Editorial

Glucose control in critically ill diabetic: Not so sweet

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It has been well-recognized that stress hyperglycemia on admission is common in critically ill patients and is associated with adverse outcome. Attempts at controlling blood sugar have met with conflicting results, probably reflecting an association rather than causality of this metabolic marker of stress. Moreover, Intensive Care Unit (ICU) case mix, for example, surgical versus medical, diabetics versus nondiabetics have a different impact on the outcome with glucose control. Diabetics both known and unknown are a subset of patients where association of hyperglycemia on admission and outcome has been variable. With increasing prevalence of diabetes in general population more so in the Indian subcontinent, this issue has become more relevant to patient care.

In a retrospective cohort study, a U-shaped curve was noted for ICU mortality and mean blood glucose in nondiabetics, whereas no such relationship was noted for diabetics.[1] Retrospective reanalysis of data from the large interventional and observational studies in glucose control in ICU have suggested that all the three domains of sugar control, i.e., hyperglycemia, hypoglycemia, and glycemic variability are affected by premorbid diabetic status of the patient. Hyperglycemia had a stronger association with mortality in critically ill patient without diabetes than with diabetes. Hypoglycemia was independently associated with mortality in both these population. Limited data suggested that increasing glycemic variability may have a stronger association with mortality in patients without diabetes than with diabetes.[2]

The observation that critically ill diabetics behave differently has also been shown in other spectrum of critical illness. In an epidemiological survey on the effect of diabetes on organ dysfunction in sepsis, it was noted that patients with diabetes were less likely to develop respiratory failure and more likely to develop renal failure as compared to nondiabetics.[3] In another observational study, it was noted that diabetes was associated with lower risk of developing acute respiratory distress syndrome than nondiabetics, and this relationship was maintained after adjusting for confounding variables.[4]

Protective mechanism from acute hyperglycemia in diabetics and the reason of adverse outcome with mild to moderate sugar control in them is unknown. It is hypothesized that diabetics develop hyperglycemia tolerance by downregulating the glucose transport mechanism and by control of blood sugar, this protective mechanism is lost.

Glycated hemoglobin (HbA1c) reflects average blood sugar of previous 3 months and is a marker of control of blood sugar in diabetics, and a diagnostic marker of undetected diabetes. Hyperglycemia on admission

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in diabetics could be due to stress hyperglycemia in controlled diabetes, uncontrolled diabetes, or both. In a recent prospective study on 1000 consecutive ICU patients, mortality increased by approximately 20% for each 18 mg/dl increase in acute glycemia in nondiabetics and in diabetics with HbA1c levels <7%, but not in patients with diabetes and HbA1c ≥7%. In fact, acute admission hyperglycemia was associated with less mortality in critically ill patients with uncontrolled diabetes suggested by high HbA1c on admission.[5]

The pathophysiology of uncontrolled diabetics tolerating stress hyperglycemia is unclear. One possibility is that the "Stress" hyperglycemia reflects the uncontrolled state of glycemia rather than the severity of stress. To differentiate stress hyperglycemia in controlled diabetics from uncontrolled diabetic state, two new metrics have been proposed recently.

The relative hyperglycemia or stress hyperglycemia ratio (SHR) is measured as admission blood glucose divided by estimated average blood glucose derived from HbA1c value. In a prospective observational study, SHR controlled for background hyperglycemia was a better biomarker of a critical illness than absolute hyperglycemia.[6]

Another concept is of the glycemic gap which is measured by calculating the difference between admission glucose and Hb A1c derived average glucose (ADAG). The HbA1c levels were converted to the ADAG by the equation, $ADAG = (28.7 \times HbA1c) - 46.7$. In a prospective study, the addition of the glycemic gap to the Acute Physiologic Assessment and Chronic Health Evaluation II score significantly improved the ability to predict ICU mortality.[7]

The impact of patients with unknown diabetes (increased HbA1c on admission, without any history of diabetes) may be a confounding factor in analyzing the effect of premorbid diabetic state, acute hyperglycemia, and effect of glucose control in ICU. In a recently published study, 9% of all admission HbA1c of more than 6% were from unknown diabetics. The impact of acute hyperglycemia on mortality was highest in patients with unknown diabetics than in nondiabetics, controlled diabetics, and uncontrolled diabetics.[8]

In this issue of the journal, investigators from Iran studied 500 surgical ICU patients.[9] They noted that the risk of death doubled with increase of HbA1c level irrespective of premorbid diabetic state. Many of their patients had secondary diabetes due to corticosteroid intake. Three important observations may be surmised from this study:

First, the importance of specific subset of critically ill patient, i.e., surgical as a subgroup more vulnerable to effects of hyperglycemia; second, secondary diabetics are equally vulnerable to effect of hyperglycemia as their primary counterpart; and third, increasing HbA1c level irrespective of premorbid diabetic state is detrimental.

Take home message from this and other studies is that all patients in ICU on admission should have their blood sugar checked and a history of premorbid diabetic status noted. Patients with admission blood sugar of >140 mg/dl should have their HbA1c level measured. These patients should be categorized on admission as nondiabetic with stress hyperglycemia, diabetic and stress hyperglycemia, controlled diabetics, uncontrolled diabetics, and unknown diabetics. A higher sugar control threshold (exact range not yet known) should be adopted for uncontrolled and unknown diabetics. It is suggested that future trials of insulin treatment in the intensive care patient should stratify management and outcome by premorbid diabetic status.

The bottom line is that in acutely ill patient target sugar should be individualized based on their premorbid glycemic status. Diabetics specially uncontrolled diabetics require a different blood sugar target than nondiabetics in ICU.

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