



# Feasibility of ERAS in Patients With Gastric Cancer Complicated by Diabetes Mellitus

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## Abstract

Enhanced Recovery After Surgery (ERAS) is the integration of multiple perioperative evidence-based medical practices into a single pathway aimed at eliminating surgical liabilities and improving treatment accuracy to enhance patients' postoperative outcomes. The ERAS Society has been developing guidelines that are widely applicable in the surgical field. ERAS pathways in selective and noncomplicated cases are extensively practiced. However, the ERAS literature excludes patients with comorbidities, such as gastric cancer complicated with diabetes mellitus (DM). Current ERAS guidelines exclude patients with DM in enhanced recovery programs because of insufficient evidence-based medicine on the molecular physiology of the patients in response to surgical insult. Therefore, it is important to implement accelerated rehabilitation surgery for patients with gastric cancer and DM. This review discusses the feasibility and necessity of applying ERAS guidelines to patients with gastric cancer complicated by DM. In addition, we documented the need to lay a logical foundation for enhanced recovery after surgery in patients with gastric cancer complicated by DM.

## Keywords

enhanced recovery after surgery, gastric cancer complicated with diabetes mellitus, logic foundation, feasibility, necessity

## Abbreviations

ERAS, Enhanced Recovery After Surgery; DM, diabetes mellitus

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## Introduction

Enhanced Recovery After Surgery (ERAS) is the integration of multiple perioperative evidence-based medical practices into a single pathway aiming to eliminate surgical liabilities and improve treatment accuracy towards enhancing patients' postoperative outcome.<sup>1</sup> Kehlet<sup>2</sup> identified the lacunae in surgical practice and initiated a multimodal protocol designed to control undesirable sequelae in elective surgeries by inhibiting perioperative risk factors through the understanding the pathophysiological response to surgery. ERAS literature systemized perioperative management by counteracting preexisting diseases, malnutrition, lifestyle modifications, surgical stress, intraoperative hypothermia, perioperative blood transfusion, postoperative pain, hypoxemia, energy levels, drains and feeding tubes, postoperative nausea and vomiting, postoperative-mobilization, and discharge. ERAS society has been developing guidelines widely feasible in the surgical field. ERAS pathways in selective and

noncomplicated cases are extensively practiced. However, the ERAS literature excludes patients with comorbidities, such as gastric cancer complicated with diabetes mellitus (type 1 or type 2 DM). Current ERAS guidelines exclude patients with DM in enhanced recovery programs because of insufficient evidence-based medicine on the molecular physiology of DM in response to surgical insult. A substantial literature has established clear links between surgical stress, blood glucose levels, and DM.<sup>3</sup> Stress is an important cause of abnormal perioperative blood glucose fluctuations. In addition, it increases complications in

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patients with diabetes and delays recovery. Stress reduction is the core mechanism for accelerating rehabilitation surgery. Therefore, it is important to implement accelerated rehabilitation surgery for patients with gastric cancer and DM. Remarkably, the ERAS pathway reduces perioperative stress in the target patient and stabilizes the patient's blood glucose, thereby achieving the goal of reducing perioperative complications and mortality in patients with gastric cancer with DM. Despite insufficient literature on comorbid ERAS patients, we suggest that it is feasible to implement ERAS in patients with gastric cancer complicated by DM. This article discusses the feasibility and necessity of applying ERAS guidelines to patients with gastric cancer complicated by DM. In addition, we documented the need to lay a logical foundation for enhanced recovery after surgery in patients with gastric cancer complicated by DM.

### **The Necessity of ERAS in Patients With Gastric Resections Complicated by DM**

Most patients undergoing gastric surgery are in pathophysiological need of perioperative recovery programs. Having DM should not be a barrier to inclusion in the ERAS guidelines, but rather a necessity. Gastric resection is one of the most successful treatment options for patients with diabetes; Type 2 DM is thought to be one of the most common cases where the metabolic gastric bypass is the most ideal treatment option. It is also reported that gastric cancer cases complicated by DM are also common.<sup>4</sup> Secondly, blood glucose fluctuation caused by pathogenic factors is similar to that of gastric surgery itself. Surgical stress plays a significant role in endocrine metabolic fluctuations and in inflammatory cascades. Postoperative complications in patients with gastric cancer complicated by DM require strict perioperative care with targeted blood glucose control measures.<sup>5</sup> Therefore, perioperative pathways to reduce stress and inflammation, improve insulin, and reduce insulin resistance are conducive to patients' surgical recovery, and are precisely an advantage that practitioners should not neglect in reference to patients with DM. Modifications favoring blood glucose control practiced in the ERAS guidelines could meet the pathophysiological demands in patients with DM.

### **Epidemiology of DM and Gastric Cancer**

The surgical curve related to age is shifting towards older age since modalities to ensure safe perioperative periods in different age groups are made possible with advancements in technology and adherence to current evidence-based medicine. However, perioperative challenges lie ahead, as older patients usually succumb to comorbidities such as gastric resections complicated by DM.

DM has become a global public health problem and is one of the 3 chronic noncommunicable diseases endangering human health.<sup>6</sup> The incidence of DM increased from 108 million to 422 million in 34 years due to population growth, bad lifestyle

habits, improved medical armamentarium, and aging society.<sup>7</sup>  $\beta$ -cell destruction from T-cells (type-1) DM caused by (type-IV) hypersensitivity due to loss of self-tolerance among T-cells resulting in less insulin production accounts for 5% to 10% cases of diabetes, while insulin resistance, failure of cells to respond to insulin due to lack of proper placement of glucose transporters to their cell membranes, failure of pancreatic normal function causing a disturbance in insulin production is known as type-2 DM which has an occurrence rate of 90% to 95%.<sup>8</sup> In 2017, there are estimated 374 million people worldwide with impaired glucose intolerance; moreover, this value is expected to increase by 10% in 2045.<sup>9</sup> Studies have reported an increase in DM cases that require surgery compared to non-DM.<sup>10</sup> Several pieces of literature have studied the effect of DM during surgical interventions.<sup>11</sup> Chronic metabolic conditions with inflammatory characteristics are linked with different types of malignancies. Diabetes is considered a chronic metabolic pathway that can lead to various diseases. Song narrated an association between autoimmune diseases and gastric cancer from 52 observational studies.<sup>12</sup> It is assumed that the limited sensation in patients with DM might influence their increased salt consumption, which might provide a favorable environment for H-pylori growth. Although studies have concluded no absolute correlation between gastric cancer and DM,<sup>13</sup> it is clear that patients with DM experience several physiological changes that could influence their susceptibility to carcinogenesis.

Additionally, DM medications have also been bridged between gastric malignancies and DM.<sup>4,14</sup> Generally, patients with gastric cancer with DM have an increased risk of disease progression and fatality compared to those without DM.<sup>15</sup> The lack of sufficient ERAS literature with established criteria and guidelines for DM management associated with gastric malignancies is significantly higher compared to DM and gastric cancer independently. Most surgical DM cases are managed according to hospital norms and doctors' experiences. Largely, the postsurgical period of gastric cancer takes approximately 10 to 14 days for the patient to be discharged and a recovery period of approximately 50 to 60 days to return to the preoperative state. However, due to metabolic insufficiency, perioperative fasting and traumatic stress cause perioperative blood glucose levels to fluctuate rapidly. Thus, the degree of insulin resistance became severe after surgery. Consequently, the incidence of perioperative complications is higher, causing delayed recovery. Adjustments in management according to the patient's physiological conditions are imperative for enhancing patient recovery.

### **Blood Glucose Control can Effectively Reduce Postoperative Complications**

The core principle of ERAS is evidence-based perioperative optimization and rehabilitation. The ERAS guidelines have the advantage of improving early clinical outcomes of patients with gastric cancer, postoperative hospital stay, and survival.<sup>16</sup> DM has a tendency to increase postoperative complications if not well controlled perioperatively. DM is not only a

preexisting preoperative condition; postoperative DM is also common. Approaches to reduce stress, improve insulin levels before surgery, and reduce insulin resistance after surgery have been reported in ERAS. These positive outcomes are beneficial for patient recovery.<sup>17</sup> A recent randomized control trial has presented favorable results among ERAS guidelines compared to conventional perioperative guidelines in gastric cancer.<sup>16</sup> Previous study suggests that patients who will not benefit from ERAS are those with underlying comorbidities that could propagate undesirable outcomes; on the contrary, ERAS protocols such as carbohydrate loading, minimal invasive procedure, and minimal opioid use followed by targeted blood glucose levels can result in a better prognosis. The inclusion of DM in ERAS is a problem that needs attention and direction that the ERAS society should consider. The existing literature is yet to fully standardize the ERAS pathways in patients with DM.<sup>18</sup>

### **Feasibility of ERAS in Patients With Gastric Cancer Complicated by DM**

A sizeable compilation of evidence shows that ERAS pathways are now implemented in pediatric, adult, and aged patients in several high-risk operations in different surgical disciplines including cerebrovascular, cardiovascular, gastroesophageal, and gastrointestinal cancer resections, including clean-to-clean contaminated operations, and have all benefited from ERAS pathways.<sup>19–24</sup> Despite the extensive application of ERAS in several high-risk procedures, impediments such as DM are still considered liabilities that ERAS pathways are not capable of controlling. At present, many studies on the ERAS concept have considered patients with complications, such as DM, in the ERAS exclusion criteria. It is known that blood glucose levels are difficult to control, and high blood glucose levels would increase the risk of intraoperative and postoperative complications. The fact that uncontrolled blood glucose levels increase surgical risks and delay recovery makes it necessary to modulate standard evidence pathways that would limit unwanted pathophysiological outcomes. ERAS protocols make it feasible for patients with DM to be included in the ERAS programs. Studies show that ERAS pathways decrease hospital stay by limiting postoperative complications through strategic perioperative planning and implementation programs.<sup>25–27</sup> ERAS study presented by Festejo Villamiel et al<sup>28</sup> found that 28% of colorectal surgery inpatients suffered from DM. Interestingly, these ERAS patients showed no significant difference in terms of length of hospital stay and complications between patients with and without DM.

### **Safety of Carbohydrates Load Before Surgery**

It is vital to maintain glycosylated hemoglobin in the blood glucose range, as failure to control glycosylated hemoglobin as a postoperative complication could be an inevitable outcome.<sup>29</sup> Previously, it was signified that carbohydrate administration prior to surgery would lead to the retention of

fluid in the stomach cavity, which would lead to aspiration and suffocation during anesthesia. It is now understood that these assumptions are not based on scientific evidence. To verify this hypothesis, scholars have conducted some studies, and the latest research has shown that glycosylated hemoglobin of less than 7% does not affect gastric emptying. Hence, it is safe to drink carbohydrate fluid before surgery in patients with gastric cancer complicated by diabetes. Generally, if blood glucose can be controlled at an appropriate level, it is safe to drink carbohydrate fluid before surgery in patients with gastric cancer complicated by DM. Preoperative carbohydrates play a positive role in controlling insulin resistance.<sup>30,31</sup>

### **Oral Carbohydrates Before Surgery can Improve Insulin Resistance**

Surgery impacts alterations in metabolic states, which could deprive glucose metabolism by interfering with the insulin resistance pathway.<sup>32</sup> A randomized controlled study by Tewari et al<sup>33</sup> showed that oral carbohydrates can minimize the rate of insulin resistance among surgical patients. The most obvious difference between ERAS and the old surgical doctrine is preoperative carbohydrate loading. ERAS excludes patients with DM, anticipating that oral carbohydrates before surgery would cause fluctuations in blood glucose, consequently affecting surgical prognosis. Oral carbohydrates before surgery can significantly increase the synthesis and secretion of insulin and reduce insulin resistance after surgery, which is conducive to the stabilization of blood glucose after surgery. Hence, it is relatively safe to administer carbohydrates before surgery.<sup>11</sup> ERAS studies suggest that surgical patients should not fast, and oral carbohydrates should be administered up to 2 to 3 preoperative hours.<sup>5</sup> We have adopted a strategy in the general surgery unit of our hospital for both DM and non-DM cases as part of our modified ERAS guidelines, and we have recorded positive effects on regulating blood glucose levels and improving insulin resistance. A study conducted by Fujikuni et al<sup>34</sup> showed the superiority of ERAS guidelines over traditional doctrines in terms of nutritional outcomes and blood glucose control.

### **Convenient Blood Glucose Control for Patients With Gastric Cancer Complicated by DM**

To date, available guidelines suggest that elective surgeries, including both minor and major procedures, only require general perioperative management of blood glucose. In other words, a random blood glucose level of less than 10 mmol/L and a fasting blood glucose of less than 7.8 mmol/L is sufficient to undergo a surgery. Furthermore, most of the patients on whom we have performed gastric cancer surgery had progressive cancer, and a life expectancy of less than 5 years accounted for the majority. For these patients, blood glucose control required a fasting blood glucose upper limit of 10 mmol/L and postprandial blood glucose within 13.9 mmol/L. Therefore, for all

patients with gastric cancer complicated by diabetes, blood glucose levels can be controlled. Consequently, from the perspective of controlling blood glucose, it is also convenient and feasible for patients with gastric cancer complicated by diabetes to undergo ERAS pathways.

## **The Strategy of Blood Glucose Control in the Perioperative Period**

As explained above, it is feasible to control DM using strategic ERAS principles, such as long-term preoperative assessment and preoperative carbohydrate interventions. If ERAS is feasible for metabolic gastric resections as well as in patients with gastric cancer, what could possibly be the fundamental disadvantage of including patients with DM with gastric cancer under the ERAS guidelines? To answer this question, it is essential to understand the core distinction between patients with diabetes and our average ERAS patients. The most fundamental difference is the blood glucose control. Therefore, in patients with gastric cancer complicated by DM, the primary obstacle is the incorporation of blood glucose management and the implementation of ERAS pathways that can maintain blood glucose levels. Standard blood glucose control measures should be applied to patients with ERAS until the day of the surgery. In cases where the blood glucose level is poorly controlled, an insulin pump or insulin should be used.

Blood glucose monitoring and regulation of ERAS in patients with gastric cancer complicated by DM are mainly to maintain the original blood glucose control method as far as possible and insulin use during operation, and monitor the whole process; if the blood glucose is not well controlled, adjustments should be made in time.

### ***Preoperative Blood Glucose Control***

If blood glucose can be controlled and stabilized by oral drugs, they will be administered until the morning of the operation. If the blood glucose control of oral drugs is unstable, subcutaneous insulin injections are administered. When the blood glucose control level reaches the target value, subcutaneous insulin is administered until the morning of the operation. For those who had received insulin injections before and whose blood glucose control level reached the inclusion standard, the insulin injection plan would not be adjusted until the morning of the operation. For patients with poor blood glucose control, the insulin pump should be considered. The initial daily dose must be set according to the patient's blood glucose level, with 50% as the basic dose, and the hourly dose must be determined according to the whole-day dose distribution table of the insulin pump. The remaining 50% should be administered as premeal doses before 3 meals.

### ***Operative Blood Glucose Control***

Patients with the original oral medication should stop taking the medication on the morning of the operation and decide whether

to inject insulin subcutaneously according to their blood glucose level. Patients who received subcutaneous insulin injections should decide whether to reduce or stop insulin injections according to the blood glucose level on the morning of the operation. Patients with an insulin pump will be administered a basic insulin pump during the operation. During the operation, the patient's blood glucose (Q1h) should be closely monitored and insulin pumped intravenously, and the infusion speed and insulin dose should be adjusted according to the blood glucose level. If the blood glucose is lower than 4 mmol/L, a glucose injection is mandatory.

### ***Postoperative Operation***

If patients use oral medications and inject insulin to control blood glucose before surgery; these patients should be administered intravenous infusion and additional subcutaneous insulin injection (in the case of blood glucose levels > 10 mmol/L). Patients using a preoperative insulin pump to control blood glucose should use an insulin pump and inject subcutaneous insulin injections (if blood glucose is > 10 mmol/L). The insulin dose should be adjusted in a timely manner according to postoperative blood glucose changes in patients (monitoring blood glucose Q2h) to prevent diabetic ketosis and hypoglycemia; these eligible patients take should sips of water after awaking, oral nutritional supplements (electrolyte formula for special medical use) 6 h postoperatively, fluid diet, and oral nutritional supplements on the first postoperative day, gradually increasing.

### ***The Use of Insulin Pump***

Insulin pumps should be used to control blood sugar levels in patients with fluctuating blood glucose levels and those who experience difficulties in controlling blood sugar levels. This is because in the perioperative period, especially after the operation, patients tend to have an irregular diet and intravenous infusion of glucose water. It is conceivable that, although the absolute value of blood glucose is not very high, the fluctuation is more severe. Some studies have shown that the safety management of insulin pumps and dietary intervention can effectively control blood glucose, reduce the dosage of insulin, shorten the time to meet the standard of blood glucose, and reduce the occurrence of hypoglycemia in patients with gastric cancer complicated with DM.

### ***The Application of Instant Blood Glucose Meter in Patients With Gastric Cancer With DM***

The core of ERAS in gastric cancer complicated by DM lies in the control of blood glucose levels during the perioperative period. The basis of blood glucose control is the effective monitoring of blood glucose. Our ideal blood glucose monitoring program is to monitor patients' blood sugar at any time; unfortunately, according to the traditional method, blood sugar can only

**Table 1.** Standard and ERAS Items Considered.

	Enhanced recovery after surgery protocol	Conventional group protocol
<b>Preoperative</b>		
Health education	Preoperative counseling and education about the ERAS protocol; written, informed consent	Routinely sign preoperative consent
Bowel preparation	Functional bowel preparation, change to a scum-free diet 2 days before surgery	Traditional mechanical bowel preparation
Preoperative fasting	Fast for 6 and 2 h before surgery, and drink “Lefu” (electrolyte formula food for special medical purposes) 350 and 200 mL on the night before and 2 h before surgery, respectively	12 h for solids and 8 h for clear, before surgery
Anesthesia preparation	Patient evaluation and analgesia education; preoperative gastric ultrasound evaluation performed the day, preoperation; ultrasound measurement of gastric antrum and ultrasound-guided TAP block performed when entering the room	Traditional anesthesia visit, risk assessment, and signature
<b>Intraoperative</b>		
Anesthesia	Thoracic epidural anesthesia combined with general intravenous anesthesia, deep muscle relaxation, and muscle relaxation monitoring	General anesthesia
Urinary catheter	Urinary catheter insertion after anesthesia, removal within 24-48 h, post-operation	Urinary catheter removal on the 3-7 postoperative day
Body temperature management	Infusion warmer and warming blanket	Not standardized
Fluids	Goal-directed fluid management (intravenous fluids 3-6 mL/kg/h, urine volume 2 mL/kg/h), < 3000 mL during the day of surgery)	Not standardized
Abdominal drain	No drains left routinely	Drains left routinely. Removal depending on the drainage volume (24 h drainage flow is less than 100 mL)
Nasogastric tube	In principle, no nasogastric tubes postoperatively or removal of nasogastric tube within 24 h	Routine placement; remove after the oral diet.
<b>Postoperative</b>		
Analgesia	Multimodal: TAP block and PICA	Treat symptomatically; inject opioids intramuscularly in case of pain.
Prevention and treatment of nausea and vomiting	Use a variety of perioperative strategies combined with postoperative intravenous infusion of serotonin receptor antagonists, if necessary. Metoclopramide is injected intramuscularly.	Symptomatic treatment, intramuscular injection, or intravenous infusion of metoclopramide for nausea and vomiting
Diet	Sips of water after patient awakens, oral nutritional supplement 6 h postoperatively, fluid diet, and oral nutritional supplements on the first postoperative day, gradually increase	Not standardized
Mobilization	Getting out of bed with assistance as soon as possible; ambulation with assistance on the first postoperation day, if tolerable (60 m), then gradually extend, and set a daily activity goal	Not standardized

Abbreviations: ERAS, Enhanced Recovery After Surgery; PICA, patient-controlled intravenous analgesia.

be measured every 2 h at most. Because of the pain or disturbance in the rest of the patient, blood sugar cannot be tested frequently. Hence, the feasibility of frequent blood glucose monitoring is less widely adopted. Blood glucose measured every 2 h requires 12 blood glucose tests per day. Patients experience sleep interruption, leading to additional psychological stress. Notably, patients cannot undergo regular blood glucose surveillance. Therefore, we used an instant blood glucose meter.

The transient blood glucose meter has several advantages. First, it can be used for 14 days. The initial calculation is based

on the period of 4 days before the operation and 10 days after the operation, dynamic observation of blood glucose levels, and understanding of the trends and regularity of blood glucose changes. Second, stress caused by the device occurs during the commencement of the intervention. Third, the cost of routine use by the patient is similar to the cost of our Q4h blood glucose test (excluding the instrument). Finally, the patient can achieve real-time data transmission, which is advantageous to our clinical research on blood glucose monitoring. However, this method has drawbacks. The instantaneous blood glucose

meter measures blood glucose in the tissue fluid; in the presence of postoperative edema and other conditions, certain errors may occur. Measurements of regular blood sugar levels once or twice a day should be performed for comparison. When clinical manifestations such as hypoglycemia do not match the blood glucose test results, regular blood sugar tests are also needed.

### Standard and ERAS Protocols

The standard and ERAS protocols are described in Table 1, which summarizes the differences between them.

### Conclusion

Patients with gastric cancer have benefited from ERAS pathways; however, patients with DM are contraindicated under the current guidelines. ERAS is safe, necessary, and feasible for patients with gastric resections complicated by DM. The most obvious difference compared to normal patients with ERAS is glycemic control during the perioperative period, and perioperative management can safely control patients' blood glucose levels. We believe that patients with gastric resections complicated by DM will benefit from ERAS.

### Study Limitations

There were certain limitations associated with this review. There is a lack of high-level evidence of gastric cancer cases with diabetes to implement the ERAS project; thus, high-quality clinical research is needed. At the same time, we need to explore specific blood glucose management schemes for these patients. Based on clinical research, we need to formulate a detailed implementation of the ERAS plan to benefit patients, which is also conducive to the promotion of the ERAS project. Transient blood glucose measurement is expensive, which increases the financial burden on these patients. Relevant papers might have been neglected by us because they shared the same scientific logic.

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### Ethical Approval

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