Biomarkers are used to establish a diagnosis, provide prognostic information, and guide therapeutic interventions in patients with acute coronary syndromes. In acute myocardial infarction (AMI), white blood cell count, creatine kinase–MB isoenzymes, myoglobin, and troponin are measured for 1 or more of these purposes. Recently, brain natriuretic peptide (a measure of hemodynamic stress), interleukin-6, C-reactive protein, and soluble CD40 ligand (indices of inflammation) have been added. The plasma glucose level at the time of AMI has been a curious but distant cousin to this list. The level of glycemia correlates with short- and long-term prognosis and can also serve as a target for intervention (with insulin). In addition, the glycemic response to the stress of AMI provides important information about the metabolic status of the patient. As a result of the increasing prevalence of insulin-resistant states, hyperglycemia will be encountered more frequently in patients with AMI.1–3 Many cardiologists may be intimidated by the implications of hyperglycemia because glucose metabolism is not part of the core curriculum of cardiology today. In this issue of Circulation, Kosiborod et al4 studied the interactions between levels of glycemia and cardiovascular outcomes during AMI.

Article p 1018

It is well known that, in the setting of an AMI, hyperglycemia is associated with adverse outcomes, even after adjustment for numerous “cardiac” variables linked to outcome. Previous studies have shown that an elevated plasma glucose level on admission is a major independent predictor of in-hospital and long-term outcome in patients with AMI.5,6 Moreover, fasting glucose level on the day after admission and failure of an elevated glucose level to fall within 24 hours of admission have been shown to be better predictors of early death in patients with AMI than the glucose level on admission.7,8 At these time points in the course of AMI, the absolute level and directional change of glucose parallels the information provided by other biomarkers such as creatine kinase–MB, troponin, and brain natriuretic peptide. Does this article by Kosiborod et al4 elevate glucose level to the ranks of these other commonly measured biomarkers in AMI?

Kosiborod et al4 demonstrate that measures of persistent hyperglycemia during AMI hospitalization are better predictors of mortality than the admission glucose level. Their study analyzed a cohort of patients with and without type 2 diabetes mellitus presenting with AMI to relate a variety of measurements of glycemia to outcome. The authors selected several glucometric evaluations and analyzed each of these measurements over different time periods during hospitalization (first 24 hours, first 48 hours, and the entire duration of hospitalization). Mean glucose, time-averaged glucose, and hyperglycemic index were evaluated and compared with admission glucose alone. Unadjusted analyses demonstrated that higher plasma glucose levels were strongly associated with increased risk of in-hospital mortality for all glucose metrics used. After adjustment for confounders, all average glucose metrics were found to be better predictors of in-hospital mortality than admission glucose. Interestingly, the study demonstrated that the in-hospital mortality rate was higher in patients without type 2 diabetes mellitus than in patients with type 2 diabetes mellitus at similar glucose levels. The authors also found that the adverse prognostic impact of elevated glucose extended throughout the entire hospitalization. Furthermore, although measures of glucose such as hyperglycemic index and time-averaged glucose have higher discriminating ability to independently predict in-hospital mortality, mean glucose was the most practical summary measure providing this prognostic information. Why might this be so? Is the level of glycemia a marker or mediator or both of outcome?

Acute hyperglycemia is associated with endothelial dysfunction, platelet hyperreactivity, impaired microcirculatory function, increased cytokine activation, increased free fatty acid levels, and increased oxidative stress, all of which adversely affect outcome in AMI.9,10 The oxidative stress induced by increasing levels of intranuclear nuclear factor-κB and by activation of proinflammatory transcription factors is also associated with hyperglycemia. Furthermore, in patients with AMI, acute hyperglycemia is associated with decreased microvascular perfusion, as demonstrated by reduced Thrombolysis in Myocardial Infarction flow and myocardial blush grades.11 Importantly, however, there is a U-shaped relationship between blood glucose and cardiovascular outcomes, with hypoglycemia during hospitalization for acute coronary syndrome being an independent correlate of higher mortality risk.12,13

In the absence of clinical trials to support a higher level of evidence, both the American College of Cardiology/American Heart Association and American Diabetes Association/American College of Endocrinology approach glycemic control in patients with acute coronary syndrome as a Class IIa
recommendation. In these guidelines, level B evidence supports the use of intensive insulin therapy to attain normoglycemia, but these recommendations are not universally employed in clinical practice. Algorithms to achieve this goal have been reviewed. Several realistic barriers stand in the way of cardiologists following such recommendations. These include (1) a fear of insulin-induced hypoglycemia in AMI, (2) inexperience in managing glycemia in the hospital, (3) lack of resources (usually staff) to monitor glucose at frequent intervals, and (4) most importantly, lack of clinical trial data unequivocally supporting normoglycemia as a mandatory treatment target. These factors have protected cardiologists from confronting this issue.

Despite these considerations, the study by Kosiborod et al adds more support to the notion that the management of hyperglycemia at the time of AMI should be considered more strongly. In general, cardiometabolic regulation in AMI has largely taken 2 forms. One approach is to deliver a metabolic "cocktail" (such as glucose-insulin-potassium [GIK]) to all patients without regard to the level of glycemia, and the other is specifically targeted only to those patients with hyperglycemia (with a "physiological" continuous infusion of insulin). Prior studies based on the work of Sodi-Pallares et al indicated that GIK infusions could protect the myocardium by a reduction of free fatty acid concentrations and subsequent improvement in myocardial utilization of glucose. However, after the report of another trial that linked hyperglycemia with poor prognosis after AMI and showed no benefit of GIK in ST-segment–elevation myocardial infarction (STEMI), the idea of metabolic regulation with insulin infusion during AMI was questioned. In addition, an analysis of combined data from 2 trials in patients with AMI showed no benefit and potential harm of GIK infusion during AMI was questioned. In addition, an analysis of combined data from 2 trials in patients with AMI showed no benefit and potential harm of GIK infusion possibly due to infusion-related hyperglycemia, hyperkalemia, fluid overload, and delivery of GIK after reperfusion therapy.

In contrast with GIK infusion, recent studies have shown that "physiologically tolerable" doses of insulin infusion can provide an antiinflammatory, profibrinolytic, antioxidant, and myocardial protective effect in hyperglycemic patients with AMI despite elevated free fatty acid levels. Insulin has been shown to increase microvascular blood flow through the release of nitric oxide by the endothelium and to suppress the expression of inflammatory mediators such as intracellular adhesion molecule-1, monocyte chemotactic protein-1, and nuclear factor-κB binding. Overall, insulin promotes beneficial effects in endothelial and platelet function, which can ultimately be a potential pharmacological tool beyond glycemic control to improve cardiovascular outcomes in the setting of AMI. The delivery of intravenous insulin to normalize glucose levels has been shown to improve outcomes in STEMI and in patients in intensive care unit settings. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study, an insulin infusion regimen designed to achieve glucose levels from 70 to 180 mg/dL reduced reinfarction and heart failure but not mortality. This study also demonstrated a reduction in C-reactive protein levels in the insulin infusion group. Importantly, recent studies have also shown the potentially harmful effect of hypoglycemia in combination with intensive insulin therapy, especially when given for prolonged periods.

The much-needed evidence that will determine whether cardiometabolic treatment of AMI patients can reduce mortality safely will be available soon. The Immediate Metabolic Myocardial Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) study evaluates prererefusion GIK delivery in patients with STEMI. The Intensive Insulin Therapy and Size of Infarct as a Visual End-point by cardiac magnetic resonance imaging (INTENSIVE) trial will evaluate the use of intensive insulin infusion therapy compared with standard glycemic control in hyperglycemic patients presenting with AMI.

Over the past 2 decades, cardiac biomarkers have provided physicians with important information for managing patients with AMI. At present, glucose levels are not used to guide therapy. However, the evidence that the plasma glucose level can predict risk and that a therapeutic strategy aimed at achieving normoglycemia may affect outcomes in patients with AMI should at least encourage cardiologists to be cognizant of the glucose level and consider it another biomarker to be reckoned with in this setting. Glucometrics that incorporate glucose values over longer time periods may provide prognostic information superior to admission glucose level and may be a better tool on which to devise algorithms incorporating intravenous insulin to treat hyperglycemia (pending results from ongoing trials in AMI). The report by Kosiborod et al provides additional evidence that the level of glycemia is an important "cardiometabolic" biomarker that should be added to the other biomarkers cardiologists now incorporate in the evaluation and management of patients with AMI.

Disclosures

Dr Nesto has served on the Speakers Bureau of Sanofi-Aventis. Dr Lago has no conflict of interest to report.

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