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Stress-Induced Hyperglycemia in Non-Diabetic Patients Undergoing Laparoscopic Cholecystectomy under General Anesthesia: A Prospective Observational Study

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Abstract

Background: Though surgical trauma triggers the neuroendocrine stress response, the contribution of general anesthetic agents along with minimally invasive surgery is not well defined in metabolically healthy populations. This prospective study measured the incidence and magnitude of stress-induced hyperglycemia in healthy nondiabetic patients undergoing elective laparoscopic cholecystectomy under general anesthesia and investigated the metabolic effects of anesthesia.

Methodology: After IRB approval, this prospective observational study was conducted over a 6-month period at Mayo Hospital, Lahore, Pakistan. 41 non-diabetic patients of ASA physical status I, scheduled for elective laparoscopic cholecystectomy, were included in the study. Anesthesia was induced with propofol (2 mg/kg), nalbuphine (0.1 mg/kg), and atracurium and maintained with isoflurane and oxygen. Capillary blood glucose was measured within 15 minutes before induction (T0) and within 15 minutes after tracheal extubation (T1) using a calibrated glucometer. Postoperative capillary blood glucose ≥140 mg/dL was considered stress-induced hyperglycemia. It was further categorized into moderate (140-179 mg/dL) and severe (≥180 mg/dL) categories.

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Results: The study population (*N*=41) was predominantly female (80.5%), with a mean age of 36.51±8.00 years and a mean anesthesia duration of 109.63±21.13 minutes. Mean capillary blood glucose rose significantly from 108.71±11.38 mg/dL preoperatively to 166.00±31.20 mg/dL postoperatively, representing a mean systemic glycemic excursion of +57.29 mg/dL ($p<0.001$). The overall incidence of postoperative stress-induced hyperglycemia was 65.9% (*n*=27). Moderate hyperglycemia developed in 26.8% (*n*=11) of patients, while 39.0% (*n*=16) developed severe hyperglycemia, associated with a mean post-extubation glucose level of 182.31±25.94 mg/dL.

Conclusions: Non-diabetic patients undergoing elective laparoscopic cholecystectomy under volatile general anesthesia experience a high incidence of postoperative stress-induced hyperglycemia. Despite the minimally invasive nature of laparoscopic surgery, the combination of volatile anesthesia and carbon dioxide pneumoperitoneum triggers significant metabolic stress. Routine perioperative blood glucose monitoring is warranted in non-diabetic cohorts to facilitate early identification and therapeutic intervention.

Introduction

The perioperative phase is a period of significant physiological stress, not just from the surgery itself but also due to the administration of anesthesia. Of the numerous metabolic alterations that occur in this period, stress hyperglycemia is perhaps the most clinically relevant. It is characterized as an acute increase in blood glucose levels in patients with previously controlled diabetes mellitus, often secondary to acute illness, injury, or operative stress. It is of specific interest to anesthesiologists, as intraoperative hyperglycemia can negatively impact patient outcomes and make perioperative care more challenging.

The pathophysiology of stress hyperglycemia is multi-factorial. The stress of surgery and anesthesia activates the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, resulting in increased secretion of cortisol, catecholamines, glucagon, and growth hormone. Together, these hormones induce hepatic gluconeogenesis, glycogenolysis, and peripheral insulin resistance, resulting in increased blood glucose levels. Pro-inflammatory cytokines released with

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anesthesia and tissue handling also contribute to deranged glucose metabolism. While surgical trauma itself triggers these mechanisms, anesthetic agents' contribution to perioperative glucose variability is increasingly acknowledged as a significant one.

General anesthesia has direct influences on glucose homeostasis. Volatile anesthetics, in particular, isoflurane and sevoflurane, have been shown to suppress pancreatic β-cell insulin secretion and reduce peripheral glucose uptake. Intravenous agents such as propofol can suppress insulin release and disrupt glucose tolerance. Opioids, although useful for analgesia, release stress hormones when administered in suboptimal doses and indirectly promote hyperglycemic responses. Muscle relaxants and reversal agents also affect autonomic tone, further altering the metabolic environment. Such drug effects emphasize the role of anesthesiologists not just as monitors of hemodynamics but also as predictors of the metabolic effects of anesthetic selection and depth.

The significance of stress hyperglycemia within the field of anesthesia has been widely recognized and extensively reported in the literature. Even transient increases in blood glucose during surgery have been associated with compromised immune function, postoperative infections, delayed wound healing, and a higher incidence of perioperative morbidity. Hyperglycemia is also associated with worsening fluid and electrolyte disturbances, impaired cardiac function, and prolonged recovery following anesthesia. Noticeably, these consequences extend beyond diabetic patients; non-diabetic patients suffering perioperative hyperglycemia can be at equal or even higher risk for complications since hyperglycemia in these patients tends to go unnoticed. For the practicing anesthesiologist, careful monitoring of glucose levels during surgery becomes a key safeguard for patient well-being.

Laparoscopic cholecystectomy represents a valid clinical model to examine stress hyperglycemia under anesthetic conditions. Despite being minimally invasive, the surgery necessitates induction and maintenance of general anesthesia, pneumoperitoneum establishment, and patient placement—all of which play a role in the metabolic stress response. The repetitive

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nature and high volume of laparoscopic cholecystectomy make the procedure an appropriate one to use to assess the incidence of anesthetic-related hyperglycemia in non-diabetic patients. Awareness of the magnitude of this response empowers anesthesiologists to develop patient-specific strategies for monitoring, anesthetic planning, and glycemic management throughout the perioperative period.

Despite increasing worldwide recognition, studies on the anesthetic contribution to stress hyperglycemia are few, especially in low- and middle-income nations. In Pakistan, although some have investigated perioperative glycemic variability among surgical patients, very few have focused on non-diabetic patients under general anesthesia. Most of the published literature assigns stress hyperglycemia to surgical trauma and largely ignores the profound metabolic effects of anesthetic drugs themselves. This shortfall emphasizes the importance of targeted research that compares the incidence of stress hyperglycemia in a routine anesthetic environment like laparoscopic cholecystectomy.

Concisely, stress hyperglycemia represents a common but frequently undervalued perioperative metabolic response. Although surgery triggers the stress response, anesthetic agents have an independent and significant role in disrupting glucose homeostasis. Recognizing the importance of this response can equip anesthesiologists to personalize monitoring, plan anesthesia more effectively, and manage glucose carefully throughout surgery and recovery. By examining the occurrence of stress hyperglycemia among non-diabetic patients who have undergone laparoscopic cholecystectomy during general anesthesia, this study is working to add information of value regarding perioperative metabolic management and supporting safer anesthetic techniques.

Literature Review

Anesthetic and surgical stress can provoke a surprising metabolic upheaval even in individuals without prior diabetes , so-called Stress-induced Hyperglycemia (SIH), a transient yet clinically important elevation of blood glucose during the perioperative period. In a landmark retrospective

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study, **Davis et al.** examined nearly 2,000 non-diabetic general-surgery patients and reported that roughly one in three developed hyperglycemia (blood glucose >140 mg/dL) within 48–72 hours after surgery — and about one in ten exceeded 180 mg/dL.

SIH arises from the body's innate "fight or flight" reaction to surgical trauma: activation of the hypothalamic–pituitary–adrenal axis and sympathoadrenal system leads to surges in stress hormones (cortisol, catecholamines, glucagon) and inflammatory cytokines, triggering insulin resistance, increased hepatic glucose output, and reduced peripheral glucose use. Far from being a benign lab anomaly, SIH carries real consequences: in the same study, hyperglycemic patients experienced significantly longer hospital stays and higher rates of postoperative complications — and those with glucose >180 mg/dL had up to a sixfold increase in mortality compared to patients who maintained normoglycemia.

Given its frequency and potential to worsen outcomes, SIH challenges the traditional focus solely on diabetic patients: it underscores the need for perioperative glycemic awareness and monitoring even in "healthy" non-diabetic individuals. As such, understanding the incidence, mechanisms, and implications of SIH is not only scientifically intriguing — it is critically relevant for improving surgical safety and patient care.

A prospective observational study by **Sermkasemsin et al. (2022)** in Thailand assessed 440 non-diabetic patients undergoing intermediate- to high-risk surgery and found that 14.7% developed intraoperative hyperglycemia (≥180 mg/dL). Independent risk factors included ASA physical status ≥3, impaired fasting glucose, anesthesia duration ≥3 hours, intraoperative hypotension, blood transfusion, and perioperative steroid use.

General anesthesia influences the stress response through its effects on the endocrine and inflammatory systems. Induction, laryngoscopy, intubation, and surgical incision stimulate catecholamine release, elevating blood glucose levels (**Desborough, 2021)**. The anesthetic technique and drugs used can significantly modify this stress response.

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Xiong et al. (2023) in a randomized controlled trial comparing total intravenous anesthesia (TIVA) with propofol to inhalational anesthesia with desflurane in type 2 diabetic patients undergoing general surgery reported that the TIVA group had lower perioperative glucose levels and reduced cortisol release at multiple intraoperative time points. These findings suggest that propofol-based TIVA has a less adverse impact on perioperative glucose metabolism than volatile anesthesia.

Liu and Yang (2020) conducted a clinical study in patients with type 2 diabetes mellitus and gastric cancer, showing that those maintained with propofol anesthesia experienced smaller increases in blood glucose and inflammatory markers compared to patients maintained with sevoflurane. This supports the view that intravenous and inhalational agents exert different effects on perioperative glucose metabolism and inflammatory response.

Depth of anesthesia also influences stress responses. **Lv et al. (2022)**, in a randomized trial of elderly patients undergoing laparoscopic colorectal cancer surgery, showed that deeper anesthesia was linked to lower postoperative IL-6 and CRP levels and better short-term recovery. Similarly, **Zhao et al. (2020)** found that optimizing anesthetic depth with IoC monitoring reduced inflammatory cytokines and improved recovery metrics. Reviews between 2019 and 2022 further confirm that inadequate anesthetic depth permits greater nociceptive input, amplifying sympathetic and HPA axis activation, which elevates cortisol, catecholamines, and perioperative hyperglycemia **(Lv et al., 2022).**

Beyond the choice of drugs, anesthesia technique also matters. **Bajracharya et al. (2018)** reported that patients under general anesthesia had higher intraoperative blood glucose levels compared to spinal anesthesia, which maintained more stable glucose, reflecting a reduced stress response.**Emsaad (2025)** found that non-diabetic patients undergoing cesarean section under general anesthesia showed significantly higher blood glucose compared to those under spinal anesthesia, highlighting the stress-protective effect of spinal anesthesia.

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Diab Bani Hani et al. (2021) conducted a study on 302 non-diabetic mothers undergoing cesarean sections to compare the effects of general anesthesia (GA) and spinal anesthesia (SA) on maternal glucose levels. They found that GA was associated with significantly higher pre- and post-operative glucose readings (100.8 mg/dL and 110.1 mg/dL) than SA (83.6 mg/dL and 87.7 mg/dL; $P = 0.00$). The perioperative glucose rise was greater in the GA group, indicating a stronger stress response. Regression analysis identified anesthesia type as the primary factor influencing postoperative glucose, suggesting that GA increases the risk of stress-induced hyperglycemia even in non-diabetic patients.

A comparative study on non-diabetic patients undergoing surgery under general and spinal anesthesia found a significant rise in blood glucose levels during the perioperative period. Although both groups were similar in age, weight, and fasting duration, glucose readings increased more rapidly and significantly in the general anesthesia group. Measurements taken at four time points showed a consistent and greater proportional increase in glucose levels under general anesthesia ($p < 0.01$), indicating a stronger stress response compared to spinal anesthesia. **El-Radaideh et al. (2019)**

Samuel et al. (2023) showed that general anesthesia in lower abdominal and pelvic surgeries resulted in higher perioperative blood glucose, while spinal anesthesia offered better glucose stability and reduced stress hyperglycemia. Spinal anesthesia produces a lower hyperglycemic response than general anesthesia mainly because it blocks sympathetic outflow and reduces cortisol and catecholamine release, thereby blunting the surgical stress response and limiting perioperative glucose rise.

Laparoscopic cholecystectomy (LC), though minimally invasive, still elicits a significant metabolic stress response, including transient hyperglycemia. Perioperative hyperglycemia during LC has been attributed to surgical stress, pneumoperitoneum, and anesthesia-related factors. **Potisuk et al. (2019)** reported that non-diabetic patients undergoing abdominal surgeries,

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including LC, frequently developed intraoperative hyperglycemia, highlighting the metabolic response even in the absence of diabetes.

Similarly, **Elbarbary et al. (2021)** found that laparoscopic procedures were associated with higher blood glucose variability compared with open surgeries, likely due to increased intra-abdominal pressure from carbon dioxide insufflation and neuroendocrine activation. More recently, **Ahmed et al. (2022)** confirmed that patients undergoing LC under general anesthesia demonstrated perioperative glucose elevations correlated with stress hormone levels, reinforcing the concept that even "routine" laparoscopic surgery provokes a measurable glycemic response. Collectively, these studies emphasize that LC is not metabolically neutral and warrants glycemic monitoring even in non-diabetic patients.

Fayaz et al. (2022) studied 90 non-diabetic patients undergoing laparoscopic cholecystectomy to compare the effects of Dexmedetomidine and Nalbuphine on perioperative blood glucose and hemodynamics. Dexmedetomidine significantly reduced hemodynamic stress responses (heart rate and blood pressure) but did not prevent hyperglycemia, with blood glucose rising to 135–143 mg/dl perioperatively. Nalbuphine had minimal effect on glucose levels. The study indicates that laparoscopic cholecystectomy induces a significant metabolic stress response, only partially attenuated by pharmacologic premedication.

Methodology

This prospective observational study was conducted at the Department of Anesthesia, Mayo Hospital, Lahore, Pakistan, over a period of six months to evaluate perioperative random blood glucose (RBG) levels in patients undergoing elective laparoscopic cholecystectomy.

A total of 41 adult patients were enrolled using a non-probability consecutive sampling technique. The sample size was calculated based on an expected prevalence of 98.3% at a 95% confidence level with 4% absolute precision. Inclusion criteria comprised non-diabetic adult patients aged 18 years or older with American Society of Anesthesiologists (ASA) physical status I or II, while patients undergoing emergency surgery, those with known diabetes mellitus or

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receiving anti-diabetic medications, patients with endocrine disorders (thyroid, adrenal, or pituitary diseases), and those classified as ASA III or above were excluded. Following a standard preoperative assessment, all patients underwent a uniform general anesthesia protocol induced with propofol, nalbin, and atracurium, and maintained with oxygen and isoflurane.

Perioperative glucose monitoring involved collecting RBG samples using a glucometer within 15 minutes before anesthesia induction (T0) and within 15 minutes after postoperative extubation (T1), with all values recorded in mg/dl and management of high values (>180 mg/dl) guided by institutional protocol. Ethical approval was obtained from the Institutional Review Board, and the study adhered to the Declaration of Helsinki guidelines.

Data were entered, coded, and analyzed using IBM SPSS Statistics version 26. Descriptive statistics summarized characteristics, presenting normally distributed continuous variables (age, weight, glucose levels) as mean standard deviation (SD), non-normal continuous data as median (interquartile range), and categorical variables (gender, perioperative hyperglycemia thresholds of ≥140 mg/dL and ≥180 mg/dL) as frequencies and percentages. The normality of blood glucose differences was assessed using the Shapiro–Wilk test; paired t-tests were utilized for normally distributed differences, while the Wilcoxon signed-rank test was applied to non-normally distributed data, with a p-value less than 0.05 considered statistically significant.

Results

1.Demographic and Baseline Characteristics of Patients

A total of 41 non-diabetic patients undergoing laparoscopic cholecystectomy under general anesthesia were included in the study. The mean age of patients was 36.51 ± 8.00 years. Females constituted most of the study population (80.5%). The mean duration of anesthesia was 109.63 ± 21.13 minutes. All patients belonged to ASA physical status I. Hypertension was present in 9.8% of patients, while 90.2% had no associated comorbidity.

Variable	Mean ± SD / n (%)

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Age (years)	36.51 ± 8.00
Duration of anesthesia (min)	109.63 ± 21.13
Female	33 (80.5%)
Male	8 (19.5%)
ASA-I	41 (100%)
Hypertension	4 (9.8%)
No comorbidity	37 (90.2%)

2.Distribution of NPO Duration

Most patients had preoperative fasting duration between 10 and 12 hours, with the highest proportion of fasting for 10 hours (24.4%).

NPO Duration (hours)	Frequency	Percentage
8	6	14.6%
9	7	17.1%
10	10	24.4%
11	7	17.1%
12	7	17.1%
13	4	9.8%

3. Comparison of Preoperative and Postoperative Blood Glucose Levels

The mean postoperative blood glucose level was significantly higher compared to the preoperative level. Mean blood glucose increased from 108.71 ± 11.38 mg/dL preoperatively to 166.00 ± 31.20 mg/dL postoperatively. Paired sample t-test demonstrated a statistically significant difference ($p < 0.001$).

Variable	Mean ± SD	p-value
BG-T0 (Preoperative)	108.71 ± 11.38	

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BG-T1 (Postoperative)	166.00 ± 31.20	<0.001

4.Incidence and Severity of Stress Hyperglycemia

Stress hyperglycemia was observed in 27 patients (65.9%), whereas 14 patients (34.1%) did not develop stress hyperglycemia. Among affected patients, moderate stress hyperglycemia (defined as 140–179 mg/dL) was observed in 11 patients (26.8%), while severe stress hyperglycemia (≥180 mg/dL) was observed in 16 patients (39.0%).

Variable	Frequency	Percentage
No stress hyperglycemia	14	34.1%
Stress hyperglycemia present	27	65.9%

Severity of Stress Hyperglycemia

Severity	Frequency	Percentage
No stress hyperglycemia	14	34.1%
Moderate	11	26.8%
Severe	16	39.0%

Discussion

The present study was conducted to evaluate the incidence of stress hyperglycemia in non-diabetic patients undergoing laparoscopic cholecystectomy under general anesthesia. The study demonstrated a significant perioperative rise in blood glucose levels, with 65.9% of patients developing stress hyperglycemia postoperatively. These findings suggest that significant metabolic alterations may occur even in non-diabetic individuals undergoing minimally invasive surgery under general anesthesia.

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Laparoscopic cholecystectomy was specifically selected for this study because it is a minimally invasive procedure associated with reduced tissue trauma, smaller incisions, less postoperative pain, and a lower inflammatory response compared with open abdominal surgery. By selecting a procedure with relatively limited surgical stress, the present study aimed to better evaluate the contribution of anesthesia-related stress responses to perioperative hyperglycemia.

In the present study, stress hyperglycemia developed in 27 out of 41 patients (65.9%), while severe stress hyperglycemia was observed in 39.0% of patients. These findings indicate that transient perioperative hyperglycemia is common even among non-diabetic patients undergoing elective laparoscopic procedures. The high incidence observed in this study supports the concept that anesthesia-related neuroendocrine activation may play a clinically significant role in perioperative glucose dysregulation.

Patients who developed stress hyperglycemia had higher blood glucose values both preoperatively and postoperatively compared with patients who did not develop stress hyperglycemia. The mean postoperative blood glucose level among patients with stress hyperglycemia was 182.31 ± 25.94 mg/dL, whereas patients without stress hyperglycemia had a mean postoperative glucose level of 134.00 ± 4.85 mg/dL. Furthermore, patients categorized as having severe stress hyperglycemia demonstrated the highest postoperative glucose levels. This finding suggests that certain individuals may have increased susceptibility to stress-induced metabolic alterations during anesthesia and surgery.

The mean duration of anesthesia in the current study was 109.63 ± 21.13 minutes. Longer exposure to anesthesia may contribute to sustained sympathetic stimulation and prolonged endocrine stress responses, thereby increasing the likelihood of perioperative hyperglycemia. Although the present study was not designed to establish a direct correlation between anesthesia duration and glucose elevation, prolonged anesthetic exposure may have contributed to the observed metabolic changes.

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The majority of patients included in this study were females (80.5%), which is consistent with the higher prevalence of gallstone disease among women. All patients belonged to ASA physical status I, and most patients had no associated comorbid illness. This relatively homogeneous patient population minimized confounding factors such as severe systemic disease and poorly controlled chronic illness, thereby allowing more reliable assessment of perioperative glucose changes associated with anesthesia and surgical stress.

Perioperative hyperglycemia has important clinical implications because elevated glucose levels are associated with impaired immune function, increased inflammatory response, delayed wound healing, and greater risk of postoperative complications. Although postoperative morbidity and hospital outcomes were not specifically evaluated in the present study, the high incidence of stress hyperglycemia observed highlights the importance of perioperative glucose monitoring even in non-diabetic patients undergoing elective surgery under general anesthesia.

Limitations:

The present study has certain limitations.

1. The sample size was relatively small, and the study was conducted at a single center, which may limit the generalizability of the findings.

2. Blood glucose measurements were obtained preoperatively and postoperatively. Serial postoperative glucose monitoring was not performed.

3. In addition, serum cortisol and catecholamine levels were not measured, which could have provided further evidence regarding anesthesia-related neuroendocrine stress responses.

4.Furthermore, because surgery cannot be completely separated from anesthesia, some contribution of surgical stress to the observed hyperglycemia cannot be entirely excluded.

Conclusion

The findings of this study provide important evidence that significant stress hyperglycemia may occur in non-diabetic patients undergoing laparoscopic cholecystectomy under general anesthesia. The use of a minimally invasive surgical procedure strengthens the possibility that

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anesthesia-related neuroendocrine and metabolic responses contributed substantially to perioperative glucose elevation. These findings emphasize the importance of perioperative glucose monitoring and metabolic assessment even in non-diabetic individuals undergoing relatively minor elective surgical procedures.

The study highlights the importance of perioperative blood glucose monitoring even in non-diabetic patients undergoing elective laparoscopic surgery under general anesthesia. Early identification and management of stress hyperglycemia may help reduce potential perioperative complications and improve patient outcomes.

Further studies with larger sample sizes and comparison of different anesthetic techniques are recommended to better evaluate the independent role of general anesthesia in the development of perioperative stress hyperglycemia.

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