally proved that acute hyperglycemia can serve as a trigger factor for the process of apoptosis. Later, the authors proved their hypothesis in mouse models with artificially induced DM [14]. The reverse state-hypoglycemia-also has an unfavorable effect on the course of ACS in patients with DM, manifested by cardiac arrhythmias, including fatal ones [1-7]. The negative effect of severe hypoglycemia, especially iatrogenic hypoglycemia, on myocardial contractility was observed when inadequate doses of insulin were administered during insulin therapy in patients with DM [15]. The existing dissonance in the questions of possible mechanisms of the influence of hyper- and hypoglycemia on the course of MI in patients with DM supports the interest of researchers in further study of this issue.

6442

Conclusions

Establishing the significant role of a cardiologist in the management of a patient with type 2 diabetes is a matter of clinical necessity. The WHO Global Report on Diabetes Mellitus (2016) indicates that to achieve better results, capacity-building efforts in the diagnosis and treatment of DM should be undertaken in the context of integrated management of noncommunicable diseases, in particular by combining DM and cardiovascular diseases. In this regard, the cardiologist should have sufficient knowledge in the field of prevention, diagnosis, treatment of diabetes and its complications, including knowledge of not only the known effects of the main classes of antidiabetic drugs, but also their pleiotropic cardiovascular effects, as well as the possibility of using lipid-lowering and antihypertensive therapy in patients with DM2. The most important condition for modern treatment of DM2 is early diagnosis of this disease, since an increase in the duration of "untreated" diabetes significantly worsens the patient's prognosis. A cardiologist and general practitioner are often "first contact" doctors who



detect glucose metabolism disorders in people with cardiovascular diseases. It is known that about 30% of patients admitted to specialized clinics with a diagnosis of ACS have a history of impaired glucose tolerance or have recently been diagnosed with diabetes. A cardiologist should have in-depth knowledge and skills on healthy nutrition, adequate physical activity, and correction of CVD risk factors such as smoking, hypertension, and dyslipidemia. In this regard, treatment of a patient with DM2, along with long-term maintenance of glycemic targets, should be aimed at managing the prognosis of patients in terms of the risk of developing cardiovascular complications.

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