Review Article

# Glycemic control in critically ill: A moving target

**Subhash Todi**

**Abstract**

Glycemic control targets in intensive care units (ICUs) have three distinct domains. Firstly, excessive hyperglycemia needs to be avoided. The upper limit of this varies depending on the patient population studied and diabetic status of the patients. Surgical patients particularly cardiac surgery patients tend to benefit from a lower upper limit of glycemic control, which is not evident in medically ill patient. Patient with premorbid diabetic status tends to tolerate higher blood sugar level better than normoglycemics. Secondly, hypoglycemia is clearly detrimental in all groups of critically ill patient and all measures to avoid this catastrophe need to be a part of any glycemic control protocol. Thirdly, glycemic variability has increasingly been shown to be detrimental in this patient population. Glycemic control protocols need to take this into consideration and target to reduce any of the available metrics of glycemic variability. Newer technologies including continuous glucose monitoring techniques will help in titrating all these three domains within a desirable range.

**Keywords:** Diabetes, glycemic variability, hypoglycemia, hyperglycemia, intensive care unit

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## Introduction

The hallmark of critical illness is an acute derangement of homeostasis secondary to a known or unknown insult. The magnitude of this derangement is dependent upon various intrinsic and extrinsic factors. This physiological response has evolved to counter the initiating insult and has a survival advantage. It is only when this response becomes disproportionate that single or multiple organ failure ensues. Various interventions in critical care are aimed to normalize the homeostasis with the hope of a better outcome. As mentioned earlier, complete normality may not be desirable during the acute phase of illness and the degree to which the disturbance in physiological variables are acceptable has been an area of major controversy and research in critical care literature. This concept is applicable to most of the common physiological variables measured at the bedside like mean arterial pressure, oxygenation, carbon dioxide levels, and so forth, and blood glucose is no exception.

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Target blood glucose level has been a fertile field of research in critical care after the seminal Leuven paper in 2001. This review will focus on the current literature pertaining to this subject and discuss areas of agreement, areas of uncertainty, and future direction.

## Areas of Agreement

Hyperglycemia is an adaptive response to critical illness and is seen in 52% of all ICU admissions.[1] There is a substantial body of evidence that disproportionate hyperglycemia increases morbidity and mortality in a heterogenous group of critically ill patient. In an observational study of 1826 mixed medical and surgical patients, hospital mortality increased progressively with increasing mean blood glucose levels. The lowest hospital mortality of 9.6% was observed in cohort of patients with mean blood glucose between 80-99 mg/dl that increased to 42.5% with mean blood glucose exceeding 300 mg/dl. The result was applicable to patients across all severity of illness and different subcategories of pulmonary, cardiac, neurological, surgical, and trauma patients. Logistic regression analysis confirmed mean blood glucose to be an independent marker of hospital mortality and added to the predictive value of Acute Physiology and Chronic Health Evaluation II (APACHE II) for prognosticating outcome in this population. Similar results were obtained

when peak instead of mean blood glucose was analyzed.[2] Similar observations are also reported from studies of a homogenous population of burn, trauma, stroke, head injury, myocardial infarction, and perioperative patients.[3-6] Based on these observations, the control arm (reflecting standard of care) of randomized glucose control studies in ICU have the upper limit of glucose target in the 180-200 mg/dl range.[7-9] Thus, there is a general consensus that the disproportionate hyperglycemia is detrimental to all categories of critically ill patient and all efforts should be made for not allowing blood glucose to go too high (>180 mg/dl) in ICU.

Moderate to severe hypoglycemia is detrimental to critically ill patient. In a retrospective database review of 102 patients with severe hypoglycemia (defined as blood glucose <40 mg/dl) during anytime of their ICU stay, mortality was 55.9% as opposed to 39.5% in 306 controls. Multivariable logistic regression analysis identified that even a single episode of severe hypoglycemia was independently associated with increased risk of hospital mortality.[10] In another database review, all first episode of hypoglycemia (blood glucose <45 mg/dl) was analyzed in 154,015 glucose values in a mixed medical/surgical ICU. Incidence of at least one episode of hypoglycemia was identified in 4.8% of observations. The incidence rate of death in patients exposed to hypoglycemia was 40/1000 ICU days compared with 17/1000 ICU days in patients without exposure. The adjusted incidence rate ratio for ICU death was 2.1 (95% confidence interval (CI), 1.6-2.8; $P < 0.001$), which might indicate a causal relationship. In tight glycemic control studies, hypoglycemia was significantly more common in intensive glucose arm and varied between 5-18%. In Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE SUGAR) study, moderate hypoglycemia (40-70 mg/dl) was observed in 45% of all patients of whom 85% were in the intensive therapy group. Severe hypoglycemia (<40 mg/dl) likewise was more common in the intensive therapy group and constituted 93% of total incidence (3.7%). In this study, irrespective of the assigned group, mortality was 23.5% in patients who did not have hypoglycemia, 28.5% in moderate hypoglycemia, and 35% in severe hypoglycemia. The adjusted hazard ratios for death in patients who had moderate or severe hypoglycemia as compared with those without hypoglycemia were 1.41 (95% CI, 1.21-1.62).

Variability of blood sugar is the third domain of glycemic control in ICU, which has shown to adversely affect patient outcome. Observational studies in noncritically ill hospitalized patients have shown an increased mortality of 8% for every 10 mg/dl increase in standard deviation (SD) of blood glucose, a measure of glycemic variability. This effect was independent of mean blood glucose and hypoglycemia occurrence during hospitalization.[11] In a large database of 168,337 glucose measurements in adult ICU patients, SD was an independent risk factor for ICU and hospital mortality.[12] In adult patients with sepsis, glucose variability was an independent predictor of mortality.[13] In a retrospective analysis of 66184 adult admission to 24 ICUs in Australia and New Zealand, glycemic variability in first 24 h was noted in 2.9% of patients. It was significantly associated with greater odds of ICU and hospital mortality.[14] A retrospective analysis was conducted of dataset from two large prospective trial on intensive glucose in medical and surgical patients from Leuven, Belgium. It was observed that large blood glucose amplitude variation and pattern irregularity were independently associated with mortality irrespective of blood glucose level. Intensive insulin strategy increased mean daily delta blood glucose while not affecting SD of blood glucose.[15] In a retrospective database analysis of 194,772 patients with an ICU stay of more than 48 h, the relative risk of mortality increased with greater duration of hyperglycemia and increased variability of blood sugar. The relative risk for the highest compared with the lowest quintile of variability was 1.61 (1.47-1.78).[16] In a study of 18,563 acute myocardial infarction patients, glycemic variability was associated with increased mortality in an unadjusted analysis, though after controlling for various patient factors including mean blood glucose, glycemic variabilty was not an independent predictor of mortality.[17] In a study from China in severe acute pancreatitis, it was observed that glycemic lability index was a significantly better predictor of ICU and hospital mortality than mean blood glucose.[18] The effect of glycemic variability on mortality was assessed in 748 hospitalized patients with congestive cardiac failure and glycemic lability index was found to be an independent risk factor.[19] In a study of moderate to severe burn injury patients, glycemic variability assessed by daily glucose excursion was significantly associated with incidence of sepsis and mortality even when the mean daily glucose was within the acceptable range of glycemia. There was an increased amplitude of glycemic excursion near the onset of hemodynamic instability in these patients.[20,21] In a retrospective cohort study of 5278 patients, high glucose variability combined with high mean glucose values was associated with highest ICU mortality. In patients with strict glycemic control, low glucose variability seemed protective, even when mean glucose remain elevated.[22] Overcorrection of

hypoglycemia with 50% dextrose is one of the factors contributing to glycemic variability. Implementing a nurse-driven protocol has been found to reduce the coefficient of variation, a measure of glycemic variability, significantly in the post-protocol group.[23] Thus, it is obvious from the above studies that glycemic variability is an important variable that need to be considered in strategies of glucose control in ICU.

## Areas of Uncertainty

Current recommendation of glycemic control in ICU as per American Diabetic Association is to initiate insulin therapy for blood sugar at or above 180 mg/dl and to keep the glucose range between 140-180 mg/dl for majority of critically ill patient.[24] These recommendations are based on recent intervention studies comparing intensive glucose control with less intensive control in this population. In a recent meta-analysis of 26 trials involving 13,567 patients on intensive insulin therapy (IIT) and mortality, it was observed that IIT did not confer mortality benefit in ICU. The mean target of blood sugar in IIT was 100 mg/dl and conventional arm was 150 mg/dl. In order to achieve statistical significance, the intervention studies usually separate the two arms significantly, but in clinical practice there is a gray area of values between these two extremes.[25] In this meta-analysis, patients in surgical ICUs tend to have more benefit from IIT. Despite limitations, earlier IIT trials in surgical patients have shown mortality benefit, and in medical patients who stayed in ICU for more than three days a significant decrease in morbidity and a trend toward decreased mortality was observed.[7,8] Moreover, if significant hypoglycemia is prevented, blood glucose values between these two extremes may also be beneficial and remains to be investigated.

Diabetic patients are exposed to effects of chronic hyperglycemia and may have a different adaptive response to stress-induced acute hyperglycemia in ICU. They also have multiple associated comorbidities and effect of glucose control in them may be different from nondiabetics. The three major domains of glycemic control, namely, hyperglycemia, hypoglycemia, and glycemic variability have been studied in critically ill diabetic subject and the outcome compared with nondiabetics. Moreover, the differential effect of intensive glucose control in diabetics have also been studied.[26]

In a retrospective cohort study of admission, hyperglycemia in ICU patient with history of diabetes had an adjusted odd ratio of death of 0.81 compared with 1.76 in nondiabetics. This trend was observed across multiple demographic subgroup including cardiac surgery patient. in another retrospective study.[27,28] In a subset analysis of a multicenter European observational study, patients with history of insulin-treated diabetics were more severely ill and more likely to have renal failure, but it was not associated with increased mortality.[29] In a study of interaction of chronic and acute hyperglycemia on mortality, patients with high preadmission hemoglobin A1c (HbA1c) (>7%), reflecting chronic hyperglycemia, had a lower hospital mortality compared with preadmission HbA1c of <7%.[30] On the contrary, in a systematic review and meta-analysis, no association between mortality risk and diabetes was found. Subset analysis revealed that the outcome was worst for diabetics in surgical ICU including cardiac surgery.[31] In emergency department patient with sepsis, presence of diabetes significantly modified the effect of hyperglycemia and hypoglycemia on mortality. Initial high glucose levels (>200 mg/dl) were associated with higher mortality in nondiabetic only, whereas glucose levels less than 100 mg/dl was associated with more adverse outcome in diabetics.[32] In a retrospective study of a large database of adult critically ill patient, the relationship between glycemic variability and mortality was found to be strongest in patients in the euglycemic range.[33] An international multicenter cohort study has found an increase in glycemic variability defined by coefficient of variation >20% was independently associated with increased risk of mortality only in patients without diabetes.[34]

From these large observational studies, the effect of acute hyperglycemia seems to be different in diabetics than in nondiabetics. The current recommendation of blood sugar control in ICU is mainly applicable to nondiabetics, and there is uncertainty regarding the desirable glucose range in diabetic subsets.

With increasing importance of glycemic variability as an important domain of glycemic control, the best metrics to measure this variable remains uncertain. In a systemic review on metrics of glucose variability, 13 variability measures were studied. SD and presense of both hypoglycemia and hyperglycemia was the most common indicator. All studies reported a statistically significant association between mortality and at least one glucose variability indicator.[35]

## Future Direction

As outlined above, unintended hypoglycemic episodes while aiming for a tight glucose control in ICU has been the major setback for this strategy, which earlier showed great promise. With improvement in glucose monitoring

technology, this harmful consequence of IIT may be mitigated and glucose control tailored to individual patient may be achieved. Microdialysis technique for measuring continuous glucose with feedback loop is also being investigated.[36] There are multiple glucose protocols both static and dynamic that are used in practice worldwide without much standardization and validation. Time spent in the desirable range of blood sugar is low with these protocols. Computerized decision support system are being developed to incorporate these variables.[37] A large-scale study with patient centered outcome needs to be carried out with these continuous monitoring devices to study their safe implementation, effective sugar control in the desirable range, avoidance of hypoglycemia, and effect on morbidity and mortality.

As it is evident that the three domains of glycemic control are equally important and may also have additive impact on outcome, a large randomized study with the present standard of care as per current guidelines with an intervention arm to control all three domains of glycemic control preferably through a point of care continuous glucose monitoring technology may add to our knowledge and improve further the outcome in ICU. A beneficial result will explain that hyperglycemia, hypoglycemia, and glucose variability are not only an epiphenomenon reflecting underlying disease severity but a causative factor of poor prognosis, and their control can improve the outcome of these patients.

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