Glycemic control in critically ill patients

Chien-Wei Hsu

Chien-Wei Hsu, Department of Medicine, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan, China
Chien-Wei Hsu, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan, China

Author contributions: Hsu CW solely contributed to this paper.
Correspondence to: Chien-Wei Hsu, MD, Assistant Professor, Attending Physician, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan, China. cwhsu2003@yahoo.com
Telephone: +886-7342121-2081 Fax: +886-73420243
Received: June 24, 2011 Revised: November 10, 2011
Accepted: December 21, 2011
Published online: February 4, 2012

Abstract

Hyperglycemia is common in critically ill patients and can be caused by various mechanisms, including nutrition, medications, and insufficient insulin. In the past, hyperglycemia was thought to be an adaptive response to stress, but hyperglycemia is no longer considered a benign condition in patients with critical illnesses. Indeed, hyperglycemia can increase morbidity and mortality in critically ill patients. Correction of hyperglycemia may improve clinical outcomes. To date, a definite answer with regard to glucose management in general intensive care unit patients, including treatment thresholds and glucose target is undetermined. Meta-analyses of randomized controlled trials suggested no survival benefit of tight glycemic control and a significantly increased incidence of hypoglycemia. Studies have shown a J- or U-shaped relationship between average glucose values and mortality; maintaining glucose levels between 100 and 150 mg/dL was likely to be associated with the lowest mortality rates. Recent studies have shown glycemic control < 180 mg/dL is not inferior to near-normal glycemia in critically ill patients and is clearly safer. Glycemic variability is also an important aspect of glucose management in the critically ill patients. Higher glycemic variability may increase the mortality rate, even in patients with the same mean glucose level. Decreasing glucose variability is an important issue for glycemic control in critically ill patients. Continuous measurements with automatic closed-loop systems could be considered to ensure that blood glucose levels are controlled within a specific range and with minimal variability.

© 2012 Baishideng. All rights reserved.

Key words: Critical care; Glycemic control; Hyperglycemia; Hypoglycemia; Insulin

Peer reviewer: Philip C Spinella, MD, FCCM, Associate Professor, Director, Translational Research Program, Washington University School of Medicine, Pediatric Critical Care Medicine, Campus Box 8116 - NW Tower 10th floor, 1 Children’s Place, St. Louis, MO 63110, United States

INTRODUCTION

Hyperglycemia is common in critically ill patients, even those patients who have not been previously diagnosed with diabetes[1,2]. Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiological or benign condition[3-7]. Alterations in glucose metabolism occur during critical illness and are mediated by various factors, including increased insulin resistance, change in hormone production, and activation of cytokines[8]. In critically ill patients a hypermetabolic state exists[9], with the predominant cause being the intense activation of counter-regulatory hormones and cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6, which may be important mediators of insulin resistance and result in hyperglycemia[10]. Clinicians have increasingly
appreciated the impact of hyperglycemia in patients with diabetes, as well as stress-induced hyperglycemia (SIH) or hospital-related hyperglycemia. The vast majority of patients in the intensive care unit (ICU) have SIH, which refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes. Patients without diabetes have a higher mortality risk when admitted to the hospital than do patients with diabetes.

Hyperglycemia is independently associated with increased ICU mortality. Strict control of the blood glucose concentration is considered important because strict control of the blood glucose concentration may reduce mortality and morbidity; however, hypoglycemia is significantly higher in patients with tight glucose control using intensive insulin therapy. Glycemic control to a moderately tight range is not inferior to euglycemia and clearly safer in critically ill patients. A less than strict approach to managing critical illness-related hyperglycemia while avoiding hypoglycemia is becoming the standard approach in most ICUs.

**Epidemiology**

The prevalence of hyperglycemia in critically ill patients is difficult to estimate because the diagnosis is variably defined. Approximately 75% of all patients, including diabetics, have blood glucose concentrations > 110 mg/dL at the time of admission, and 12% of all patients have blood glucose concentrations > 200 mg/dL. Another study showed that > 60%, 38% and 23% of patients had blood glucose concentrations > 110 mg/dL, > 150 mg/dL, and > 200 mg/dL after admission in the medical ICU of a tertiary care medical center, respectively. Glucose values > 140 mg/dL occur in 51%-58% of patients presenting with acute myocardial infarctions (MIs). Latham et al. found that 21% of cardiothoracic surgery patients developed post-operative blood glucose levels of > 200 mg/dL. The prevalence rates of hyperglycemia were 86.7%, 61% and 35.2% for pediatric patients with maximal glucose levels of > 110 mg/dL, > 150 mg/dL, and > 200 mg/dL, respectively. Faustino et al. reported prevalence data of 75%, 50.1%, and 26.3% in pediatric patients with cut-off values of 120, 150 and 200 mg/dL, respectively.

**Causes of Hyperglycemia and Pathophysiology**

The factors contributing to hyperglycemia in patients with critical illnesses include the release of stress hormones and the use of medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers). Overfeeding, intravenous dextrose, commonly used parenteral nutrition, dialysis solutions, and antibiotic solutions, also contribute to hyperglycemia. Insufficient insulin or volume depletion can cause hyperglycemia. Bed rest, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake and promotes peripheral insulin resistance; simple bed rest can further aggravate SIH.

In patients with diabetes, the cause of hyperglycemia is a combination of insulin resistance and pancreatic β-cell secretory defects. In patients with SIH, the cause of hyperglycemia is a complex interaction of counter-regulatory hormones, cytokines and insulin resistance. Glucagon, epinephrine, and cortisol increase gluconeogenesis and glycogenolysis. Gluconeogenesis is triggered to a greater extent by glucagon than by epinephrine and cortisol. TNF-α may promote gluconeogenesis by stimulating glucagon production. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol.

Insulin resistance may be associated with impaired insulin receptor binding or impairment in the activation of early or intermediate components of the insulin signaling pathway and/or with defects in glucose transporter 4. Epinephrine can inhibit insulin-stimulated glucose transport in skeletal muscle. The action of counter-regulatory hormones on insulin resistance in skeletal muscles may be mediated through an elevation in the circulating free fatty acid level in patients with critical illness, despite hypoinsulinemia. Cytokines such as TNF-α and IL-1, inhibit post-receptor insulin signaling. The severity of illness is associated with a proportional rise in serum cytokines and insulin resistance.

**Adverse Effects of Hyperglycemia**

It has been reported that pronounced hyperglycemia might lead to complications or a poor clinical outcome. Elevated blood glucose concentrations are associated with increased morbidity and mortality after burns, surgery, strokes, MI's and head trauma. In the pediatric ICU, peak blood glucose levels and the duration of hyperglycemia are independently associated with mortality. Hyperglycemia can cause polymorphonuclear neutrophil dysfunction, and decreased intracellular bacterial activity and opsonic activity, which plays a role in the increased incidence of infections in patients with hyperglycemia. High glucose concentrations in cells can damage mitochondrial protein and stimulate glucagon production. High glucose concentrations also reduce vascular reactivity and endothelial nitric oxide production, which may compromise blood flow to the periphery. In addition, acute hyperglycemia enhances proteolysis and is associated with an increased risk of cardiac complications, hemodynamic and electromyocardial disturbances, acute renal failure, and death.

**Insulin Therapy Protocols**

Use of a validated protocol to help maintain the glucose level is effective in critically ill patients. The protocol should be developed by a core group of clinicians, in-
ICU protocol for glycemic management

**Goal**
The goal of this protocol is to maintain the glucose level between 140 and 160 mg/dL.

**Monitoring**
The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable.

**Management of insulin infusion**
Continuous insulin infusion (100 IU of Actrapid HM in 99 mL of 0.9% NaCl) with the use of a pump is started when the blood glucose is > 180 mg/dL on two successive measurements.

Blood glucose levels are controlled by the neuro-fuzzy method. The first row at the top of the chart in the appendix displays the range of blood glucose values measured, while the first column on the left displays the range of possible blood glucose values measured 1-4 h previously. The adjusted infusion rate is at the intersection between the perpendicular lines drawn from the present blood glucose values and the blood glucose values found 1-4 h previously.

**Present blood glucose value (mg/dL)**

| Present blood glucose value (mg/dL) | ≤ 80 | 81-100 | 101-120 | 121-140 | 141-160 | 161-180 | 181-200 | 201-220 | 212-240 | 221-240 | 241-260 | > 260 |
|-----------------------------------|------|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|--------|
| Preceding blood glucose value (mg/dL) | | | | | | | | | | | | 1-4 h before |
| ≤ 80 | 0.3 | 0 | 0.1 | 0.5 | 0.8 | 1.2 | 1.3 | 1.4 | 1.5 | 1.5 | 1.5 |
| 81-100 | -0.5 | -0.4 | -0.2 | 0.2 | 0.6 | 1 | 1.2 | 1.4 | 1.4 | 1.5 | 1.5 |
| 101-120 | -0.7 | -0.7 | -0.4 | 0 | 0.4 | 0.8 | 1.1 | 1.3 | 1.4 | 1.4 |
| 121-140 | -0.9 | -0.8 | -0.6 | -0.3 | 0.2 | 0.6 | 1 | 1.2 | 1.3 | 1.4 | 1.4 |
| 141-160 | -1 | -1 | -0.6 | -0.5 | 0.0 | 0.6 | 0.9 | 1.1 | 1.3 | 1.4 | 1.4 |
| 161-180 | -1.2 | -1.1 | -1 | -0.7 | -0.2 | 0.3 | 0.7 | 1 | 1.2 | 1.3 | 1.4 |
| 181-200 | -1.3 | -1.3 | -1.1 | -0.8 | -0.4 | 0.1 | 0.6 | 0.9 | 1.2 | 1.3 | 1.4 |
| 201-220 | -1.4 | -1.4 | -1.2 | -1.0 | -0.8 | -0.1 | 0.4 | 0.8 | 1.1 | 1.3 | 1.4 |
| 221-240 | -1.4 | -1.4 | -1.3 | -1.1 | -0.5 | -0.3 | 0.2 | 0.7 | 1 | 1.2 | 1.3 |
| 241-260 | -1.5 | -1.5 | -1.4 | -1.2 | -0.6 | -0.5 | 0.1 | 0.6 | 0.9 | 1.2 | 1.3 |
| > 260 | -1.5 | -1.5 | -1.4 | -1.3 | -1 | -0.6 | 0 | 0.5 | 0.9 | 1.1 | 1.3 |

**Management of hypoglycemia**
If the blood glucose concentration is ≤ 60 mg/dL, the protocol directs the nurses to stop the insulin infusion, and notifies physicians to administer 50% dextrose immediately, with blood glucose measurements repeated after 30 min.

Switch to subcutaneous insulin-injection
If the insulin dose is < below 3 IU/h, a conversion of the intravenous infusion to a subcutaneous insulin injection is considered. The insulin infusion is often discontinued before the patient is discharged from the ICU.

**Figure 1  Example of glycemic control protocol in an adult intensive care unit. ICU: Intensive care unit.**

including physicians, nurses, pharmacists, and dietitians with guidelines that provide targeting a specific glucose level, insulin dose adjustment, the interval of glucose monitoring, and time for stopping infusion or decreasing the infusion rate to accommodate changes in patient feeding regimes for tests or medications. The risks of complications, such as hypoglycemia, must be addressed. Intravenous insulin therapy is suggested. The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable. A protocol is shown in Figure 1 as an example which can be modified for local needs.

Published glycemic management protocols have been documented to significantly improve glucose levels without a significant increase in the risk of hypoglycemia. The advantages of an algorithm or protocol include more consistent glucose control, less of a trial-and-error pattern of treatment, the ability to maintain glycemic control closer to the target range of near-normal, and earlier intervention for hypoglycemia. A lack of protocol-based care might be expected to increase glycemic variability.

Regular measurement of blood glucose is a burden for nurses; glycemic control by continuous glucose monitoring with automatic closed-loop systems can reduce the clinical burden. Glycemic management protocols in the ICU should focus more on the variability of glycemic control as the treatment target, because glycemic management is related to patient outcome. Continuous monitoring of glucose would allow for the early identification of rapid fluctuations in status associated with changes in insulin requirements. Continuous monitoring of glucose may help prevent the extremes of glucose variability and can maintain optimal blood levels without causing hypoglycemia, thus decreasing the variability in blood glucose concentrations in patients admitted to the ICU. Conversion of an intravenous infusion to subcutaneous insulin injection therapy is often necessary before or at the time of discharge from the ICU.
Hsu CW. Glycemic control in critically ill patients

OUTCOMES

Hyperglycemia has been linked to worse outcomes in critically ill patients. The SPRINT study showed that tight glycemic control to a mean of 6.0 mmol/L mitigated organ failure faster than conventional control at a higher mean level of 7.2 mmol/L. In 2001, van den Berghe et al. published the Leuven study, which demonstrated that tight glycemic control with a target of blood glucose level between 80 and 110 mg/dL had better outcome than conventional control in critically ill surgical patients. ICU mortality, the risk of multi-organ failure, systemic infection and sepsis, the incidence of acute renal failure, critical illness-related polyneuropathy, the need for blood transfusion, and the need for prolonged mechanical ventilator support were reduced from 8% to 4.6%, 34%, 40%, 41%, 44%, 50%, and 50%, respectively. Based on the Leuven study, tight glycemic control was adopted as the standard for critical care patients worldwide. In 2004, Krinsley et al. demonstrated that patients in whom the blood glucose concentrations were controlled to < 140 mg/dL had superior survival rates than did patients in whom the blood glucose concentrations were controlled to < 200 mg/dL in medical-surgical ICUs. In 2006, Van den Berghe et al. repeated the Leuven study in a medical ICU, but did not demonstrate a survival benefit with tight glycemic control in all critically ill medical patients; however, better outcomes, including ICU, ventilator, and hospital days were noted. For patients in the ICU > 3 d, a survival benefit was reported in the tight glycemic control group. Other studies in which tight glycemic control in the ICU was achieved did not demonstrate a lower mortality rate, less frequent acute renal failure, decreased need for renal replacement therapy, decreased vasopressors, and a lower number of ventilator-free days in the intensive insulin treatment group. A significantly higher mortality rate was reported in the NICE-SUGAR study. Furthermore, the NICE-SUGAR study did not demonstrate a lower mortality rate compared with usual care, and there was also no significant difference in mortality when stratified by glucose goals. Another meta-analysis study showed that intensive insulin therapy may be beneficial in patients admitted to the surgical ICU, but not the medical ICU or a mixed ICU.

Patients with SH had worse outcomes than patients with a known diabetic history. Umpierrez et al. reported that newly diagnosed hyperglycemia (admission or fasting glucose level > 125 mg/dL or random glucose level > 200 mg/dL) was associated with a 16% mortality rate compared to a mortality rate of 3% among patients with known diabetes and a rate of 1.7% among patients without hyperglycemia. Three cohorts of ICU patients concluded that hyperglycemia during an ICU admission had a more significant impact on the risk of mortality among patients without diabetes than among patients with diabetes.

GLYCEMIC VARIABILITY

Blood glucose levels in critically ill patients fluctuate widely, even when continuous feeding and an insulin infusion are used. Glycemic variability is usually expressed as the standard deviation around the mean glucose value or as the mean amplitude of glycemic excursions. Glycemic variability is also associated with outcome in critically ill patients; specifically, greater glycemic variability is associated with a significantly higher mortality rate. Non-survivors of critical illnesses were shown to have a higher standard deviation and coefficient of variation (CV) of glucose (standard deviation/mean glucose level) during the ICU stay. A blood glucose level standard deviation > 20 mg/dL was associated with a 9.6-fold increase in mortality compared with a blood glucose level standard deviation < 20 mg/dL. A deleterious effect resulting from increased glycemic variability was noted among non-diabetic patients, but not among patients with diabetes. The mortality rate among non-diabetic patients with a mean glucose level of 70-99 mg/dL during the ICU stay was 10.2% for patients with a glucose CV of < 15% vs 58.3% for patients with a glucose CV above 50%.[86] Increased glycemic variability not only increased the mortality rate, but also morbidity, such as nosocomial infections and hospital length of stay.[86] In a recent retrospective study involving surgical ICU patients, Hermansides and co-workers reported serum glucose variance and combined with high serum glucose levels was associated with the highest mortality, and glucose variability was more important than glucose levels in predicting outcome.[86] Dossett et al. reported that glucose variability was associated with increased mortality, but the mean blood glucose level was not associated with increased mortality in patients with sepsis.

Why is glycemic variability associated with poorer outcomes? Glycemic variability may reflect more attention to detail in medical and nursing care, which may be the real determinants of better outcomes. Less glycemic variability may be associated with severe illness. Induced fluctuation in glycemic levels is more likely to produce apoptosis than sustained hyperglycemia.[87,88] These effects may be mediated via wide changes in osmolarity that in turn could affect cellular and organ function.[89] Oxidative stress was produced in much higher concentrations by alterations in glycemic levels than by sustained hyperglycemia.[87,89] Indeed, increased oxidative stress can result in endothelial dysfunction and contributed to vascular damage. Oxidative stress may be one of the unifying mechanisms underpinning the vasoconstriction, microvascular thrombosis, and inflammation associated...
with hyperglycemia and glycemic variability. Rapid changes in glucose levels can also induce monocyte adhesion to endothelial cells. Another reason why increased glycemic variability may be associated with poorer ICU outcomes is the fact that significant hypoglycemia could occur undetected.

In past trials involving intensive insulin therapy, there were discrepancies in mortality outcomes. All of the data regarding glycemic variability were unavailable in these trials; however, glycemic variability may account for the different mortality rates.

HYPOGLYCEMIA
A plasma glucose concentration < 70 mg/dL is the most common threshold used to define hypoglycemia; however, most of the studies involving glucose control in the ICU have defined severe hypoglycemia arbitrarily as values < 40 mg/dL, whether or not the patients had associated symptoms. Emerging data suggest that hypoglycemia may have a negative impact on the clinical status and outcome of ICU patients. ICU patients may tolerate hypoglycemia poorly and also exhibit impaired counter-regulatory responses or have delayed detection of hypoglycemia. The most severe complications of severe hypoglycemia, such as seizures and death, are easy to measure; more subtle manifestations of neuroglycopenia, such as headaches, fatigue, confusion, dysarthria, or impaired judgment, may be difficult or impossible to diagnose in critically ill patients. Hypoglycemia is more common in medical and septic sub-groups of patients. Female gender, a history of diabetes, the APACHE II score, mechanical ventilation, continuous veno-venous hemodialysis, and ICU length of stay are independent predictors of hypoglycemia. Spontaneous episodes of severe hypoglycemia are rare and observed mainly in patients with fulminant hepatic failure and adrenal failure secondary to septic shock, and especially in patients with severe co-morbidities, such as liver cirrhosis, chronic renal failure, and malnutrition.

Based on the Leuven study in 2001, intensive insulin therapy was widely used in many ICUs. Many studies have shown that intensive insulin therapy is associated with significantly more episodes of severe hypoglycemia than conventional insulin therapy. In the VISEP and Glucocontrol trials, the studies were terminated early because of significantly more hypoglycemic episodes in the intensive insulin treatment group. In two meta-analyses studies, intensive insulin therapy also showed a significantly increased risk of hypoglycemia. Because intensive insulin therapy has been associated with a significantly higher risk of hypoglycemia, there is increased concern about the safety of intensive insulin therapy, which has become an obstacle to strict glycemic control.

Is the hypoglycemic episode directly responsible for an increased risk of death in patients with critical illnesses? One study revealed the degree of hypoglycemia parallels the increase in the risk of death. Even a single episode of severe hypoglycemia is independently associated with an increased risk of mortality; however, some studies have shown that the occurrence of hypoglycemia is not associated with an increased risk of mortality.

GLYCEMIC GOAL
Considerable uncertainty remains regarding the optimal target levels of glucose for patients in the ICU. A safe upper limit for blood glucose level during insulin therapy has not been precisely determined in critically ill patients. The Surviving Sepsis Campaign Guidelines advocate a goal of glucose control < 150 mg/dL, in part to limit hypoglycemia. A large body of observational cohort study data from heterogeneous populations strongly suggests that a J- or U-shaped mortality curve exists among acutely and critically ill patients. Both high and low blood glucose values are independently associated with hospital mortality, with the lowest mortality occurring among those patients with mean glucose levels during their stay in the range of 5.60-8.69 mmol/L and higher rates of mortality for those patients with levels below or above this range. In a recent study, moderate glycemic control was superior to tight glycemic control with decreased mortality and major complications for patients undergoing isolated coronary artery bypass grafting. Patients with a glucose level of 127-179 mg/dL had the lowest mortality and major complications; specifically, sepsis, prolonged ventilation, post-operative renal failure, and the need for new dialysis were highest in the tight glucose control group. Another study also showed that a glucose level of 140-180 mg/dL was associated with the best risk-benefit ratio. The American Association of Clinical Endocrinologists and the American Diabetes Association have increased the treatment threshold to values > 180 mg/dL and a target glucose level between 140 and 180 mg/dL for ICU patients.

CONCLUSION
Acute hyperglycemia associated with insulin resistance is common in critically ill patients. Both hyperglycemia and hypoglycemia harm our patients. The appropriate glycemic target has not been established and may indeed be different for different patient populations. At the same mean blood glucose value, the nature of glycemic control can be quite different with respect to glycemic variability. Not only is the glucose level important, but glycemic variability is also important. An attempt to minimize glycemic variability might have a significant beneficial impact on the outcomes of patients without diabetes. New strategies should be developed to achieve glycemic control with a minimal risk of hypoglycemia and large glucose variations. More effort should be focused on the quality of blood glucose measurement devices and blood glucose monitoring modalities.
REFERENCES

1. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. *Diabetes Care* 1998; 21: 246-249

2. Umpierrez GE, Issacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87: 978-982

3. Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care* 1999; 22: 1827-1831

4. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; 355: 773-778

5. Levetan CS, Magee MF. Hospital management of diabetes. *Endocrinol Metab Clin North Am* 2000; 29: 745-770

6. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merryl H, Cox JL. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol* 2002; 40: 1748-1754

7. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003; 290: 2041-2047

8. Robinson LE, van Soeren MH. Insulin resistance and hyperglycaemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues* 2004; 15: 45-62

9. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycaemia. *Crit Care Clin* 2001; 17: 107-124

10. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab* 2001; 15: 533-551

11. Palumbo PJ. Blood glucose control during surgery. *Anesthesiology* 1981; 55: 94-95

12. Pomposelli JJ, Baxter JK, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, Bistrian BR. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr* 1998; 22: 77-81

13. Wallis LF, Miller J, Davidson MB, Brown J. Perioperative management of diabetes mellitus. *Anesthesiology* 1981; 55: 104-109

14. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; 373: 1798-1807

15. Knapik P, Nadzijakiewicz P, Urbanska E, Saucha W, Herdyska M, Zembala M. Cardiopulmonary bypass increases postoperative glycemia and insulin consumption after coronary surgery. *Annu Thorac Surg* 2009; 87: 1859-1865

16. Estrada CA, Young JA, Nifong LW, Chitwood WR. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Annu Thorac Surg* 2003; 75: 1392-1399

17. McAlister FA, Man J, Bizritz L, Amad H, Tandon P. Diabetes and coronary artery bypass surgery: an examination of perioperative glycemic control and outcomes. *Diabetes Care* 2003; 26: 1518-1524

18. Jones KW, Cain AS, Mitchell JH, Millar RC, Rimmash HL, French TK, Abbate SL, Roberts CA, Stevenson SR, Marshall D, Lappé DL. Hyperglycaemia predicts mortality after CABG: postoperative hyperglycaemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. *J Diabetes Complications* 2008; 22: 365-370

19. Mitchell I, Knight E, Gissane J, Tamhane R, Kolli R, Leditschke IA, Bellomo R, Finer S. A phase II randomised controlled trial of intensive insulin therapy in general intensive care patients. *Crit Care Resusc* 2006; 8: 289-293

20. Cournis DB, Connery LE, Ketzler JT. Perioperative diabetic and hyperglycemic management issues. *Crit Care Med* 2004; 32: SI16-SI25

21. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *DIAGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ* 1997; 314: 1512-1515

22. Orford N, Stow P, Green D, Corke C. Safety and feasibility of an insulin adjustment protocol to maintain blood glucose concentrations within a narrow range in critically ill patients in an Australian level III adult intensive care unit. *Crit Care Resusc* 2004; 6: 92-98

23. Orford NR. Intensive insulin therapy in septic shock. *Crit Care Resusc* 2006; 8: 230-234

24. van den Bergh G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinand P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359-1367

25. Van den Bergh G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354: 449-461

26. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter I, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-1297

27. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, Ailawadi G. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2011; 141: 543-551

28. Cely CM, Arora P, Quartin AA, Kett DH, Schein RM. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest* 2004; 126: 879-887

29. Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek EP, Krumholz HM. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 2005; 111: 3078-3086

30. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, Masoudi FA, Marso SP, Spertus JA. Glycemic metrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation* 2008; 117: 1018-1027

31. Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol* 2001; 22: 607-612

32. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics* 2006; 118: 173-179

33. Faustino EV, Apkon M. Persistent hyperglycaemia in critically ill children. *J Pediatr* 2005; 146: 30-34

34. Kovalaske MA, Gandhi GY. Glycemic control in the medical intensive care unit. *J Diabetes Sci Technol* 2009; 3: 1380-1341

35. Stuart CA, Shangraw RE, Prince MJ, Peters EJ, Wolfe RR. Bed-rest-induced insulin resistance occurs primarily in muscle. *Metabolism* 1988; 37: 802-806

36. Lena D, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. *Anesthesiology* 2011; 114: 438-444

37. Lang CH, Bagby GJ, Blakesley HL, Spitzer J. Importance of hyperglycagomia in eliciting the sepsis-induced increase in glucose production. *Crit Care Med* 1989; 22: 181-191

38. McGuinness OP, Shau V, Benson EM, Lewis M, Snowden RT, Greene JE, Neal DW, Cherrington AD. Role of epineph-
rine and norepinephrine in the metabolic response to stress hormone infusion in the conscious dog. Am J Physiol 1997; 273: E674-E681

39 Fujisawa T, Cherrington AD, Neal DN, McGuinness OP. Role of cortisol in the metabolic response to stress hormone infusion in the conscious dog. Metabolism 1996; 45: 571-578

40 Blumberg D, Hochwald S, Burt M, Donner D, Brennan MF. Tumor necrosis factor alpha stimulates gluconeogenesis from alanine in vivo. J Surg Oncol 1995; 59: 220-224; discussion 224-225

41 Fan J, Li YH, Wojnar MM, Lang CH. Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1, and MAP kinase in skeletal muscle. Shock 1996; 6: 164-170

42 Fink RL, Wallace P, Brechtel G, Olefsky JM. Evidence that glucose transport is rate-limiting for in vivo glucose uptake. Metabolism 1992; 41: 897-902

43 McGuinness OP, Snowden RT, Moran C, Neal DW, Fujiwara T, Cherrington AD. Impact of acute epinephrine removal on hepatic glucose metabolism during stress hormone infusion. Metabolism 1999; 48: 910-914

44 Ishizuka K, Usui I, Kanatani Y, Bukhari A, He J, Fujiyama S, Yamazaki Y, Suzuki H, Hiratani K, Ishiki M, Iwata M, Urakaze M, Haruta T, Kobayashi M. Chronic tumor necrosis factor-alpha treatment causes insulin resistance via insulin receptor substrate-1 serine phosphorylation and suppressor of cytokine signaling-3 induction in 3T3-L1 adipocytes. Endocrinology 2007; 148: 2994-3003

45 He J, Usui I, Ishizuka K, Kanatani Y, Hiratani K, Iwata M, Bukhari A, Haruta T, Sasaoka T, Kobayashi M. Interleukin-1alpha inhibits insulin signaling with phosphorylating insulin receptor substrate-1 on serine residues in 3T3-L1 adipocytes. Endocrinology 2006; 147: 114-124

46 Whitcomb BW, Pradhan EK, Pittas AG, Rohnmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med 2005; 33: 2772-2777

47 Zauner A, Nimmerrichter P, Anderwald C, Bischof M, Schiermeier M, Ratheiser K, Schneweiss B, Zauner C. Severity of insulin resistance in critically ill medical patients. Metabolism 2007; 56: 1-5

48 Gore DC, Chinks D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma 2001; 51: 540-544

49 Ljungqvist O, Nygren J, Treffel A. Insulin resistance and elective surgery. Surgery 2000; 128: 757-760

50 Kaganovsky N, Levy S, Knobler H. The role of hyperglycemia in acute stroke. Arch Neurol 2001; 58: 1209-1212

51 Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 2002; 52: 20-28

52 Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. BMJ 1997; 314: 1303-1306

53 Malmberg K, Norhammar A, Wedel H, Ryden L. Glycemic control in patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation 1999; 99: 2626-2632

54 Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. Neurology 2002; 59: 67-71

55 Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatr Crit Care Med 2004; 5: 329-336

56 Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 1999; 88: 1011-1016

57 Nielson CP, Hindson DA. Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentrations in vitro. Diabetes 1989; 38: 1031-1035

58 Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med 2003; 29: 642-645

59 Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Necheimias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med 1982; 72: 430-450

60 Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? J Clin Invest 2004; 114: 1187-1195

61 Amour J, Brzezinska AK, Jager Z, Sullivan C, Weirhaur D, Du J, Vladic N, Shi Y, Wartlter DC, Pratt PF, Kersten JR. Hyperglycemia adversely modulates endothelial nitric oxide synthase during anesthetic preconditioning through tetrahydrobiopterin- and heat shock protein 90-mediated mechanisms. Anesthesiology 2010; 112: 576-585

62 Nazir FS, Almen M, Small M, Connell JM, Lees KR, Walters MR, Cleland SL. Blunted response to systemic nitric oxide synthase inhibition in the cerebral circulation of patients with Type 2 diabetes. Diabet Med 2006; 23: 398-402

63 Flakoll PJ, Hill JO, Abumrad NN. Acute hyperglycemia enhances proteolysis in normal man. Am J Physiol 1993; 265: E715-E721

64 Cheung NW, Napier B, Zaccaria C, Fletcher JP. Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. Diabetes Care 2005; 28: 2367-2371

65 Burkett E, Keijzers G, Lind J. The relationship between blood glucose level and QTc duration in the critically ill. Crit Care Resusc 2009; 11: 8-13

66 Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sercravsky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327

67 Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004; 79: 992-1000

68 Davidson PC, Steed RD, Bode BW. Glucocomander: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation. Diabetes Care 2005; 28: 2418-2423

69 Brown G, Dodek P. Intravenous insulin nomogram improves blood glucose control in the critically ill. Crit Care Med 2001; 29: 1714-1719

70 Egi M, Bellomo R, Stachowski E, French CJ, Hart G, Stow P. Circadian rhythm of blood glucose values in critically ill patients. Crit Care Med 2007; 35: 416-421

71 Signal M, Pretty CG, Chase JG, Le Compte A, Shaw GM. Continuous glucose monitors and the burden of tight glycaemic control in critical care: can they cure the time cost? Diabet Technol 2010; 4: 625-635

72 Yatabe T, Yamazaki R, Kitagawa H, Okabayashi T, Yamashita K, Hanazaki K, Yokoyama M. The evaluation of the ability of closed-loop glycemic control device to maintain the blood glucose concentration in intensive care unit patients. Crit Care Med 2011; 39: 575-578

73 Moghissi ES. Addressing hypoglycemia from hospital admission to discharge. Curr Med Res Opin 2010; 26: 589-598
Hsu CW. Glycemic control in critically ill patients

74 Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hегa¬ry C, Bailey M. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 2008; 36: 2249-2255

75 Worthley MJ, Shrive FM, Anderson TJ, Traboulsi M. Prog¬nostic implication of hyperglycemia in myocardial infarction and primary angioplasty. Am J Med 2007; 120: 643.e1-643.e7

76 Fogelholm R, Murros K, Rissanan A, Avikainen S. Admis¬sion blood glucose and short term survival in primary in¬tracerebral haemorrhage: a population based study. J Neurol Neurosurg Psychiatry 2005; 76: 349-353

77 Chase JG, Pretty CG, Pleifer L, Shaw GM, Preiser JC, Le Compte AJ, Lin J, Hewett D, Moorhead KT, Desaive T. Or¬gan failure and tight glycemic control in the SPRINT study. Crit Care 2010; 14: R154

78 Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrant P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenström A. Intense metabolic control by means of insu¬lin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005; 26: 650-661

79 Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemer AA, Memish ZA, Haddad SH, Syd Sj, Giridhar RH, Rishu AH, Al-Daker MO, Kahoul SH, Brits RJ, Sakkijra MH. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med 2008; 36: 3190-3197

80 National Institute of Health. Glucose Control Study: Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients. Available from: URL: http://www.clinicaltrial.gov/show/NCT00107601. Access: Jun 12, 2011

81 Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Reinhart K, Engel C, Bloos F, Meier-Hellmann A. Hypoglycemia unawareness. Crit Care Med 2009; 37: S503-S507

82 Griesdale DE, de Souza RJ, van Dam RM, Heysland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mor¬tality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009; 180: 821-827

83 Rady MJ, Johnson DJ, Patel BM, Larson JS, Helmers RA. In¬fluence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabe¬tes mellitus. Mayo Clin Proc 2010; 85: 1559-1567

84 Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients be¬fore and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg 2006; 18: 317-325

85 Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med 2008; 36: 308-313

86 Ali NA, O’Brien JM, Dungan K, Phillips G, Marsh CB, Lemes¬how S, Connors AF, Preiser JC. Glucose variability and mortality in patients with sepsis. Crit Care Med 2008; 36: 2316-2321

87 Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. J Diabetes Sci Technol 2009; 3: 1292-1301

88 Waeschle RM, Moerter O, Hilgers R, Herrmann P, Neumann P, Quintel M. The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. Crit Care 2008; 12: R129

89 Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hypergly¬cemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med 2008; 9: 361-366

90 Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoeistra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. Crit Care Med 2010; 38: 838-842

91 Dossett LA, Cao H, Mowery NT, Dorch MJ, Morris JM, May AK. Blood glucose variability is associated with mortality in the surgical intensive care unit. Am Surg 2008; 74: 679-685; discussion 685

92 Egi M, Bellomo R, Reade MC. Is reducing variability of blood glucose the real but hidden target of intensive insulin therapy? Crit Care 2009; 13: 302

93 Rissio A, Mercuri F, Quagliaro L, Damante G, Ceriello A. Intermittent high glucose enhances apoptosis in human um¬bilical vein endothelial cells in culture. Am J Physiol Endocri¬nol Metab 2001; 281: E924-E930

94 Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceri¬ello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activa¬tion. Diabetes 2003; 52: 2795-2804

95 Otto NM, Schindler R, Lun A, Boenisch O, Frei U, Oppert M. Hyperosmotic stress enhances cytokine production and decreases phagocytosis in vitro. Crit Care 2008; 12: R107

96 Schiekofer S, Andrassey M, Chen J, Rudofsky G, Schneider J, Wendi T, Stefan N, Humpert P, Frätsche A, Stumvoll M, Schleicher E, Häring HU, Nawroth PP, Bierhaus A. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. Diabetes 2003; 52: 621-633

97 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hypergly¬cemia in patients with type 2 diabetes. JAMA 2006; 295: 1681-1687

98 Hirsch IB. Glycemic variability: it’s not just about A1C any¬more! Diabetes Technol Ther 2005; 7: 780-783

99 Watada H, Azuma K, Kawamori R. Glucose fluctuation on the progression of diabetic macroangiopathy—new findings from monocyte adhesion to endothelial cells. Diabetes Res Clin Pract 2007; 77 Suppl 1: S58-S61

100 Krinsley J, Preiser JC. Intensive insulin therapy to control hyperglycemia in the critically ill: a look back at the evidence shapes the challenges ahead. Crit Care 2010; 14: 530

101 Cryer PE, Davis SN, Shamoan H. Hypoglycemia in diabetes. Diabetes Care 2003; 26: 1902-1912

102 Preiser JC, Devos P. Clinical experience with tight glucose control by intensive insulin therapy. Crit Care Med 2007; 35: S503-S507

103 Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007; 35: 2262-2267

104 Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitra¬kou A. Hypoglycemia unawareness. Endocr Rev 1991; 12: 356-371

105 Boord JB, Graber AL, Christman JW, Powers AC. Practical management of diabetes in critically ill patients. Ann Intern Med 2001; 134: 1763-1767

106 Bagshaw SM, Egi M, George C, Bellomo R. Early blood glu¬cose control and mortality in critically ill patients in Austra¬lia. Crit Care Med 2009; 37: 463-470

107 Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with in¬tensive insulin therapy in critically ill patients: predisposing
factors and association with mortality. Crit Care Med 2009; 37: 2536-2544

109 Bagshaw SM, Bellomo R, Jacka MJ, Egi M, Hart GK, George C. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. Crit Care 2009; 13: R91

110 Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med 2003; 31: 359-366

111 Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc 2010; 85: 217-224

112 Vriesendorp TM, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, Schultz MJ, Rosendaal FR, Hoekstra JB. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. Crit Care Med 2006; 34: 2714-2718

113 Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003; 78: 1471-1478

114 Falciglia M, Freyberg RW, Almenoff PL, D’Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009; 37: 3001-3009

115 Kavanagh BP, McCowen KC. Clinical practice. Glycemic control in the ICU. N Engl J Med 2010; 363: 2540-2546

S- Editor Wang JL  L- Editor Webster JR  E- Editor Zheng XM

Hsu CW. Glycemic control in critically ill patients