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Serum Glucose Levels and Hospital Outcomes in the Setting of Acute Myocardial Infarction in Patients Not Known to Have Diabetes: A Community-Wide Perspective

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Serum Glucose Levels and Hospital Outcomes in the Setting of Acute Myocardial Infarction in Patients Not Known to Have Diabetes: A Community-Wide Perspective

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Background: Elevated serum glucose levels during hospital admission for acute myocardial infarction (AMI) have been associated with an increased risk of adverse short-term outcomes in diabetic patients (Capes, 2000; Oswald, 1986; Wahab, 2002). Although diabetics, compared with non-diabetics, have a worse prognosis after AMI (Mak, 1997; Herlitz, 1986; Miettinen, 1998), recent studies have suggested that hyperglycemia is also associated with an increased risk of various clinical complications and death in non-diabetic patients (Capes, 2000; Wahab, 2002; Sewardsen, 1989). While the pathophysiologic substrates responsible for these associations remain poorly understood, it appears that neither a catecholamine-induced stress response nor underlying impaired glucose tolerance are the only mechanisms involved (Wong, 2004; Marfella, 2003; Ceriello, 2005).

While several recent studies have demonstrated the prognostic importance of elevated glucose levels in non-diabetic patients hospitalized with AMI (Norhammar, 1999; Tenerz, 2003; Timmer 2004), few investigations have examined the characteristics and hospital management practices of patients with varying levels of serum glucose and the relation of elevated glucose levels to hospital outcomes. None of these studies have assessed changes in these endpoints over time. In addition to the use of different glucose cutpoints in prior investigations, previous studies have examined relatively few strata of patients with varying glucose levels, making interpretation of the role of serum glucose in the pathogenesis of AMI difficult. Moreover, few of these investigations have been carried out from the more generalizable perspective of a community-wide investigation.

Objectives: The purpose of this population-based study is to examine the overall, and potentially changing, relation between levels of serum glucose at the time of hospital admission for AMI, occurrence of AMI associated complications, and the risk of dying during hospitalization in patients hospitalized with AMI without previously diagnosed diabetes. A secondary objective of this study is to examine the demographic and clinical characteristics of patients who present with different serum glucose levels as well as the overall, and potentially changing, hospital management of patients with AMI according to admission serum glucose levels. Patients hospitalized with AMI at all greater Worcester (MA) hospitals in 5 biennial periods between 1995 and 2003, and not known to have previously diagnosed diabetes, comprised the population of interest.

Methods: The Worcester Heart Attack Study is an ongoing population-based investigation examining changes over time in the hospital incidence and case-fatality rates of AMI in residents of the Worcester metropolitan area. The medical records of all greater Worcester residents hospitalized for possible AMI at all area medical centers were individually reviewed and validated by trained study physicians and nurses according to predefined diagnostic criteria. These criteria take into account clinical presentation, increases in serum enzyme levels, and serial electrocardiographic findings. Demographic and clinical data including age, sex, comorbidities (e.g., history of angina, heart failure, hypertension, or stroke), order of the AMI (initial vs prior event) and type (Q-wave vs non–Q-wave AMI), use of cardiac medications and coronary revascularization procedures during hospitalization, and hospital discharge status were abstracted from hospital medical records by trained nurse and physician reviewers. The 3,601 patients without a history of previously diagnosed diabetes, based on the review of information contained in hospital medical records, included in the present analysis were hospitalized in 5 biennial periods between 1995 and 2003.

Data analysis: Patients with independently validated AMI and without a history of diabetes were stratified into quintiles based on the initial serum glucose level recorded at the time of hospital admission. These quintiles consisted of the following: quintile 1: <120 mg/dl; quintile 2: 120 to 139 mg/dl; quintile 3: 140-159 mg/dl; quintile 4: 160 to 179 mg/dl; and quintile 5: ≥180 mg/dl. We also categorized patients' serum glucose levels into 2 additional strata at the extremes of this distribution (<100 and ≥200 mg/dl) for purposes of further characterizing the distribution of serum glucose levels in the study sample. Logistic regression analysis was used to assess the independence of the association between serum glucose levels and the development of heart failure, cardiogenic shock, and death during hospitalization while controlling for several potentially confounding prognostic variables.

Our initial regression model controlled for the effects of age and sex only. A second regression model controlled for medical history, AMI associated characteristics, and time (cohort year) in addition to age and sex. A third model controlled for these variables in addition to hospital use of effective cardiac medications (angiotensin converting enzyme (ACE) inhibitors, aspirin, beta blockers, lipid lowering agents, and thrombolytics) and hospital use of coronary angioplasty. Multivariable adjusted odds ratios and accompanying 95% confidence intervals were calculated in a standard manner.

Results: Approximately one-third of patients presented with glucose levels <120 mg/dl while one-quarter had serum glucose levels ≥160 mg/dl. Patients in the uppermost quintiles of serum glucose were significantly more likely to develop heart failure, cardiogenic shock, and die during hospitalization than patients with lower serum glucose levels. Patients with the highest glucose levels were less aggressively treated with effective cardiac medications and coronary interventions. The results of this population-based investigation provide insights to the magnitude and impact of hyperglycemia in patients not known to have diabetes hospitalized with AMI. Increased surveillance and more aggressive treatment strategies remain needed to improve the outlook of patients with elevated glucose levels.

Discussion: Numerous studies have demonstrated that patients with elevated serum glucose levels in the setting of AMI, irrespective of diabetes status, are more likely to experience adverse hospital outcomes. A limited number of studies have suggested that this risk may be exaggerated in non-diabetic patients in comparison to those with established diabetes (Wahab, 2002; Sewardsen, 1989). While early studies hypothesized that the presence of hyperglycemia in the setting of AMI in patients without previously diagnosed diabetes may represent a combination of underlying impaired glucose tolerance and a catecholamine-induced stress response to myocardial damage (Oswald, 1986; Wahab, 2002; Sewardsen, 1989), current research suggests a more complex pathophysiologic mosaic (Ceriello, 2005). Evidence that strict glycemic control with insulin significantly decreases mortality in diabetic patients with AMI further suggests that hyperglycemia in the setting of AMI is not purely an epiphenomenon of the stress response (Malmberg, 1997; Malmberg, 1999, Fath-Ordoubadi, 1997).

Our data supports previous findings that an elevated serum glucose upon admission for AMI is a significant risk factor for heart failure, cardiogenic shock, and dying during the acute hospitalization. Increased attention to serum glucose levels should assist in the risk stratification of patients with AMI, especially in non-diabetics where serum glucose levels may go largely ignored. Further risk stratification regarding patients' underlying glycometabolic status, and need for short as well as long-term risk factor modification, is also warranted.

Although the mechanisms remain unclear, tight glycemic control with glucose-insulin infusions during the first 24 hours of an AMI has been shown to improve both short and long-term outcomes in patients with diabetes (Malmberg, 1997; Malmberg, 1999, Fath-Ordoubadi, 1997). The survival benefit has been found to be greatest in those not already receiving insulin treatment (Malmberg, 1995). These findings, coupled with the universally adverse outcomes experienced by non-diabetic patients who present with both hyperglycemia and AMI in our

study and others, suggest that tight glycemic control in the acute care setting may play an important role in improving the clinical outcomes of non-diabetic patients hospitalized with AMI.

Study Strengths and Limitations: The strengths of the present study include the large number of patients with independently validated AMI from several relatively recent periods of investigation and inclusion of patients from a representative Northeast metropolitan area whose socioeconomic characteristics reflect those of the U.S. population as a whole, reinforcing the generalizability of the present findings. A primary limitation of this observational study is that admission serum glucose levels in the setting of AMI can fluctuate widely, due to factors such as time and content of last meal, and due to acute myocardial damage. While one recent study showed fasting glucose to be superior to admission glucose in the assessment of short-term mortality risk among patients admitted with AMI (Suleiman, 2005), there is significant support for the efficacy of aggressive glucose management on the basis of admission blood glucose levels (Malmberg, 1995). Neither HbA1c levels, systematically collected fasting blood sugars, nor glucose tolerance test results were available to further assess chronic glycometabolic status and to assess the true prevalence of impaired glucose tolerance or frank diabetes in our study population.

Conclusion: The results of the present investigation confirm that, even among non-diabetic patients, the prevalence of elevated serum glucose levels upon admission for AMI is high. Furthermore, these patients are consistently less likely to receive optimal treatment for AMI, while experiencing significantly higher rates of clinical complications, including in-hospital mortality, in comparison to patients with lower serum glucose levels. These and other data suggest the need for a randomized controlled trial of tight glycemic control in non-diabetic patients with AMI presenting with hyperglycemia on admission for purposes of assessing the optimal treatment of these high-risk patients.