Inpatient Management of Diabetes and Hyperglycemia

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ABSTRACT

Illness, particularly when severe, leads to increased concentrations of counter-regulatory factors which induce insulin resistance and predispose patients to stress hyperglycemia. Elevated glucose concentrations are common in hospitalized patients, both those with as well as without recognized diabetes. Substantial data has emerged over the past decade that quality glucose management in these individuals actually improves clinical outcomes. Controlling glucose in this setting is challenging, given the phenotypic variability amongst patients, with fluctuating courses of acute illnesses and unpredictable nutritional schedules. We review the evidence basis that has informed national standards and glucose targets in both critically and non-critically ill patients. In the intensive care setting, insulin infusions are now widely endorsed to quickly achieve and maintain glucose control. On the hospital wards, physiological subcutaneous insulin therapy, incorporating both basal and nutritional components, is emerging as the optimal treatment strategy. The transition to outpatient care is another important aspect of any hospital glycemic management program. (*Clin Ther.* 2013;35: 724–733) © 2013 Published by Elsevier HS Journals, Inc.

Key words: diabetes, hyperglycemia, hospital, inpatient, critical care, insulin infusion

INTRODUCTION

Hyperglycemia in hospitalized patients with or without overt diabetes presents complex management issues. Questions arise about the degree of intensity to which glucose levels should be maintained in the critical care setting, step-down units, and general medical-surgical wards, as well as the optimal strategies for subsequent transitions to outpatient care.

Glucose Control During Critical Care

There is a well-recognized relationship between glucose levels and adverse clinical outcomes in the critically ill. In 2003, Krinsley et al[1] reported that in a mixed medical-surgical intensive care unit (ICU), mortality increased progressively as mean blood glucose concentrations increased. For example, mortality was 9.6% in patients whose mean ICU glucose concentration fell between 80 and 99 mg/dL but was >4-fold higher (42.5%) in those whose mean glucose exceeded 300 mg/dL. Similarly, Kosiborod et al[2] in 2008 reported that in patients hospitalized for acute myocardial infarction (AMI), mortality increased progressively with every 10-mg/dL glucose increase above 120 mg/dL, after controlling for a variety of important clinical variables (**Slide 1**). This relationship was particularly striking in those without an antecedent history of diabetes. These data were consistent with those from an early observational study from Umpierrez et al[3] involving 2030 ICU patients, which concluded that those with newly identified hyperglycemia had significantly higher mortality (31%) than did patients with known diabetes (11%). Notably, in the Kosiborod analysis,[4] an increase in mortality was also seen when mean blood glucose fell below 70 mg/dL.

These studies raise the possibility that controlling blood glucose in the setting of critical illness may improve clinical outcomes but also that overly intensive approaches might be counterproductive. Yet observational data alone can be misleading and are influenced by confounding factors that are either not easily assessed or not initially considered to be relevant by the investigators. So, it remained unknown as to whether hyperglycemia merely serves as a marker of poor clinical outcomes or represents a true mediator of these adverse events. It is well-recognized that illness by itself, particularly when severe, leads to "stress hyperglycemia" through the activation of counter-regulatory hormones, primarily cortisol and epinephrine, which increase endogenous glucose production and decrease glucose uptake into peripheral tissues, while also elevating circulating levels of free fatty acids

Accepted for publication April 19, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.04.008
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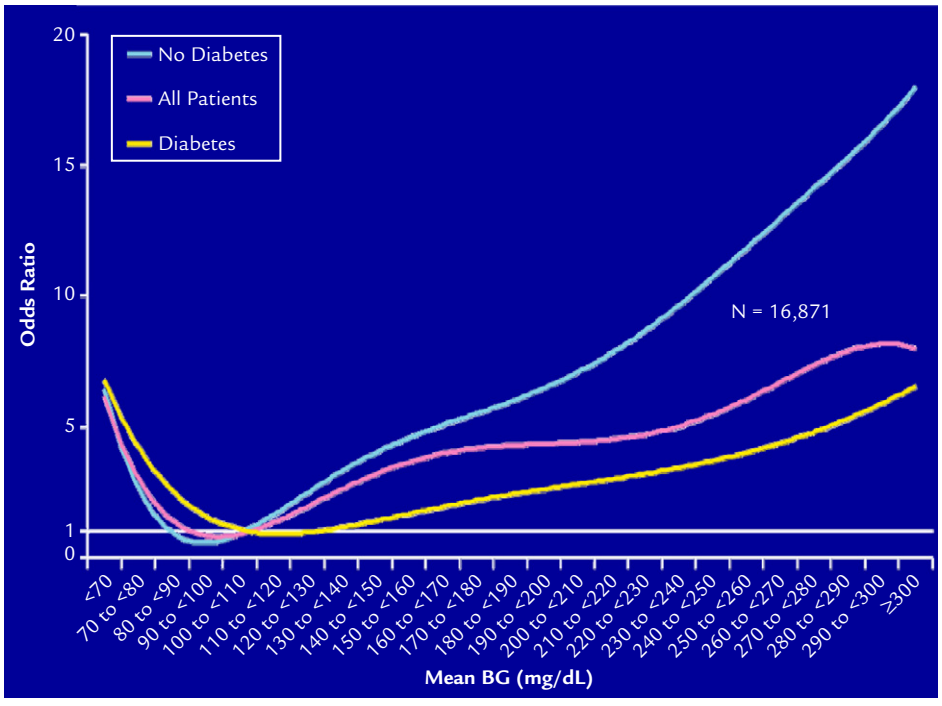

Slide 1. Relationship between mean glucose levels and mortality during hospitalization for nearly 17,000 acute myocardial infarction patients. Hyperglycemia is associated with more adverse outcomes, especially in nondiabetic individuals. Reprinted with permission from Kosiborod M *et al. Circulation* 2008;117:1018–1027.[2]

through the stimulation of lipolysis (Slide 2). Conversely, increased glucose and fatty acids may secondarily exacerbate illness through altered tissue metabolism, oxidative stress, hypercoagulability, and suppressed immunity and wound healing.

The first study to explore the notion of controlling glucose in the ICU to improve patient outcomes was conducted by cardiothoracic surgeons, led by Funary.[5] In this nonrandomized trial, patients undergoing cardiac surgery were placed on an insulin-infusion regimen for 3 days postoperatively, targeting a glucose level of 151 to 200 mg/dL. Their outcomes were compared to those from a historical control group who were mainly managed conventionally with subcutaneous regular human insulin (every 4 hours on a sliding scale with a target of ~200 mg/dL). Deep sternal wound infections occurred in 0.8% of the study group and in 2.0% of the controls (relative risk [RR] reduction, 66%; $P = 0.01$). Impressively, the annual rates of deep sternal wound infections in diabetic patients at the end of the study had reached the rates similar to those in nondiabetic individuals. The nonrandomized nature of this study, however, limited the conclusiveness of its findings.

The DIGAMI (Diabetes Insulin-Glucose Infusion in Acute Myocardial Infarction) study[6] examined the short- and long-term effects of intensive insulin treatment in patients with diabetes during and soon after AMI. A total of 360 patients were randomly assigned within 24 hours of admission to receive an intravenous infusion of insulin (and glucose) for 48 hours, with a target blood glucose level of 126 to 196 mg/dL, followed by multidose subcutaneous insulin injections for 3 months. A total of 314 patients in the control group received conventional diabetes care. An 11% absolute and a 28% relative mortality risk reduction was dem-