Review Article

CME Scientific Principles and Clinical Implications of Perioperative Glucose Regulation and Control

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Development of hyperglycemia after major operations is very common and is modulated by many factors. These factors include perioperative metabolic state, intraoperative management of the patient, and neuroendocrine stress response to surgery. Acute insulin resistance also develops perioperatively and contributes significantly to hyperglycemia. Hyperglycemia is associated with poor outcomes in critically ill and postsurgical patients. A majority of the investigations use the term "hyperglycemia" very loosely and use varying thresholds for initiating treatment. Initial studies demonstrated improved outcomes in critically ill, postsurgical patients who received intensive glycemic control (IGC) (target serum glucose <110 mg/dL). These results were quickly extrapolated to other clinical areas, and IGC was enthusiastically recommended in the perioperative period. However, there are few studies investigating the value of intraoperative glycemic control. Moreover, recent prospective trials have not been able to show the benefit of IGC; neither an appropriate therapeutic glycemic target nor the true efficacy of perioperative glycemic control has been fully determined. Practitioners should also appreciate technical nuances of various glucose measurement techniques. IGC increases the risk of hypoglycemia significantly, which is not inconsequential in critically ill patients. Until further specific data are accumulated, it is prudent to maintain glucose levels <180 mg/dL in the perioperative period, and glycemic control should always be accompanied by close glucose monitoring.

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Fasting plasma glucose (FPG) levels are tightly regulated typically between 60 and 90 mg/dL, and postprandial glycemic excursions to >140 mg/dL are unusual in normal healthy individuals. Chronic hyperglycemia has significant long-term deleterious health effects.[1] According to the current guidelines by the American College of Endocrinology and the American Diabetes Association (ADA), individuals with an FPG of 100 to 125 mg/dL are considered prediabetic, whereas those with FPG levels ≥126 mg/dL have diabetes mellitus.[2] Based on the current National Health and Nutritional Examination Survey, the crude prevalence of diabetes (diagnosed and undiagnosed) in the United States is 12.9% of the population older than 20 years, and approximately 40% of these individuals are unaware of the diagnosis.[3] A further 26% of the population has impaired fasting glucose (which increases the risk of diabetes), making the burden of disease to be 73 million people. Between 60% and 70% of patients with prediabetes will progress to develop frank diabetes.[4] Eighty percent of the cases in North America and Western Europe are Type 2 diabetes, which is characterized by variable degrees of insulin deficiency and resistance. Type 1 diabetes accounts for another 5% to 10% of cases and is characterized by pancreatic β-cell destruction and absolute requirement of insulin. Other diseases such as genetic defects, malfunction of the exocrine pancreas, other endocrinopathies, certain medications, and gestation may cause the other 5% to 10% of the cases of diabetes.

Although patients with diabetes have a higher incidence of operative complications,[5,6] development of acute hyperglycemia perioperatively per se (i.e., even in those with previously normal glucose tolerance) is also recognized as a predictor of adverse

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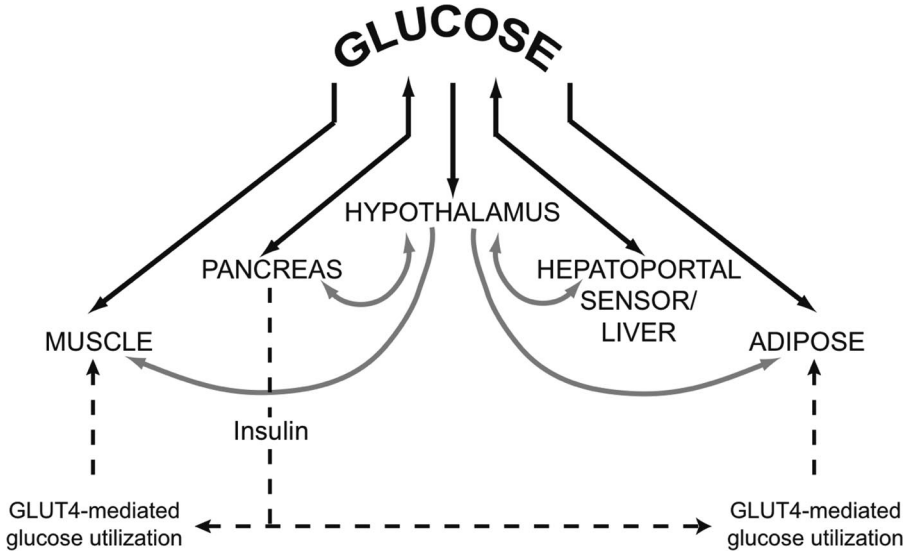

Figure 1. Principal organs that are involved in glucose sensing and communication. Hypothalamus, liver, hepatoportal sensor, pancreas, adipocytes, and muscle are involved in glucose sensing and communicate with each other via neuronal pathways, hormones, or changes in glucose levels. Liver uptakes glucose postprandially as well as produces glucose during fasting. Black lines represent glucose-mediated (solid) or hormone-mediated (dotted) communication. Gray lines represent neural-mediated communications. GLUT-4 = glucose transporter 4.

outcomes.[7–9] This association implies, but certainly does not prove, that controlling hyperglycemia during and after surgery may lead to improved outcomes, and has been the focus of recent reviews.[4,10] A number of articles advocating "intensive glycemic control" (IGC) in the perioperative and hospital setting have been published, but the potential clinical benefit of IGC during and after surgery has not been tested rigorously. Thus, there is significant allocation of resources and adoption of perioperative practices that have not been substantiated by large, randomized clinical trials. Moreover, according to a recent, large multicenter trial involving mixed medical/surgical intensive care unit (ICU) patients, there may be some harm associated with IGC.[11] This review discusses our current understanding of glucose homeostasis, the scientific basis for hyperglycemia in the perioperative period, and critically analyzes the contemporary literature addressing perioperative glycemic control.

PHYSIOLOGY OF GLYCEMIC CONTROL

Glucose Transport

The principal organs involved in glucose homeostasis include the brain, pancreas, muscle, adipose tissue, liver and sensors in the hepatoportal area, and the kidneys[12] (Fig. 1). The interactions of these organs to maintain stable glycemia are complex.[12,13] Glucose enters the cell by 1 of 2 methods: facilitated diffusion or active transport. Facilitated diffusion requires specific glucose transporters (GLUTs) (GLUT-1 to -12, H+/myoinositol transporter, and sodium-dependent glucose cotransporters 1–6).[14] Insulin is one of several hormones involved in glucose homeostasis, albeit the most important. However, all cells are not dependent on insulin for glucose transport. Insulin-independent glucose transport is most notable in the pancreas, brain, and immune and endothelial cells. In contrast, cells that are dependent on insulin for glucose transport include skeletal and cardiac muscle, adipose tissue (where GLUT-4 predominates), and the liver, whose glucose uptake is primarily regulated by GLUT-2. Glucose transport into muscle and adipose tissue via a pool of GLUT-4 membrane proteins that move rapidly to the cell surface upon activation of the insulin receptor (IR) is the rate-limiting step in insulin-mediated glucose disposal[15] (Fig. 2). Hence, any condition that reduces the amount of insulin secretion or decreases the cellular sensitivity to insulin's action, or both, will result in hyperglycemia.[16]

Insulin Secretion and Its Regulation

Increased levels of glucose in the plasma trigger the release of insulin from β-cells in the pancreatic islets of Langerhans. The basal rate of insulin secretion is on the order of 0.4 to 0.7 U/h, increasing rapidly by 4- to 5-fold after ingestion of food.[17,18] The half-life of insulin in the blood is approximately 5 to 6 minutes, although its cellular activity upon binding to the IR is substantially longer.

The secretion of insulin is not exclusively governed by the plasma glucose level. It is also modulated by other pancreatic hormones (glucagon, somatostatin, and pancreatic polypeptide) and by intestinal hormones collectively known as incretins (glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1).[18] Other intestinal hormones such as cholecystokinin and gastrin promote islet cell neogenesis and may indirectly influence glucose homeostasis.[18] Insulin-like growth factors (IGF-1 and IGF-2) also seem to affect glucose metabolism, but their importance in humans remains unclear. Glucose homeostasis results from the complex interaction between each of these factors, the nature of which continues to be revealed.[18] For example, the more recently discovered modulatory role of the incretins explains the higher levels of insulin that are observed after oral administration of carbohydrates than after an equivalent amount of IV administered dextrose.[18,19]

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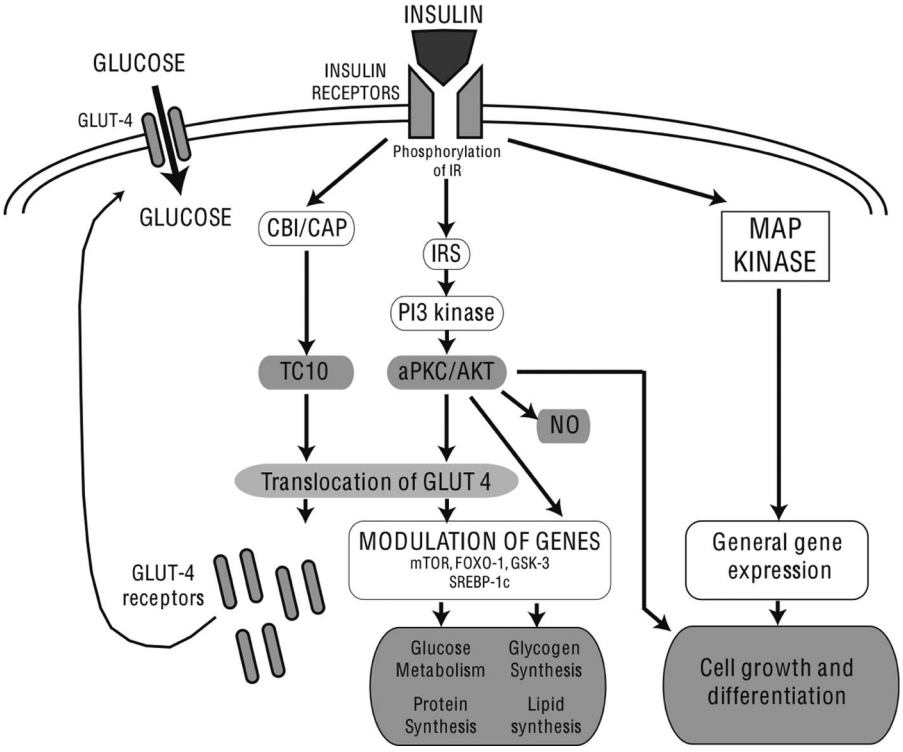

Figure 2. Signal transduction pathway of insulin. Insulin exerts its action through the cell-surface insulin receptor (IR). Binding of insulin to its receptor activates multiple downstream substrates through a series of complex phosphorylation reactions. Activation of these substrates triggers other downstream pathways, which can be loosely grouped into metabolic pathway and proliferative pathways, although they are not mutually exclusive. Metabolic pathway involves phosphatidylinositol-3 (PI3) kinase and casitas b-lineage protooncogene (CBl), whereas the proliferative ones involve mitogen-activated protein kinase (MAP kinase). IRS = insulin receptor substrate; CBl/CAP = an oncoprotein; aPKC/AKT = atypical protein kinase C; GLUT-4 = glucose transporter 4; FOXO-1 = forkhead transcription factor-1; TC10 = small GTPase Tc10; NO = nitric oxide; mTOR = mammalian target of rapamycin; GSK-3 = glycogen synthase kinase 3; SREBP-1c = sterol response element-binding protein-1c.

Additional factors affect insulin secretion: nitric oxide, arginine, leucine, and β-keto acids, which can each stimulate pancreatic insulin output.[19] Any agent that increases cytosolic cyclic adenosine monophosphate and hence intracellular calcium can also potentially enhance insulin secretion. These agents include β-adrenergic agonists and phosphodiesterase inhibitors such as theophylline.[19] Intracellular calcium can also be increased by acetylcholine; hence, vagal stimulation may also increase insulin secretion.[19,20]

Conversely, sympathetic stimulation inhibits insulin secretion. This action is mediated by norepinephrine and galanin (a protein that activates K_{ATP} channels).[20] Catecholamines also inhibit insulin secretion via α-2 adrenergic receptor stimulation. Hence, the net effect of epinephrine and norepinephrine is inhibition of insulin secretion. However, in the setting of α-blockade, these catecholamines may actually enhance insulin secretion via unopposed β-adrenergic stimulation.[19] Intracellular potassium depletion also attenuates pancreatic insulin output.[19]

Inhaled anesthetics depress glucose-stimulated insulin release, an effect that seems to be relatively consistent among the various agents.[21–29] Isoflurane and sevoflurane impair glucose tolerance in this manner,[30,31] but it remains unclear whether the effect is dose dependent.[23] One study suggested that the effect is independent of the dose up to 1.5 minimum alveolar concentration.[30] Desflurane/remifentanil anesthesia maintained insulin levels; however, glucose levels still increased modestly, likely because of a superimposed decrease in insulin sensitivity.[32] Propofol and opioids blunt the neuroendocrine response, and various combinations of other IV anesthetics have also demonstrated this effect.[33–35] However, this response is restricted to the intraoperative period because the anesthetics are discontinued or administered at a much lower dose in the postoperative period.[33] Clonidine can blunt the neuroendocrine response through its α_2-agonist action, but it may promote perioperative hyperglycemia by decreasing insulin secretion from the pancreatic β-cells.[36,37] For reasons that are unclear, an increase in plasma glucose has not been observed with the use of dexmedetomidine, even though it may also decrease insulin secretion.[38]

Signal Transduction

Insulin exerts its action through the cell surface IR. Notably, IRs are not only limited to the cells that are intricately involved in glucose transport but are also present in many other cells. These include endothelial cells, lymphocytes, macrophages, and monocytes. Binding of insulin to its receptor activates multiple

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downstream substrates through a series of complex intracellular phosphorylation reactions.[39] Activation of these substrates triggers other downstream pathways, which can be loosely grouped into metabolic and proliferative (mitogenic) pathways, although they are not always mutually exclusive. Metabolic pathways involve signaling via phosphatidylinositol-3 (PI3) kinase and casitas b-lineage proteins, whereas the proliferative ones involve signaling through mitogen-activated protein kinase (MAPK)[40,41] (Fig. 2).

Metabolic Effects of Insulin

Activation of the PI3 kinase pathway has 3 principal actions on glucose metabolism: (1) promotion of glucose uptake in insulin-sensitive cells by translocation of a specific glucose transporter (GLUT-4) to the cell membrane; (2) promotion of glycogen synthesis, the chief storage form of intracellular glucose; and (3) phosphorylation of transcription factor (forkhead transcription factor-1), which regulates expression of genes involved in the adaptation to fasting and feeding (gluconeogenesis, glycolysis, lipogenic and sterol synthetic pathways, and hepatic insulin sensitivity).[42,43] The PI3 kinase pathway also stimulates transcription factors that affect nitric oxide production, lipogenesis, and protein synthesis (Fig. 2). Physiologically, insulin reduces circulating glucose concentrations by increasing the uptake of glucose into peripheral tissues, especially skeletal muscle. In the liver, insulin activates glucokinase and decreases endogenous (primarily hepatic) glucose production by reducing gluconeogenesis and glycogenolysis.

Nonmetabolic Effects of Insulin

Some of the beneficial effects of insulin are attributed to its nonmetabolic actions, exerted primarily, although not exclusively, through the MAPK pathway (Fig. 2). It suppresses several proinflammatory transcription factors (nuclear factor-κB, early growth response-1, and activating protein-1) and decreases the expression of endotoxin-mediated inflammatory mediators (interleukin [IL]-1β, IL-6, macrophage migration inhibitor factor, and tumor necrosis factor [TNF]-α).[44,45] Furthermore, inhibitory factor-κB expression is increased (which counters the actions of proinflammatory intracellular signal, nuclear factor-κB).[45] Insulin augments nitric oxide production (via the PI3 kinase pathway) in both platelets and the endothelium, thereby acting as an inhibitor of platelet aggregation and a selective vasodilator (Fig. 2). Insulin decreases expression of tissue factor, plasminogen activator inhibitor-1, reactive oxygen species, intracellular adhesion molecule-1, and monocyte chemotactic protein-1 generation, highlighting its antioxidant, antithrombotic, and antifibrinolytic properties.[41] Antiapoptotic properties of insulin have also been well described.[46] In contrast, insulin also increases endothelin-1 expression via the activation of the MAPK pathway. However, in the setting of "selective insulin resistance" as seen in obesity and diabetes, this pathway likely remains intact and, in the setting of hyperglycemia and hyperinsulinemia, may manifest insulin's vasoconstrictive and, potentially, its proatherosclerotic actions.[44]

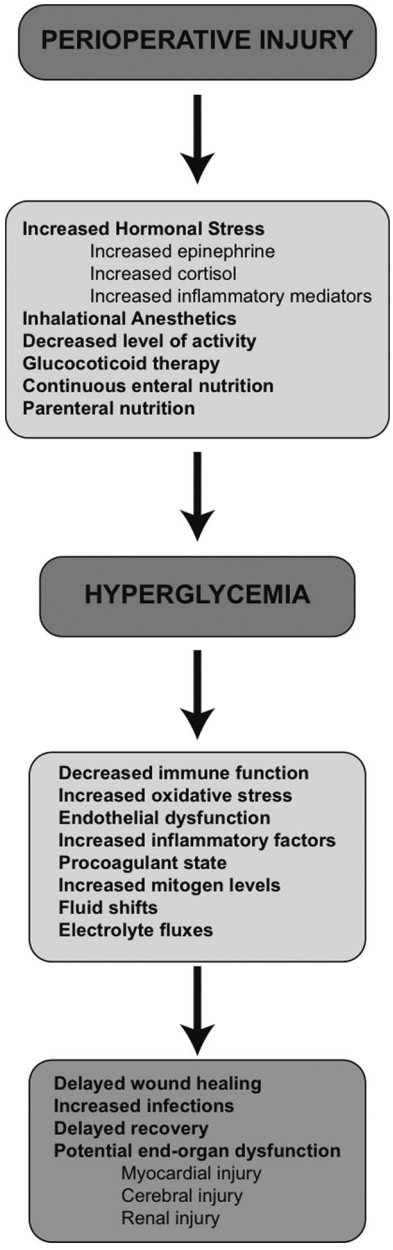

Figure 3. The relationship among perioperative injury, hyperglycemia, and outcomes.

Detrimental Effects of Acute Hyperglycemia

Diabetic patients have significant cardiovascular disease and compromised immune function, which makes them prone to perioperative cardiac complications and surgical wound infection.[47,48] However, acute hyperglycemia may also have its own deleterious effects that can lead to poor perioperative outcomes (Fig. 3). It can suppress various aspects of immune function (chemotaxis, phagocytosis, generation of reactive oxygen species, and intracellular killing of bacteria) and increase the

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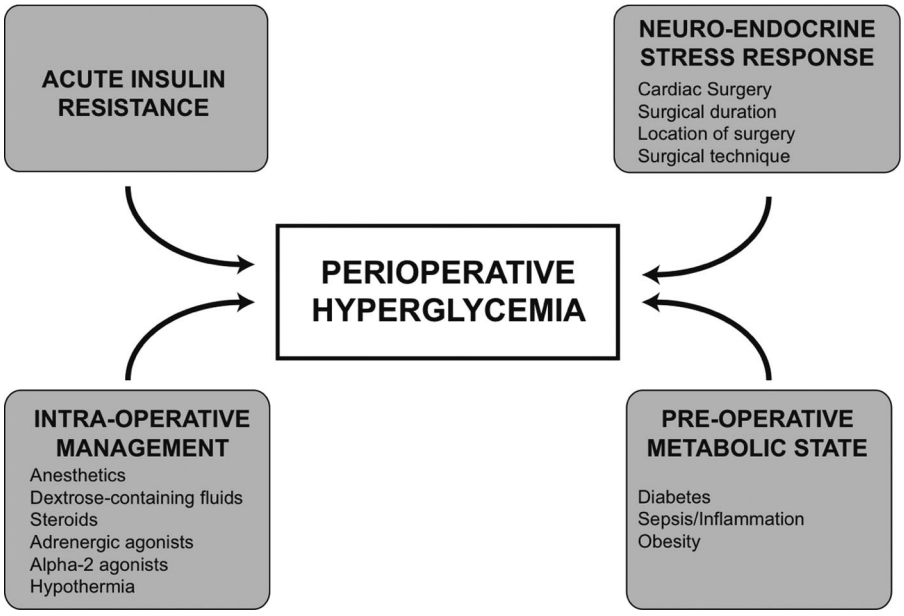

Figure 4. Modulators of perioperative hyperglycemia.

circulating inflammatory cytokine concentration.[1,49] Some of the effects of hyperglycemia are reported at glucose concentrations >200 mg/dL.[50–52] Decreased nitric oxide production, increased angiotensin II levels, and increased systemic vascular resistance can lead to altered vascular reactivity in hyperglycemia.[44] Once the renal threshold is crossed, osmotic diuresis leads to dehydration and electrolyte and acid-base imbalance. Hyperosmolality leads to central nervous system dysfunction, and its rapid correction can worsen cerebral edema.

MODULATORS OF HYPERGLYCEMIA IN THE PERIOPERATIVE PERIOD

Hyperglycemia is a ubiquitous phenomenon in the perioperative period, linked to the preoperative metabolic state of the patient, neuroendocrine stress response, and acute perioperative insulin resistance, as well as his or her intraoperative management.[6,53,54] These factors are not necessarily independent of each other (Fig. 4). Patients with diabetes, metabolic syndrome, preexisting insulin resistance (due to obesity, etc.) or those with underlying β-cell dysfunction (previously unrecognized under basal conditions) are more likely to develop perioperative hyperglycemia.[55] However, development of stress-induced hyperglycemia in patients without diabetes portends poorer outcomes than those in patients with diabetes.[56–58]

Activation of the neuroendocrine system contributes significantly to perioperative hyperglycemia. Glucagon, epinephrine, and cortisol (counterregulatory hormones) are the primary hormones that are secreted in the setting of perioperative stress. These counterregulatory hormones work in concert to maintain hyperglycemia by targeting substrate supply, capacity of the liver to take up gluconeogenic precursors, mobilization of glycogen stores in the perioperative fasting state, and facilitation of glucose release by the liver, while minimizing hepatic glucose entry.[6] Gluconeogenesis contributes >90% to the total glucose production under perioperative conditions.[53] Glucose production increases by approximately 30% after surgery, whereas glucose clearance decreases.[53] The reduction in glucose clearance is related to decreased glucose use by the skeletal muscle, which is secondary to increased insulin resistance.[6] Endotoxin also contributes to hyperglycemia by stimulating the adrenergic system and increasing the levels of cytokines that cause insulin resistance.[59]

Insulin resistance is a state of decreased biological effect to any given concentration of insulin.[60] When it occurs acutely, in some individuals, the pancreas may not be able to respond with appropriate hyperinsulinemia, and the result is hyperglycemia. Insulin resistance is affected by age, genetic predisposition, ethnicity, physical activity level, and body weight. Poor perioperative caloric intake and negative nitrogen balance also increase insulin resistance.[6] Insulin resistance is also mediated by proinflammatory molecules, free fatty acids, and counterregulatory hormones.[61] During surgical or traumatic injury, peripheral resistance to the action of insulin may be profound at the level of the prime controllers of glucose (adipose tissue, liver, heart, and skeletal system).[59,62]

The exact mechanism of insulin resistance in the inflammatory and perioperative state is far from settled. It is most likely attributable to many factors acting at various levels of the signal transduction pathways. Of note is a decrease in tyrosine phosphorylation of IR substrate (IRS) and activation of proteins that suppress cytokine signaling, called suppressor of cytokine signal.[62] TNF-α has been shown to induce phosphorylation of IRS-1, which in turn phosphorylates the IR, making it resistant to normal phosphorylation by insulin.[62] In addition, TNF-α and IL-6 have been shown to induce suppressor of cytokine signal-3

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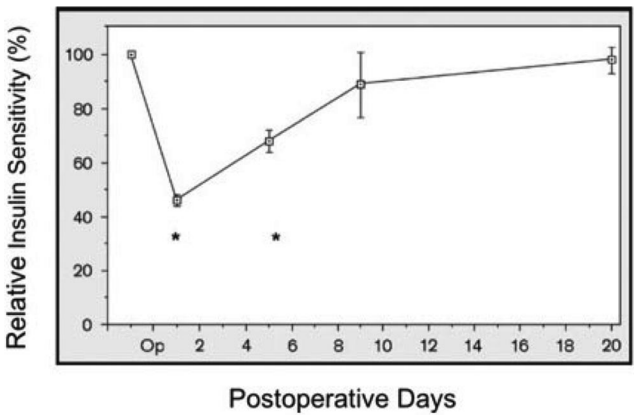

Figure 5. Time course for postoperative insulin resistance in patients undergoing open cholecystectomy. Relative insulin sensitivity represented as percentage (%) that is calculated as postoperative insulin sensitivity/perioperative insulin sensitivity × 100. Insulin sensitivity was determined within 5 days preoperatively and at days 1 (n = 9), 5, 9, and 20 (n = 5) postoperatively. Statistically significant difference presented with an asterisk; Op = day of the operation. (Reproduced from Thorell et al.[65] with permission.)

protein, which also interferes with tyrosine phosphorylation of IR and IRS-1, and degradation of IRS-1. Decreased IRS-1 function not only decreases subsequent GLUT-4 translocation via Akt activation but also affects nitric oxide production.[62] Indeed, alteration in insulin-mediated translocation of GLUT-4 has been noted in patients who underwent total hip replacement.[63] The increased amount of free fatty acids may further enhance the inflammatory cascade, decrease PI3 kinase activity that ultimately leads to failure of GLUT-4 translocation, and contributes to insulin resistance.[64] The insulin-resistant state can further enhance lipolysis, increase free fatty acids, and create a vicious cycle.

Significant insulin resistance develops intraoperatively during cardiac surgery and has been demonstrated as early as 2 hours after the completion of noncardiac operations of intermediate risk and duration.[29] Thorell et al.[65] studied 10 patients undergoing elective open cholecystectomy surgery under general anesthesia and showed that insulin resistance was most noticeable on the first postoperative day (insulin sensitivity decreased by approximately 50%), persisted up to 5 days, and reverted back to normal 9 to 21 days after surgery (Fig. 5).

Insulin resistance and the hyperglycemic response are also directly related to the degree of surgical trauma.[66,67] Operations involving the thorax and abdomen elicit a more profound and prolonged hyperglycemic response than lower-risk peripheral or diagnostic procedures.[66] Similarly, less hyperglycemia is noted in the setting of laparoscopic surgery versus open procedures, even in the setting of a similar neuroendocrine response.[68] Even the operative approach in a particular surgery can modify the perioperative glucose response.[69] Blood loss during surgery is also positively correlated with insulin resistance.[54]

The degree of hyperglycemia is also dependent on the medications used during surgery (e.g., steroids, epinephrine, or IV fluids containing dextrose) and the dextrose in pump prime fluid during cardiopulmonary bypass.[70–72] Patients who undergo cardiac surgery with cardiopulmonary bypass, especially under deep hypothermic circulatory arrest, frequently develop hyperglycemia.[73] This is likely due to the profound inflammatory and stress response of cardiopulmonary bypass and/or hypothermia, which decrease insulin secretion and further augment insulin resistance.[71] Hyperglycemia during cardiopulmonary bypass may also be related to increased reabsorption of glucose in the renal tubules.[74]

It is predictable that any anesthetic technique that modifies the neuroendocrine stress response intraoperatively could also modulate the subsequent metabolic sequelae and mitigate perioperative hyperglycemia. In operations involving the lower part of the body, spinal and epidural anesthesia can blunt such a stress response.[27,75] In contrast, for upper abdominal surgeries, neuraxial anesthetic techniques seem to be less efficient in doing so.[76] Propofol and opioids blunt the neuroendocrine response, and various combinations of IV anesthetics have also demonstrated this effect; however, the modulation of the stress response in this manner is restricted to the intraoperative period, likely because such drugs are either discontinued or administered at a much lower dose in the postoperative period.[33,35] Generally, the metabolic effects of noncardiac surgery are most evident postoperatively.[77] Furthermore, postoperative alterations in physical activity (which has a major impact on glucose utilization) and medications (which directly interfere with insulin secretion or enhance insulin resistance) affect postoperative glycemic levels.

To summarize, the perioperative stress response leads to insulin resistance. This may be modulated further by many factors, including anesthetic technique, perioperative medications, surgical location and extent, and operative duration and technique. Insulin secretion is also directly affected by anesthetics and various vasoactive medications. It is therefore not surprising that hyperglycemia is extremely common in the postoperative setting.

HYPERGLYCEMIA AND PERIOPERATIVE OUTCOMES

Recognizing the potential deleterious effects of hyperglycemia, its association with poor perioperative outcomes and salutary effects of insulin, it would be logical to advocate glycemic control in the perioperative period. Currently, there is no unified or well-accepted value to define perioperative "hyperglycemia." Investigators have used serum glucose values of >100 mg/dL to >270 mg/dL to define clinically relevant hyperglycemia in adult surgical populations.[78,79] Similarly, the therapeutic threshold to treat glucose levels in adults perioperatively has ranged from >110 mg/dL to >200 mg/dL. In

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the context of this review, the term "intensive glycemic control (IGC)" means the attempt to maintain all glucose levels >70 to 80 mg/dL and <110 mg/dL, and the discussion focuses predominantly on the adult surgical population, unless specifically mentioned. Most of the evidence for the improved outcomes of glycemic control is derived from retrospective or prospective observational studies. There have been few prospective randomized controlled trials, and even fewer studies have focused specifically on the intraoperative period. For the purpose of this review, first we discuss retrospective studies, followed by prospective trials. To highlight the level of evidence for each phase in the perioperative period, we further divide the discussion into the preoperative, intraoperative, and postoperative periods.

Retrospective Studies

Preoperative Hyperglycemia

Patients with diabetes have an established association with adverse perioperative outcomes.[47,80] However, 10% to 15% of patients without diagnosed diabetes may present with hyperglycemia preoperatively. A number of studies have shown a strong association between perioperative hyperglycemia (>200 mg/dL) and poor perioperative outcomes, regardless of diabetic status (Table 1).[80,82,86] A retrospective analysis of 1201 patients who underwent carotid endarterectomy revealed that perioperative glucose >200 mg/dL on the day of surgery and increasing levels of operative-day glucose were associated with increased risk of perioperative (30-day) stroke, myocardial infarction, and death.[85] A case-control retrospective study of 108,593 patients who underwent noncardiac, nonvascular surgery showed that perioperative hyperglycemia (>200 mg/dL) was associated with increased mortality (odds ratio [OR], 1.7).[80] Similarly, abnormal hemoglobin (Hb)$A1_c$ (>7%) is associated with increased risk of infection and morbidity after cardiac and noncardiac surgeries.[86,105]

Intraoperative Hyperglycemia

A number of retrospective studies in cardiac surgery patients have demonstrated a link between intraoperative glycemic levels and adverse outcomes. This association was not clearly established in earlier studies, but[89] more recent investigations have been able to show a strong association between glycemic levels and outcomes.[78,90,91,106] With the exception of one study, all retrospective studies in cardiac surgery patients have used a glucose level of >110 mg/dL as their association or therapeutic cutoff threshold (Table 1).[83,84,87,88,93,97] An initial retrospective analysis of 409 patients revealed that for each 20 mg/dL increase in serum glucose levels >100 mg/dL, the risk for adverse events increased by 30%.[78] These results, however, were not supported by a subsequent prospective study from the same group.[107] Ouattara et al.[106] analyzed 200 diabetic patients who underwent cardiac surgery and demonstrated an association between intraoperative hyperglycemia (defined as >4 consecutive values >200 mg/dL despite treatment) and poor cardiac and noncardiac outcomes. Doenst et al. assessed the influence of hyperglycemia (highest glucose level) during cardiopulmonary bypass on perioperative morbidity and mortality in patients with or without diabetes. A peak glucose level >360 mg/dL during cardiopulmonary bypass was an independent predictor of mortality both in patients with diabetes (OR, 1.2) and in those without diabetes (OR, 1.12). These investigators determined that a peak intraoperative glucose level <270 mg/dL during cardiopulmonary bypass was not associated with poor outcomes.[79] In an interventional trial by Furnary et al.[90] of glycemic control in 3550 diabetic patients undergoing cardiac surgery, outcomes were compared with historical controls. Insulin was initiated intraoperatively and continued for 3 days postoperatively. A significant reduction in mortality and a decrease in cardiovascular morbidity and infection were demonstrated compared with historical controls who received insulin subcutaneously. However, IGC was not the aim of this study, and glucose levels were initially targeted to <200 mg/dL, but during subsequent years of the study, to 100 to 150 g/dL.

There are few retrospective studies in the noncardiac surgery literature that only correlate intraoperative glycemic levels with outcomes. A recent post hoc analysis of the Intraoperative Hypothermia for Aneurysm Surgery Trial suggested an association of increased neurologic deficits with hyperglycemia (>129 mg/dL) at the time of cerebral aneurysm clipping.[108] In patients with severe traumatic brain injury, IGC was associated with increased markers of cellular stress; however, no difference in mortality or functional outcomes was noted.[81] Thus, the evidence in support of IGC intraoperatively, even in retrospective and observational studies, remains scant.

Postoperative Hyperglycemia

A metabolic impact of neuroendocrine perturbations secondary to surgical stress is most noticeable postoperatively. Postoperative hyperglycemia is associated with poor outcomes. Most patients studied are status post–cardiac surgery, although there are some data on vascular, neurosurgical, and trauma patients as well.[8,96,98,101–103,109] Two studies, one in a trauma ICU[99] and another in a mixed medical-surgical ICU, were able to show a correlation between better clinical outcomes and lower glucose level (<140 mg/dL).[96] One investigation in a neurosurgical ICU did not show a difference in outcomes in the first week of admission, although there was a decreased infection rate and a statistical decrease in the intracranial pressure in the second week in glycemic controlled patients.[102] Another recent study investigated the effect of glycemic control (<120 mg/dL) in 834 patients with aneurysmal subarachnoid hemorrhage and did not

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Table 1. Retrospective Studies

Study	Study type	Number and type of patients	Design	Glycemic goal or range	Salient findings
Preoperative					
Aristedis and Serafim[81]	Retrospective case-control	267 patients, head trauma	Nonstandardized protocol	None	Severity of head injury correlated with admission and postoperative glucose levels. Only postoperative glucose levels >200 mg/dL were predictors of poor outcomes
Yendamuri et al.[82]	Retrospective	738 patients, trauma	Nonstandardized protocol	None	Admission glucose >200 mg/dL was associated with increased mortality, increased hospital and ICU LOS, and increased rate of infection
Laird et al.[83]	Retrospective	516 patients, trauma	Nonstandardized protocol	None	Hyperglycemia (glucose >200 mg/dL) was associated with higher rate of infection and mortality
Sung et al.[84]	Prospective observational	1003 patients, trauma	Nonstandardized protocol	None	Hyperglycemia (glucose >200 mg/dL) had higher incidence of infection and hospital LOS
McGirt et al.[85]	Retrospective	1201 patients, carotid endarterectomy	Nonstandardized protocol	<200 mg/dL	Preoperative glucose >250 mg/dL was associated with increased incidence of stroke, TIA, MI, and death. Mild hyperglycemia (150–199 mg/dL) was not associated with difference in the incidence of stroke, TIA, MI, and death
Dronge et al.[86]	Retrospective	647 patients, noncardiac surgery	Nonstandardized protocol	HbA_{1c}	A $HbA_{1c} < 7\%$ associated with decreased incidence of infectious complications
Noordzij et al.[80]	Retrospective, case-control	904 patients, noncardiac, nonvascular surgery	Nonstandardized protocol	None	In patients with prediabetes 3-fold increase while in patients with diabetes 4-fold increase in cardiovascular mortality
Intraoperative					
Hill et al.[87]	Retrospective	2862 patients, CABG	Nonstandardized glucose management	None	No association between maximum blood glucose concentration and mortality (univariate analysis)
Guvener et al.[88]	Retrospective	1090 patients, CABG	Nonstandardized glucose management	150–200 mg/dL	Patients with diabetes were more prone to infectious complications. Preoperative hyperglycemia was an independent predictor of short-term infectious complications and the total hospital LOS
Estrada et al.[89]	Retrospective	1574 patients, CABG	Nonstandardized glucose management		Hyperglycemia did not predict increased mortality
Furnary et al.[90]	Prospective observational	3554 patients, CABG	SQ insulin versus continuous IV insulin	150–200 mg/dL, 125–175 mg/dL, and 100–150 mg/dL	Continuous IV insulin therapy (prebypass to 3 d postoperative) improved survival (2.5% vs 5.3%)
Doenst et al.[79]	Retrospective	6280 patients, cardiac surgery	Insulin by bolus during CPB	>270 mg/dL	Peak glucose >360 mg/dL was associated with adverse events and mortality
Gandhi et al.[78]	Retrospective	409 patients, cardiac surgery	Nonstandardized glucose management	N/A	Maximal and mean intraoperative glucose predicted increased morbidity and mortality (multivariate analysis). Increase in mean intraoperative glucose level (20 mg/dL) associated with an increase occurrence (30%) of an adverse event
D'Alessandro et al.[91]	Prospective observational	600 patients, CABG	Insulin by standardized protocol pre, intra, and postoperatively	150–200 mg/dL	No difference in cardiac, pulmonary, neurological, renal, and infectious complications. Decreased mortality in treatment group (1.3% vs 4.0%)
Puskas et al.[7]	Retrospective	525 patients, CABG	Nonstandardized glucose management	N/A	At 6 wk, nondiabetics patients, glucose >200 mg/dL was associated with decreased cognitive dysfunction. In patients with diabetes, hyperglycemia had no effect on cognitive dysfunction

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Table 1. Continued

Study	Study type	Number and type of patients	Design	Glycemic goal or range	Salient findings
Postoperative					
Finney et al.[92]	Prospective observational	523 patients, medical (12%), surgical (88%) ICU	Insulin by nonstandardized protocol	90–145 mg/dL	Patients divided into 6 groups. Best outcomes noted in patients with glucose levels between 145 and 180 mg/dL. In all glucose groups, insulin administration was associated with increased risk of death
McAlister et al.[93]	Retrospective	291 patients, CABG	92% received IV insulin by protocol	164–209 mg/dL	Hyperglycemia on POD-1 was an independent predictor of adverse outcomes
Vriesendorp et al.[94]	Retrospective	275 patients, vascular surgery	Nonstandardized protocol	None	Postoperative infection rate correlated with hyperglycemia
Krinsley[95]	Retrospective observational	1600 patients, medical (65%)/ surgical (35%) ICU	Insulin by standardized protocol	<140 mg/dL	Lower incidence of mortality (20.9% vs 14.8%), renal dysfunction (3% vs 12%), and PRBC transfusion (20.5% vs 25.5%). No difference in infection and LOS. No benefit of hyperglycemic control if APACHE score >35
Bochicchio et al.[8]	Prospective observational	942 patients, trauma	Nonstandardized protocol	None	High (glucose > 220 mg/dL), worsening, or highly variable glucose levels associated with increased risk of infection, ICU-LOS, H-LOS, and mortality
Gale et al.[96]	Retrospective	103 patients, trauma ICU	SQ insulin by standardized protocol	<140 mg/dL	Blood glucose level >140 mg/dL was associated with increased morbidity and mortality
Schmeltz et al.[97]	Retrospective	614 patients, cardiothoracic surgery	Insulin by standardized protocol	80–110 mg/dL	Blood glucose level >200 mg/dL on admission to the ICU was associated with increased morbidity and mortality
Reed et al.[98]	Retrospective	7261 patients, trauma	Progressively stringent insulin protocol	Mean glucose decreased from 141 to 129	Decreased incidence of intraabdominal abscesses. Decreased number of days on the ventilator
Wahl et al.[99]	Prospective observational	513 patients, trauma	Insulin by standardized protocol	<140 mg/dL	Mean blood glucose levels >140 mg/dL were strongly associated with mortality but not with infection rate
Ascione et al.[100]	Retrospective	8727 patients, cardiac surgery	Insulin by standardized protocol	90–144 mg/dL	Glucose level >200 mg/dL anytime during the first 5 d was associated with increased in-hospital morbidity and mortality
Treggiari et al.[101]	Retrospective	10,456 patients, medical/ surgical	Progressively stringent insulin protocol	None 80–130 mg/dL 80–110 mg/dL	No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control
Meier et al.[102]	Retrospective	228 patients, neurotrauma	Insulin by standardized protocol	70–130 mg/dL	No difference in outcome during the first week. Decreased ICP and infection rate in the second week
Ramos et al.[103]	Retrospective	995 patients, general/ vascular surgery	Nonstandardized protocol	None	Postoperative infection rate was associated postoperative hyperglycemia
Thiele et al.[104]	Retrospective	834 neurosurgical points with SAH	Insulin by standardized protocol	<120 mg/dL	No difference in inhospital mortality

ICU = intensive care unit; LOS = length of stay; TIA = transient ischemic attack; MI = myocardial infarction; HbA1c = hemoglobin A1c; PRBC = packed red blood cells; CABG = coronary artery bypass surgery; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; ICP = intracranial pressure; SAH = subarachnoid hemorrhage; POD = postoperative day.

show an effect on in-hospital mortality.[104] In cardiac surgery patients, blood glucose levels >200 mg/dL on admission to the ICU or anytime between 1 to 5 days after the procedure were correlated with morbidity and mortality.[100] Another investigation involving 521 patients, of whom 88% were postsurgical cardiac patients, divided the cohort into 6 groups (≤79, 80–110, 111–144, 145–180, 181–200, and ≥200 mg/dL); the investigators were able to demonstrate better outcomes in those patients with glucose levels between 145 and 180 mg/dL than in those patients with higher levels.[92] Although increased postoperative blood glucose levels were associated with poor outcomes, the glucose thresholds associated with good outcomes seemed to be much higher than 110 mg/dL.[92]

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Collective analysis of retrospective studies suggests a strong association between perioperative hyperglycemia and patient outcome. However, a majority of the investigations use the term "hyperglycemia" very loosely and establish the association with poor perioperative outcomes to glucose levels that are much higher than 110 mg/dL. In addition, it remains unclear from such investigations whether correcting the hyperglycemia will improve clinical outcomes. That is, it remains poorly understood whether hyperglycemia mediates poor operative outcomes or whether it is simply an "innocent bystander," i.e., a marker of the sickest patients or those with, or predisposed to, the most underlying metabolic derangements.

Prospective Studies

Preoperative

There has been no prospective, randomized control trial that has demonstrated that controlling glucose or decreasing $HbA1_c$ to a given level, for a certain duration, before elective surgery improves the overall perioperative outcomes. Practically, anesthesiologists are unlikely to have a significant role in managing chronic perioperative hyperglycemia. However, perioperative evaluation provides a unique opportunity to screen patients for hyperglycemia. Clearly, patients presenting with very poor glycemic control, especially if exhibiting features of ketoacidosis or hyperosmolar state, should not undergo elective procedures and would benefit from aggressive stabilization before surgery. However, it is less clear whether there is any value in acutely controlling hyperglycemia in those who are chronically hyperglycemic, especially for short, minimally stressful outpatient procedures. Most of the recent randomized clinical trials have been conducted on cardiac surgery patients with the aim of controlling glucose levels or administering insulin intraoperatively and/or postoperatively (Table 2).[115]

Intraoperative

In the contemporary noncardiac surgical literature, prospective, randomized, controlled data investigating the efficacy of intraoperative IGC are lacking. A recent trial of 236 patients undergoing vascular surgery showed a decrease in major cardiovascular events when glucose was maintained between 100 and 150 mg/dL with continuous insulin infusion.[120] However, the trial had to be terminated early for logistical reasons and was underpowered.[121] A trial of 78 patients involving aneurysm clipping after acute subarachnoid hemorrhage did not show a mortality benefit of IGC.[117] Notably, the brain is particularly sensitive to hypoglycemia, with evidence that glucose levels both <80 mg/dL and >170 mg/dL can be harmful.[122] Larger, well-designed trials are required to confirm the therapeutic benefit of IGC intraoperatively in neurosurgical and other noncardiac surgery patients.

Insulin in combination with glucose (and potassium) has been used for myocardial protection in patients presenting with myocardial ischemia or infarction[123] and has also been tested with variable success for decades during cardiac surgery. Most of the earlier trials did not control for glucose levels; however, some recent studies have adopted an IGC approach. A decrease in inflammatory markers (IL-6, IL-8, and TNF-α) has been shown with high-dose insulin treatment (approximately 21 U/h for a 70-kg person or 5 $mU \cdot kg^{-1} \cdot min^{-1}$) while maintaining glucose between 80 and 110 mg/dL with exogenous dextrose.[124] Other reports have shown increased phagocytic capacity[110] or improved myocardial function with intraoperative insulin use.[113] However, no difference was noted in clinical outcomes. Larger studies by Rao et al.[111] (1127 patients receiving insulin during cardioplegia) and Butterworth et al.[112] (381 patients) were unable to show any difference in myocardial injury and/or low cardiac output states or neurologic complications, respectively.

There is only one study that has assessed the value of intraoperative IGC prospectively.[107] Four hundred cardiac surgery patients were randomly assigned to receive either continuous insulin infusion to maintain glucose levels between 80 and 100 mg/dL or conventional treatment to treat glucose levels >200 mg/dL. Postoperatively, both the treatment group and the control group received insulin to maintain normoglycemia after surgery. No significant difference was noted in the composite outcomes (death, sternal wound infection, prolonged infection, cardiac arrhythmias, stroke, and renal failure) between the treatment (44%) and conventional (46%) groups. ICU and hospital length of stay were also not significantly different. Importantly, more deaths (4 vs 0) and strokes (8 vs 1) were actually noted in the IGC group. Although it is a single-center study with low frequency of mortality and inability to differentiate between diabetics and nondiabetics, the study questions the utility of intensive intraoperative glycemic control in patients undergoing surgery.

Postoperative

The strongest support for IGC therapy comes from a single-center study of 1548 mechanically ventilated patients (predominantly cardiac surgical ICU patients) by van den Berghe.[114] It was a prospective, randomized, controlled trial. The treatment group received IGC by IV infusion for the duration of the ICU stay, whereas in the control group, plasma glucose was treated only if >215 mg/dL and was maintained in a conservative range of 180 to 210 mg/dL. During the trial, the mean morning blood glucose in the 2 IGC and control groups was 103 and 153 mg/dL, respectively. The authors demonstrated a significant decrease in ICU mortality, renal dysfunction, need for dialysis, and neuropathic changes in the IGC group. However, caregivers were not blinded to therapy, all

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Table 2. Prospective Studies

Study	Study type	Number of patients	Study design	Glycemic goal or range	Salient findings
Intraoperative					
Rassias et al.[110]	RCT	30 patients, CABG	Insulin by standardized protocol	75–125 mg/dL	Increased total neutrophil phagocytic capacity in insulin treatment group
Rao et al.[111]	RCT	1127 patients, CABG	Insulin during cardioplegia	None	No difference in myocardial injury and/or low cardiac output syndromes between treatment and control groups
Butterworth et al.[112]	Prospective	381 patients, CABG	Insulin by standardized protocol	<100 mg/dL	No difference in short- and long-term neurological complications between the groups
Koskenkari et al.[113]	RCT	40 patients, CABG + AVR	Insulin by standardized protocol	108–180 mg/dL	Improved myocardial contractile function and decreased inotropic support. No difference in clinical outcomes
Gandhi et al.[107]	RCT	400 patients, CABG	Intraoperative insulin by standardized protocol	80–100 mg/dL	No difference in composite outcomes. Increased number of deaths (4 vs 0) and stroke (8 vs 1) in the intensive insulin group
Postoperative					
van den Berghe et al.[114]	RCT	1548 patients, surgical ICU	Intensive insulin by standardized protocol	<110 mg/dL	Significant difference in morbidity and mortality, in patients who stayed >5 d. No difference in mortality in patients who stayed <5 d (1.7% vs 1.8%)
Grey and Perdrizet[115]	RCT	61 patients, general surgery	Intensive insulin by standardized protocol	80–120 mg/dL	Decrease in nosocomial infection rate
Hoedemaekers et al.[116]	RCT	20 patients, postcardiac surgery	Insulin by standardized protocol	80–110 mg/dL	No difference in outcomes between treatment groups (PRBC transfusion, time on ventilator, ICU-LOS, or renal dysfunction). No difference in IL-10, and IL-6 levels between treatment groups
Bilotta et al.[117]	RCT	78 patients, aneurysm clipping/ neurosurgery	Insulin by standardized protocol	80–120 mg/dL	Infection rate was lower in treatment group. No difference in postoperative vasospasm, neurologic outcome, and mortality rates
Bilotta et al.[118]	RCT	97 patients, traumatic brain injury requiring surgery	Insulin by standardized protocol	80–120 mg/dL	Decreased length of ICU stay. No difference in infection rate and mortality
Bilotta et al.[119]	RCT	483 patients, neurosurgery	Insulin by standardized protocol	80–110 mg/dL	Decreased length of ICU stay and infection rate. No difference in mortality and Glasgow outcome scale at 6 mo
Finfer et al.[11]	RCT	6104 patients, medical/ surgical ICU	Insulin by standardized protocol	81–108 mg/dL	Increased mortality in IGC group. No difference in number of days in the ICU, hospital, on mechanical ventilation, or renal replacement therapy
Subramaniam et al.[120]	RCT (unblinded)	236 patients, vascular surgery	Continuous insulin infusion versus SQ, started intraoperatively and continued 48 h	100–150 mg/dL	Decreased major cardiovascular events in patients who received continuous insulin infusion

ICU = intensive care unit; LOS = length of stay; PRBC = packed red blood cells; CABG = coronary artery bypass surgery; AVR = aortic valve replacement; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; IL-6 = interleukin 6; IL-10 = interleukin 10; IGC = intensive glucose control; RCT = randomized controlled trial.

patients had received a significant amount of exogenous glucose (>160 g/d) and enteral/parenteral nutrition, and there was also an unusually high mortality in the control group, based on disease severity.[125] These results were initially supported by other observational studies.[95] A meta-analysis of 35 randomized, controlled trials in critically ill hospitalized patients showed significant benefit of insulin therapy.[126] Of the 35 trials included in this meta-analysis, 14 trials involved postoperative patients, and 11 of these 14 trials used glucose-insulin-potassium infusions. Another meta-analysis involving 14 trials in surgical patients showed some benefit of perioperative insulin infusion on mortality (risk ratio [RR], 0.69; confidence interval [CI], 0.51–0.94).[127] No data from medical ICUs were included in either of these meta-analyses.

Collectively, the results from the study by van den Berghe in predominantly surgical patients, in conjunction with other retrospective cardiac surgery studies, were quickly extrapolated to imply that IGC is

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strongly effective in critically ill postsurgical patients. However, subsequent randomized trials by the same group and others have not been able to replicate the improved outcomes in other ICU settings.[116–118,128,129] Van den Berghe's own group showed no mortality benefit using the same protocol in the medical ICU, although in-hospital mortality was reduced in those patients who stayed in the ICU for at least 3 days.[130] The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis and the Glucontrol trials conducted in mixed medical/surgical patients, the former involving solely those with sepsis, were not able to show significant benefit of IGC.[128,131] Of the patients enrolled in the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial, 52% underwent at least one elective or emergent surgical procedure. Another recent trial in postoperative neurosurgical patients showed decreased length of hospital stay and infection rate but no difference in overall survival or neurologic outcomes at 6 months postoperatively.[119]

Recently, the results of the much-awaited landmark Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial have become available.[11] This was a multicenter, multinational, randomized, nonblinded trial conducted in a mixed medical/surgical population of 6104 patients, of whom 35% were admitted to the ICU after emergent or elective surgery. IGC (glucose 81–108 mg/dL) was compared with conventional glycemic control (144–180 mg/dL). No difference was noted in 90-day mortality, number of days in the hospital, number of days in the ICU, days on mechanical ventilation, and need for renal replacement therapy between the groups. Unlike the study by van den Berghe, higher mortality was actually noted in the IGC group (27.5%) versus the conventional treatment group (24.9%) (OR for IGC = 1.14, CI 1.02–1.28, P = 0.02). On subgroup analysis, no significant difference was noted in the surgical population. Furthermore, a 13 times higher incidence of severe hypoglycemia (<40 mg/dL) was noted in the IGC group. The authors have not yet disclosed the relationship between hypoglycemia in NICE-SUGAR and mortality. The negative results of a recent meta-analysis,[132] other trials,[119,128,129] and now the NICE-SUGAR[11] study clearly bring into question the utility of IGC in ICU patients.

A meta-analysis involving 34 trials in both medical and surgical intensive care patients did show a benefit of IGC in decreasing the risk for sepsis, especially in the surgical population. In contrast to the previous meta-analyses,[126,127] however, it was not able to show a clear benefit of IGC on in-hospital mortality (21.6% vs 23.3%; RR, 0.93; 95% CI, 0.85–1.03). There was also no significant difference in mortality when patients were stratified by glucose goal or ICU setting ([1] surgical: 8.8% vs 10.8%; RR, 0.88; 95% CI, 0.63–1.22; [2] medical: 26.9% vs 29.7%; RR, 0.92; 95% CI, 0.82–1.04; or [3] medical-surgical: 26.1% vs 27.0%; RR, 0.95; 95% CI, 0.80–1.13). The meta-analysis confirmed a 5-fold increase in the incidence of significant hypoglycemia (glucose ≤40 mg/dL; 13.7% vs 2.5%; RR, 5.13; 95% CI, 4.09–6.43).[132] A meta-analysis of 26 trials, which included the NICE-SUGAR study data, did not show a significant benefit of IGC (RR, 0.93; CI, 0.83–1.04), and the incidence of hypoglycemia was 6-fold higher.[133] However the study did show an improvement in surgical ICU patients (RR, 0.63; CI, 0.44–0.91).

In summary, the association between perioperative hyperglycemia and poor outcomes is strong. However, the value of IGC preoperatively has not been tested prospectively and has not been proven intraoperatively and postoperatively. Therefore, IGC cannot be advocated for perioperative patients at the present time.[134]

HYPOGLYCEMIA

Low glucose levels initiate a compensatory stress response and a typical set of symptoms. However, in the perioperative period and during critical illness, the signs of hypoglycemia may be masked, the compensatory response may be blunted, and the affected patients may be incapable of communicating the symptoms. The ischemic brain reverts to anaerobic metabolism and lactate production and is dependent on lactate for its source of energy. Decreasing glucose levels rapidly and acutely may decrease the lactate supply to the ischemic brain and potentially exacerbate brain injury.[135] Moreover, unrecognized hypoglycemia can have deleterious consequences and has been associated with increased mortality.[136,137]

Hypoglycemia may be a complication of aggressively and rapidly treating hyperglycemia, especially if tight glucose control is desired. The incidence of severe hypoglycemia (defined as <40 mg/dL), in various ICU studies, ranges from 5.1% to 25.3% of patients in IGC groups and is between 3 and 13 times more common in patients in the intensive control arms of these trials.[47,94,114,128,130,132,136] A higher incidence of mortality in ICU patients who develop hypoglycemia has also been reported.[138] It is not known whether the higher mortality noted is related to increased levels of insulin (which can lead to sympathetic discharge, sodium retention, and various mitogenic actions) or to hypoglycemia.[139] One recent report from the cardiac literature suggests that hypoglycemia after insulin therapy carries with it no subsequent effect on post-myocardial infarction mortality, whereas the same was not true for spontaneous hypoglycemia, likely reflecting underlying comorbidities.[140] In addition, there is some inherent variability in the point-of-care monitoring techniques that are currently in use.[141] Significantly low blood glucose levels may develop without the practitioners realizing the severity of the hypoglycemia.[141,142] Continuous glucose monitors may improve hyperglycemia detection and facilitate more intensive glucose lowering. However, more rigorous data are required before their use can be advocated.

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Certain patients may be more prone to hypoglycemia, and special attention and modifications to the insulin protocol may be warranted. Independent risk factors include female gender, sepsis, history of diabetes, interrupted or reduced nutritional support without adjustment of insulin dose, continuous venovenous hemofiltration, especially with bicarbonate-based substitution fluid, and need for inotropic support.[109] Patients with significant hepatic, renal, or adrenal insufficiency are prone to hypoglycemia, irrespective of intensive insulin therapy. Insulin, when improperly used, is dangerous, has the highest rate of errors,[143] and is considered 1 of the 5 most common drugs associated with medication errors of clinical significance.[144]

AREAS OF UNCERTAINTY

It is becoming increasingly clear that the ideal glucose levels <110 mg/dL that were advocated for critically ill patients and were quickly extrapolated to the perioperative period may have been too rigorous and are not strongly substantiated in multicenter clinical trials. However, this does not imply that glucose control should be totally abandoned and that any hyperglycemic levels are acceptable.[139] Moreover, many questions remain unanswered.

First, the ideal intraoperative and postoperative glycemic target is unknown. Whether clinicians should use mean glucose levels or absolute peak glucose levels as markers of glycemic control is also poorly understood. Some investigators have shown a good correlation of outcomes with decreased glycemic variability, which may be more important than maintaining the blood glucose within a certain range.[145–148] Glucose fluctuations may trigger adverse physiologic events (increased apoptosis, cytokine expression, and oxidative stress) beyond those sustained from chronic hyperglycemia.[4]

Second, if used, the ideal duration of more intensive insulin therapy and glycemic control is also unknown.[149] In cardiac surgery, investigators have used a multitude of different protocols for variable durations. The Portland protocol adopted in the study by Furnary et al.[90] advocates at least 3 days of IV insulin therapy during and after surgery. The ICU protocols typically treat patients only for the duration of ICU stay. Once the patients are transferred to the floor, protocols for glucose monitoring are less stringent, and episodes of hypoglycemia may be missed.[4]

Third, there has been less vigorous discussion of the risk/benefit ratio of IGC interventions. Egi et al.[150] studied patients from their large prospective database who were closely matched to the control patients in the van den Berghe surgical ICU population and calculated the number of patients who would need to be treated with IGC to save one life (number needed to treat [NNT]) and to cause harm (number needed to harm [NNH]). NNT varied between 38 and 125, whereas NNH varied from 7 to 13 between institutions. In the NICE-SUGAR study, which predominantly enrolled patients in Australia and New Zealand, a 3.6% increase in mortality rate was noted in the IGC group.[11] Even in the patients studied by Van den Berghe, the NNT was very similar to NNH.[151] Although the potential benefits and potential harm may not be equivalent, such analyses suggest that the beneficial effects of IGC may not be universal, may come at some cost, and can vary significantly among populations and institutions. That is, the NNH might be lower than the NNT in certain cohorts; hence, harm could occur more frequently than benefit. One should also realize that there is significant variation in perioperative outcomes in different regions of the world. Although significant hyperglycemia should be addressed, the aggressiveness of IGC and the need for intensive insulin therapy may ultimately be determined by local practices and the overall morbidity and mortality of the selected patient population.

Fourth, lack of evidence for tight glycemic control may not be a function of glycemic control per se, but may be related to limitation in the glucose monitoring and management technologies.[4] Current commercially available technology does not enable us to consistently achieve IGC without overshooting glycemic goals (with potential detrimental consequences such as significant hypoglycemia). Improvement in glucose monitoring technology and insulin delivery devices in the future may allow smoother achievement of IGC and improved outcomes, without the current incidence of 3 to 6 times higher hypoglycemic episodes.

Finally, the investigations and discussions have centered predominantly on "hyperglycemia" and not necessarily on "patients with diabetes." The value of short-term tight glycemic control in patients with diabetes has not been proven,[152] and IGC seems to be less effective in critically ill patients with diabetes than in patients without diabetes.[57,58,153,154] In patients with diabetes, intraoperative hyperglycemia does not seem to influence postoperative cognitive dysfunction,[7] and higher glucose levels may not be as deleterious as in patients without diabetes. This may be related to the chronic adaptive changes to hyperglycemia in patients with diabetes.[155] Thus, it is difficult to advocate the same glucose threshold for patients with diabetes as for patients without diabetes. There is a clear difference in the management of patients with Type 1 versus Type 2 diabetes and especially patients who receive insulin (because of Type 1 or advanced Type 2 diabetes). Patients with Type 1 diabetes are prone to ketosis and will require a basal level of insulin throughout the perioperative period either via long-acting insulin or insulin infusion. The value of IGC in patients with Type 1 diabetes in the perioperative period has not been specifically addressed in any of the trials.

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PRACTICAL MANAGEMENT OF PERIOPERATIVE HYPERGLYCEMIA

Glucose Measurement and Monitoring

Ideally, blood glucose should be determined by the central laboratory or onsite blood-gas analyzers; as a rule, point-of-care capillary meters are less reliable, especially in hypoperfused, hypothermic, or anemic patients. The practitioners should keep in mind that the accuracy varies with each modality and some error is allowed when accuracy of these devices is tested.[156,157] The National Committee for Clinical Laboratory Standards recommends the difference between a glucose meter and a conventional laboratory meter not exceed ±15% for glucose concentrations <100 mg/dL and ±20% for glucose concentrations >100 mg/dL.[156] Although not typically considered, such errors may be significant when trying to establish tight glycemic control. The actual concentration of glucose (amount of glucose per volume of specimen) differs significantly between plasma and whole blood[158] because glucose dissolves in the aqueous but not the solid components of the specimen. The plasma glucose concentration is approximately 11% higher than that in whole blood.[159] The majority of bedside/home glucose meters actually convert their whole blood glucose results to the higher plasma equivalents by a multiplying factor of approximately 1.12 depending on the meter.

Glucose levels in arterial blood are higher than in the venous or capillary blood (because glucose has not yet been extracted by the tissues). Furthermore, the hemodynamic state of a patient may also affect the accuracy of the blood glucose measurement by the point-of-care devices.[160–163] In hemodynamically stable patients, point-of-care measurements correlate well with laboratory reference values. However, in patients with poor peripheral perfusion and shock, there is significant variation between laboratory reference values and point-of care measurements. A recent study showed that 15% of the capillary blood glucose values differed by >20% from the laboratory reference value in hemodynamically compromised patients.[164] Therefore, there is a real possibility of overdosing or underdosing a critically ill patient with insulin.[141,165] Other factors, such as variation in sample volume, may also affect point-of-care measurements. Excess sample volume can result in spuriously high levels, whereas too small a sample volume may result in low glucose levels. Worsening anemia may result in spuriously high levels of glucose (because of increased volume of plasma). Some medications and conditions also may interfere with glucose measurements. These include L-dopa, dopamine, mannitol, acetaminophen, severe unconjugated bilirubin, severe hyperlipidemia, increased uric acid, maltose (present in immunoglobin solution), and icodextrin (present in peritoneal dialysis fluid).[166]

In view of the variations between point-of-care devices, it is important that care providers know whether the device in their hospital reports true whole blood glucose or converts to plasma glucose. In addition, individual institutions should specify blood glucose targets based on the institutional methodology of glucose testing and use devices approved by the Food and Drug Administration. It is imperative that in any circumstance in which there is a discrepancy between the measured glucose level and a patient's clinical condition, that the glucose concentration be confirmed by central laboratory measurement.

Insulin Protocols for Perioperative Glycemic Control

In view of the complex nature of glycemic control in the perioperative period, maintaining glucose levels within a specific range is resource intensive.[167] By some estimates, each point-of-care glucose measurement adds 3.5 to 9 minutes to patient care.[168] Aggregate time spent by the caregivers to monitor glucose and achieve target glucose levels safely may be substantial. The narrower the desired glycemic range, the more resource intensive the protocol will be. Many protocols have been tried and advocated, and many institutions have established their own regimens. Discussion of each protocol is beyond the scope of this review.[149] Subcutaneous insulin administration is not recommended in the intraoperative and immediate perioperative periods and in critically ill postoperative patients because there is a significant variation in skin perfusion and, therefore, absorption. In addition, the onset of action for subcutaneously administered insulin, even the rapid-acting analogs, may be too sluggish for this setting.[164] Most study protocols that have achieved desirable glycemic control (regardless of therapeutic benefit) in acute care settings have used continuous IV insulin infusion combined with IV bolus injections. Targeted glucose levels can be achieved successfully and in a timely manner using these dynamic scale protocols, considering the rate of change in blood glucose levels, combined with frequent blood glucose determinations.

Perioperative Glycemic Goals

The National Health and Nutritional Examination Survey data suggest that 30% to 40% of the population has impaired glycemic control and can be classified as having either diabetes or prediabetes.[169] Thus, a significant proportion of patients presenting for perioperative evaluation are likely to have unrecognized impaired glycemic control and are also more likely to develop intraoperative and postoperative hyperglycemia. Perioperative physicians recognize the multisystem impact of diabetes (chronic hyperglycemia) and its relationship to poor perioperative outcomes. Modification of oral hypoglycemic and insulin regimens is an integral component of the perioperative preparation of patients diagnosed with diabetes. However, the preoperative visit also provides a unique opportunity

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Table 3. Recommendations for Glycemic Control in the Perioperative Period

Location	American College of Endocrinology[171]	Canadian Diabetes Association[172]	American Diabetes Association[171]	American Heart Association/ American College of Cardiology[a][173]	Society of Thoracic Surgeons (for cardiac surgery)[174]
Intensive care unit	Between 140 and 180 mg/dL; generally <180 mg/dL	<110mg/dL	Between 140 and 180 mg/dL; generally <180 mg/dL	110–180 mg/dL	Generally; <180 mg/dL ventilator dependent in ICU >3 d; <150 mg/dL
Intraoperative	<150 mg/dL	90–180 mg/dL	<150 mg/dL		<180 mg/dL
Perioperative	<140 mg/dL premeal or <180 mg/dL (random)	90–180 mg/dL	<140 mg/dL premeal or <180 mg/dL (random)	NA	<180 mg/dL

NA= not addressed specifically; ICU = intensive care unit.

[a] Guidelines were based on earlier studies and older recommendations from the American College of Endocrinology and the American Diabetes Association.

to screen for diabetes and prediabetes in specific risk groups. The ADA recommends that the following individuals be screened for diabetes: patients who are older than 45 years; patients who have a body mass index >25 kg/m^2 and have the following additional risk factors: first-degree relatives with diabetes, women with gestational diabetes or history of delivering a baby >4.1 kg, hypertension, history of cardiovascular disease, high-density lipoprotein cholesterol <35 mg/dL or triglycerides >250 mg/dL, women with polycystic ovarian syndrome, or physical inactivity.[3]

Preoperative measurement of $HbA1_C$ is used as a marker for long-term glycemic control and may identify patients with chronic hyperglycemia. However, practitioners should recognize that it is not currently endorsed by the ADA, American College of Endocrinology, or the World Health Organization to diagnose diabetes. Some have suggested that high $HbA1_C$ (>6%) should lead to more formal evaluation for diabetes. No prospective study has shown that decreasing $HbA1_C$ preoperatively to a certain level will improve outcomes. The effect of acute glycemic control preoperatively (<100 mg/dL) is unknown and unlikely to be advocated based on current evidence. However, it is hoped that identifying patients with impaired glycemic control can lead to their early medical management and improved long-term outcomes.[170]

Elective surgery should be avoided in the presence of ketoacidosis or a hyperglycemic hyperosmolar state. Although a fasting glucose level >100 mg/dL is considered abnormal in the nonoperative setting, as discussed earlier, it has been difficult to assign a specific glucose level that should trigger treatment in the perioperative period. There is a significant heterogeneity in recommendations that have been proposed by various organizations, which include the American College of Endocrinology, Canadian Diabetes Association, ADA, American Heart Association, and the Society of Thoracic Surgeons (Table 3).[172–176] In light of the recent data, older recommendations by the American College of Endocrinology and the ADA have been revised.[171] A general theme that emerges in these guidelines is to at least maintain glucose levels <180 mg/dL perioperatively. Although it is recommended to maintain a glucose level of <150 mg/dL in cardiac surgery patients with a complicated ICU course, it should be recognized that the recommendation is not based on a high level of evidence.[174] Similarly, the authors believe that in the intraoperative period, there is no evidence to compel IGC. Maintaining glucose levels to <180 mg/dL intraoperatively is a reasonable goal in most situations. This would potentially decrease the probability of hypoglycemia. Furthermore, in view of recent negative studies and 5-fold increased probability of severe hypoglycemia, IGC (<110 mg/dL) in critically ill postoperative patients cannot be advocated.

The Surgical Care Improvement Project has adopted a new measure that requires glucose levels to be <200 mg/dL by 6:00 AM of the second postoperative day in cardiac surgical patients.[177] Although it is possible to institute protocols for glucose control that can be followed by nurses without much physician input, the practice can be significantly resource intensive. Necessary resources should be allocated to achieve the goals safely.

CONCLUSION

Perturbations in glycemic control after intermediate- to high-risk surgery are dependent on many factors and can lead to increased glucose levels perioperatively. A patient's perioperative metabolic state, intraoperative anesthetic management, exogenous glucose administration, endogenous glucose production and utilization, neuroendocrine response, development of acute insulin resistance, and variations in endogenous insulin secretion all determine the absolute perioperative glucose level. Irrespective of the cause, hyperglycemia is associated with poor perioperative outcomes, but

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whether correction of hyperglycemia reduces surgical morbidity and mortality is not entirely clear. Moreover, neither a universally appropriate therapeutic glycemic target nor the true efficacy of perioperative glycemic control has been fully determined. Although a number of studies to assess this question have been conducted (especially in the postoperative period), significant heterogeneity in patient populations, glucose targets, and measurement protocols for glucose still leave many questions unanswered. To answer some of the lingering questions pertaining to IGC, several trials are currently underway.[178–181] The efficacy of perioperative IGC (<110 mg/dL) is unproven, as underscored by several recent negative trials, and it increases the risk for hypoglycemia by 3- to 6-fold, which is not inconsequential in critically ill patients. IGC is also resource intensive. Although the potential benefits and harm of IGC may not be equivalent, such analyses suggest that the beneficial effects of IGC may not be universal and can vary significantly among populations and institutions. Currently, it is not advisable to abandon glucose control altogether and until further specific data are accumulated, it is prudent to maintain glucose levels <180 mg/dL in the perioperative period. Insulin therapy should preferably be administered IV in the perioperative period and should always be accompanied by close glucose monitoring. Improvement in glucose monitoring technology and insulin delivery devices in the future may allow better-controlled achievement of IGC with improved outcomes in specific patient populations.

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