GLUCOSE METABOLISM DISORDERS IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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SUMMARY – Glucose metabolism disorders in acutely ill patients include oscillations in plasma glucose concentration outside the range of reference values. These disorders include both hyperglycemia and hypoglycemia, regardless of previous diagnosis of diabetes in a particular patient. Hyperglycemia is frequent in acute patients due to the increased release of stress hormones such as catecholamines and cortisol, but also as an effect of a cascade of proinflammatory cytokines in emergencies such as acute coronary syndrome, pulmonary edema, pulmonary embolism, injuries, severe infections and sepsis. Hyperglycemia occurs often even in patients in whom diabetes was not previously diagnosed, and in diabetic patients requirement for hypoglycemic medication may be temporarily increased. Hyperglycemia in cardiac emergencies is associated with more frequent adverse major cardiovascular events and worse prognosis. Hypoglycemia occurs seldom in these patients, its origin is almost always iatrogenic, and it worsens the patient's prognosis even more than moderate hyperglycemia. Good regulation of glycemia is necessary in the management of these patients; therefore plasma glucose determination and close monitoring are obligatory, and therapy with short acting insulin should be introduced if plasma glucose concentration exceeds 10 mmol/L, regardless of the risk of hypoglycemia. It is also useful to determine the acid-base status and blood or urine ketones.

Key words: *Acute coronary syndrome; Hyperglycemia; Hypoglycemia; Major adverse cardiovascular events*

Introduction

Coronary artery disease (CAD) is the leading cause of death and physical inability. So far, many risk factors have been established, such as male sex, older age, smoking, obesity, physical inactivity, comorbidities like arterial hypertension, diabetes mellitus, hyperlipidemia and hypercoagulable states. All of them are leading to advanced stages of atherosclerosis with prominent intravascular plaques. Rupture of instable plaques may lead to consecutive thrombosis and stenosis or occlusion of the specific vessel. If collat-

eral blood perfusion is insufficient, some form of acute coronary syndrome occurs.

Despite many advances in the treatment of acute coronary syndrome, prevention and appropriate treatment of risk factors remain the best way to prevent death and major cardiovascular adverse events[1].

Diabetes Mellitus and Coronary Heart Disease

Diabetes mellitus has an important impact on vascular disease. It is a major risk factor for heart attack, stroke, and lower extremity vascular disease, and the leading cause of blindness and end-stage renal disease. It is also a major cause of painful peripheral neuropathy, leading to physical disability[2-4].

About three-quarters of diabetic patients die from cardiovascular disease and two-thirds of these

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die from the manifestations of ischemic heart disease, promoting coronary artery disease to the leading cause of morbidity and mortality in patients with diabetes mellitus. Patients with type 2 diabetes have an equivalent cardiovascular risk to that of a non-diabetic patient who has already experienced a coronary event[5,6].

Patients with diabetes are more likely to experience acute myocardial infarction (AMI) and heart failure, and are at a greater risk of dying from an acute cardiac event than patients without diabetes. These differences may be related to the severity and extent of coronary heart disease in diabetic patients, the extent of left ventricular remodeling, and the presence of significant ventricular arrhythmias[7-9].

However, the main reason for increased prehospital, intrahospital and 1-year post-hospital mortality in diabetic patients is the development of heart failure after AMI. Sudden death and fatal ventricular arrhythmias contribute to a lesser extent to the increased mortality rate[7].

Over the past few years, several new methods of treating CAD and acute coronary syndrome (ACS) have been introduced, but patients with diabetes have not enjoyed the same decline in CAD-related mortality as nondiabetic individuals. Poor prognosis associated with diabetes after AMI has been observed in several studies despite adjustment for age, treatment, sex, additional comorbidities, and coronary risk factors[2].

The negative prognostic implications of diabetes apply to patients with different manifestations of ACS, including unstable angina, non-ST segment elevation AMI (NSTEMI), and ST-segment elevation AMI (STEMI). In addition, since patients with diabetes who develop ACS appear to sustain worse outcomes than those without diabetes, it is important to determine if they are receiving proven cardiac interventions under current practices.

There is also mounting evidence that people with coronary heart disease often have undiagnosed type 2 diabetes, impaired glucose tolerance or impaired fasting glucose, which is indicative of an early stage in the pathophysiology of type 2 diabetes[10].

Nondiabetic Glucose Disturbances and Acute Coronary Syndromes

Abnormalities in glucose control can be detected early after AMI and are strong risk factors for cardiovascular morbidity and mortality, even in nondiabetic patients. Usually, glucose disturbances are detected at hospital admission by routine blood glucose measurement. While hypoglycemia is quite rare, hyperglycemia occurs often. Hyperglycemia at admission is a common finding in diabetics with ACS and it is a consequence of transiently increased insulin resistance due to elevated levels of stress hormones and cytokines, as shown in Figure 1.

Hyperglycemia may also occur in patients without prior history of diabetes. In some, it is transient and may normalize in the following days (therefore called 'stress hyperglycemia'), but in others it is persistent reflecting the presence of diabetes mellitus[11].

Stress hyperglycemia is not an event exclusively specific for ACS. In almost all other states of acute illness, like in stroke, sepsis, etc., blood glucose levels my bee elevated[12].

Surprisingly, despite the fact that stress hyperglycemia is a common event, it still lacks a widely accepted definition. Most authors consider hospital admission plasma glucose as a relevant finding, but the threshold value for stress induced elevated plasma glucose is still under dispute. However, most authors simply use definitions of non-stress hyperglycemia, according to ADA, WHO/IDF or EASD/ESC[13], as shown in Table 1.

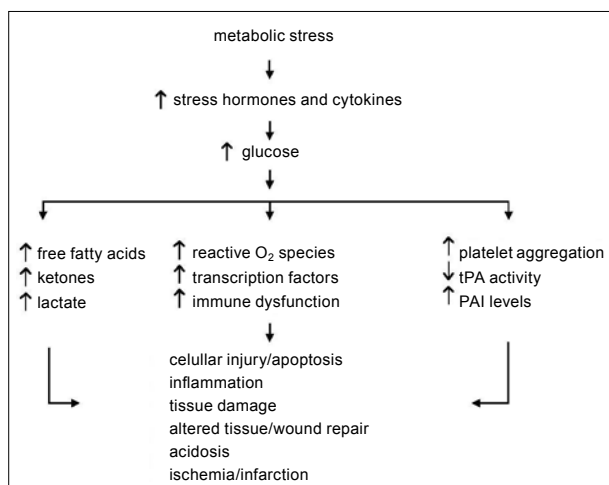Stress hyperglycemia during critical illness has long been considered essential to provide fuel for vi-

Fig. 1. Pathophysiological impact of hyperglycemia

tal organs and hence was interpreted as a beneficial adaptation. Evidence is now growing against this notion as hyperglycemia is identified as an independent risk factor for adverse outcome of numerous surgical and medical conditions, and avoiding hyperglycemia with intensive therapy has been shown to improve the outcome[14-16].

The association of higher glucose levels with mortality in patients with unstable angina, NSTEMI and STEMI has been described, but not yet widely recognized.

Several studies have demonstrated hyperglycemia, with or without pre-existing diabetes mellitus, to be associated with adverse outcomes in patients with ACS, like death, recurrent myocardial infarction or heart failure. Stress hyperglycemia is associated with higher rates of infarction-related artery occlusion[17]. In patients who underwent primary percutaneous coronary interventions (pPCI), the incidence of restenosis was higher in patients with blood glucose abnormalities[18,19].

The underlying pathophysiology relating adverse clinical outcomes to hyperglycemia is unclear, and it is still uncertain whether increased plasma glucose is simply a marker of adverse outcomes or their cause.

Endothelial dysfunction is characteristically seen in diabetes and *in vivo* studies have demonstrated that hyperglycemic spikes induce endothelial dysfunction in both normal and diabetic subjects. It is also known that acute glycemic excursions lead to a series of coagulation abnormalities likely to induce thrombosis.

Atherosclerosis is now considered an inflammatory disease, and there are studies demonstrating that acute hyperglycemia can increase the production of highly sensitive C-reactive protein, plasma interleukin-6, interleukin-18 and tumor necrosis factor-α[20,21].

One potential mechanism whereby hyperglycemia may mediate adverse clinical outcomes could be the adverse impact of hyperglycemia on platelet function. Increased platelet activation and aggregation occur in diabetic and acutely hyperglycemic patients due to increased platelet degranulation, thromboxane synthesis, impaired nitric oxide effect, and insensitivity to aspirin. Furthermore, deleterious changes in fibrinolysis and coagulation secondary to the metabolic derangements of type 2 diabetes have emerged as the likely mechanisms underlying the increased cardiovascular risk. Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of the fibrinolytic system. Thus, elevated concentrations of PAI-1 promote persistence of clots and may have great impact on the prognosis in patients with ACS. Concentrations of PAI-1 are elevated in the blood and vessel walls of patients with type 2 diabetes or other insulin-resistant states[22,23]. Another possible mechanism leading to increased mortality in patients with stress hyperglycemia is its negative impact on left ventricular remodeling, as some echocardiographic studies have shown. Changes in end-diastolic volume, as well as in end-systolic volume were lesser in patients without stress hyperglycemia in the period up to one year after myocardial infarction. Decreased ejection fraction was more profound in patients with

Table 1. Criteria for hyperglycemic glucose metabolism disorders

	EASD/ESC	ADA	WHO/IDF
Normal range fasting:	≤6.0 mmol/L	≤5.5 mmol/L	≤6.0 mmol/L
2 h glucose load:	<7.8 mmol/L	<7.8 mmol/L	<7.8 mmol/L
Impaired fasting glucose fasting:	6.1-6.9 mmol/L	5.6-6.9 mmol/L	6.1-6.9 mmol/L
2 h glucose load:	<7.8 mmol/L	<7.8 mmol/L	<7.8 mmol/L
Impaired glucose tolerance fasting:	<7.0 mmol/L ≥7.8 and <11.0	<7.0 mmol/L ≥7.8 and <11.0	<7.0 mmol/L ≥7.8 and <11.0
2 h glucose load:	mmol/L	mmol/L	mmol/L
Diabetes mellitus fasting:	≥7.0 mmol/L	≥7.0 mmol/L	≥7.0 mmol/L
2 h glucose load:	≥11.0 mmol/L	≥11.0 mmol/L	≥11.0 mmol/L

higher levels of stress hyperglycemia. This finding can explain the larger proportion of heart failure in the group of patients with stress hyperglycemia[8].

A prolonged heart rate adjusted QT interval (QT_c) has been shown to be predictive of sudden death and to correlate with measures of CAD. In a study looking at the effect of acute hyperglycemia induced by intravenous glucose load on the QT_c interval, it was found that QT_c and several sympathetic tone dependent hemodynamic parameters were increased in response to this acute rise in glucose. This suggests that exaggerated glycemic surges, as seen in the postprandial state, can enhance the risk of sudden death in vulnerable persons by enhancing the sympathetic tone and prolonging the QT_c interval[9].

The influence of stress hyperglycemia on mortality in patients with ACS seems to be independent even of the presence of previously diagnosed diabetes. Elevated blood glucose levels at admission in patients with ACS were an important independent predictor of in-hospital mortality, even more important for patients without previously known diabetes, as reported in some studies[24].

It has to be commented that, compared with euglycemic patients, those with stress hyperglycemia were older, with higher heart rates, prevalence of hypertension, congestive heart failure and diabetes, but less tobacco use[25].

According to some other papers, patients with previously known and well-controlled diabetes had similar rates of in-hospital adverse events to the patients without diabetes and without stress hyperglycemia[26].

While stress hyperglycemia seems to be recognized as an important predictor of short-term, in-hospital adverse events, fasting hyperglycemia and its impact on mortality has not been so often commented in the literature.

However, the use of fasting blood glucose for risk stratification after AMI remains important. Fasting blood glucose after MI is particularly relevant because it also shows strong association with short-term prognosis after MI, as well as admission glycemia. Furthermore, even in non-diabetic patients with AMI, fasting blood glucose is an independent predictor of abnormal glucose tolerance as well as admission hyperglycemia[27].

Persistent hyperglycemia in comparison to both admission hyperglycemia and fasting hyperglycemia, perhaps has the strongest relation to early cardiovascular events[24].

The Role of Hypoglycemia

Not only hyperglycemia, but also hypoglycemia is a harmful event for diabetics suffering from ACS, as evidenced most recently by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[28]. The intensive glucose lowering arm of this trial was stopped prematurely due to a higher rate of mortality in patients in the intensive arm *versus* those in the standard arm. However, there are some objections to this conclusion because the intensive glucose lowering arm included more patients with a prior history of AMI and they were more often treated with rosiglitazone. In two similar trials, ADVANCE (Action in Diabetes and Vascular Disease) and VADT (Veterans Affairs Diabetes Trial)[29], there was no benefit in the reduction of major cardiovascular events in the intense glucose lowering arms, probably due to the higher rate of hypoglycemia. In a smaller study, patients with hypoglycemia and ACS had lower body weight and were more often diabetic.

The relationship of blood glucose and mortality seemed to be U-shaped among patients with ST-elevation myocardial infarction, with similar rates between patients with hypoglycemia and moderate hyperglycemia, as shown in Figure 2[28-31].
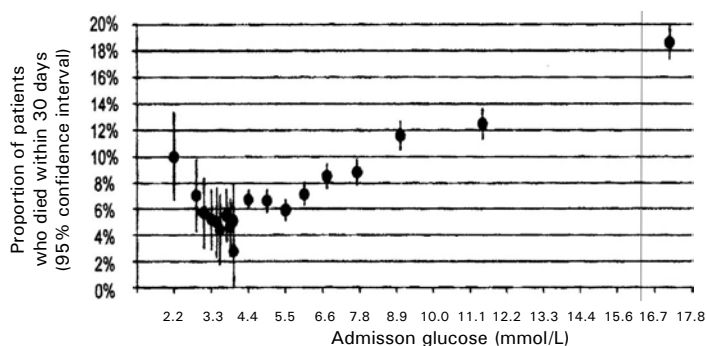

Fig. 2. Impact of admission glucose on short-term mortality in patients with acute myocardial infarction (adapted from Kosiborod et al.[31]).

Treatment of Blood Glucose Disturbances in Acute Cardiac Patients

The management of glucose disturbances in acute states differs largely from common diabetic therapies in outpatients.

The basic medications required for blood glucose regulation in all emergencies are short acting insulins (or recently introduced ultra-short acting insulin analogs), glucagon, crystalloid solutions of saline, glucose solution of different concentrations, and liquid potassium salts. It is worth noting that all these medications should be applied parenterally, while oral administration of glucose lowering drugs, although theoretically possible, shows serious shortcomings. Sulfonylureas and related medications are not a good choice in emergencies due to the relatively slow onset of effects, and a relatively long half-life (for some of them, the effect lasts up to 24 hours). These drugs are also relatively less effective in states with a higher degree of insulin resistance. Their performances are also not desirable in all intensive care units dealing with instable patients because of a relatively high risk of hypoglycemia. Medications like biguanides and thiazolidinediones are contraindicated in heart failure. Furthermore, some thiazolidinediones like rosiglitazone are withdrawn because of the increased incidence of major adverse cardiovascular events. Administration of longer acting insulin and insulin analogs, as well as premixed insulin combinations is not contraindicated, but may be less suitable for instable patients due to the long biological half-life of these insulin subgroups[32-34].

Special attention needs to be paid to adequate hydration and correction of electrolytic disorders in patients with hyperglycemia, which may be a therapeutic problem since the insufficient cardiac function may limit parenteral hydration[34].

It remains unclear, however, to what extent maintaining normoglycemia and glycemia-independent actions of insulin account for the different clinical benefits of intensive insulin therapy in the critically ill. *Post hoc* analyses of randomized controlled studies of intensive insulin therapy in surgical intensive care patients have suggested that blood glucose control best explains the clinical benefits of the intervention.

Several mechanisms may be involved in improving cardiovascular outcomes. The protective effect of insulin on the endothelium has been suggested to play a key role in the survival benefit of intensive insulin therapy. Endothelial protection is likely to improve microcirculation in vital organs, whereby their function may be protected and hence the risk of death reduced. Avoiding direct toxicity of glucose to endothelial cells, but perhaps also to other cells that take up glucose independently of insulin, such as neurons and hepatocytes, may contribute to the survival benefit achieved with tight blood glucose control. The cardiovascular system appears to be crucially affected by intensive insulin therapy. It was demonstrated that high levels of insulin ameliorated myocardial contractility but only when normoglycemia was maintained concomitantly. This observation is of relevance to the controversy surrounding GIK (glucose + insulin + potassium infusion) therapy. GIK traditionally focuses on insulin as the key component of a metabolic cocktail, which is thought to beneficially modulate myocardial metabolism. Insulin is thought to have direct inotropic effect by economizing and ameliorating myocardial performance. In the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction)-1 study, GIK promoted survival of patients with diabetes and AMI. In this study, patients in the GIK arm had significantly lower blood glucose levels. However, after hospital discharge, there was no benefit shown for patients receiving intensive insulin therapy in comparison to patients given other therapies (DIGAMI 2 study)[30].

Conclusion

Blood glucose levels should be routinely assessed among patients with ACS to possibly aid risk stratification and tailoring of therapy. It seems that strict blood glucose control (glucose value should be close to the physiological values) is an imperative not only in the prevention but also in the treatment of ACS and prevention of reinfarction and heart failure. Finally, and perhaps most important of all, is the need for ACS patients with hyperglycemia to be properly evaluated for diabetes. Fasting glucose, HbA_{1c} and glucose tolerance testing 2 hours after oral administration of 75 g glucose load are helpful investigations in identifying and treating the existing prediabetes or diabetes[34].

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Sažetak

POREMEĆAJI METABOLIZMA GLUKOZE U BOLESNIKA S AKUTNIM KORONARNIM SINDROMOM

V. Altabas, K. Altabas, M. Berković–Cigrovski, S. Maloševac, M. Vrkljan i *V. Nikolić Heitzler*

Poremećaji metabolizma glukoze u akutnih bolesnika uključuju poremećaje poput hiperglikemije i hipoglikemije, od-nosno odstupanja koncentracija glukoze u plazmi izvan referentnih raspona. Pritom je nevažno boluje li bolesnik od ranije dijagnosticirane šećerne bolesti. Hiperglikemija je česta kod ovakvih bolesnika zbog prolazno povišenih koncentracija kateholamina i kortizola, kao i niza proupalnih citokina, a može se javiti kod bolesti poput akutnog koronarnog sindroma, plućnog edema, plućne embolije, povreda, te teških infekcija i sepsa. Često se javlja kod bolesnika bez šećerne bolesti, kod dijabetičara može zahtijevati prolazno povišenje doza antidijabetičnih lijekova. Hipoglikemija se javlja mnogo rjeđe, po svom postanku je gotovo uvijek jatrogena. Hiperglikemija i hipoglikemija pogoršavaju prognozu akutnih bolesnika, te je u bolničkim uvjetima praćenje razine glukoze u krvi obvezno, uz uvođenje terapije kratkodjelujućim inzulinom kod hiper-glikemije iznad 10 mmol/L. Dodatne informacije pruža određivanje acidobaznog statusa i ketona.

Ključne riječi: *Akutni koronarni sindrom; Hiperglikemija; Hipoglikemija; Veći neželjeni kardiovaskularni ispadi*