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# Stress Hyperglycemia During Surgery and Anesthesia: Pathogenesis and Clinical Implications

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**Abstract** Numerous studies have demonstrated an association between hyperglycemia in the perioperative period and adverse clinical outcomes. Many patients who experience hyperglycemia while hospitalized do not have a known history of diabetes and experience a transient phenomenon often described as "stress hyperglycemia" (SH). We discuss the epidemiology and pathogenesis of SH as well as evidence to date regarding predisposing factors and outcomes. Further research is needed to identify the long-term sequelae of SH as well as perioperative measures that may modulate glucose elevations and optimal treatment strategies.

**Keywords** Stress hyperglycemia · Inpatient diabetes · Insulin · Critical illness · Perioperative glucose management · Insulin resistance

## Introduction: Outcomes and Epidemiology of Newly Recognized Hyperglycemia in Hospitalized Patients

A substantial body of literature demonstrates a clear association between hyperglycemia in hospitalized patients and an increase in morbidity and mortality. This association occurs regardless of a diagnosis of diabetes prior to hospitalization. In fact, patients without a history of diabetes appear to have worse outcomes than those with known diabetes [1••, 2–4, 5••, 6••]. In one large study of 2030 patients admitted to general hospital wards, 38 % of patients were found to have hyperglycemia, with 26 % having a prior diagnosis of diabetes. Patients with newly discovered hyperglycemia were found to have a significantly higher rate of in-hospital mortality (16 %) compared to those patients with a prior history of diabetes

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(3 %) and those with normoglycemia (1.7 %) [1••]. It was postulated that the hyperglycemia per se could not be the sole driver of mortality as the glucose levels were overall higher in patients with known diabetes, leading to the conclusion that newly recognized hyperglycemia served as a marker of severity of illness. In the case of ischemic and hemorrhagic stroke, a review of the literature showed that hyperglycemia (glucose 110–126 mg/dL) was associated with an increased risk of both in-hospital and 30-day mortality only in patients without prior diabetes [2]. Moreover, patients with admission hyperglycemia (glucose 121–144 mg/dL) and no prior diabetes had a greater risk of poor functional recovery following hemorrhagic stroke [2]. Other studies have highlighted differences in outcomes when patients with hyperglycemia are stratified based on a history of diabetes. In a non-randomized, observational study in a mixed medical and surgical ICU, outcomes in patients with and without diabetes were compared after implementation of an insulin infusion protocol [3]. In this study, even modest hyperglycemia (glucose 140–179 mg/dL) was a strong risk factor for mortality in patients without diabetes, while only severe hyperglycemia (glucose >180 mg/dL) was a risk factor for mortality among patients with diabetes. This indicates that a history of diabetes may mitigate some of the acute effects of hyperglycemia.

Patients without a prior diagnosis of diabetes who are found to be hyperglycemic in the hospital represent two populations: those with pre-existing diabetes or abnormal glucose tolerance which had not been previously recognized and those with true "stress hyperglycemia" who manifest hyperglycemia in acute illness but normal glucose tolerance on subsequent testing [1••, 7••]. Stress hyperglycemia by definition is a transient phenomenon and therefore several studies have performed repeat glucose testing in patients after hospital discharge to evaluate rates of previously undiagnosed diabetes [8–11]. In one study of patients admitted after non-ST elevation myocardial infarction, patients without known diabetes underwent an oral glucose tolerance test (OGTT) prior to discharge and at 3 months post-discharge. Abnormal glucose tolerance, including diabetes, was detected in 61 % of patients on admission and 41 % of patients at 3 months [8]. A similar study performed in patients admitted for acute stroke found the OGTT on admission was consistent with diabetes in 24 % of patients, while 37 % had impaired glucose tolerance (IGT) [9]. At 3 months, those patients with hyperglycemia on admission were re-evaluated, and 14 % were found to have diabetes, while 27 % had IGT [9].

Studies evaluating hyperglycemia and hospital outcomes rarely have longitudinal data to determine if the hyperglycemia is transient, thus whether these two populations of patients with newly recognized hyperglycemia are in fact similar in terms of acute and long-term outcomes is unknown. It is reasonable to consider that there may be relevant differences. For example, if hyperglycemia on admission in patients with previously normal glucose tolerance correlates to severity of illness, then the acute risks for these patients may be greater but they may have less metabolic long-term disease. Patients who present with diabetes that was not previously diagnosed may have had limited access to healthcare and may be found to have a number of chronic untreated conditions that affect their long-term health. The inability to distinguish between these two populations in the current outcomes literature leaves these questions so far unanswered.

## Pathogenesis of Perioperative Hyperglycemia

The etiology of hyperglycemia in the perioperative period is multifactorial (Fig. 1). During physiologic stress, there is an increase in sympathetic stimulation and a subsequent rise in catecholamines, cortisol, glucagon, and growth hormones levels [12, 13]. This escalation in counter-regulatory hormones leads to an increase in endogenous glucose production via gluconeogenesis (predominately hepatic) and glycogenolysis. Under normal physiologic conditions, glucose homeostasis is tightly regulated via insulin-mediated glucose uptake in peripheral tissues (skeletal, cardiac muscle, adipose (GLUT 4) and liver (GLUT2) and inhibition of hepatic glucose production [14–18, 19••]. However, during the perioperative period, transient insulin resistance and impaired insulin signaling appear to contribute to hyperglycemia in patients both with and without diabetes. This phenomenon is thought to be due in part to excess circulating proinflammatory cytokines (TNF-alpha, IL-1, IL-6) and the aforementioned counter-regulatory hormones [17].

Literature suggests this transient decrease in physiologic response to circulating insulin levels is most pronounced on the first postoperative day and may persist for days or weeks following the procedure [20]. In a study of patients undergoing elective abdominal surgery, Thorell et al. described an average decrease of 50 % in insulin sensitivity for up to 5 days postoperatively and the time to normalization ranged from 9–21 days following surgery [20]. Anatomic location and invasiveness of the procedure as well as intraoperative fluids and anesthetics have also been linked with the degree of glucose elevation and duration of stress hyperglycemia. Surgeries involving the thorax and abdomen were associated with a more pronounced and prolonged duration of hyperglycemia when compared to peripheral procedures [20, 21]. Additionally, less invasive procedures (laparoscopic vs. open) have been associated with less of an increase in insulin resistance [22].

There has been ongoing interest in investigating the choice of anesthetic and sedative techniques for patients with impaired glucose tolerance with hopes of modulating sympathetic activity and subsequently post-procedure hyperglycemia (Table 1). Procedures with epidural or regional anesthesia have been associated with lower insulin resistance when

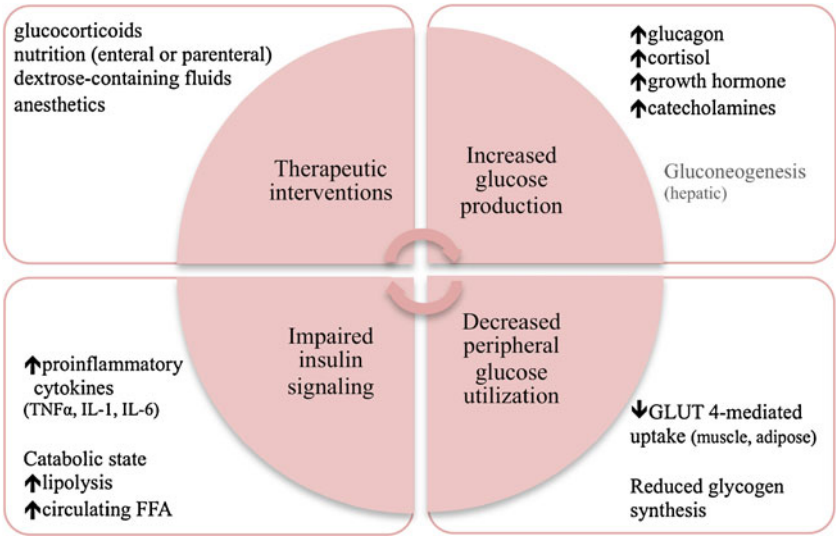


**Fig. 1** Pathogenesis of stress hyperglycemia. *FFA* free fatty acids, *GLUT* glucose transporter type, *IL* interleukin, *TNF-α* tumor necrosis factor-α

compared to those with general anesthesia [23, 24]. Additionally, certain anesthetics such as etomidate [25] and benzodiazepines [26] decrease ACTH and cortisol levels and their use has been shown to blunt perioperative hyperglycemia. Decreased sympathetic tone with alpha-2 adrenergic agonists has been of recent interest, especially for patients with impaired glucose tolerance. Behoula et al. reported premedication with clonidine improved glycemic control and decreased insulin requirements during ophthalmic surgery [27]; however, the effect of clonidine on the HPA axis remains controversial as when studied in patients without known diabetes, this effect has not been consistently observed [28–30]. Dexmedetomidine [31, 32] and opiates [33] have shown the most favorable post-procedure glucose profile and are considered by some experts as the anesthetic agent of choice for patients with diabetes and impaired glucose tolerance. Conversely, several studies have shown substantial impairment in glucose tolerance and insulin secretion with volatile anesthetics [34, 35]. This adverse consequence is thought to be due to inhibition of adenosine triphosphate-sensitive potassium channels on beta cells. In a recent study by Jung et al, a higher-dose propofol infusion showed attenuation in glucose and norepinephrine levels and lower perioperative glucose levels in patients undergoing lung surgery [36]. Additionally, the choice of intraoperative fluids (<5 % and ideally 1–2.5 % dextrose) may also play a role in modulating postoperative glucose levels and insulin resistance [37]. Some investigators have also examined the role of preoperative glucose infusions (vs. fasting) and effect of postoperative insulin resistance. Ljungqvist et al. reported decreased postoperative insulin resistance in patients undergoing elective open cholecystectomy when given glucose infusion preoperatively as compared to patients with traditional preoperative overnight fasting [38]. Many therapeutic interventions such as glucocorticoids, enteral or parenteral nutrition, and postoperative physical inactivity can directly contribute to or exacerbate stress hyperglycemia.

**Table 1** Predictors of stress hyperglycemia

| | |
|---|---|
| Surgical | More invasive procedure (open vs. laparoscopic)<br>Anatomic location involving thorax and abdomen<br>General anesthesia (vs. epidural)<br>Intraoperative fluids with >5% dextrose |
| Perioperative | Glucocorticoids<br>Parenteral/enteral nutrition<br>Physical inactivity |
| Patient factors | Degree of illness<br>Pre-existing state of insulin resistance and/or deficiency<br>Advanced age<br>Higher BMI<br>Higher HbA1c<br>Baseline glucose on day of procedure |

Patient factors will play a role, including the degree of illness and the patient's pre-existing state of insulin resistance and/or deficiency.

Several studies have demonstrated a clear association between stress hyperglycemia, specifically glucose levels exceeding 180 mg/dL, and adverse clinical outcomes in the perioperative period including impaired immune function, surgical site infections, delayed wound healing, and increased length of stay [39••]. It is also well documented in the medical literature that hyperglycemia can lead to endothelial dysfunction [40], platelet aggregation, and thrombus formation [41]. In a retrospective cohort study, Malmstedt et al. showed the frequency of infection was proportional to the degree of hyperglycemia in vascular surgery patients [42]. Similar findings have been described in orthopedic, hepato-biliary, pancreatic cancer, and colorectal surgeries, demonstrating a direct relationship to hyperglycemia and complications [43–45]. Vilar-Compte et al. described serum glucose levels >150 mg/dL as associated with an increased risk in surgical site infections in mastectomy patients (OR 3.05) [46]. In a recent study by Mohan et al., 3514 patients without established diabetes and serum glucose levels over 180 mg/dL had a greater risk of superficial surgical site infection [45].

## Clinical Predictors of Hyperglycemia in the Perioperative Period

As mentioned above, baseline patient factors influence the likelihood of perioperative hyperglycemia (Table 2). Several prospective and retrospective studies have sought to identify these characteristics. Increasing age and a high body mass index (BMI) are most consistently implicated. Sato et al. described an association between HbA1c, BMI, and intraoperative insulin resistance [47]. Cammu et al. found a higher BMI predicted larger perioperative insulin requirement [48]. Gianchandani et al. found preoperative HbA1c was an independent predictor of postoperative hyperglycemia ($p = 0.02$) [49•]. Using the immediate postoperative duration of the insulin infusion as a surrogate for recovery from surgical stress among 61 patients who met criteria for initiating an insulin infusion immediately after surgery, those with a high preoperative mean BMI and higher insulin resistance (insulin levels and HOMA-IR) ($p = 0.004$, $p = 0.048$) had longer durations of the infusion [49•]. Male gender, previous cardiac surgery, and poor left ventricular ejection fraction are some weaker predictors that have been described in other studies [50].

**Table 2** Anesthetics and effect on perioperative glucose

| Anesthetic Agents | Proposed Mechanism | Effect on Glucose |
|---|---|---|
| Etomidate [25] | ↓ adrenal steroidogenesis | ++ |
| Benzodiazepines [26] | ↓ ACTH<br>↓ cortisol | ++ |
| Alpha- 2 adrenergic agonists:<br>Clonidine* [27-30]<br>Dexmedetomidine [30,31] | ↓ sympathetic tone<br>↓ norepinephrine<br>↓ ACTH<br>↓ cortisol | + |
| Opiates [33] | ↓ sympathetic tone and effect on hypothalamic-pituitary axis | + |
| Volatile anesthetics[34,35] | Inhibition of ATP sensitive potassium channels on beta cells | +++ |
| Propofol [36] | ↓ norepinephrine | + |

* Some conflicting evidence

Abbreviations: ACTH: adrenocorticotropin hormone; ATP: adenosine triphosphate

The use of insulin or sulfonylureas, an HbA1c >6.5 % or a random BG of >120 mg/dL predicted periprocedural hyperglycemia in a cohort of patients with diabetes undergoing percutaneous coronary interventions. Similar predictors for stress hyperglycemia have been described [50]. In a recent study in patients with and without diabetes who underwent knee and hip replacements, preoperative HbA1c and fasting glucose on the day of surgery were associated with postoperative hyperglycemia. HbA1c levels of 6.1–6.4 % doubled the risk of hyperglycemia, and baseline glucose on the day of surgery ≥126 mg/dL compared to ≤100 mg/dL markedly increased the odds of hyperglycemia (adjusted OR = 17 (1.6–1.78)) [51]. The incidence and persistence of dysglycemia after surgery depends on which diagnostic criteria are used (FPG, 2 h postprandial after an OGTT or HbA1c). Very few studies evaluate the persistence of hyperglycemia. Gianchandani et al. found among patients identified perioperatively with stress hyperglycemia, 59 % had prediabetes and 10 % had newly identified diabetes by one or more diagnostic criteria and continued to be dysglycemic 3 months postoperatively [49•]. Although HbA1c identified the largest group of patients with dysglycemia, 2 h postprandial glucose after an OGTT had the highest pre and postoperative correlation ($r = 0.39$, $p < 0.001$). This was a short follow-up and studies with longer duration of follow-up are needed.

## Perioperative Glucose Targets in Patients With and Without Diabetes

Data in the critical care literature suggests that optimal glycemic ranges may differ in patients with and without diabetes, and recent studies in the perioperative literature have similar implications. Kotgal et al. evaluated perioperative (highest BG intraoperative and within 24 h postoperatively) BG levels in 40,000 patients in a Veterans Administration database [52••]. Although more adverse events were noted in the diabetes patients overall, the group without known diabetes had a dose response relationship with the level of BG elevation (OR = 1.3, 95 % CI, 1.1–1.5, for BG 125–180 mg/dL and OR 1.6, CI, 1.3–2.1 for BG >180 mg/dL) [50]. Similar findings were noted in the subanalysis of the GLUCO-CABG trial during which BG was controlled perioperatively using a computerized algorithm. Patients with stress hyperglycemia had better outcomes at glucose range of 110–140 mg/dL compared to 140–180 mg/dL while patients with diabetes had similar outcomes in both groups [53••]. This difference in outcomes may be attributed to the ability of patients with diabetes to physiologically adapt to glucose variability, although the details of this are unclear and not supported by all studies involving CABG patients [54, 55]. The Kotgal group also noted the underuse of insulin in patients without diabetes and hypothesized that hyperglycemia indicated higher levels of stress in patients without diabetes when compared to those with diabetes. In a large retrospective study evaluating intraoperative BG control in cardiac surgery patients, Duncan et al. found that outcomes were best in patients without diabetes when glucose ranged within 140–170 mg/dL [56]. Those with severe intraoperative hyperglycemia (glucose >200 mg/dL) had an increase in morbidity and mortality, similar to patients with BG less than 140 mg/dL [56]. Since hypoglycemia rates were low, it could not explain poor outcomes in the lower ranges. In cardiac surgery patients evaluated by Blaha et al., tight glucose control (80–110 mg/dL) maintained perioperatively (starting during surgery and continuing postoperatively) reduced morbidity in patients without diabetes [5••]. These studies together may suggest that patients with and without diabetes may benefit from separate glucose thresholds at which to initiate insulin infusions intraoperatively and possibly distinct intraoperative blood glucose target ranges. Active research in this area is needed in future clinical trials.

## Conclusions

Perioperative stress hyperglycemia is a common clinical problem due to a transient decrease in insulin responsiveness and may persist for days or weeks following a surgical procedure. As reviewed above, several factors influence the timing, severity, and duration of SH, including the type of procedure, the anesthetic used, as well as preoperative glucose tolerance. Currently available data suggest that patients without established diabetes who develop SH are at higher risk of poor outcomes, but it remains unclear if this distinction warrants unique treatment strategies for these patients. Additional studies are needed to test the hypothesis and to address other important outcomes. These outcomes include cost, given that hospitalizations of patients with perioperative hyperglycemia cost nearly four times more than those of their normoglycemic counterparts [57]. Despite some inconsistency in the literature, the consistent finding from numerous studies investigating perioperative hyperglycemia supports the use of insulin therapy to achieve metabolic control in order to optimize postoperative outcomes.

### Compliance with Ethical Standard

**Conflict of Interest** Nadine E. Palermo, Roma Y. Gianchandani, Marie E. McDonnell, and Sara M. Alexanian declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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