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Review article

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# Perioperative insulin therapy

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**Abstract**

Surgical patients commonly develop hyperglycemia secondary to the neuroendocrine stress response. Insulin treatment of hyperglycemia is required to overcome the perioperative catabolic state and acute insulin resistance. Besides its metabolic actions on glucose metabolism, insulin also displays nonmetabolic physiological effects. Preoperative glycemic assessment, maintenance of normoglycemia, and avoidance of glucose variability are paramount to optimize surgical outcomes. This review discusses the basic physiology and effects of insulin as well as practical issues pertaining to its management during the perioperative period.

**Keywords:** blood glucose, diabetes mellitus, hyperglycemia, insulins, perioperative care

Hyperglycemia is associated with adverse outcomes in surgical and critically ill patients. Unfortunately, perioperative physicians often underestimate the neuroendocrine stress response in surgical patients and, as a result, overlook the importance of blood glucose management. Insulin constitutes the most reliable hypoglycemic agent for the perioperative period. This review provides an overview of the basic physiology and effects of insulin as well as practical issues pertaining to its perioperative use.

## Physiology of insulin: synthesis and secretion

Insulin is a peptide hormone synthetized and secreted by β-cells of pancreatic islets of Langerhans. It promotes glucose homeostasis by facilitating cellular glucose uptake and by regulating carbohydrate, lipid, and protein metabolism.

Initially, synthetized as preproinsulin, the prohormone is first processed to proinsulin and subsequently converted to insulin and C-peptide, which are both stored in secretory granules and released into the circulation in equimolar amounts [1, 2].

Secretion of insulin is controlled by both nutrient and non-nutrient factors [1, 3]. Inside β-cells, glucokinase phosphorylates glucose to glucose-6-phosphate, thereby generating a significant amount of adenosine triphosphate (ATP). Consequently, closure of $K^+$-ATP-dependent channels, membrane depolarization, opening of voltage-dependent calcium channels, and exocytosis of insulin-containing granules occur. The uptake of cationic amino acids, L-arginine and L-ornithine, into the β-cells results in membrane depolarization, thereby causing activation of voltage-dependent calcium channels and enhancing insulin release. Other mechanisms of insulin secretion are regulated by non-nutrient mediators. Peptide hormones such as vasoactive intestinal peptide (VIP), glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) activate adenylyl

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cyclase activity and protein kinase A. In the cholinergic pathway, acetylcholine stimulates phospholipases and protein kinase C.

Inhibition of insulin release is mediated by several mediators such as somatostatin, galanin, prostaglandins, and catecholamines (through the α2-adrenergic pathway) and involves activation of G proteins [3, 4].

Pancreatic β-cells secrete approximately 0.4–1.0 international units (IU) of insulin/kg/day in healthy adults and 0.5–0.7 IU/kg/day in patients with insulin-sensitive diabetes [5, 6]. The basal insulin secretion accounts for approximately 50% of the total daily insulin production [7]. Thus, the basal rates of insulin secretion range from 0.4 to 0.7 IU/h [8]. These rates are sufficient for insulin-dependent cellular uptake of glucose and the maintenance of normal fasting blood glucose levels by limiting gluconeogenesis and preventing uncontrolled hydrolysis of triglycerides.

## Actions of insulin

Insulin plays an essential role in the transport of glucose into insulin-dependent cells such as myocytes and adipocytes. Insulin binds its receptors and thereby activates tyrosine kinase activity and phosphorylation of insulin-responsive substrates (IRSs). In turn, the phosphorylated IRS proteins bind to signaling molecules, such as phosphatidylinositol-3 kinase (PI-3 kinase). The latter promotes translation of glucose transporters (GLUTs) to the cell membrane resulting in antilipolysis and synthesis of glycogen, lipid, and protein [3, 8–10].

Anti-inflammatory, antioxidant, antithrombotic, antiatherosclerotic [11], and antiapoptotic effects of insulin have been documented [12–14]. Insulin produces its nonmetabolic action by binding to insulin receptors in endothelial cells, platelet, lymphocytes, macrophages, and monocytes. Inside vascular endothelial cells and platelets, insulin stimulates nitric oxide synthase and enhances nitric oxide production via the PI-3 kinase pathway, thereby causing vasodilation and inhibiting platelet aggregation. Through the mitogen-activated protein kinase (MAPK) pathway, insulin can also suppress several proinflammatory transcription factors and decrease the expression of endotoxin-mediated inflammatory mediators [15].

## Insulin therapy

Human insulin and insulin analogs can be used to manage hyperglycemia. Structurally, synthetic human insulin is identical to its natural endogenous counterpart. Insulin analogs have been developed by modifying the amino acid sequence of the insulin molecule. Differences between human insulin and insulin analogs are inconsequential for the management of type 1 and type 2 diabetes as well as diabetic ketoacidosis (DKA) [16, 17].

Insulins are classified according to their pharmacokinetic profiles (**Table 1**). Long-acting analogs are commonly used as basal agents to mimic endogenous insulin, which is physiologically secreted to control blood glucose levels during periods of fasting. By contrast, rapid- and short-acting preparations are intermittently administered to prevent or treat postprandial and stress-induced hyperglycemia. Alternately, continuous subcutaneous and intravenous infusions of rapid- and short-acting insulin also provide a basal insulin regimen; moreover, they can be adjusted in response to a specific blood glucose concentration.

**Table 1.** Pharmacokinetics, role of treatment, and dosing of insulin preparations [18–21]

| Insulin type | Onset | Peak | Effective duration | Role of treatment | Dosing |
|---|---|---|---|---|---|
| Rapid acting | 5–15 min | 30–90 min | 2–5 h | Bolus | Postprandial |
| Aspart (NovoRapid) | 5–15 min | 30–90 min | 2–5 h | Bolus | Postprandial |
| Lispro (Humalog) | | | | | |
| Short acting | 30–60 min | 2–3 h | 5–8 h | Bolus | Postprandial |
| Regular (Humulin R) | | | | | |
| Intermediate acting | 1–2 h | 4–10 h | 10–16 h | Basal | Twice daily |
| NPH (Humulin N) | 1–2 h | 4–12 h | 12–18 h | Basal | Twice daily |
| Lente (Monotard) | | | | | |
| Long acting | 2–3 h | 4–8 h | 8–24 h | Basal | Twice daily |
| Ultralente (Humulin U) | 2–4 h | No peak | 20–24 h | Basal | Once daily |
| Glargine (Lantus) | 3–4 h | 6–8 h | Up to 20–24 h | Basal | Once/twice daily |
| Detemir (Levemir) | 30–90 min | No peak | Up to 42 h | Basal | Once daily |
| Degludec | | | | | |

Onset varies significantly according to injection site. Duration of long-acting analogs is dose dependent [22].
NPH, neutral protamine Hagedorn insulin

## Route of delivery

Endogenous insulin is released from pancreatic β-cells into the portal venous system; subsequently, approximately 60% undergoes hepatic extraction. Therefore, the insulin concentration in the portal veins can be 3 times higher than that in the peripheral circulation. When exogenous insulin is parenterally administered, it distributes throughout the circulation thus resulting in a high level peripherally, but a low concentration in the liver [23]. This relative insulin deficiency in the portal circulation attenuates hepatic glycogenolysis and gluconeogenesis during fasting and compromises suppression of glucagon secretion in the fed state.

Subcutaneous administration of rapid-acting insulin has been shown to provide similar glycemic control as intravenous infusion of regular insulin [24–26]. The accumulation of repeated doses of subcutaneous insulin can be a concern: therefore, additional doses should not be administered until after the time-to-peak effect [27]. Although the subcutaneous basal–bolus insulin regimen constitutes the preferred method for maintaining target glycemia in hospitalized, noncritically ill patients, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) and American Diabetes Association (ADA) recommend the intravenous infusion of regular insulin in critically ill patients and those undergoing major surgical procedures [28, 29].

Regular insulin administered intravenously displays a faster onset and shorter duration of action compared with that given subcutaneously and intramuscularly [30, 31]. A bolus dose of intravenous insulin lowers the blood glucose within minutes with the maximum effect occurring after 20–30 min. Because the plasmatic half-life of insulin is about 4–6 min and the hypoglycemic effect lasts only about 1 h, a continuous intravenous infusion is required to maintain a basal insulin level [32].

## Perioperative insulin dosing

The effective dose of insulin depends on the extent of the patient's insulin resistance and the target blood glucose. Insulin sensitivity is reflected by the patient's total daily dose and is predicted by plasma HbA1c level [33]. Target blood glucose levels are listed in diabetes management guidelines disseminated by various organizations (**Table 2**).

For a basal–bolus insulin regimen, the calculated total daily dose of insulin ranges between 0.2 and 0.5 IU/kg based on the patient's age, renal function, and blood glucose concentration [34]. This calculated dose is equally partitioned into basal and prandial components [7].

**Table 2.** Recommendations for glycemic control during perioperative period

| | Perioperative care | Intensive care |
|---|---|---|
| ADA (2017) [28] | 80–180 mg/dL | 140–180 mg/dL with insulin therapy, generally <180 mg/dL |
| AACE/ACE (2015) [29] | <140 mg/dL for premeal glucose<br><180 mg/dL for random glucose | 140–180 mg/dL |
| AAGBI (2015) [38] | 108–180 mg/dL | Not available |
| CDA (2013) [73] | 90–144 mg/dL for premeal glucose<br><180 mg/dL for random glucose | 144–180 mg/dL |
| JBDS (2012) [74] | 108–180 mg/dL<br>72–216 mg/dL is acceptable | Not available |
| SAMBA (2010) [27] | 90–130 mg/dL for premeal glucose<br><180 mg/dL for random glucose | Not available |

AACE/ACE, The American Association of Clinical Endocrinologists/American College of Endocrinology; AAGBI, The Association of Anaesthetists of Great Britain & Ireland; ADA, The American Diabetes Association; CDA, The Canadian Diabetes Association; JBDS, The Joint British Diabetes Society; SAMBA, The Society of Ambulatory Anesthesia

For supplemental insulin, the initial bolus dose of regular insulin ranges between 2 and 10 IU [34] or is based on the "rule of 1500" for surgical patients. The latter strategy divides 1500 by the total daily insulin dose. The result predicts the expected decrease in glycemia with 1 unit of insulin [27].

For continuous regimens, the insulin starts at 1–2 IU/h, which mimics basal endogenous secretion [3]. Insulin is administered simultaneously with a continuous infusion of dextrose (2 g/kg/day) [35–37]. Blood glucose should be checked before the infusion and monitored hourly (or more frequently if the results fall out of the target range) [38]. Both insulin and dextrose rates are titrated to maintain normoglycemia and reduce glycemic variability.

Insulin is considered 1 of the top 5 high-alert medications [39]. Errors in insulin prescribing and administration can be high because of the prevalence of insulin use and its narrow therapeutic index. Insulin orders written with abbreviations such as "u", "iu", and "U" have been misinterpreted as "0" or "10" and have caused from 10 to 100 times dosing errors [40]. Preparation of insulin with normal syringes potentially generates confusion and results in 10-fold overdose errors [41]. Thus, only insulin syringes should be employed.

## Perioperative benefits of insulin

Surgery, anesthesia, acute illness, and fasting constitute stressors, which lead to metabolic perturbation. Perioperative hyperglycemia is associated with the stress-induced release of counter-regulatory hormones and proinflammatory cytokines, which, in turn, result in increased endogenous glucose production [42] and a state of impaired insulin sensitivity. This transient insulin resistance, the so-called "diabetes of injury" [43], is most pronounced on the first postoperative day and may persist for days or weeks after surgery depending on the anatomic location and invasiveness of the intervention [44, 45]. These metabolic derangements contribute to hyperglycemia in both diabetic and nondiabetic patients. Significant amounts of insulin are required to overcome this state of insulin resistance and hyperglycemia. Concurrent administration of high doses of insulin together with dextrose to achieve normoglycemia provides significant benefits stemming from insulin's metabolic and nonmetabolic properties [36, 46].

The cardioprotective effect of insulin can improve clinical outcomes for patients undergoing cardiac surgery. For instance, perioperative insulin administration, coupled with glucose and insulin administration while maintaining normoglycemia (i.e., the GIN therapy), and the glucose–insulin–potassium (GIK) concept have been shown to improve left ventricular function in coronary artery bypass graft (CABG) surgery [47, 48], attenuate the degree of myocardial injury in off-pump coronary artery bypass (OPCAB) surgery [49], reduce the incidence of low cardiac output state, and the need for inotropic support in patients with aortic stenosis undergoing aortic valve replacement [50] as well as prevent myocardial oxidative stress in patients with acute coronary syndrome who are undergoing percutaneous coronary intervention [51].

Hyperglycemic crises, DKA, and hyperosmolar hyperglycemia are precipitated by surgical stress, fasting, and inadequate or discontinued insulin therapy. Blood or urine ketone levels should be measured to differentiate these conditions. Insulin administration is essential for the treatment of hyperglycemic crises, because it promotes glucose utilization, diminishes glycogenolysis as well as gluconeogenesis, and suppresses ketogenesis. Intravenous infusion remains the preferred route of insulin delivery for patients with DKA [52].

## Perioperative risks of insulin

Hypoglycemia represents one of the most common complications in surgical and critically ill patients. Blood glucose levels below 65–70 mg/dL usually serve as a threshold for activation of glucagon and epinephrine secretion. Symptoms of hypoglycemia are predominantly neurological and adrenergic in nature: they include sweating, tachycardia, tremors, convulsion, and coma. Tight glycemic control can lead to hypoglycemia desensitization and reduced recognition of symptoms, thus risking an even more pronounced drop in blood glucose [53]. Expectedly, most clinical symptoms are masked during anesthesia and can be blunted by postoperative sedation. Therefore, blood glucose should be regularly monitored during the perioperative period.

Several electrolytic disorders (e.g., hypokalemia, hypophosphatemia, and hypomagnesemia) are associated with insulin therapy [54]. The latter stimulates the $Na^+$–$K^+$-ATPase pump activity and subsequently redistributes potassium into intracellular compartment. Moreover, it promotes transport of both glucose and phosphate into skeletal muscle and hepatic cells. Hypokalemia, hypophosphatemia, and acidosis (in the setting of DKA) cause urinary loss of magnesium. Administration of insulin leads only to a slight decrease in serum levels of potassium, phosphate, and magnesium. However, severe depletion of potassium and phosphate can occur during the treatment of severe hyperglycemia [52].

## Assessment of insulin's effects

Metabolic and nonmetabolic effects of insulin can be detected with clinical and laboratory evaluations (**Table 3**).

## Perioperative implications

Robust literature from recent decades has repeatedly linked perioperative hyperglycemia to increased rates of complications and hospital mortality [55–58]. Conversely, studies in critically ill patients [59], cardiac surgery [60–61], and non-cardiac surgery [56–58, 62–67] have demonstrated that improved glycemic control mitigates the risk of developing multi-organ failure, curtails systemic as well as wound infections, and reduces short- and long-term mortality.

Glucose variability (i.e., the fluctuation of glucose concentrations) has been suggested as an important predictor of morbidity and mortality after cardiac surgery [68], liver transplantation [69], and in critically ill patients [70, 71]. The increased risk of adverse outcomes associated with glucose fluctuation could be related to the activation of oxidative stress [72]. During the intraoperative period, one should expect glucose fluctuation to increase because of the stress-induced acute insulin resistance.

Unfortunately, to date, the optimal glucose level required for improved clinical outcomes remains unknown: hence,

**Table 3.** Assessment points for effects of insulin

| Effect | Potential case | Assessment | |
|---|---|---|---|
| | | Clinical | Investigation |
| **Metabolic effect** | | | |
| Glucose lowering | Fasting<br>Use of oral hypoglycemic<br>Renal and hepatic impairment<br>Alcohol consumption | Sweating<br>Tachycardia<br>Tremors<br>Convulsion<br>Coma | Blood glucose |
| Hypokalemia | Mineralocorticoid excess (Cushing syndrome, primary hyperaldosteronism, use of corticosteroids)<br>Parenteral or enteral nutrition<br>Thiazide or loop diuretics use | Fatigue<br>Weakness<br>Arrhythmia<br>Polyuria | Serum/urine electrolytes<br>Electrocardiogram |
| Hypophosphatemia | Hyperparathyroidism<br>Parenteral or enteral nutrition | Weakness (diplopia, dysphagia)<br>Confusion | Serum electrolyte |
| Protein anabolism | – | – | Serum albumin<br>Nitrogen balance |
| Antilipolysis | – | – | Serum-free fatty acids<br>Acid–base balance |
| **Cardiovascular effect** | | | |
| Vasodilation | Concomitant use of vasodilators | Increased blood flow to skeletal, myocardial, cerebral tissues | Blood pressure<br>Vascular resistance |
| Positive inotropic | – | – | Cardiac output |

there exist various published guidelines for glycemic control in critically ill and surgical patients (**Table 2**).

## Preoperative period

Preoperative hyperglycemia correlates with poor postoperative outcomes for diabetic and nondiabetic patients [75, 76]. Preoperative assessment and optimization of diabetes should therefore be focused to prevent such consequences. The prevalence of nondiabetic patients showing an increased preoperative fasting blood glucose is approximately 21%–25% [77, 78]. Indeed, undiagnosed diabetic patients show higher risks of perioperative morbidity and mortality than their known diabetic counterparts [62, 79–80].

Preoperative glycemic management depends on the type and duration of diabetes, the type of antidiabetic medications, the level of glycemic control, the duration of fasting, and the nature of the proposed surgical intervention.

In addition to being an indicator of blood glucose control during the previous 3–4 months [81], plasma glycated hemoglobin A (HbA1c) constitutes an independent predictor of postoperative outcomes after major colorectal [82, 83], cardiac [84], and vascular surgery [85]. Moreover, the preoperative HbA1c levels help predict intraoperative insulin sensitivity [33] which, in turn, provides a marker for surgical stress with potential relevance for postoperative outcomes and recovery [86, 87]. A recommended HbA1c goal for adults is <7% [28]. If the preoperative HbA1c exceeds 8.5%, elective surgery may be delayed, and the diabetes specialist team should be consulted for preoperative optimization [38, 74]. Preoperative blood glucose and HbA1c levels should be verified in diabetic patients at the time of referral for surgery. However, unless clinical suspicion suggests otherwise, these tests are not recommended as routine screening for patients without documented diabetes [38, 88, 89].

Preoperative insulin therapy in well-controlled diabetic patients undergoing nonmajor surgery should simply be managed by modifying their usual diabetes medications [27, 38]. Basal glycemic control with a daily dose of long-acting insulin should be reduced by 20% on the day before the surgery. On the surgical day, blood glucose level must be checked and the long-acting background insulin should be continued at 80% of its usual dose even though intravenous insulin infusion is required. The rapid- and short-acting insulin used for prandial glycemic control must be held during the perioperative fasting period. For type 1 diabetic patients receiving subcutaneous insulin pump therapy, continuation of the basal infusion at 80–100% of the usual rate is recommended upon an initiation of fasting [90]. However, the accuracy of the basal rate must be assessed preoperatively by the diabetes specialist team.

Insulin-treated patients with suboptimal glycemic control or subjects scheduled for major elective surgery should be

admitted 2–3 days before the surgery to optimize blood glucose levels and other diabetes-related conditions such as impaired cardiac function and electrolyte abnormalities [37]. Subcutaneous intermediate-acting insulin with preprandial short- or rapid-acting insulin is administered and titrated to obtain the daily insulin requirement [91]. During the perioperative period, continuous intravenous glucose–insulin infusions are recommended for basal and correctional therapy because of their titratability and predictable absorption [92]. For insulin-naïve and nondiabetic patients, perioperative insulin therapy may be considered if the blood glucose levels are significantly elevated [27].

## Intraoperative period

Several strategies have been proposed to attenuate the stress-induced catabolic state and acute insulin resistance triggered by surgical tissue trauma. Combined administration of insulin and dextrose can be implemented intraoperatively [93]. The conventional "insulin sliding scale" provides a simple titration scheme to achieve a target glycemic range; despite its popularity, this strategy is reactive, as it attempts to treat hyperglycemic episodes after their occurrence. By contrast, a preemptive infusion of high-dose insulin with rate adjustment of dextrose to maintain targeted blood glucose levels will preserve normoglycemia during major abdominal [94] and cardiac surgery [95]. In addition, supraphysiological doses of insulin provide benefits derived from insulin's nonmetabolic properties [47, 96, 97].

During insulin therapy, blood glucose must be closely monitored. Generally, a blood gas analyzer and glucose meter are used to measure intraoperative glucose levels. The accuracy of capillary blood glucose analysis using glucose meters depends on several factors including hematocrit, blood pressure, temperature, pH, anesthetic technique, medications, and glucose meter technology. With the newer technologies, the glucose meters provide acceptable accuracy for intraoperative subcutaneous insulin dosing, which lead to ameliorating of glycemic control efficacy [98, 99]. Moreover, improved control of glucose variability has been demonstrated after cardiac surgery when a continuous glucose monitoring was used [100, 101]. However, the efficacy and reliability of continuous glucose monitoring during the perioperative period require further elucidation [28, 102].

Intraoperative hyper- and hypoglycemia must be avoided. In type 1 diabetic patients, the basal rate of insulin must be continued throughout surgery to prevent DKA. If glycemia exceeds 200 mg/dL, ketone levels should be measured and the treatment of hyperglycemia should be implemented based on potential etiology and clinical and laboratory tests [28, 38]. Blood glucose levels <70 mg/dL should be corrected with 15–20 g of glucose, and glycemia should be assessed 15 min after the implementation of treatment [28].

The judicious choice of intraoperative anesthetic technique can also help minimize the catabolic state seen in surgical patients. For instance, neuraxial blocks are reputed to blunt the neuroendocrine stress response and attenuate insulin resistance [103]. This facilitates glucose utilization and reduces protein loss and hyperglycemia.

## Postoperative period

Oral intake should be restarted as soon as possible. In non-critically ill patients undergoing minor surgery, the preoperative subcutaneous insulin regimen may be reinstituted upon resuming enteral nutrition [38, 104]. For ambulatory patients, subcutaneous rapid-acting insulin is preferred to its regular counterpart, because it will shorten the duration of observation for hypoglycemia postoperatively [27]. For patients undergoing major surgery with intraoperative use of insulin, the latter should be continued along with a dextrose infusion or parenteral nutrition during periods of uncertain alimentation. When the patient is able to tolerate a normal diet, the intravenous insulin infusion can be transitioned to a subcutaneous regimen. The subcutaneous insulin is started with the first meal and the intravenous insulin terminated shortly thereafter to ensure that baseline insulin requirements are always met (especially in type 1 diabetic patients) [91].

During the patient's hospital stay, postoperative stress-induced hyperglycemia should be treated with rapid- or short-acting insulin. The dose is calculated by dividing the daily insulin requirement by 30 for every 50 mg/dL above the glycemic goal [91]. The total dose of insulin and adequacy of oral intake should be reviewed on a daily basis. If carbohydrate intake is unreliable, the basal–bolus insulin regimen should be selected.

## Conclusion

Perioperative metabolic perturbation and its adverse consequences result from the transient hypercatabolic state and insulin resistance, which are both induced by surgical stress. Awareness and appropriate metabolic intervention are key components of modern perioperative care. Adequate insulin and glucose administration should be provided to maintain normal blood glucose level and control its variability.

Despite the existing evidence of benefits from metabolic effects of insulin, clinical evidence supporting its nonmetabolic properties remains lacking. Future research into the mechanism and potential benefits of insulin therapy in organ protection is required to understand more fully its therapeutic role during the perioperative period.

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