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SHOULD TARGET GLYCEMIC RANGE BE EXACTLY THE SAME FOR PATIENTS WITH ACUTE MYOCARDIAL INFARCTION VERSUS WITHOUT DIABETES?



To the Editor:

Pronounced hyperglycemia by itself is a dangerous condition, but it is particularly dangerous when accompanied by ketoacidosis or a hyperglycemic hyperosmolar state (1). The measurement of glycemia is universally available and inexpensive. Glycemia is often measured in the emergency department (ED); in almost 20% of patients, glucose concentration in serum is evaluated, and capillary glucose measurement is required in an additional large number of patients (2). Another rationale for measuring glycemia in the ED is the fact that every fourth patient in the ED has diabetes mellitus (DM) (3).

Glycemic control (and therefore the target range) are important things to be aware of in the ED (2,4–17). High serum glucose concentration in the ED is a valid marker of in-hospital morbidity and mortality (4,5). Despite the prognostic significance of hyperglycemia in the ED, its management in the ED is clearly suboptimal (5). It may be advantageous to start proper hypoglycemic treatment in the ED because it results in faster achievement of the glycemic target(s).

The *Journal of Emergency Medicine* published the Rush Emergency Department Hyperglycemia Intervention protocol for ED treatment of hyperglycemia using subcutaneous insulin before hospital admission or discharge. This protocol was safe and reduced the in-hospital length of stay (8). The Rush Emergency Department Hyperglycemia Intervention protocol was cited as valid in the Consensus Statement on Inpatient Glycemic Control of the American Association of Clinical Endocrinologists and the American Diabetes Association (13). Furthermore, Bernard et al. have demonstrated that use of the standardized insulin protocol in the ED and in the hospital can provide better results compared with the usual care (9). In addition, as far as acute myocardial infarction (AMI) is concerned, the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial that was performed before admission and in the ED has demonstrated that glucose infusion with insulin and potassium reduced the size of the myocardial infarction (MI) after 30 days of follow-up (18). Moreover, a triple endpoint (cardiac arrest, mortality, or heart failure), or hospitalization within 1 year of follow-up was reduced in ST-elevation AMI patients in this trial (18). Therefore, parameters that are already measured in the ED, such as glycemia, ought to be used for treatment. For example, in a patient with DM and chest pain (without ST elevation or other electrocardiographic abnormalities typical of non-ST-segment elevation acute coronary syndrome), who has a high capillary glucose level measured, insulin treatment can be started in the ED while waiting for the troponin result. Indeed, marked hyperglycemia (with or without ketoacidosis or a hyperglycemic hyperosmolar state) is much more dangerous in the AMI setting without insulin. The numerous studies published to date have confirmed the rational expectation that hyperglycemia, both at admission (admission blood glucose), fasting, and during the hospital stay, is a valid prognosticator of poor in-hospital outcome in patients with AMI (19,20).

Arterial blood gases can be a valid prognostic marker for patients with AMI, even for a follow-up of 20 years (21). Also, AMI has been known for a long time (since 1931) to worsen glycemic control (22). There is little doubt that acute control of hyperglycemia in AMI is beneficial. For example, in the Japanese Acute Coronary

Syndrome Study the optimal glycemic range in patients with AMI without DM was <108 mg/dL (<6 mmol/L), and the nadir of the U-shaped curve was between 162 and 198 mg/dL (9–11 mmol/L) in diabetics with AMI (23). Low, but different, glycemic cutoffs for in-hospital mortality were reported in the meta-analysis of Capes et al. as 110 mg/dL (6.1 mmol/L) for patients with AMI without DM and 180 mg/dL (10.0 mmol/L) for patients with AMI with DM (24). Therefore, it is important to treat high glucose concentration in patients with AMI. Moreover, not a single trial has been performed in a placebo-controlled manner because it has been considered unethical. Finally, current guidelines on the topic suggest treating hyperglycemia (with some differences in threshold and target concentrations) (25–28). Indeed, protocols recommend various doses of insulin to treat hyperglycemia in the ED and in-hospital, depending (among other determinants) on the target glycemic range. The common target in the ED is to decrease glycemia below 200 mg/dL (11.1 mmol/L) (8,9).

The same in-hospital glycemic targets (e.g., 126–180 mg/dL, 7.0–10.0 mmol/L) have been suggested for patients with AMI both with and without DM (29). This might not be for the following reasons.

First, the average hemoglobin A1c (HbA1c) is higher in patients with AMI with known DM vs. those without a previous DM diagnosis. In patients with AMI with high admission blood glucose levels, many with DM have chronic hyperglycemia, while those with previous normoglycemia (as judged by normal HbA1c) have acute hyperglycemia. This is a result of stress caused by fear, severe pain, and large myocardial injury, with eventual heart failure, with consequent catecholamine and cortisol surge, and sympathetic overactivity (30).

Second, the glycemic profile of patients with and without DM differs in AMI (6,7). For example, most patients with AMI without DM have glycemia levels between 126 and 144 mg/dL (7–8 mmol/L), while the majority of those with DM have much higher glycemia—in the range of 198 to 234 mg/dL (11–13 mmol/L) (23).

Third, the prognostic cut-off glucose concentrations (which optimally discriminate survivors from nonsurvivors) are also higher in patients with AMI with DM (24,31–34).

Fourth, the glycemic range associated with optimal survival differs between patients with DM and patients without DM (23). For example, in patients with AMI without DM, the optimal range was <108 mg/dL (<6 mmol/L) vs. 162 to 180 mg/dL (9–10 mmol/L) in patients with DM (23). Therefore, the optimal glycemic range is much higher ($>50\%$) in patients with AMI with DM.

Finally, in-hospital mortality is linearly related to glycemia (the lower, the better) in patients with AMI without DM, while the “U-shaped” curve is revealed in diabetic patients with AMI, meaning higher mortality either with low or high glycemia (23,35).

There are two good illustrations of the aforementioned essential differences between DM and non-DM patients with AMI. First, glycemia of 5 mmol/L (90 mg/dL) in AMI is good for non-DM patients, but it may be too low for diabetics (i.e., associated with higher mortality—although not necessarily causally) (23). Second and similarly, if we look into Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial data, the average blood glucose level for patients with AMI with DM was 11.44 mmol/L (206 mg/dL), but already the values >8.278 mmol/L (149 mg/dL) were associated with increased mortality in non-DM patients (33).

The most plausible explanation is that patients with DM simply adapt and acclimate to higher glycemia (36). Supporting this scenario, HbA1c (which reflects glycemia in the previous 2–3 months) has consistently been higher in DM vs. non-DM patients (37). Therefore, the same target glycemic level in AMI might have been favorable or unfavorable. It is favorable if correction of blood glucose occurs from acutely raised values (because of the stress of AMI) to preinfarction glucose values; it is unfavorable if the blood glucose level decreases to a far lower glycemic level than this individual diabetic patient has had for years (this may be relative hypoglycemia for the patient). Indeed, hypoglycemia is dangerous in AMI (29). Moreover, a meta-analysis found a statistically significant relative risk of no less than 13.4 (95% confidence interval 3.7–48.6) (38). In addition, a too-rapid rate of glycemic reduction could be a factor in adverse cardiovascular outcomes (39). Therefore, the optimal glycemic range (possibly causally) related to survival in AMI is higher in patients with DM compared with non-DM patients (23). Clearly, the target glycemic range should not be exactly the same for patients with vs. without previous DM. An analogy or similar mistake that was practiced for decades was to have a single glycemic cut-off for the prognosis of all AMI patients, regardless of DM status (32,40).

In conclusion, an important point is that patients with AMI with DM (both those with known, previously diagnosed DM and those with undiagnosed but obviously present DM, as recognized by high HbA1c) have chronic hyperglycemia. On the other hand, patients with AMI with normal HbA1c obviously do not have chronic hyperglycemia, but some of them have an acute increase in blood glucose concentration. In AMI, the optimal glycemic range is higher in patients with DM who become adapted to hyperglycemia than in previously normoglycemic

individuals. Therefore, the target glyceemic range ought to be higher for patients with AMI with vs. without DM.

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