# Optimal Glucose Management in the Perioperative Period

Charity H. Evans, MD, MHCM*, Jane Lee, MD, PhD,
Melissa K. Ruhlman, MD

**KEYWORDS**

• Blood glucose • Glucose management • Glycemic control • Hyperglycemia
• Hypoglycemia • Perioperative • Surgical • Tight glycemic control

**KEY POINTS**

- Hyperglycemia, defined as a level of blood glucose (BG) greater than 180 mg/dL, in the perioperative period is associated with poor clinical outcomes; treating hyperglycemia in critically ill patients can lead to decreased morbidity and mortality.
- The gold standard for BG measurement is a venous plasma sample evaluated through the clinical laboratory.
- Intensive insulin therapy, defined as a target treatment BG range of 80 to 110 mg/dL, significantly increases the incidence of hypoglycemia and has not been proven to be beneficial in surgical patients.
- When determining when to treat surgical patients for hyperglycemia and what target BG to achieve, the surgeon must take into account the patient's clinical status, because the evidence has shown optimal benefit at different levels.
- In critically ill and noncritically ill surgical patients, insulin therapy should be used with a goal BG of 140 to 180 mg/dL.

## INTRODUCTION

Hyperglycemia is a common finding in patients undergoing surgery. Up to 40% of noncardiac surgery patients have a postoperative level of blood glucose (BG) greater than 140 mg/dL, with 25% of those patients having a level greater than 180 mg/dL.[1] Perioperative hyperglycemia has been associated with increased morbidity, decreased survival, and increased resource utilization.[2–4] For example, McConnell and researchers[5] found a mean 48-hour postoperative glucose greater than

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Department of Surgery, University of Nebraska Medical Center, 983280 Nebraska Medical Center, Omaha, NE 68198-3280, USA
* Corresponding author.
*E-mail address:* charity.evans@unmc.edu

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200 mg/dL in patients after colorectal surgery was associated with an increased incidence of surgical site infection. Similar associations have been found in patients following total joint arthroplasty, infra-inguinal vascular surgery, orthopedic spinal surgery, hepato-biliary-pancreatic surgery, and mastectomy.[6–10] As a treatable and therefore preventable complication, optimal perioperative glycemic control is quickly becoming standard of care.

Evidence suggesting hyperglycemia is a modifiable and independent predictor of adverse outcomes in surgical patients led to widespread implementation of intensive insulin therapy (IIT) with perioperative BG targets of 80 to 110 mg/dL. However, further investigation into the use of IIT failed to show a survival benefit, leading researchers to question what constitutes "normoglycemia" in the perioperative period. The purpose of this review is to summarize the pertinent research on perioperative glucose management, evaluate the pathophysiology of glucose control and glycemic disturbances, discuss the workup and assessment of preoperative patients, and analyze optimal management strategies.

## NATURE OF THE PROBLEM

Hyperglycemia in the critically ill was once viewed as a normal adaptive response to the stress placed on the body by disease. Insulin resistance was thought to be causative factor, because it has been demonstrated in greater than 80% of all critically ill patients.[11] Additional research showed that hyperglycemia is the clinical endpoint of multiple physiologic processes, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis.[12] Once viewed as an adaptive response essential for survival, hyperglycemia was not routinely monitored or controlled in the perioperative patient.

In the late 1980s, researchers discovered improved cardiac function with glucose-insulin-potassium (GIK) infusion for 48 hours after coronary artery bypass grafting.[13] GIK was found to be safe and effective in the treatment of refractory left ventricular failure after grafting. Early studies involving GIK emphasized the importance of glucose and insulin in surgical patients, but offered little insight to glycemic control. The beneficial effect of GIK on cardiac function was likely due to the metabolic effects of insulin, including the ability to promote the use of glucose as a primary myocardial energy substrate. However, these effects were unrelated to glycemic control because BG was not corrected or controlled.

The adverse outcomes of individuals with diabetes were established in the early 1990s and were thought to be secondary to the direct effect of hyperglycemia on immune function, pathogen growth, and vascular permeability, and the indirect effect via the long-term consequences of hyperglycemia on the microvascular system.[14,15] In critically ill patients in the intensive care unit (ICU), levels of BG greater than 180 mg/dL are associated with impaired neutrophil function, increased infection risk, longer hospital stays, and increased mortality.[3] Further studies showed that IIT with intravenous (IV) insulin to a level of target glucose less than 150 mg/dL reduced the incidence of myocardial infarction (MI) and cerebrovascular accidents (CVA) in diabetics with known atherosclerosis. MI and CVA constituted most of the postoperative complications in diabetics. Therefore, researchers proposed that better glycemic control may improve other perioperative complications in patients with diabetes. Early studies focused on perioperative glycemic control and the risk of infectious complications after coronary artery bypass surgery. Researchers showed that postoperative hyperglycemia is an independent predictor of short-term infectious complications and recommended a glucose target level of less than 200 mg/dL to reduce the risk of infection.[16]

In 2001, Brownlee[17] demonstrated under experimental conditions that concentrations of glucose greater than 300 mg/dL were clearly deleterious, mediated by a hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain. These studies were completed in animals, but provided the only scientific guidance for glycemic targets in humans. A landmark study published by van den Berghe and colleagues in 2001 then changed the long-held beliefs about stress hyperglycemia. In contrast to earlier beliefs that hyperglycemia was just a normal adaptive response to the stress placed on the body by disease, the Leuvin I researchers postulated that elevations in serum glucose contributed to the pathophysiology of critical illness. Leuvin I compared the conventional management in which BG was treated only when greater than 200 mg/dL to IIT regimen targeting a level of BG between 80 and 110 mg/dL. Van den Berghe and colleagues[18] demonstrated a 4% decrease in the mortality of surgical critical care patients randomized to the IIT group. This study included mostly surgical patients, of which 63% underwent a cardiac procedure.

The Leuven II study published in 2006 focused on nonsurgical patients. Similar to the Leuven I study, patients were randomly assigned to strict normalization of BG between 80 and 110 mg/dL with the use of insulin infusion or to conventional therapy, with insulin administered when level of BG exceeded 215 mg/dL, with the infusion tapered when the level decreased to less than 180 mg/dL. This study was unable to show the mortality benefit seen in the Leuven I study because IIT reduced levels of BG but did not significantly reduce mortality.[19] The external validity of the Leuven studies has been questioned and may explain why the results are considered inconclusive. Although inconclusive, the Leuven trials clearly showed that a level of BG higher than 180 mg/dL cannot be considered acceptable. Additional retrospective trials by Krinsley[20] and Finney and colleagues[21] in 2003 and 2004, respectively, found that when BG was controlled less than 150 mg/dL, patients had better outcomes than those with higher levels.

The external validity of the Leuven studies led researchers to question the evidence. In the late 2000s, several large single-center and multicenter prospective trials were completed to further evaluate target BG ranges. All studies to date titrated insulin therapy to maintain a level of BG between 80 and 110 mg/dL in the intervention group. Prior studies, including Leuven I and II, managed the control groups with insulin to a BG range of 180 to 200 mg/dL. In comparison, the NICE-SUGAR and GluControl trials used a control target value of 140 to 180 mg/dL. Review of pertinent trials of tight glucose control by IIT (**Table 1**) revealed no significant difference in primary outcome, specifically mortality, between the 2 groups, with the exception of the Leuven I and NICE-SUGAR studies, in opposite directions. A significant secondary outcome revealed in several studies is tight glucose control by IIT, associated with a 4-fold to 6-fold increase in the incidence of hypoglycemia.[22,23]

Guidelines for perioperative glycemic control are limited by the available evidence. However, when viewed as a whole, the evidence clearly shows that perioperative hyperglycemia is associated with worse outcomes. There is insufficient evidence to support tight glucose control to a target of 80 to 120 mg/dL over conventional glucose control to a target of less than 180 mg/dL in the perioperative period.

## PATHOPHYSIOLOGY

Fasting plasma glucose (FPG) is tightly regulated in healthy nondiabetic individuals with levels between 60 and 90 mg/dL and rarely increases to greater than 140 mg/dL in the postprandial period. According to the current guidelines of the American College of

**Table 1**
**Summary of pertinent prospective randomized controlled trials of tight glucose control by intensive insulin therapy**

| Publish Year | Papers | No of Subjects (Intervention and Control) | Subject Classification | Study Design | Intervention (BG Target, mg/dL) | Control (BG Target, mg/dL) | Primary Outcome Variable | Significant Secondary Outcomes |
|---|---|---|---|---|---|---|---|---|
| 2001 | Van den Berghe, et al. (Leuven I) | 765/783 | Surgical | Single center, single blind | 80–110 | 180–200 | ICU mortality (4% decrease) | Multiorgan failure (decreased) |
| 2006 | Van den Berghe, et al. (Leuven II) | 595/605 | Medical | Single center, single blind | 80–110 | 180–200 | ICU mortality (no significant change) | Acute kidney injury (decreased) |
| 2008 | Arabi | 266/257 | Medical (~80%) Surgical (~20%) | Single center, single blind | 80–110 | 180–200 | ICU mortality (no significant change, increased hypoglycemia) | Hypoglycemic episodes (increased) |
| 2008 | De La Rosa | 254/250 | Medical (~50%) Surgical (~50%) | Single center, single blind | 80–110 | 180–200 | 28-d mortality (no significant change) | Hypoglycemic episodes (increased) |
| 2009 | Brunkhorst, et al. (VISEP) | 247/289 | Medical (46.9%) Surgical (52.9%) | Multicenter, single blind | 80–110 | 180–200 | 28-d mortality (no significant change) | Hypoglycemic episodes (increased) |
| 2009 | Finfer, et al. (NICE-SUGAR) | 3054/3050 | Medical (~63%) Surgical (~37%) | Multicenter, single blind | 80–110 | 140–180 | 90-d mortality (increased in intervention group) | Hypoglycemic episodes (increased) |
| 2009 | Preiser, et al. (GluControl) | 542/536 | Medical (~42%) Surgical (~58%) | Multicenter, single blind | 80–110 | 140–180 | ICU mortality (lack of benefit in intervention group) | Hypoglycemic episodes (increased) |

*Data from* Refs.[18,19,22,23,64–66]

Endocrinology and the American Diabetes Association, individuals with FPG levels greater than 126 mg/dL or hemoglobin A1c greater than 5.7% have diabetes mellitus (DM).[24] The aforementioned studies identified these individuals as having increased incidence of operative complications, thus leading to the concept that tight glucose control during the perioperative period in both healthy and diabetic patients may lead to improved outcomes. However, it became evident that understanding the pathophysiology of the disease was required to develop a comprehensive perioperative glucose control model.

The principal organs involved in glucose control include the brain, pancreas, muscle, adipose tissue, liver, and kidneys.[25] The interactions between these organs have been elucidated as outlined in **Fig. 1**, but the understanding is far from complete. Insulin mediates glucose control by regulating the transport of glucose into cells either by facilitated diffusion or by active transport. Glucose transport is facilitated by specific glucose transporters, which include GLUT 1–12, $H^+$/myoinositol transporter, and sodium-dependent glucose cotransporter 1–6.[26] Activation of the insulin receptor is the rate-limiting step in moving glucose out of the serum into the cells to maintain FPG levels; therefore, both insulin level regulation and insulin receptor sensitivity are involved in maintaining glucose homeostasis.

Insulin is secreted from β-cells in the pancreatic islets of Langerhans, with a half-life of 4 to 6 minutes. Basal rate of 0.5 to 0.7 U/h is secreted constitutively and increases acutely with increased levels of glucose. Glucose levels are detected by pancreatic cells via binding of glucose with GLUT2.[27] The secretion of insulin is directly modulated by other hormones, including those from the pancreas (glucagon, somatostatin,

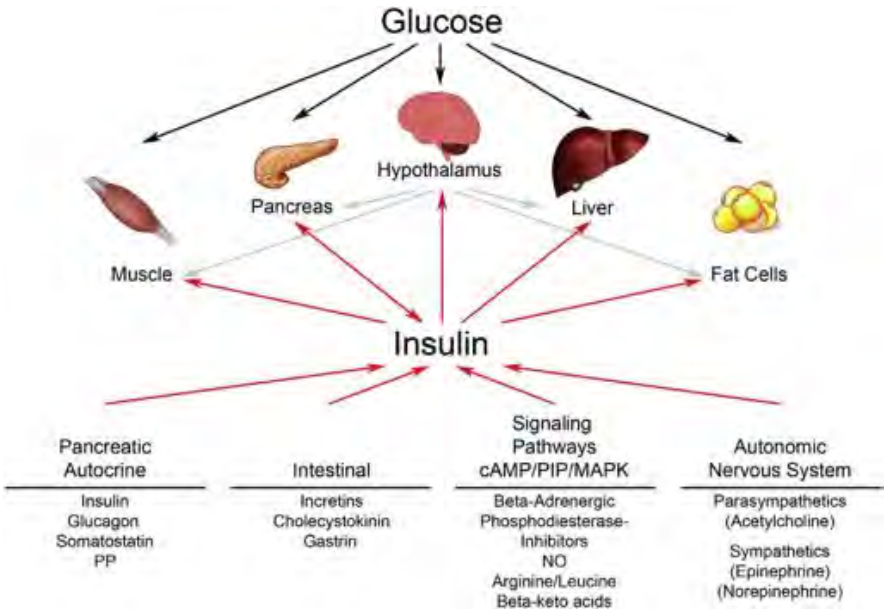


**Fig. 1.** Modulation of the secretion of insulin. Interactions between glucose, insulin, and multiple organ systems. Glucose had direct effects on various systems through glucose-specific receptors (*black arrows*). Multiple organ systems communicate with each other through their neural pathways (*gray arrows*). Insulin release is activated by both glucose and various other mechanisms as summarized in the figure (*red arrows*). cAMP, cyclic adenosine monophosphate; PIP, phosphatidylinositol phosphate; NO, nitric oxide; PP, pancreatic polypeptide.

and pancreatic polypeptide) and intestine (incretins), as depicted in Fig. 1.[28] Indirect modulation occurs through other hormones that promote islet cells neogenesis (cholecystokinin and gastrin) and growth factors (insulin-like growth factor-1 and insulin-like growth factor-2). Other factors that increase insulin release are those that activate cytosolic cyclin adenosine monophosphate, which results in increases in intracellular calcium levels, such as nitric oxide (NO), arginine, leucine, and β-keto acids. Increases in intracellular calcium can also affect parasympathetic signaling pathways, such as those activated by acetylcholine. Conversely, sympathetic pathways mediated by catecholamines decrease insulin levels.[29] The physiology of insulin regulation brings light to how operative stress and various agents used in the perioperative period can influence glucose levels.

Insulin affects glucose transport via binding of Insulin Receptor (IR) in organ systems involved in glucose regulation, and IRs present other organ systems through activation of downstream signaling pathways, which can be loosely categorized as proliferative (mitogenic) and metabolic. These pathways are not mutually exclusive and many times synergistic. IRs are present on cells involved in hemostasis and inflammation, which activate the proliferative pathways through mitogen-activated protein kinase (MAPK).[30] These pathways affect the immune system by suppressing proinflammatory transcription factors and endotoxin-mediated inflammatory mediators. Metabolic pathways are activated by phosphatidylinositol-3 kinase, which affects growth, adaptation to fasting and feeding, and response to stress.[31] In addition, PI3 kinase increases NO production,[32] which affects both platelets and endothelium and decreases expression of several factors that ultimately highlight insulin's antioxidant, antithrombotic, and antifibrinolytic properties, all of which are also affected through the MAPK pathway as well.[33] Given insulin's broad actions, it becomes evident how hyperinsulinemia in the perioperative period can affect patient outcomes.

Hyperglycemia, which results from normal physiologic response to stress through actions of sympathetic response or underlying insulin insensitively, has its own pathologic effects,[12] including suppression of various aspects of immune function and activation of proinflammatory cytokines, which affect wound healing and immunologic defensive function.[34] These effects have been reported in levels of glucose greater than 200 mg/dL. In addition, hyperglycemia is known to decrease NO, increase angiotensin II levels, and ultimately affect systemic vascular resistance.[35] Hyperglycemia causes hyperosmolality, which has renal and neurologic consequences. Hyperosmolality can cause dieresis, which leads to dehydration and electrolyte and acid-base imbalances as well as central nervous system dysfunction.[36] Rapid correction of hyperosmolality can cause cerebral edema. Fig. 2 depicts how perioperative injury can cause hyperglycemia, which ultimately leads to mortality and morbidity.

## CLINICAL PRESENTATION AND EXAMINATION

The patient's history and physical examination (Table 2), along with laboratory studies (Box 1), provide the surgeon with the needed information to determine optimal perioperative glycemic management strategies.[24]

## DIAGNOSTIC PROCEDURES

Determining the best modality for evaluating BG in the perioperative period requires knowledge of the advantages and disadvantages of each. A variety of options are available for testing including hemoglobin A1c, point-of-care (POC) testing, arterial, venous, capillary, and plasma blood sampling, and continuous glucose monitoring.

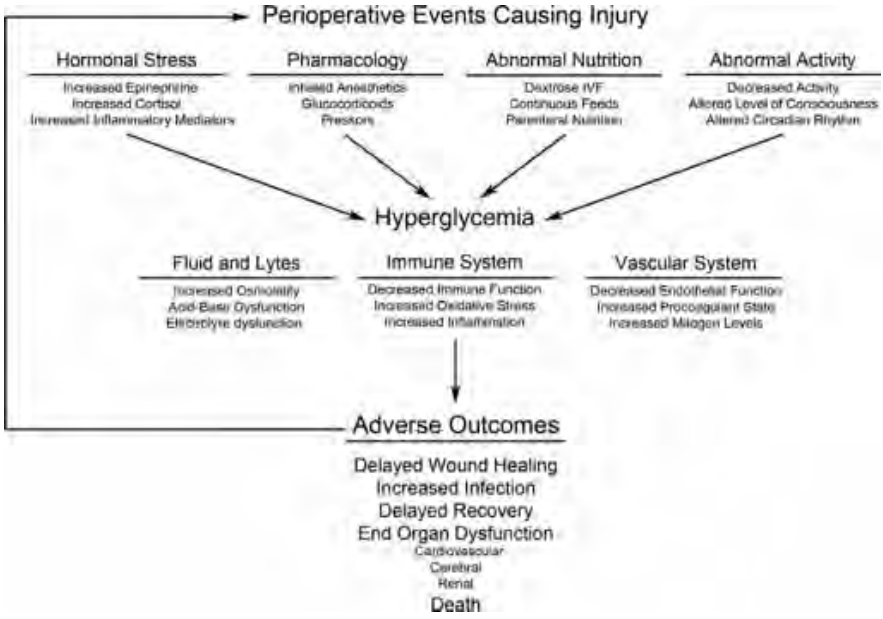


**Fig. 2.** Influence of perioperative events on hyperglycemia. Perioperative stress-related hyperglycemia may start a downward spiral resulting in significant morbidity and mortality. Perioperative stressors cause hyperglycemia, which activates mechanisms that result in adverse outcomes. Often these adverse outcomes worsen the same perioperative stressors or activate other perioperative stressors, which compounds itself, resulting in further injury and, if not controlled, eventually resulting in death. IVF, intravenous fluid.

The terms blood glucose and plasma glucose, although at times used interchangeably, can have significant variability. Plasma glucose is typically 10% to 15% higher than whole BG due to higher water concentration in plasma (93%) compared with erythrocytes (73%). Plasma glucose is a more physiologic measurement because whole BG can vary significantly with the hematocrit.[37,38] The American Diabetes Association and World Health Organization recommend the use of venous plasma glucose for measuring and reporting BG. Capillary glucose is the most imprecise measurement of BG, mostly because of the type and accuracy of devices used for measuring. The difference between venous and capillary glucose is typically small in fasting patients without major physiologic derangements. The difference in glucose values between these 2 measurements has been shown to be up to 8% higher in capillary blood after meals or glucose load. Capillary glucose also tends to underestimate whole BG in situations with poor peripheral perfusion or increased tissue extraction of glucose.[37,38] Classically, in the operating room, whole BG evaluation is obtained in conjunction with an arterial blood gas. Arterial BG is accepted to be more accurate than capillary glucose but has been shown in some cases to provide higher glucose values than either venous or capillary samples.[37]

POC devices are readily available and quick and require a minimal sample size. POC devices typically measure whole BG but most self-correct internally and report results as plasma glucose.[37] Although these devices are useful, the rapid physiologic changes that occur in the operating room and in the postoperative patient may lead to significantly less accurate results. Factors such as hemoglobin, temperature changes, fluid shifts, and hypotension can all affect the accuracy of the rapid-acting

**Table 2**
**Preoperative assessment**

| Symptoms of Hyperglycemia | Planned Operation | Risk for Perioperative Glycemic Disturbance Hyperglycemia |
|---|---|---|
| • Polyphagia<br>• Polydipsia<br>• Polyuria<br>• Blurred vision<br>• Fatigue<br>• Weight loss<br>• Poor wound healing<br>• Dry mouth | • Type of surgery<br>  ○ Cardiac<br>  ○ Noncardiac<br>• Length of surgery<br>• Planned anesthesia<br>• Timing of surgery<br>• Length of time NPO | • Diabetes<br>• Stress from acute illness<br>• Medications<br>  ○ Glucocorticoids<br>  ○ Octreotide<br>  ○ Vasopressors<br>  ○ Immunosuppressants<br>• Enteral and parenteral nutrition |
| **Past Medical History** | **Postoperative Plan** | **Hypoglycemia** |
| • Type 1 or 2 diabetes<br>• Glucose intolerance<br>• Previous hospitalizations for diabetes<br>• Outpatient glycemic control<br>**Medications**<br>• Outpatient oral glycemics or insulin<br>• Glucocorticoids<br>• Immunosuppressants | • Resume oral diet<br>• NPO<br>• Enteral nutrition<br>• Parenteral nutrition | • Insulin use<br>• Altered nutritional status<br>• Heart failure<br>• Liver or renal failure<br>• Malignancy<br>• Infection, sepsis<br>• Iatrogenic<br>  ○ Sudden reduction in steroid use while on long-acting insulin<br>  ○ NPO or decreased oral intake<br>  ○ Inappropriate timing of insulin administration<br>  ○ Decreased dextrose administration<br>• Interruptions in enteral or parenteral nutrition |

POC machines. It appears that these inaccuracies are more pronounced in the hypoglycemic range, with up to 20% variation in either direction, and in the anemic patient, with inaccuracies up to 30%. These wide variations can lead to alterations in clinical decision-making and potentially cause adverse outcomes in patient care. Clinical laboratory measurements using arterial or venous samples are much more accurate than POC meters and should be used whenever possible.[37,39] Hemoglobin A1c, or glycated hemoglobin, is a marker of long-term glucose control. A preoperative hemoglobin A1c less than 7% confers good long-term glucose control and has been associated with decreased risk of infectious complications.[40]

Continuous glucose monitoring devices can be used to obtain real-time BG analysis and allow for closer monitoring and for prevention of the deleterious effects associated with hypoglycemia. These devices can be quite accurate but require frequent calibration. This type of device might prove beneficial in a diabetic patient undergoing a long, complicated, or high-risk procedure in which frequent and accurate glucose monitoring is required.[40]

As an alternative to blood sampling, subcutaneous sensors for continuous monitoring are available and have been found to correlate with BG values. These devices may not have the needed accuracy for routine use in an acute care setting such as with surgical patients. Ellmerer and researchers[41] found good correlation of blood and subcutaneous glucose measurements in ICU postcardiac surgery patients using a subcutaneous sensor.These devices require frequent calibrations with the patient's blood, which may limit the benefit of the device.[40]

**Box 1**
**Preoperative laboratory studies**

*Patient with known diabetes*

- Hemoglobin A1C (HgA1C)
- Fasting level of BG

*Patient without diabetes*

- Based on risk factors
- Hemoglobin A1C (HgA1C)
- Fasting level of BG *IF*
  - Adults with BP greater than 135/80 mm Hg
  - Adults with body mass index greater than or equal to 25 kg/m$^2$ *AND*
    - Physical inactivity
    - First-degree relative with diabetes
    - High-risk ethnicity
    - History of gestational diabetes or delivery of baby greater than 9 lbs (4.1 kg)
    - Hypertension
    - HDL less than 35 mg/dL or triglycerides greater than 250 mg/dL
    - History of polycystic ovarian syndrome
    - History of cardiovascular disease
    - History of impaired glucose tolerance or impaired fasting glucose

## MANAGEMENT

Insulin is used in the management of perioperative hyperglycemia. Insulin requirements are determined by the balance between endogenous insulin secretion and insulin resistance. Exogenous insulin comes in several forms, typically classified as short and fast-acting, or long and slow-acting, based on the time to onset, peak activity, and duration of action of each. The time to onset, peak activity, and duration of action can only be approximated, because the degree of absorption of any dose can vary as much as 25% to 50%, leading to fluctuation in glucose control.[42,43] **Fig. 3** displays the properties of different types of insulin. The intermediate to long-acting preparations are used as a basal supplement, suppressing hepatic glucose production and maintaining normal levels of BG in the fasting state. Short-acting bolus doses of insulin are used to cover extra insulin requirements. In critically ill patients, the short-acting insulins allow the patient to reach goal BG ranges in the shortest duration of time and allows for rapid changes in doses given its short half-life.

Exogenous insulin can be delivered as a bolus, premeal or prandial, correctional, basal, or basal-bolus dose. The decision of the type of insulin dose to administer is based on the patient's basal insulin requirements, degree of hyperglycemia, level of perioperative stress, and clinical status. A description of each is provided in **Table 3**.

Exogenous insulin can be administered subcutaneously or intravenously, each with its own advantages and disadvantages (**Table 4**).

Although most surgeons agree that glycemic control is required in the perioperative period, the optimal BG range remains controversial. Review of the evidence provides surgeons with recommendations based on the clinical status of the patient, as

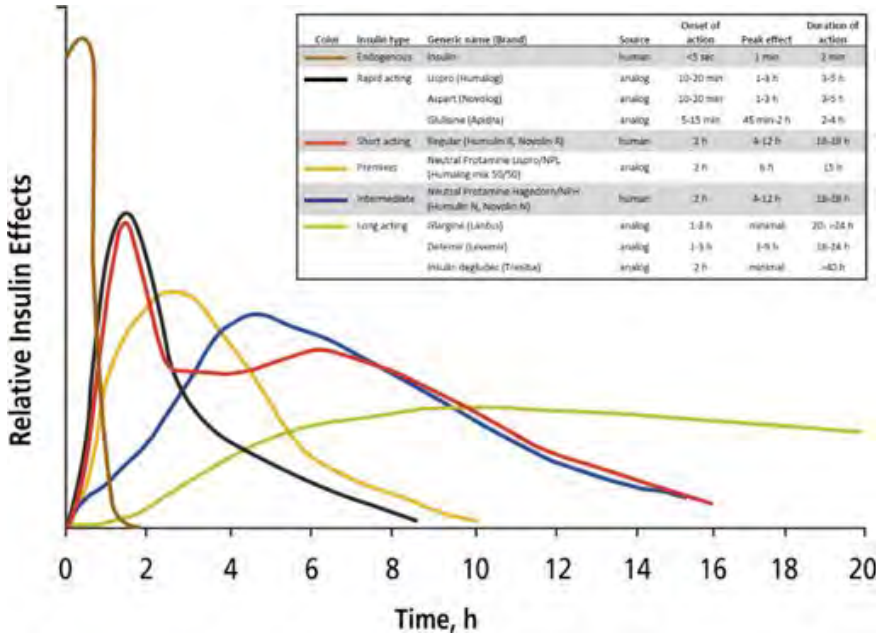


**Fig. 3.** Insulin action guideline. There are several categories of insulin that vary in time of onset and duration. Shorter-acting insulin is used in acute insulin control, such as after meals. Intermediate-acting and long-acting insulin is used to provide baseline insulin levels. Intermediate dosing is dosed several times during the day, whereas long-acting insulin is dosed once daily. Combination insulin is used for immediate action as well as providing baseline levels of insulin.

summarized in **Fig. 4** and **Box 2**. The proposed insulin infusion protocol presented in **Fig. 4** is a modified version of the protocol recommended by Goldberg and colleagues.[44]

Once the perioperative patient on IV insulin is more stable, the prehospital insulin regimen can be resumed, assuming that it was optimal in achieving glycemic targets. Because of the short half-life of IV regular insulin, the first dose of subcutaneous (SQ) insulin must be given before discontinuation of the IV insulin infusion. If intermediate-acting or long-acting insulin is used, it should be given 2 to 3 hours before stopping the infusion, whereas short-acting or rapid-acting insulin should be given 1 to 2 hours before discontinuation.

## SPECIAL POPULATIONS

The concept of perioperative glycemic control was born in the research of special populations, including patients undergoing cardiovascular surgery, pediatric population, trauma patients, patients with traumatic brain injury (TBI), and patients on steroids. The evidence and recommendations vary from the management of the critically ill and noncritically ill patients, and therefore, warrant special attention.

### *Cardiovascular*

The very concept of intense glucose control in the critically ill was first studied in cardiac patients.[18] Since this landmark article by Van den Berghe about the benefit of IIT,[45] the debate has centered on who may benefit from glucose control and to

**Table 3**
**Types of insulin doses**

| Bolus | Basal |
|---|---|
| • Commonly used for noncritical patients with or without DM<br>• Short-acting (regular) or rapid-acting (lispro, aspart, or glulisine) insulin<br>• Typically provided as a premeal bolus to cover the extra requirements after food is absorbed<br>• Does not provide patient with basal level of insulin<br>• Or as a "sliding scale" titrated to level of BG<br>• Little data to support its benefit and some evidence of potential harm when the "sliding scale" is applied in a rote fashion (Queale) | • Intermediate- to long-acting preparations (neutral protamine hagedron; neutral protamine lispro, detemir, or glargine)<br>• Typically administered once or twice daily to provide basal insulin levels to suppress hepatic glucose production and maintain near normoglycemia in the fasting state<br>• Provides patient with basal level of insulin<br>• Basal insulin levels can also be achieved by continuous infusion of a short-acting or rapid-acting insulin via an insulin pump, used almost exclusively in type 1 diabetes |
| **Correctional** | **Basal-bolus** |
| • Additional doses of short-acting or rapid-acting insulin<br>• Given premeal to patients on basal-bolus regimens to correct premeal hyperglycemia<br>• Dose of correction insulin should be based on patient characteristics such as previous level of glucose control, prior insulin requirements, and, if possible, the carbohydrate content of meals | • Combination of short-acting and long-acting insulins, given separately (not premixed)<br>• Increasing use for inpatient hyperglycemia in the noncritically ill patient (Umpierrez) |

*Data from* Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Arch Intern Med 1997;157(5):545–52; and Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a Basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care 2013;36(8):2169–74.

**Table 4**
**Comparison of subcutaneous and intravenous delivery of insulin**

| SQ Delivery of Insulin | IV Delivery of Insulin |
|---|---|
| • Most noncritically ill patients with or without DM can be treated with SQ insulin<br>• Little data showing that IV insulin is superior to SQ insulin in the noncritically ill patient<br>• Injection sites include upper arms, abdominal wall, upper legs, and buttocks<br>• Injection sites should be rotated<br>• Insulin is absorbed more rapidly when injected into the abdomen than the arms or legs<br>• The variability in absorption is increased and net absorption is reduced with increasing size of the subcutaneous depot | • Any patient with BG >180 mg/dL should be managed with IV insulin<br>• Patients with type 1 DM, especially those undergoing a long surgery, also should be treated with IV insulin<br>• Changes of IV dose have a more immediate effect compared with SQ therapy<br>• Little data showing that IV insulin is superior to SQ insulin in the noncritically ill patient<br>• The best IV insulin protocols take into account not only the prevailing BG but also its rate of change and the current insulin requirements |

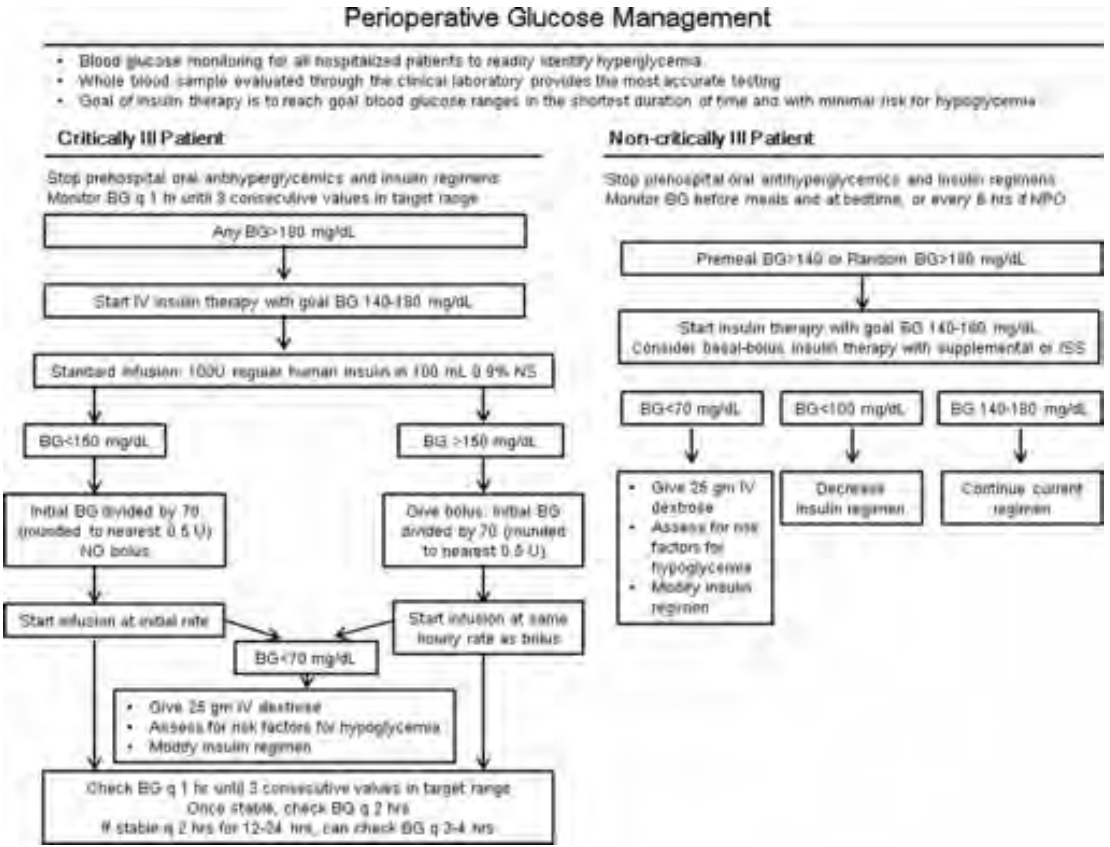


**Fig. 4.** Recommendations for perioperative glucose management. ISS, insulin sliding scale; NS, normal saline; NPO, nothing by mouth. (*Adapted from* Goldberg PA, Siegel MD, Sherwin RS, et al. Implementation of a safe and effective insulin-infusion protocol in a medical intensive care unit. Diabetes Care 2004;27:461–7.)

**Box 2**
**Indications for intravenous insulin therapy**

- Type 1 diabetics who are instructed as nothing by mouth (NPO), perioperative, or in labor and delivery
- Any ICU patient with BG greater than 180 mg/dL
- Poorly controlled hyperglycemia despite subcutaneous insulin therapy
- Patients with known diabetes status postcardiac surgery
- Patients with acute coronary syndrome or acute MI with BG greater than 180 mg/dL
- Patients with diabetic ketoacidosis or hyperosmolar hyperglycemic syndromes

what degree of glucose control is required for the benefits to outweigh the risks of hypoglycemia, also an independent risk factor for poor outcomes.[46] Hyperglycemia is postulated to be cardiotoxic because of its direct effects on the myocardium membranes and mitochondria,[47] and its indirect effects via activation of proinflammatory mediators.[48] Contrary to the seminal article on this topic, studies in both neonatal and adult cardiac surgery patients revealed that IIT contributes to severe hypoglycemia, and moderately intense glucose control has demonstrated no difference in outcome compared with IIT. Currently, the Society of Thoracic Surgeons advocate a target range of 120 to 180 mg/dL for patients undergoing cardiac bypass surgery.[49]

### *Pediatric*

Neonates, infants, and young children less than 8 years of age have a higher incidence of hypoglycemia because of poor glycogen stores in their liver and their intrinsic higher metabolism. In pediatric trauma patients, early administration of glucose-containing solutions in the form of D5 or D10 is recommended after initial resuscitation.[50] However, it is also known that hyperglycemia is associated with poor neurologic outcomes in the pediatric traumatic head-injury patients. In addition, in infants on pressor support with necrotizing enterocolitis, hyperglycemia is associated with longer lengths of stay and increased rates of death.[51] The studies that showed improved outcomes of IIT in cardiac surgery patients spurred investigations in glucose control in neonatal and infant cardiac surgery patients, which showed similar findings.[52] Researchers then focused on perioperative glucose control in the pediatric population. Several studies showed the danger of hypoglycemia in normal healthy infants and children is rare and dextrose-containing fluids should be avoided perioperatively.[53] However, neonates and patients on parenteral or continuous enteral feeds should not be categorized as normal, and administration of dextrose solution would be appropriate. D5 solutions should be avoided, but 1% to 2% dextrose solutions in normal saline or lactated Ringer is recommended at an infusion rate of 120 to 300 mg/kg/h to maintain adequate levels of glucose and to avoid lipid metabolism.[54]

### *Trauma*

Hyperglycemia is a normal metabolic response to stress and trauma due to activation of the sympathetic nervous system. Studies showed that hyperglycemia in trauma patients is more strongly associated with poor outcomes than sick patients in the ICU.[55,56] Despite these associations, trauma patients account for only a small percentage of patients addressed in studies of critically ill patients and IIT.[57] Theoretically, critically ill trauma patients can be treated as ICU patients; yet hyperglycemia in the

noncritically ill trauma patient is largely uninvestigated at this time. At the authors' institution, glucose monitoring is initiated on admission of all trauma patients regardless of diabetes or level of care status and is discontinued if levels of glucose remain within institutionally acceptable levels for 48 hours. This practice is based on the empiric knowledge of the literature and has yet to be shown to decrease mortality or morbidity in all trauma patients.

### *Neurologically Critical Ill Patients*

The brain is one of few organ systems that exclusively use glucose as an energy source. Hypoglycemia is detrimental to critically ill neurologic patients, including those who suffered TBIs. Furthermore, in congruency with the studies of critical ill patients, hyperglycemia defined as greater than 200 mg/dL has also been linked to higher mortality and worse outcomes in these patients.[58,59] Similarly, tight glucose control had been shown to not improve neurologic outcome while increasing the risk of hypoglycemia. In fact, a large body of evidence is available that shows that tight glucose control causes reduced cerebral extracellular glucose and increased incidence of brain energy crisis.[60] A microdialysis study of severe brain injury cohort demonstrated that systemic levels of glucose closely reflects to levels in the cerebrospinal fluid and, furthermore, hypoglycemia in the brain was detected even in systemic levels of glucose in the intermediate range.[61] Given that the traumatized brain has several metabolic changes including dysfunction of glucose transport mechanism, probable increased metabolic needs, and mitochondrial dysfunction, hypoglycemia defined as less than 80 mg/dL has been associated with brain energy crisis and poor outcomes, leading to the assumption that glucose control range in TBI is somewhere between 80 and 200 mg/dL. Further studies on the subject will eventually elucidate BG goals in TBI.[58]

### *Steroids*

Steroids are used perioperatively as a prophylaxis for nausea, stress steroids for patients with adrenal insufficiency, and an induction agent before organ transplantation. Steroids are released when the sympathetic nervous system is activated to mobilize energy reserves during stressful states. Incidentally, steroid boluses and drips are used as an adjunct to pressors during septic shock.[62] However, steroids can also induce hyperglycemia and insulin intolerance. Intraoperatively, steroid use has not been shown to significantly affect levels of BG and outcomes.[63] Hence, denying steroids for indicated perioperative uses for fear of hyperglycemia appears to be unsubstantiated that this time.

## SUMMARY

Hyperglycemia, defined as any level of BG greater than 140 mg/dL in the hospital setting, is a common finding in surgical patients during the perioperative period. Factors contributing to poor glycemic control include counterregulatory hormones, insulin resistance, decreased glucose uptake, immune suppression, activation of proinflammatory cytokines, use of dextrose-containing IV fluids and enteral and parenteral nutrition. Hyperglycemia in the perioperative period is associated with increased morbidity, decreased survival, and increased resource utilization. Optimal glucose management in the perioperative period contributes to reduced morbidity and mortality. To readily identify hyperglycemia, BG monitoring should be instituted for all hospitalized patients. The gold standard for BG measurement is a venous plasma sample evaluated through the clinical laboratory. When determining when to treat surgical patients for

hyperglycemia and what target BG to achieve, the surgeon must take into account the patient's clinical status, because the evidence has shown optimal benefit at different levels. IIT, defined as target treatment BG in the range of 80 to 110 mg/dL, significantly increases the incidence of hypoglycemia and has not been proven to be beneficial in surgical patients. In critically ill and noncritically ill surgical patients, insulin therapy should be used with a goal BG of 140 to 180 mg/dL. The avoidance of hypoglycemia, specifically in TBI and pediatrics, has been shown to be as significant as treating hyperglycemia. Therefore, treatment protocols must allow a margin of error when targeting the optimal BG range.

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