

## Review Article

# Stress-Induced Hyperglycemia in General Surgery: a Narrative-Review

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## Abstract

**Background:** Stress-induced hyperglycemia, also known as stress hyperglycemia, occurs after severe stress on the body, such as surgery. Awareness of this condition and its management are essential to reducing complications and mortality in patients after general surgery. This study aimed to review studies conducted on stress hyperglycemia in patients who underwent general surgery.

**Materials and Methods:** This review study investigated the outcomes and management of stress hyperglycemia in general surgery patients. From 2014 to 2024, the keywords “stress hyperglycemia” and “general surgery” were searched in the PUBMED, ELSEVIER, and CENTRAL databases.

**Results:** The incidence of stress hyperglycemia varies between studies but often occurs in more than 20% of patients. Compared with diabetic patients undergoing general surgery, patients with stress hyperglycemia have more severe rates of complications and mortality. Complications of stress hyperglycemia include infection, necrosis, organ damage, and mortality. Stress hyperglycemia can also increase the length of hospital stay.

**Conclusion:** The results of this study showed that stress hyperglycemia was common in people who had general surgery and was linked to a higher risk of complications and death compared to patients who did not have hyperglycemia or diabetes.

**Keywords:** General surgery, Hyperglycemia, Stress, Surgery

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## Introduction

Hyperglycemia frequently occurs in critically ill patients within the initial 48 hours of intensive care unit (ICU) admission in at least 50% of cases<sup>1</sup>. Stress-induced hyperglycemia, or hyperglycemia, precipitates insulin resistance and elevates blood

glucose levels via various pathways. Counterregulatory hormones impair glucose homeostasis, including catecholamines, cortisol, glucagon, and growth hormone. Moreover, elevated inflammatory cytokines exacerbate the metabolic condition of patients. Consequently, the hepatic is compromised, and glucose absorption by skeletal muscle through glucose

transporter type 4 (GLUT-4) is likewise impaired<sup>2</sup>. Numerous observational and randomized controlled trials indicate that hyperglycemia serves as an independent risk factor for hospital complications, prolonged hospital stays, elevated infection rates, and increased mortality compared with normoglycemic patients<sup>3,4</sup>. About 30% of patients who lack a diabetes history and undergo noncardiac surgery experience hyperglycemic stress, typically manifesting within 72 hours post-surgery. In these patients, hyperglycemic stress correlates with poorer outcomes compared to non-diabetic individuals and exhibits a similar rate of complications to those with diabetes<sup>5-7</sup>. General surgery may be related to hyperglycemic stress due to the physiological stress it induces. Research indicates that the onset of hyperglycemia post-general surgery is associated with a fourfold increase in complications and a twofold increase in mortality compared to patients with normal blood glucose levels<sup>4,8,9</sup>. Considering the impact of hyperglycemic stress on the outcomes of patients undergoing general surgery and the importance of managing this condition, this study reviews studies conducted on hyperglycemic stress in patients undergoing general surgery.

## Methods

This review aimed to investigate the outcomes and management of stress hyperglycemia in patients undergoing general surgery. The keywords “stress hyperglycemia” and “general surgery” were searched in PUBMED, ELSEVIER, and CENTRAL databases from 2014 to 2024. Review studies, editorials, and case reports were excluded from this review. Studies that included patients other than general surgery were also excluded.

## Results

Ten studies assessed hyperglycemic stress in general surgery patients during the period. The study by Yang et al. aimed to determine the impact of hyperglycemic stress on clinical outcomes in patients with acute pancreatitis. 967 nondiabetic and 114 diabetic patients (10.5%) met the inclusion criteria, and clinical outcomes were not significantly different between the two groups. Hyperglycemic stress in people without

diabetes was a blood glucose level of 180 mg/dL or higher. This level was correlated to 8.8 times higher odds of persistent organ failure ( $P < 0.001$ ). Blood glucose levels of 300 mg/dL for diabetic patients had a 7.5-fold odds ratio for persistent organ failure ( $P = 0.009$ ). Hyperglycemic stress was independently associated with persistent organ failure, acute necrosis, infection, and mortality<sup>10</sup>.

Liu et al. investigated the prevalence of hyperglycemic stress in patients with A-type acute aortic dissection (ATAAD) without diabetes and its impact on short-term and long-term clinical outcomes. The study enrolled 1098 patients with a confirmed diagnosis of ATAAD. The patients were put into three groups based on their blood glucose levels: the normoglycemic group ( $BG < 7.8$  mmol/L), the mild to moderate hyperglycemic stress group ( $7.8$  mmol/L  $\leq$   $BG < 11.1$  mmol/L), and the severe hyperglycemic stress group ( $BG \geq 11.1$ ). 421 ATAAD patients (38.3%) had hyperglycemic stress, of which 361 (32.9%) were in the mild to moderate group and 60 (5.46%) were in the severe group. People in the hyperglycemic stress group were more likely to have high-risk symptoms and needed conservative treatment than people in the normoglycemic stress group. Severe hyperglycemic stress was associated with a higher risk of 30-day ( $P = 0.04$ ) and 1-year ( $P = 0.04$ ) mortality<sup>11</sup>. The study by Fiorillo et al. aimed to investigate the effects of postoperative hyperglycemia in nondiabetic patients undergoing gastric cancer surgery. A total of 193 patients underwent gastrectomy. Patients with diabetes and individuals who had undergone pancreatic resection were excluded. Blood glucose levels were assessed in the postoperative period within 72 hours following surgery. The evaluation focused on postoperative complications, mortality, and the postoperative period in hyperglycemic patients (blood glucose level  $> 125$  mg/dL) in comparison to euglycemic patients (glucose level  $\leq 125$  mg/dL). The difference between mild hyperglycemic stress (blood glucose levels ranging from 125 to 200 mg/dL) and severe hyperglycemic stress (blood glucose levels of 200 mg/dL or higher) was analyzed. Ninety-six patients (5%/55) exhibited postoperative hyperglycemia. Severe postoperative hyperglycemia occurred in 11 patients, representing 6.4% of the cohort. A postoperative glucose level exceeding 200 mg/dL correlated with poorer outcomes when compared to euglycemic

patients and those with mild postoperative hyperglycemia. The rate of postoperative complications was 24.8%, with a significantly higher incidence observed in patients experiencing severe postoperative hyperglycemia compared to those with mild hyperglycemia and normoglycemic people<sup>12</sup>.

Abdelmalak et al. studied preoperative blood glucose levels and their impact on postoperative outcomes in elective noncardiac surgery. A total of 61,536 patients were analyzed. The main outcome was a composite measure of in-hospital severe complications and mortality rates. The secondary primary outcome was mortality at one year. The crude incidence of the composite in-hospital outcome showed a significant association with preoperative glucose levels; however, this association was not present after adjusting for variables ( $P=0.40$ ). The association did not show a significant difference between patients with diabetes and those without ( $P=0.09$ ). One-year mortality demonstrated a significant association with preoperative blood glucose levels, both in univariate analysis ( $P<0.001$ ) and following adjustment for confounding variables ( $P<0.001$ ). Patients diagnosed with diabetes who maintained euglycemia preoperatively exhibited a higher overall 1-year mortality rate compared to patients without diabetes experiencing hyperglycemic stress. Hyperglycemic patients with diabetes exhibited significantly lower 1-year mortality compared to hyperglycemic patients without diabetes ( $P<0.001$ )<sup>13</sup>.

Davis et al. assessed the prevalence of hyperglycemic stress and related complications in general surgery patients without a diabetes history. Hospital outcomes were evaluated in general surgery patients classified as normoglycemic preoperatively (blood glucose  $<140$  mg/dL) who subsequently experienced hyperglycemic stress (blood glucose  $>140$  mg/dL or  $>180$  mg/dL) within 48 hours post-surgery. A total of 415 patients (21%) exhibited blood glucose levels between 140 and 180 mg/dL, while 206 patients (10.5%) had blood glucose levels exceeding 180 mg/dL. The median duration of hospital stay was 9 days for patients with blood glucose levels between 140 and 180 mg/dL and 12 days for those exceeding 180 mg/dL, compared to normoglycemic patients ( $P<0.001$ ). Patients exhibiting blood glucose levels between 140 and 180 mg/dL experienced an increased rate of complications

compared to normoglycemic patients. Those with levels exceeding 180 mg/dL faced a greater incidence of complications and elevated mortality rates in comparison to normoglycemic patients and the other group<sup>7</sup>.

Mohan et al. assessed the relationship between elevated blood glucose levels during the early postoperative phase and the occurrence of surgical site infections (SSIs), sepsis, and mortality following colorectal surgery. A total of 5145 patients were examined, and 1072 were diagnosed with diabetes. In diabetic patients, the unadjusted analysis revealed a significant association between elevated blood glucose and superficial SSI; however, this was not present in the adjusted analysis ( $P=0.39$ ). No significant association was found between elevated blood glucose levels and deep surgical site infections, limb surgical site infections, sepsis, or mortality in diabetic patients. In nondiabetic patients, a significant association was observed between elevated blood glucose levels and superficial surgical site infections, sepsis, and mortality (all  $P<0.05$ )<sup>14</sup>.

Mexsen et al. aimed to assess the predictive value of preoperative hyperglycemia on surgical outcomes. Patients were categorized into four groups according to preoperative blood glucose levels: less than 100 mg/dL ( $n=184$ ), 100–140 mg/dL ( $n=207$ ), 140–180 mg/dL ( $n=41$ ), and greater than 180 mg/dL ( $n=16$ ). The study cohort comprised 478 patients. This study found that older age ( $P=0.0085$ ), higher body mass index, diabetes, and hypertension were significantly associated with elevated glucose levels ( $P<0.05$ ). The complication rate varied from 26% for glucose levels below 100 mg/dL to 94% for levels exceeding 180 mg/dL, whereas the recurrence rate ranged from 10% at glucose levels below 100 mg/dL to 37% for levels between 140 and 180 mg/dL. Preoperative glucose significantly influenced the overall complication rate, major complication rate, and recurrence rate independently<sup>15</sup>.

The study conducted by Shiffermiller et al. aimed to compare the length of stay (LOS) following noncardiac surgery in patients experiencing hyperglycemic stress versus those with diabetic hyperglycemia. Patients experiencing hyperglycemic stress had no prior history of diabetes before the surgical procedure. A total of 270 patients with hyperglycemia were analyzed, comprising

82 individuals in the hyperglycemic stress group and 188 in the diabetic hyperglycemic group. The LOS was greater in the hyperglycemic stress group compared to the diabetic hyperglycemic group (10.4 days vs. 7.3 days;  $P = 0.03$ ). No association was identified between LOS and prompt treatment of hyperglycemia within 12 hours ( $P = 0.43$ ), daily insulin dose ( $P = 0.89$ ), or mean total glucose ( $P = 0.13$ ) in the hyperglycemic stress group<sup>16</sup>.

Gianotti et al. evaluated the relationship between postoperative blood glucose level trends and the incidence of surgical-related infections. Adult patients without diabetes who were eligible for elective abdominal surgery were examined. A total of 6078 blood glucose measurements were collected at various time points in 452 patients. Blood glucose levels exceeding 100 mg/dL at admission were associated with an approximately threefold increase in the risk of hyperglycemia ( $P < 0.001$ ). Increased initial and secondary blood glucose levels correlate with a heightened risk of infection<sup>17</sup>.

A study by Fayfman et al. investigated the potential of sitagliptin to mitigate intraoperative hyperglycemic stress in patients lacking a diabetes history who were undergoing general surgery. Patients were randomly assigned to receive either sitagliptin ( $n=44$ ) or placebo ( $n=36$ ), with the treatment administered from the day before surgery until discharge. Postoperatively, 44 patients (55%) exhibited blood glucose levels exceeding 140 mg/dL. The hyperglycemic stress rates were comparable between the placebo and sitagliptin groups (56 and 55%, respectively). Blood glucose levels exceeding 180 mg/dL were noted in 19% of patients receiving placebo and 11% of those treated with sitagliptin. Both treatment groups exhibited comparable postoperative blood glucose levels, recorded at  $148.9 \pm 29.4$  mg/dL for placebo and  $146.9 \pm 35.2$  mg/dL for sitagliptin. No significant differences were observed in LOS (4 vs. 3 days), ICU admission rates (3% vs. 5%), hypoglycemia incidence (6% vs. 11%), or complication rates (14% vs. 5%) between the two groups. Sitagliptin exhibited no impact on hyperglycemic stress<sup>18</sup>.

## Discussion

This review assessed the findings of existing studies regarding hyperglycemic stress in patients undergoing

general surgery. Many studies indicate that patients undergoing general surgery may experience hyperglycemic stress, with the incidence varying across research but often exceeding 20% of patients<sup>7, 10, 12, 15</sup>. In these patients, a significant observation was that, in contrast to diabetic patients undergoing general surgery, those experiencing hyperglycemic stress exhibited earlier and greater morbidity and mortality. This phenomenon may be attributed to the differential tolerance of cells to the toxic effects of hyperglycemic stress in comparison to diabetic patients. In diabetic individuals, cellular adaptation to blood sugar occurs over time. Conversely, in normoglycemic patients experiencing hyperglycemic stress, cells have not undergone such adaptation, resulting in heightened toxicity from high blood glucose levels and an increased rate of complications in these patients<sup>19</sup>. Patients experiencing hyperglycemic stress may encounter complications such as infection, necrosis, organ damage, and potentially death<sup>7, 10-12, 14-17</sup>.

Counterregulatory hormones and proinflammatory cytokines contribute to the metabolic environment established during hyperglycemic stress. Gluconeogenesis and insulin resistance significantly contribute to the onset of inflammatory reactions. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are inflammatory cytokines that induce insulin resistance and inhibit insulin secretion. Elevated serum IL-6 levels correlate with insulin resistance, increasing blood glucose levels by releasing glucose from hepatic glycogen stores. Moreover, hyperglycemia elevates blood IL-6 levels, presumably due to enhanced production by monocytes. TNF- $\alpha$  correlates with sepsis severity and is an early mediator in its development. TNF- $\alpha$  induces insulin resistance in animals, spontaneously or by elevating circulating free fatty acids<sup>20-22</sup>.

The hypothalamic-pituitary-adrenal (HPA) axis activation occurs during hyperglycemic stress, resulting in elevated cortisol secretion from the adrenal gland. Cortisol synthesis is crucial for the maintenance of cellular homeostasis and the proper functioning of various bodily systems. Cortisol, catecholamines, glucagon, and growth hormone function as counterregulatory hormones can reduce insulin secretion by enhancing the activity of pancreatic alpha cells. Catecholamines and cytokines regulate hepatic

gluconeogenesis. Catecholamines and their binding to insulin inhibit insulin activation by reducing tyrosine kinase activity and peripheral glucose uptake via GLUT-4. Glucocorticoids restrict glucose uptake in peripheral tissues, while growth hormone inhibits insulin activation on tyrosine residues<sup>23, 24</sup>.

Studies indicate that hyperglycemic stress affects over 50% of patients, regardless of diabetes status, and correlates with elevated surgical complication rates and increased mortality among individuals without a diabetes history. Reports indicate that 30-day mortality rates were elevated for nondiabetic patients experiencing hyperglycemic stress following noncardiac surgery in comparison to normoglycemic patients with a history of diabetes<sup>3, 4, 8</sup>. The Surgical Care and Outcomes Evaluation Program, encompassing patients with and without diabetes, identified that hyperglycemia occurred in 29% of patients within 2 days post-surgery, correlating with a higher incidence of postoperative complications than nonhyperglycemic patients<sup>8</sup>. The reviewed studies indicated that hyperglycemic stress had a greater impact on nondiabetic patients compared to diabetic patients<sup>10, 14, 16</sup>.

Identifying patients experiencing hyperglycemic stress is crucial, as prior research indicates that prompt intervention in non-diabetic individuals with hyperglycemic stress mitigates complications and enhances overall patient outcomes. Von Loeffelholz et al. and Umpierrez et al. demonstrated that intensive insulin therapy did not influence outcomes in diabetic patients; however, patients experiencing hyperglycemic stress exhibited notable improvements in complications with this treatment<sup>25-27</sup>. Shiffmiller et al. indicated that insulin therapy had no impact on the duration of hospital stays for patients experiencing hyperglycemic stress<sup>16</sup>.

Effective management of blood glucose levels is essential for enhancing patient clinical outcomes. Numerous studies indicate effective management strategies for hyperglycemic stress. Nonetheless, consensus on a glycemic target is controversial. A significant number of healthcare providers lack a structured method for managing hyperglycemic stress. A study indicated that each 10 mg/dL rise in blood glucose levels exceeding 120 mg/dL correlated with a gradual increase in patient mortality. Consequently, it

is advisable to use insulin to manage glucose levels in postoperative patients<sup>28</sup>.

Continuous intravenous insulin infusion (CIIT) is frequently utilized in critically ill patients within the ICU setting. Insulin possesses a brief half-life, typically under 15 minutes. Consequently, it can swiftly modulate glucose levels and achieve the target range within four to eight hours<sup>29</sup>. Secondary agents combined with insulin may be beneficial in managing hyperglycemic stress; however, research on this topic is limited. Heidary et al. examined the impact of magnesium on insulin resistance in ICU patients experiencing hyperglycemic stress. Seventy patients with hyperglycemic stress received either magnesium (7.5 g magnesium sulfate in 500 ml normal saline administered as an intravenous infusion over eight hours) or a placebo. The research indicated that a single bolus dose of magnesium decreased insulin resistance and enhanced the condition of the patients<sup>30</sup>. Fayfman et al. conducted a study of oral sitagliptin therapy for hyperglycemic stress, concluding that it had no impact on managing this condition<sup>18</sup>. The optimal treatment protocol must ensure stable blood glucose levels, effectively reach and sustain target levels, adapt to rapid fluctuations, and reduce the risk of hypoglycemia; nonetheless, the formulation of a suitable protocol remains under investigation<sup>31</sup>.

Conversely, transferring patients from the ICU complicates the administration of intravenous insulin. A transition to a subcutaneous insulin regimen is advised. The American College of Endocrinology recommends administering 80% of the 24-hour insulin infusion regimen, allocating half for the basal dose and the remaining portion for bolus dosing. Critically ill patients outside the ICU with blood glucose levels exceeding 10 mmol/L require treatment with intravenous insulin<sup>32</sup>.

## Conclusion

Hyperglycemic stress has a significant prevalence exceeding 20%, highlighting the necessity for focused management of general surgery patients experiencing this condition. Hyperglycemic stress elevates the risk of infection, necrosis, organ damage, and mortality, with complication rates surpassing those observed in diabetic patients. Timely management can mitigate these risks. Insulin is the primary treatment for

managing patients experiencing hyperglycemic stress.

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## Conflict of interest

The authors further declare that they have no conflict of interest.

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