



Dysglycemia in ICU Patients

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Abstract

Dysglycemia has emerged as a very common challenge in critically ill patients, especially with regard to current coronavirus disease 2019 pandemic. Prediabetes, poorly controlled diabetes, pharmaceutical intervention in intensive care unit (ICU) with glucocorticoids, catecholamines and other medicines, and stress response all contribute to dysglycemia in critically ill patients. Early identification and management are the key to prevent further complications. Patient prognosis in terms of clinical outcome, length of ICU stay, and in-hospital morbidity/mortality are adversely affected by patient's dysglycemic status. Apart from hyperglycemia, the other three important pillars of dysglycemia are discussed in this article. Synopsis of early intervention have been captured from India-specific practice guidelines. Important landmark trials have also been captured in this article to provide a clarity on certain aspects of managing dysglycemia in ICUs. Hence, this review article is an attempt to bring forth the salient aspects in diagnosing and managing dysglycemia in critical care settings.

Keywords

- ▶ intensive care unit
- ▶ glycemic variability
- ▶ blood glucose

Introduction

Critical illness results in hyperinflammation, secretion of stress hormones/insulin, and excessive substrate metabolism. Polytherapy, including steroids also, impacts metabolism of body substrates like proteins, fats, and carbohydrates. Dysglycemia is a manifestation of altered carbohydrate metabolism and improper handling of carbohydrate metabolites by the body. Dysglycemia in the form of hyperglycemia hypoglycemia or glycemic variability (GV) manifests commonly in critical illness and is seen even in patients without diabetes. Patients with dysglycemia are more prone to intensive care unit (ICU) admissions. This is especially with regard to severe acute respiratory syndrome coronavirus pandemic causing coronavirus disease 2019 (COVID-19) disease that dysglycemia is very common in patients admitted in ICUs. Higher oxidative stress and reduced immunity

are outcomes of dysglycemia, which worsen the critical illness. Vicious cycle soon establishes between critical state and dysglycemia, so that one state is worsening other.

Numerous studies have found dysglycemia as independent factor associated with significant morbidity and mortality. Cellular hypoxia due to critical illness (especially with regard to COVID-19) exacerbates reperfusion/oxidative injury due to circulating high blood glucose (BG). Hence, it appears to be a preventable risk, if dysglycemia is controlled. Management of dysglycemia needs a holistic approach. Pharmaceutical management and appropriate nutrition intervention are the two pillars of dysglycemia management in ICU patients.

After van den Berghe et al's publication in 2001,¹ intensive glycemic control in ICUs was followed for the next 15 years. The population studied in the trial was critical surgical patients. Later large trials could not replicate the results of

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van den Berghe et al and found that this intensive control is not suitable for all critically ill patients, as it caused unacceptable levels of hypoglycemia in few patients. Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) showed a significant increase in mortality in patients who received intensive treatment with insulin.²

Now, dysglycemia is known to be a conglomerate of three well-known variables, namely hypoglycemia, hyperglycemia, GV, and the recently known fourth variable, time in target range (TITR)

Four Pillars of Dysglycemia

Stress Hyperglycemia

This is commonly seen in critically ill patients, even in absence of patient's diabetes history. It can be caused due to myriad of interventions done in ICU like catecholamine/dextrose/glucocorticoid infusion or even antibiotics. Systemic inflammation causes immune-alteration as well as stress hormones release, which are antagonistic to insulin, like cortisol, catecholamines, and glucagon. The result is higher rates of glycogenolysis and gluconeogenesis causing stress hyperglycemia. Insulin resistance also develops secondary to systemic inflammation.³

Hypoglycemia

Yamada et al⁴ found intensive insulin therapy as the most prominent reason behind hypoglycemia in ICU. NICE-SUGAR study found that around 45% of studied population experienced hypoglycemia (82.4% in the intensive group with insulin). The mortality rate in patients without hypoglycemia was 23.5%, whereas it was 28.5 and 35.4% in patients with moderate and severe hypoglycemia, respectively.⁵ Krinsley et al in 2011⁶ found that at-least one episode of mild hypoglycemia was associated with increase in length of ICU stay.

Glycemic Variability

Repeated excursions in plasma glucose levels, which are higher than that for normal physiologic response, over a brief time is defined as GV.⁷ Thus, glycemic control may differ markedly, despite the similar mean plasma glucose levels. Krinsley⁸ found that as the standard deviation of plasma glucose values increased, there was an increase in mortality as well. Krinsley attributed this to GV. This association was more evident in the patients in euglycemic range (70–99 mg/dL). Research has revealed that GV triggers oxidative stress, thus causing endothelial dysfunction and vascular damage in patients with diabetes. In nondiabetics, the GV increases the apoptosis of cells.

Time in Target Range

It indicates the percentage of time in which patient's plasma glucose levels remain within the targeted range. Signal et al⁹ found that TITR more than 70% during ICU stay was associated with improved survival. Omar et al¹⁰ studied TITR in cardiac surgery patients and found that TITR more than 80%

was associated with lesser postoperative complications and reduced length of ICU stay.

Identification/Assessment of Dysglycemia in ICU

Identifying the Patients At-Risk for Developing Dysglycemia during ICU Stay

Mehta et al¹¹ recommend plasma glucose and hemoglobin A1c (HbA1c) values to identify the patients at-risk in this regard. Either an oral glucose tolerance test with 2-hour post oral glucose tolerance test BG more than 140 mg/dL or HbA1c over 6.5% even if random BG values are below 140 mg/dL indicates the patient will be at risk and will have higher chances to exhibit dysglycemia during ICU stay. Hence, if any patient exhibits random BG more than 140 mg/dL prior to/at the time of ICU admission, then HbA1c is required to be done. All diabetics patients admitted to ICU should have HbA1c reports should be made available of test done in past 2 to 3 months.

Monitoring/Assessment of Dysglycemia

Numerous studies have found the association between hyperglycemia/hypoglycemia/GV with clinical outcomes in critically ill patients. All there of above mentioned are found as independent predictors for patient prognosis and length of ICU stay. Hence, apart from routine measurement of HbA1c and BG values, GV should also be calculated. Mehta et al¹¹ recommended various metrics to be used in Indian ICUs for the assessment of dysglycemia. Important among these practice guidelines¹¹ are as follows:

- The 4-hourly blood sample should be used for detecting GV in patients on continuous feeds.
- The arterial/venous blood sample is preferable over the capillary sample for continuous monitoring of GV.
- If feasible, mean amplitude of glycemic excursions (MAGE) may be used as an additional measure.
- GV/fluctuation should be kept minimal during the entire ICU stay.
- Continuous glucose monitoring is preferable in critical care settings, if resources are available.

Acceptable Glycemic Targets in ICU Patients

Leuven I trial, that is, van den Berghe et al in 2001,¹ found intensive glycemic control reduced surgical ICU mortality and prevented organ failure, thus reducing morbidity as well. However, Leuven II study done in medical ICU patients failed to replicate the results of Leuven I study. The volume substitution and insulin therapy in severe sepsis multicenter trial ($n = 537$) and the Glucontrol multicenter trial ($n = 1101$) did not support Leuven I findings. Later NICE-SUGAR trial² found that incidences of severe hypoglycemia and higher mortality rates were found in patient groups with tight BG control. Since then, moderate glucose control is advised in ICU patients. On the basis of the analysis of all the available evidences, Mehta et al¹¹ recommended practice guidelines with respect to the acceptable glycemic targets to be followed in Indian ICUs:

- The preferred BG range for medical/surgical ICU patients is 140 to 180 mg/dL.
- Frequency of BG monitoring should be seven times a day in orally fed/bolus-fed dysglycemic patients.
- BG measurements should be done 4 hourly in continuously fed dysglycemic patients.
- Monitoring and adherence of glycemic targets are mandated and can be continued longer, if there is persistent dysglycemia or the patient is on steroids
- Hypoglycemic episodes should be minimal, and efforts should be made for keeping BG levels above 110 mg/dL.

They made the same recommendations for cardiac, neurology, renal, and respiratory compromised critically ill patients with dysglycemia.

Uncontrolled Dysglycemia in ICU Patients

Chao et al¹² in a retrospective observational study of over 1.94 lakh patients studied the association between ICU acquired dysglycemia and in-hospital mortality. They found GV in terms of both severity and duration was associated with higher mortality rates in hospital. Chao et al¹² in retrospective cohort study found that higher GV (higher MAGE >65 mg/dL) within first day of ICU admission was independently associated with higher 30-day mortality. Hence, there is a need to identify at-risk patients as well as early dysglycemia to improve patient prognosis. Studies have also found that early management of dysglycemia in ICUs is a neuroprotective strategy. It preserves neuronal viability, while preventing acute injury to brain and avoiding cognitive impairment in survivors. Olariu et al¹³ in systemic reviews found stress-induced hyperglycemia as an independent risk factor for higher rates of infections in ICU and higher length of ICU stay.

Conclusion

Dysglycemia is very common complaint in ICU patients, especially in patients with COVID-19 disease and on glucocorticoids. The four parameters of dysglycemia are independent predictor of clinical outcomes in ICU patients. Screening of at-risk patients, early identification, and timely management of dysglycemia in ICU patients require lots of resources. Proper documentation, raising danger alarms, and timely management are essential. Hence, a team effort of doctors,

paramedics, and qualified nutritionists is warranted. ICU protocols should be standardized for managing the same.

Conflict of Interest

None declared.

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