Implications and Treatment of Acute Hyperglycemia in the Setting of Acute Myocardial Infarction

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A 52-year-old obese male without a prior history of diabetes mellitus (DM) presented with angina and an anterior ST-segment-elevation myocardial infarction (STEMI). Physical examination and chest x-ray were consistent with congestive heart failure. Admission glucose was 230 mg/dL. Coronary angiography revealed an occluded left anterior descending coronary artery, and stenting reestablished TIMI grade 2 flow in that artery within 90 minutes of symptom onset. Left ventricular ejection fraction was 35% with severe anterior hypokinesis. Peak creatine kinase was 600 IU. The next day, fasting glucose was 180 mg/dL. An echocardiogram performed 6 weeks after discharge revealed an ejection fraction of 35% without change in the anterior wall motion. Fasting glucose as an outpatient was 156 mg/dL.

The scenario described above is commonly encountered and illustrates how hyperglycemia can affect the outcome of patients with STEMI. Hyperglycemia could have affected the following features of this case: (1) Congestive heart failure was present despite only modest myocardial injury by creatine kinase level; (2) despite successful percutaneous coronary intervention, subnormal coronary perfusion was observed; and (3) left ventricular recovery after STEMI did not occur. Cardiologists need to be cognizant of the hazards associated with hyperglycemia in this setting because these patients will be encountered more frequently as a result of the increasing prevalence of insulin resistance syndromes.

Prevalence and Risk of Hyperglycemia in STEMI

Acute hyperglycemia is common in patients with STEMI even in the absence of a history of type 2 DM. Hyperglycemia is encountered in up to 50% of all STEMI patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients.1 The prevalence of type 2 DM or impaired glucose tolerance may be as high as 65% in MI patients without prior DM when oral glucose tolerance testing is performed.2

Elevated plasma glucose and glycated hemoglobin levels on admission are independent prognosticators of both in-hospital and long-term outcome regardless of diabetic status.3,4 For every 18-mg/dL increase in glucose level, there is a 4% increase in mortality in nondiabetic subjects.5 When admission glucose level exceeds 200 mg/dL, mortality is similar in non-DM and DM subjects with MI. Admission glucose has been identified as a major independent predictor of both in-hospital congestive heart failure and mortality in STEMI.6

Fasting glucose the day after admission appears to be a better predictor of early mortality than glucose level on admission.7 Patients with both an elevated admission glucose and an elevated fasting glucose the next day have a 3-fold increase in mortality. Similarly, failure of an elevated glucose level to fall within 24 hours of admission is associated with excess mortality in STEMI patients without DM.8

The presence and degree of hyperglycemia may not correlate with infarct size, as is commonly thought.5 Counterregulatory hormones (catecholamines, growth hormone, glucagon, and cortisol) are released in proportion to the degree of cardiovascular stress and may cause hyperglycemia and an elevation of free fatty acids, both of which lead to an increase in hepatic gluconeogenesis and a decrease in insulin-mediated peripheral glucose disposal. As in our case study, the glycemic response to these “stress” hormones is exaggerated when super-

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imposed on insulin resistance manifest as obesity in this patient.

**Cardiovascular Effects of Acute Hyperglycemia in STEMI**

Acute hyperglycemia is associated with numerous adverse effects that contribute to a poor outcome in STEMI (Table 1). Acute hyperglycemia rapidly suppresses flow-mediated vasodilatation, likely through increased production of oxygen-derived free radicals. Hyperglycemia increases intranuclear nuclear factor-κB binding and activates proinflammatory transcription factors, which increase the expression of matrix metalloproteinases, tissue factor, and plasminogen activator inhibitor-1. The degree of oxidative stress correlates most closely with acute, not chronic, glucose fluctuations. Increased oxidative stress interferes with nitric oxide–mediated vasodilatation and reduces coronary blood flow at the microvascular level. In STEMI subjects, acute hyperglycemia is associated with reduced TIMI grade 3 flow before intervention compared with euglycemia and is the most important predictor of the absence of coronary perfusion. Similarly, diabetic subjects have reduced myocardial blush grades and diminished ST-segment resolution after successful coronary intervention in STEMI, consistent with diminished microvascular perfusion. Acute hyperglycemia is associated with impaired microcirculatory function as manifest by “no reflow” on myocardial contrast echocardiography after percutaneous coronary intervention. Preexisting HbA1c levels and diabetes status do not differ between subsets with and without no reflow, suggesting that acute, not chronic, hyperglycemia is the dominant factor. Finally, the well-known adverse effects of hyperglycemia on platelet function, fibrinolysis, coagulation, and ischemic preconditioning likely contribute to the adverse effects of acute hyperglycemia in STEMI.

Hyperglycemia is a reflection of relative insulinopenia, which is associated with increased lipolysis and free fatty acid generation, as well as diminished myocardial glucose uptake and a decrease in glycolytic substrate for myocardial energy needs in STEMI. Myocardial ischemia results in an increased rate of glycogenolysis and glucose uptake via translocation of GLUT-4 receptors to the sarcolemma. Because glucose oxidation requires less oxygen than free fatty acid oxidation per molecule of ATP produced, myocardial energetics are more efficient during the increased dependence on glucose oxidation with ischemia. With relative insulinopenia, however, the ischemic myocardium is forced to use free fatty acids instead of glucose as an energy source because myocardial glucose uptake is acutely impaired. Thus, a metabolic crisis may ensue as the hypoxic myocardium becomes less energy efficient in the setting of hyperglycemia and insulin resistance.

**Role of Aggressive Treatment of Hyperglycemia in STEMI**

The concept of a metabolic cocktail (GIK) to stabilize cell membranes through potassium influx, promote glucose oxidation, and reduce free fatty acid accumulation to protect the ischemic myocardium dates back to the work of Sodi-Pallares et al. Early studies yielded promising results, and a meta-analysis suggested that therapy with GIK may reduce mortality in STEMI. However, the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicos Latino-America (CREATE-ECLA) study showed no benefit of GIK in a large number of STEMI subjects, dampening the enthusiasm for aggressive use of a metabolic cocktail in STEMI. However, in CREATE-ECLA, glucose levels increased during the first 6 hours in the GIK-treated group, whereas there was a reduction in glucose in the control group. Subjects with the highest tertile of admission glucose levels had more than twice the mortality (14% versus 6.6%) compared with subjects in the lowest tertile. The “neutral” effect of GIK may be explained by a relative benefit of GIK (possibly the insulin component) counterbalanced by the increased risk associated with the increase in glucose levels related to GIK.

In contrast to GIK, a “cocktail” delivered regardless of glucose level, intravenous insulin delivered to normalize glucose improves outcomes in STEMI and in patients in intensive care unit settings. Insulin is associated with numerous cardiovascular benefits above and beyond a reduction in hyperglycemia (Table 2). Experimentally, hyperinsulinemia in the setting of euglycemia is associated with enhanced myocardial blood flow, whereas vasodilatory reserve is reduced in the presence of hyperglycemia. Similarly, the postprandial state is associated with reduced myocardial blood flow in diabetic subjects but is
associated with increased myocardial perfusion in normal subjects. Thus, acute hyperglycemia negates the beneficial effects of insulin on coronary vasodilatory reserve. Insulin therapy also improves functional recovery after myocardial ischemia by mechanisms distinct from improved myocardial energetics.

Myocardial protection with insulin administration at the time of reperfusion appears to be independent of the effects of insulin on glucose metabolism; rather, it is associated with activation of cell survival signaling pathways in experimental models. In humans, insulin infusion at the time of reperfusion has a profound antiinflammatory effect and reduces infarct size. Both the American Diabetes Association and the American College of Endocrinology recommend attaining a glucose target of ≤110 mg/dL while the patient is in the intensive care unit and <180 mg/dL postprandially when the patient is transferred to a less intensive care setting. Although less specific, the ACC/AHA guidelines state, “Tight glucose control in diabetics during and after STEMI has been shown to lower acute and 1-year mortality rates.” Algorithms for the management of hyperglycemia in the hospital setting have recently been reviewed.

In summary, acute hyperglycemia in the setting of STEMI worsens the prognosis in patients with and without known DM. As seen in our case study, hyperglycemia impaired microvascular flow and was associated with congestive heart failure. The upcoming National Institutes of Health–sponsored Immediate Metabolic Myocardial Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial (clinicaltrials.gov) using prehospital GIK treatment in patients with STEMI will help to further define the role of aggressive metabolic control in STEMI. In the meantime, it appears prudent for the clinician to monitor and restore normoglycemia as soon as possible to optimize outcomes in STEMI.

Disclosures

None.

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