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About the journal

The *Annals of Clinical Nutrition and Metabolism* (ACNM, eISSN: 2799-8363) is a peer-reviewed, open-access, joint official journal of the Korean Society of Surgical Metabolism and Nutrition, the Korean Society for Parenteral and Enteral Nutrition, the Asian Society for Surgical Metabolism and Nutrition, and Japanese Society for Surgical Metabolism and Nutrition. This joint journal was launched in December 2021 after merging the Journal of Clinical Nutrition (pISSN: 2289-0203) from 2007 to 2021, published by the Korean Society for Parenteral and Enteral Nutrition, and the Surgical Metabolism and Nutrition (pISSN: 2233-5765) from 2010 to 2021, published Korean Society of Surgical Metabolism and Nutrition. Its abbreviated title is Ann Clin Nutr Metab.

Aims and scope

The *Annals of Clinical Nutrition and Metabolism* (ACNM) aims to contribute to health of human being by improving clinical nutrition practice through scientific research, including basic science and clinical studies related to nutrition and metabolism.

Scope: The journal's scope includes the following in the field of nutrition, metabolism, and medicine.
- Nutritional screening and assessment
- Nutritional planning
- Perioperative nutritional care
- Nutrition therapy in acute and chronic disease
- Critical care nutrition
- Optimizing enteral and parental therapy
- State-of-the-art diagnostic techniques for nutritional care
- Innovative surgical or interventional techniques for nutritional care
- Nationwide nutrition survey
- Scientific laboratory research

Regional scope: Its regional scope is mainly Asia, but it welcomes submissions from researchers all over the world.

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Editorial

Bridging evidence and clinical practice: a practical guide for enteral nutrition from the Korean Society for Parenteral and Enteral Nutrition

Suk-Kyung Hong

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Enteral nutrition plays a crucial role in treating critically ill patients. However, administering enteral nutrition while assessing tolerance is especially challenging in patients with impaired consciousness and gastrointestinal dysfunction, including those with multi-organ failure. Consequently, this intervention must be approached with utmost caution.

International guidelines have recently been updated by the American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine [1] and the European Society for Clinical Nutrition and Metabolism [2], each supported by varying levels of evidence. However, these guidelines primarily address contentious issues affecting clinical outcomes while often overlooking safety and feasibility in real-world settings. In clinical practice, many aspects of enteral nutrition continue to require multidisciplinary consensus to ensure effective communication and implementation. Relying solely on evidence-based approaches can be challenging because they tend to focus on highly specific details without considering broader practical concerns.

In this issue of *Annals of Clinical Nutrition and Metabolism*, an article by Chang et al. [3] introduces the Korean Enteral Nutrition Practical Guide developed by the Korean Society for Parenteral and Enteral Nutrition (KSPEN) [3]. In clinical practice, challenges related to safety incidents are encountered more frequently than improvements in clinical outcomes solely attributable to enteral nutrition [4]. Therefore, it is essential for multidisciplinary teams within each institution or country to establish a systematic, updated approach through structured enteral nutrition protocols based on mutual consensus. This strategy will promote safe and effective administration in intensive care units and ultimately improve patient care and outcomes.

Studies have demonstrated that implementing enteral feeding protocols is associated with improved energy intake and a reduced incidence of enteral nutrition-related adverse events in critically ill patients [5,6]. The publication of the Korean Enteral Nutrition Practical Guide by KSPEN represents a significant advancement as an updated clinical guideline reflecting expert consensus. It is tailored to the Korean healthcare environment and is grounded in the expertise and experience of healthcare professionals in the field. This guideline marks an important step toward standardizing enteral nutrition practices in Korea, ensuring both efficacy and safety in clinical application.

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Authors' contribution

All work was done by Suk-Kyung Hong.

Conflict of interest

Suk-Kyung Hong has served as the editor of the *Annals of Clinical Nutrition and Metabolism* since 2021. However, she

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Special Article

A practical guide for enteral nutrition from the Korean Society for Parenteral and Enteral Nutrition: Part I. prescribing enteral nutrition orders

Ye Rim Chang[1], Bo-Eun Kim[2], In Seok Lee[3], Youn Soo Cho[4], Sung-Sik Han[5], Eunjung Kim[6], Hyunjung Kim[2], Jae Hak Kim[7], Jeong Wook Kim[8], Sung Shin Kim[9], Eunhee Kong[10], Ja Kyung Min[11], Chi-Min Park[12], Jeongyun Park[13], Seungwan Ryu[14], Kyung Won Seo[15], Jung Mi Song[16], Minji Seok[17], Eun-Mi Seol[18], Jinhee Yoon[19], Jeong Meen Seo[20], for KSPEN Enteral Nutrition Committee

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Introduction

To reduce complications and improve patient safety in enteral nutrition (EN), it is essential to establish and adhere to policies and standardized procedures for routine practices and decision-making throughout the EN process. Effective communication among all members of the multidisciplinary team is also crucial. An interdisciplinary group from the Korean Society for Parenteral and Enteral Nutrition (KSPEN) has developed a practice guide that is essential for healthcare professionals in ensuring the safe delivery of EN, taking into account the domestic realities of EN administration in Korea.

Methodology

To develop this document, the KSPEN EN committee first identified key questions related to EN and subsequently categorized them into relevant sections, including prescribing

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Abstract

Purpose: This study aimed to develop a comprehensive practical guide for enteral nutrition (EN) designed to enhance patient safety and reduce complications in Korea. Under the leadership of the Korean Society for Parenteral and Enteral Nutrition (KSPEN), the initiative sought to standardize EN procedures, improve decision-making, and promote effective multidisciplinary communication.
Methods: The KSPEN EN committee identified key questions related to EN practices and organized them into seven sections such as prescribing, delivery route selection, formula preparation, administration, and quality management. Twenty-one experts, selected based on their expertise, conducted a thorough literature review to formulate evidence-based recommendations. Drafts underwent peer review both within and across disciplines, with final revisions completed by the KSPEN Guideline Committee. The guide, which will be published in three installments, addresses critical elements of EN therapy and safety protocols.
Results: The practical guide recommends that EN orders include detailed elements and advocates the use of electronic medical records for communication. Standardized prescription forms and supplementary safety measures are outlined. Review frequency is adjusted according to patient condition—daily for critically ill or unstable patients and as dictated by institutional protocols for stable patients. Evidence indicates that adherence to these protocols reduces mortality, complications, and prescription errors.
Conclusion: The KSPEN practical guide offers a robust framework for the safe delivery of EN tailored to Korea's healthcare context. It emphasizes standardized protocols and interdisciplinary collaboration to improve nutritional outcomes, patient safety, and operational efficiency. Rigorous implementation and monitoring of adherence are critical for its success.

Keywords: Drug-related side effects and adverse reactions; Enteral nutrition; Iatrogenic disease; Patient safety; Republic of Korea

EN orders, selecting the delivery route and initiating EN, preparing EN formulas, general administration, safe use of EN delivery systems, medication administration, and quality management.

Twenty-one experts were assigned to address these key questions based on their expertise and experience. Following a comprehensive literature review, evidence-based practice recommendations were formulated along with rationales supported by relevant references. Draft recommendations for each key question underwent peer review within the same professional discipline and cross-review by experts from other disciplines. Finally, the KSPEN Guideline Committee conducted an additional review to finalize the Practice Guide for EN. This guide will be published in seven installments.

Practice guide

Key question 1. What elements should be included in EN therapy recommendations?

Practice recommendation

- The following elements should be included in EN orders:
  1. Indications and rationale for enteral feeding
  2. Enteral feeding formula name (generic name, e.g., high-protein standard formula, or product name), concentration (kcal/mL), caloric value, and category of EN formula
  3. Reasons for recommending or changing a specific formula
  4. Tube information, including the delivery route (e.g., nasogastric tube, nasojejunal tube, gastrostomy tube, or jejunostomy tube)
  5. Single dose volume (mL) or total daily volume (mL)
  6. Administration method (e.g., continuous infusion, intermittent infusion, or bolus feeding)
  7. Feeding rate, including initial rate, target rate, and progression schedule
  8. Flush volume and schedule
  9. Daily target or provided nutrient intake
     - Mandatory: total volume, energy, protein, and fluid intake
     - Optional: energy per body weight (kcal/kg), carbohydrate (g), and protein (g)
  10. Monitoring parameters
     - Adverse effects: refeeding syndrome, gastrointestinal complications, improper tube placement (to be monitored as early as possible)
     - Trends in blood tests
     - Trends in anthropometric measurements
     - Tolerance to enteral feeding: symptoms such as abdominal distension, vomiting, diarrhea, and constipation
- Additional infusion protocols should be provided (e.g., patient positioning, oral care, conditions requiring discontinuation of feeding).
- Electronic medical records should be used to communicate

and document responses and progress by the multidisciplinary team managing enteral-fed patients.

Rationale

Even among critically ill patients with a lower tolerance for enteral feeding, significant reductions in mortality [1], a decreased incidence of complications such as diarrhea, and improved early initiation with appropriate calorie delivery have been reported [2]. The implementation of an enteral feeding protocol in the intensive care unit resulted in a shorter time to initiate feeding, a higher rate of achieving target nutritional intake [3], and decreased reliance on parenteral nutrition [1]. Additionally, incorporating nutrition assessment findings into nutritional support recommendations [4] led to increased energy and protein intake, shorter hospital stays, and improvements in serum albumin levels and body weight [5]. The integration of nutrition assessments and prescription recommendations via electronic medical records has been reported to facilitate efficient communication among healthcare professionals and specialists, thereby contributing to improved nutritional status, better maintenance of electrolyte balance and optimal blood glucose levels, reduced medical costs, and fewer prescription errors [6].

Key question 2. What are the essential components of an enteral feeding prescription, and what adjuncts can improve patient safety?

Practice recommendation

• Standardized enteral feeding prescription form

A standardized enteral feeding prescription form should include the following essential components (Figs. 1, 2):

1. Patient information
   - Name and registration number
   - Height and weight
   - Specific considerations such as allergies that must be taken into account for enteral feeding administration
2. Total amount
   - Total energy ______ kcal/day
   - Total protein ______ g/day
   - Total carbohydrate ______ g/day
   - Total fat ______ g/day
   - Total fluid ______ mL/day
3. Enteral feeding formula
   - Name of the enteral feeding formula (e.g., high-protein standard) or product name
   - For pediatric patients, the concentration (kcal/mL) should be specified
4. Administration route and enteral access device

Patient information			
Name: ______	Registration number: ______	Age: ______	Body weight (kg): ______
Allergy information: ______			

Total amount		Enteral feeding formula	
☐ Total energy ____ kcal/day	☐ Total fat ____ g/day	☐ Standard	☐ Carbohydrate controlled
☐ Total protein ____ g/day	☐ Total fluid ____ mL/day	☐ Standard-high protein	☐ Hydrolyzed
☐ Total carbohydrate ____ g/day		☐ Standard-high calorie	☐ Immune modulating
		☐ Fiber containing	☐ Low electrolyte

Route and access		
☐ Orogastric	☐ Nasogastric	☐ Gastrostomy
☐ Oroduodenal	☐ Nasoduodenal	☐ Jejunostomy
☐ Orojejunal	☐ Nasojejunal	

Administration methods and rate	
☐ Continuous	☐ Start at rate of ____ mL/hr
	☐ Increase by ____ mL/hr every ____ hours, till target ____ mL/hr
☐ Intermittent	☐ Start by ____ mL for ____ min, ____ times per day
	☐ Increase by ____ mL per meal for ____ min, till target ____ mL per meal, ____ times per day

Others
☐ Flush feeding tube with ____ mL every ____ hours (minimum 30 mL per flush)
☐ Head of bed 30°–45°

Fig. 1. Example of an enteral feeding prescription protocol.

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Monitoring
☐ Assess gastric residual volume (GRV) before intermittent feeding or every ____ hours.
☐ If GRV is ≥500 mL, discontinue enteral nutrition for ____ hours, reassess, and resume feeding if GRV is <500 mL.
☐ Monitor tolerance to enteral nutrition every ____ hours.
☐ Assess and manage enteral feeding tube placement every ____ hours.
☐ Check body weight daily or every ____ days.
☐ Monitor blood glucose levels.
Laboratory orders
☐ Check blood tests daily or every ____ days.
☐ Check serum magnesium daily or every ____ days.
☐ Check serum phosphorus daily or every ____ days.
Supplementary orders
☐ Medications may be administered via the enteral feeding tube, but at least 15 mL of water should be flushed before and after administration.
☐ Medications should not be mixed with enteral nutrition formula.

Fig. 2. Example of supplementary orders.

- Administration route (e.g., nasogastric, gastrostomy, nasojejunal, or jejunostomy)

5. Administration method and rate
   - Method of administration (e.g., continuous infusion or intermittent feeding)
   - Volume and rate of administration
   - Guidelines for dose escalation and progression of nutritional support

• Supplementary items for patient safety

To improve patient safety, guidelines and procedures should be established to integrate the following enteral feeding prescription directives within the ordering communication system:

1. Confirmation of tube placement via radiography at the initiation of EN (except in neonates and pediatric patients with multiple inserted tubes to minimize radiation exposure)
2. Establishment of standardized methods for enteral tube flushing
3. Monitoring the appropriateness of bed elevation and EN tolerance
4. Management and evaluation of enteral access devices based on infection control guidelines
5. Monitoring parameters: biochemical test results, intake and output measurements, weight and physical examination, gastrointestinal tolerance
6. Specification of product type, prescribed amount, and administration schedule when using calorie- or nutrition-dense food products

• Consultation with the nutrition support team

Collaboration with the nutrition support team or the clinical nutrition department should be sought when necessary.

Rationale

A clear protocol outlining the essential components of an enteral feeding prescription ensures that patients receive the appropriate formula via the correct route in a timely manner. Healthcare providers should document these essential components in electronic medical records (Fig. 1). A prospective study evaluating the implementation of an ordering communication system demonstrated a significant reduction in prescription error rates after its adoption [7].

The use of enteral feeding protocols improves the delivery of energy, protein, and fluids in critically ill patients—who may experience interruptions in EN due to procedures such as intubation, extubation, gastrointestinal interventions, or imaging studies [8,9]. The nutrition support team or clinical nutrition department should determine which enteral feeding protocol is most suitable for each patient and how to effectively implement the prescription process.

Supplementary prescription orders (Fig. 2) help ensure adequate energy and protein intake, maintain patient safety, and assist healthcare providers in monitoring EN therapy. Although not mandatory, these supplementary orders enhance the clarity and accuracy of EN prescriptions.

Key question 3. How frequently should enteral feeding prescriptions be renewed?

Practice recommendation

• The frequency of reviewing EN prescriptions should be

determined based on the EN protocol of each healthcare institution.
- Every time the EN prescription is modified or re-prescribed, all items included in the prescription should be re-evaluated.
- Critically ill patients, postoperative patients, patients with poor blood sugar control, patients with unstable fluid and electrolyte status, high-risk patients with refeeding syndrome, and neonatal and pediatric intensive care patients should be monitored daily, and their EN prescriptions should be reviewed [10].
- For stable hospitalized patients, those in long-term care facilities, and home care patients, the monitoring and EN prescription review frequency should be determined according to the protocol of each healthcare institution [11,12].

Rationale

Regular review and monitoring of EN prescriptions allow early identification of clinical and metabolic complications and ensure that nutritional support is provided safely. Each healthcare institution should establish protocols for the review and renewal frequency of EN prescriptions, involving nutrition support specialists from various fields. Additionally, institutions should monitor adherence to these protocols to ensure patient safety and evaluate the effectiveness of nutritional interventions.

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Authors' contribution

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Methodology: all authors. Project administration: all authors. Visualization: all authors. Funding acquisition: Not applicable. Writing – original draft: all authors. Writing – review & editing: all authors. All authors read and approved the final manuscript.

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Supplementary materials

None.

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Review

Pathogenesis, risk factors, and management of postoperative delayed gastric emptying after distal gastrectomy: a narrative review

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Abstract

Purpose: This narrative review elucidates the complex pathogenesis, key risk factors, and effective management strategies for postoperative delayed gastric emptying (DGE) following distal gastrectomy with D2 lymphadenectomy, a definitive procedure for middle and lower gastric cancer. It also explores opportunities for improved prevention and innovative treatment options.

Current concept: DGE significantly disrupts gastric motility and presents with symptoms such as early satiety, postprandial fullness, nausea, vomiting, and gastric atony. Although rarely fatal, DGE hampers oral intake, prolongs hospital stays, and diminishes quality of life. Current evidence indicates that DGE is a multifactorial disorder resulting from an interplay of vagal nerve disruption, damage to smooth muscle and interstitial cells of Cajal, imbalances in gastrointestinal hormones, and postoperative gut microbiome dysbiosis. Patient-specific factors, including advanced age, poor nutritional status, diabetes, and preoperative pyloric obstruction, along with surgical factors (most notably Billroth II reconstruction), further increase the risk of DGE. Management involves dietary modifications, prokinetic agents (such as metoclopramide and selective 5-HT_4 agonists like prucalopride), and gastric decompression.

Conclusion: DGE is a challenging complication following gastrectomy that demands a deeper understanding of its underlying mechanisms to improve patient outcomes. Emerging therapies, including microbiota modulation and advanced pharmacological agents, offer promising new treatment avenues.

Keywords: Gastrectomy; Gastrointestinal microbiome; Gastroparesis; Risk factors; Stomach neoplasms

Introduction

Background

Distal gastrectomy with D2 lymphadenectomy is a curative surgery for middle and lower gastric cancer [1]. However, this procedure can markedly disrupt the stomach's normal anatomical and physiological functions, leading to regional abnormalities in motility and resulting in delayed gastric emptying (DGE) [2-4]. Also known as postoperative gastroparesis syndrome, DGE is characterized by early satiety, postprandial fullness, nausea, vomiting, and gastric atony, all occurring in the absence of mechanical gastric outlet obstruction [5-9]. Clinically, DGE is often observed during transitions to solid diets or when food consistency changes, highlighting the dynamic nature of postoperative gastric motility disturbances [7,10]. With an incidence rate ranging from approximately 5% to 25% [6,7], DGE is one of the major complications after gastrectomy. Although it is generally nonfatal and may be managed with nasogastric tube insertion or fasting, with or without prokinetic therapy [6], DGE can delay oral intake, ex-

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tend hospital stays, and significantly diminish patients' quality of life [2,6-8,11,12]. Furthermore, it may adversely affect oncological outcomes; for example, Zhang et al. [13] reported a mean recurrence-free survival time of 26.1 months for patients with DGE, compared to 33.4 months for those without.

The exact pathogenesis of postoperative DGE remains unclear [8]. Current evidence indicates that DGE is multifactorial, involving nerve damage, smooth muscle dysfunction, injury to interstitial cells of Cajal (ICC), hormonal imbalances, postoperative microbial dysbiosis, and other yet unidentified factors [8,14]. Moreover, the management of DGE following gastrectomy remains suboptimal and presents significant challenges [8].

Objectives

This review examines current research on the pathogenesis and risk factors associated with DGE following distal gastrectomy. It also aims to provide insights into targeted prevention strategies and highlight promising therapeutic options that may improve the management of post-gastrectomy DGE in the future.

Pathogenesis, etiology, and risk factors of postoperative DGE following distal gastrectomy

The physiology of gastric emptying is a highly coordinated process that involves the central, autonomic, and enteric nervous systems, as well as smooth muscle cells, ICC, and gastrointestinal hormones [8,15]. Contractions of the gastrointestinal smooth muscle, stimulated by intrinsic cholinergic neurons, are essential for triturating solid food and facilitating gastric emptying [16]. Additionally, endocrine regulation via gastrointestinal hormones—commonly known as brain-gut peptides (e.g., gastrin, motilin, ghrelin, cholecystokinin, vasoactive intestinal peptide, and glucagon-like peptide-1)—plays a pivotal role in controlling gastrointestinal motility [8,17].

Pathogenesis of postoperative DGE

The underlying mechanisms of postoperative DGE remain incompletely understood, but current evidence points to a multifactorial etiology. Disruption of vagal innervation, direct injury to smooth muscle fibers, and disturbances in the ICC network are all implicated in the development of DGE [8,18-20]. The vagus nerve is critical for coordinating gastric motility by regulating smooth muscle contractions and ICC activity; however, surgical procedures such as gastrectomy can impair this neural pathway [8,18]. Such disruptions compromise the effective propulsion of gastric contents, thereby contributing to DGE [8].

Recent studies have increasingly emphasized the link between gut microbiota, its metabolites, and postoperative complications [8]. A meta-analysis by Tarazi et al., which reviewed 33 gastrointestinal surgeries, found that surgical interventions often lead to alterations in the gut microbiome [8,21]. Similarly, Guyton and Alverdy reported that gastrointestinal procedures can alter the composition and structure of the intestinal flora, frequently resulting in postoperative microbial dysbiosis [8,14]. Building on these findings, Mandarino et al. suggested that gut dysbiosis may play a key role in both the initiation and progression of gastroparesis [8,22]. Several studies have demonstrated that the intestinal microbiota partly regulates gastrointestinal motility by influencing the interactions between muscularis macrophages and enteric neurons [8,23]. Alterations in the gut microbiota can affect macrophage function, indicating that microbial changes directly impact immune modulation within the gastrointestinal tract [8,24]. Muscularis macrophages, which are essential for gut motility, are classified into pro-inflammatory M1 and anti-inflammatory M2 subtypes [8,23,25]. Notably, in rat models, abdominal surgery has been shown to activate M1 macrophages within the gastrointestinal plexus, leading to increased production of pro-inflammatory cytokines [8,26]. An inverse correlation has been observed between gastric emptying and the proportion of M1 macrophages in the gastrointestinal plexus [26]. Consequently, Wang et al. [8] proposed that, in addition to direct surgical factors like vagal injury and anatomical changes, DGE may also be partially influenced by postoperative microbiome alterations. These findings are summarized in Table 1.

Etiology of postoperative DGE

Gastroparesis most commonly arises from idiopathic causes, diabetes, and post-surgical conditions. Idiopathic gastroparesis accounts for 36% of cases, followed by diabetic gastroparesis at 29% [7,27]. Post-surgical conditions, particularly those following procedures such as partial gastrectomy and pylorus-preserving pancreatoduodenectomy, represent approximately 13% of cases [7,10]. This review focuses primarily on post-gastrectomy gastroparesis, specifically postoperative DGE. Surgical trauma—including traction injuries and disruptions to the blood supply—damages gastric smooth muscle and both gastric and retroperitoneal nerve plexuses, impairing the stomach's ability to generate effective electrical rhythms and contraction waves, thereby contributing to DGE [2,4,18,28]. Additionally, surgical stress, which encompasses perioperative psychological responses (e.g., anxiety, fear, and insomnia), activates the sympathetic nervous system and inhibits the gastrointestinal nerve plexus, further exacerbating postoperative DGE [4,8,29,30]. These etiologies are summarized in Table 2.

Risk factors for post-gastrectomy DGE

The risk factors for DGE following distal gastrectomy are multifaceted and closely interrelated. Over the past decade, numerous studies have examined these factors, although their findings have been inconsistent [28]. Recent research broadly categorizes the risk factors for post-gastrectomy DGE into two groups: patient-related factors and surgery-specific attributes (Table 3).

Patient-related risk factors

Multiple studies have identified independent patient-related risk factors for DGE, including advanced age, poor nutritional status, preoperative pyloric obstruction, significant blood loss, postoperative intra-abdominal infections, and psychological factors [6,19,28,31,32]. Liu et al. [31] reported that advanced age, Helicobacter pylori infection, elevated anxiety levels, lower perioperative albumin concentrations, and preoperative pyloric obstruction significantly contribute to DGE.

Mukoyama et al. [6] further emphasized the roles of sex, diabetes, and distal gastric tumors in DGE. They noted that premenopausal women may be particularly vulnerable to impaired gastric motility due to higher levels of estrogen and progesterone, hormones known to influence gastrointestinal function.

Meng et al. [4] suggested that postoperative hypoproteinemia may result in edema of the gastrointestinal walls and anastomotic sites, causing localized dyskinesia and delaying the recovery of gastrointestinal motility, thereby increasing the risk of DGE. They also proposed that hyperglycemia plays a crucial role in gastric emptying dysfunction by inhibiting the secretion and release of motilin. This effect becomes particularly significant when blood glucose levels exceed 10 mmol/L, as hyperglycemic conditions disrupt normal elec-

Table 1. Pathogenesis of postoperative delayed gastric emptying

Pathogenesis	Description	Reference
Disruption of neural pathways	Vagal nerve impairment disrupts coordination of gastric motility, smooth muscle contractions, and interstitial cells of Cajal (ICCs) activity.	[8,18-20]
Smooth muscle and ICC damage	Direct mechanical or ischemic injury to gastric smooth muscle and ICCs disrupts the synchronization of motor activity, resulting in a loss of effective electrical rhythms and contraction waves necessary for gastric emptying.	[8,18]
Gut microbial dysbiosis	Abdominal surgery-induced dysbiosis has been shown to activate M1 macrophages in the gastrointestinal plexus, leading to increased expression of pro-inflammatory cytokines that contribute to delayed gastric emptying.	[8,23-26]

Table 2. Etiology of postoperative delayed gastric emptying

Cause	Description	Reference
Surgical trauma	Traction injuries and disruptions to the blood supply damage gastric smooth muscle and both gastric and retroperitoneal nerve plexuses, impairing the stomach's ability to generate effective electrical rhythms and contraction waves, thereby contributing to delayed gastric emptying.	[2,4,7,8,10,18,28-30]
Surgical stress	Perioperative stress reactions (e.g., anxiety, fear, insomnia) activate the sympathetic nervous system, which inhibits gastrointestinal motility.	[2,4,7,8,10,18,28-30]

Table 3. Risk factors for post-gastrectomy delayed gastric emptying

	Risk factor	Reference
Patient-related factors	Advanced age	[4,6,19,28,31,32]
	Female sex	
	Poor nutritional status: hypoproteinemia and low albumin levels	
	Preoperative pyloric obstruction	
	Diabetes mellitus	
	Higher body mass index	
	Significant intraoperative blood loss	
	Intra-abdominal infections	
Surgery-related factors	Anastomotic method: Billroth II reconstruction	[4,28,31,33]

trogastric rhythms and reduce intragastric pressure [4].

Furthermore, Pang et al. [19] identified advanced age, a high body mass index, and low preoperative albumin levels in patients with pyloric obstruction as significant predictors of DGE. Preoperative pyloric obstruction has been consistently highlighted as a key risk factor by several researchers, including Pang et al. [19], Liu et al. [31], and Meng et al. [4]. Based on these findings, Pang et al. proposed two possible mechanisms: prolonged obstruction may lead to gastric wall edema and smooth muscle damage, thereby weakening peristalsis and impairing nerve conduction; and postoperative anastomotic edema with mucosal accumulation may further disrupt gastric motility.

Surgery-specific risk factors

Several studies have examined how different surgical techniques influence the incidence of post-gastrectomy DGE.

Meng et al. [4] and Liu et al. [31] demonstrated that Billroth II anastomosis is associated with a higher incidence of DGE compared to Billroth I. Mao et al. [33] reported that patients undergoing Billroth II reconstruction were more likely to develop DGE than those receiving other types of reconstruction, with Billroth I serving as the reference group (odds ratio=1). The odds ratio for Billroth II was 7.3 ($P=0.001$), while that for Roux-en-Y was 5.9 ($P=0.15$). They suggested that, regardless of surgical technique, Billroth II reconstruction alters the digestive tract in a manner that impairs its ability to efficiently process contractile chyme and reduces gastrointestinal smooth muscle contractility. In agreement with these observations, Yu et al. [28] reported that Billroth I reconstruction reduces the risk of DGE, whereas the use of a jejunal nutrition tube increases it.

Pang et al. [19] approached the issue from a different perspective by replacing the traditional Billroth II procedure with Roux-en-Y and uncut Roux-en-Y reconstructions in favor of enhancing the anti-reflux effect and focused on the configuration of the anastomosis. Although their study found no significant difference in the overall incidence of DGE between these techniques, they observed that DGE occurred more frequently with linear anastomoses than with circular ones. More specifically, linear stapler incisions made parallel to the greater curvature were more likely to induce DGE than vertical incisions, possibly due to potential damage to the gastric fundus pacing point, which is critical for coordinating motility.

Additionally, Pang et al. [19] proposed that a smaller residual stomach volume—typically resulting from high-level vessel disconnections along the greater curvature to ensure a secure anastomosis—might predispose patients to DGE. In contrast, Mukoyama et al. hypothesized that a larger remnant stomach could become more atonic and, therefore, more susceptible to DGE [6,34]. This discrepancy may stem from variations in surgical contexts and conditions. Mukoyama et al. [6] further emphasized the need for additional research, ideally incorporating imaging techniques such as computed tomography scans, to better define the relationship between remnant stomach volume and DGE.

Kim et al. [2] identified laparoscopic distal gastrectomy as a significant risk factor for DGE, hypothesizing that the use of laparoscopic energy-based devices might cause thermal injury to the ICC, which are crucial for gastric motility. In contrast, Meng et al. [4] found no difference in the incidence of DGE between laparoscopic and open radical gastrectomy. Therefore, further research is warranted to clarify any disparities in DGE incidence between laparoscopic and open surgery, taking into account the wide range of relevant surgical factors. Moreover, since energy-based devices are now commonly used in open surgery, additional comparative studies are needed to determine whether similar risks exist in open procedures.

While these studies collectively shed light on the diverse factors influencing DGE, limitations such as variations in sample size, study design, and measurement methods across the literature must be acknowledged. These limitations underscore the need for further research to more precisely delineate the underlying mechanisms.

Diagnosis

Gastric scintigraphy is considered the gold standard for diagnosing DGE and remains the most widely used diagnostic technique [4,35]. However, in post-gastrectomy patients exhibiting symptoms of DGE, alternative imaging modalities—such as plain abdominal X-ray, an upper gastrointestinal series, or computed tomography scans—may also be employed [6]. It is important to note that the severity of symptoms and clinical presentation do not always correlate with the extent of DGE [4,36,37].

Management

The management of DGE requires a comprehensive approach that considers multiple factors to optimize patient care [27]. In the acute setting, correcting dehydration and electrolyte imbalances is essential and can be achieved via oral or intravenous routes depending on severity [35,38]. In more severe cases, gastric decompression with a nasogastric tube may be necessary to alleviate symptoms and prevent further complications [35].

Dietary modification

Dietary modification is a critical component in managing postoperative DGE [7,39]. Patients should be advised to consume several small meals while limiting fat and fiber content, as these components delay gastric emptying [7]. A meal frequency of 4 to 6 small meals per day is recommended, and high-caloric liquids can provide essential nutrition while minimizing symptoms in mild DGE [27]. Nutritional counseling by experts is vital, as DGE often leads to malnutrition due to inadequate oral intake and vomiting [27,40-42]. Patients with diabetes mellitus should maintain strict blood glucose control to reduce the risk of exacerbating gastroparesis symptoms [35,42]. Liquid nutrition is particularly beneficial because gastric emptying for liquids is generally preserved, especially when diets are low in fat and fiber [7,38]. Conversely, hypertonic foods should be avoided as they can worsen these conditions [7,38].

Prokinetic medications

Prokinetic agents play a crucial role in managing moderate to severe gastroparesis by promoting and coordinating gastrointestinal motility while alleviating symptoms [4,5,16,43]. These agents facilitate gastric emptying through specific receptor interactions, including serotonergic 5-HT_4 receptor agonists, dopamine $D_{2/3}$ receptor antagonists, and neurokinin-1 (NK1) recetpor antagonists [43]. However, their long-term use is often limited by adverse effects, drug resistance, financial burden, and psychological distress [4]. When selecting a prokinetic drug for postoperative DGE, several factors must be considered, including patient comorbidities (such as diabetes, neurological disorders, or cardiovascular disease), the severity of DGE, and altered pharmacokinetics in the gastrointestinal tract resulting from surgical anatomical and functional changes. Further research is needed to better understand these the effects of surgical changes on pharmacokinetics and to develop more effective treatment protocols. In cases of severe DGE, intravenous options may be more effective than oral medications. Additionally, the potential side effects and toxicity of the drug must be considered to ensure that treatment is safe and well-tolerated. Consequently, the pharmacological management of DGE remains suboptimal and continues to challenge healthcare providers [4]. A brief summary of these agents and their mechanisms of action is presented in Table 4.

Metoclopramide, the only medication approved for gastroparesis in the United States, is a D_2-receptor antagonist with partial 5-HT_4 receptor agonist activity that provides both prokinetic and antiemetic effects, available in oral and intravenous formulations [5,43,44]. Nevertheless, caution is warranted when administering metoclopramide to patients with postoperative DGE, as these patients are vulnerable to depression, and the drug may exacerbate this condition [7]. Moreover, because metoclopramide crosses the blood-brain barrier, it can cause central nervous system side effects—including anxiety, depression, tremors, and, in rare cases, severe extrapyramidal symptoms such as tardive dyskinesia. Consequently, the U.S. Food and Drug Administration has issued a black box warning limiting its use to a maximum of 12 weeks [5,43].

Domperidone, a dopamine receptor antagonist, offers similar efficacy to metoclopramide but is associated with fewer extrapyramidal side effects since it does not cross the blood-brain barrier [5,42,43]. However, it carries a potential risk of cardiac dysrhythmias and, in rare cases, sudden death. This risk is attributed to its inhibition of hERG (human ether-à-go-go-related gene) channel activity and the resultant QTc (corrected QT interval) prolongation [5,44,45].

Several new-generation 5-HT_4 receptor agonists—including prucalopride, velusetrag, naronapride, and felcisetrag—are highly selective and do not exhibit hERG-related effects [5,43]. Among these, prucalopride is approved in several countries, including the United States, for the treatment of chronic constipation due to its enterokinetic properties [5,43]. Recent research suggests that prucalopride also has gastrokinetic effects, improving symptoms in patients with idiopathic gastroparesis [5,43]. Additionally, prucalopride may enhance gastric neuromuscular function through its anti-inflammatory actions, such as facilitating vagal stimulation, modulating T helper cell responses, and reducing postoperative ileus [43,46]. In a study by Carbone et al. [47], 4 weeks of prucalopride treatment significantly improved symptoms, quality of life, and gastric emptying compared to placebo in patients with idiopathic gastroparesis [47].

Velusetrag, another selective 5-HT_4 receptor agonist, has demonstrated efficacy in relieving symptoms and accelerating gastric emptying in patients with diabetic and idiopathic gastroparesis [5,48].

Felcisetrag (TAK-954), when administered intravenously, has been shown to significantly accelerate gastric emptying as well as small bowel and colonic transit in patients with gastroparesis and DGE [49]. In a double-dummy, parallel-group, randomized trial, felcisetrag improved gastric retention in mechanically ventilated patients with enteral feeding intolerance (gastric residual volume ≥200 mL), outperforming metoclopramide [50].

Motilin and ghrelin, hormones secreted in the upper di-

Table 4. Overview of prokinetic agents for consideration in delayed gastric emptying management

Agent	Mechanism of action	Key benefits	Special comments and side effects	Reference
Metoclopramide	D_2-receptor antagonist, partial 5-HT_4 agonist	- Prokinetic and antiemetic effects - Available for intravenous administration	- CNS side effects (e.g., anxiety, depression, tremors); rare severe extrapyramidal symptoms (e.g., tardive dyskinesia); FDA black box warning limits use to 12 wk	[5,7,43,44]
Domperidone	Dopamine receptor antagonist	- Similar efficacy to metoclopramide; fewer CNS side effects	-Risk of cardiac dysrhythmias and sudden death due to hERG channel inhibition and QTc prolongation -Gynecomastia, galactorrhea, menstrual irregularities	[5,42–45,57]
Prucalopride	Highly selective 5-HT_4 receptor agonist	- Improvement of symptoms and gastric emptying; anti-inflammatory effects enhance neuromuscular function	-Generally approved for chronic constipation -Limited availability and long-term safety data	[5,43,46,47]
Velusetrag	Highly selective 5-HT_4 receptor agonist	- Alleviation of symptoms and acceleration of gastric emptying in diabetic and idiopathic gastroparesis	-Limited availability and long-term safety data	[5,48]
Felcisetrag	Highly selective 5-HT_4 receptor agonist	- Similar effects to those of other highly selective 5-HT4 receptor agonists - Available for intravenous administration	-Limited availability and long-term safety data	[49,50]
Erythromycin	Motilin receptor agonist	- Facilitation of gastric emptying - Available for intravenous administration	-Adverse effects: abdominal cramps, nausea, diarrhea, QTc prolongation, tachyphylaxis reversible deafness	[5,43,51–53,57]
Acotiamide	Cholinesterase inhibitor M1 and M2 muscarinic receptors antagonist	- Enhancement of gastric contractility and accommodation and alleviation of dyspepsia	-Less effective for epigastric pain and burning -Headache, diarrhea	[5,57,58]
Levosulpiride	D_2 dopamine receptor antagonist 5-HT_4 receptor agonist	- Enhancement of gastrointestinal motility through dual prokinetic action via dopaminergic and serotonergic pathways	-Limited to short-duration use to avoid side effects -Drug-induced parkinsonism, galactorrhea and menstrual abnormalities	[5,57,59]

CNS, central nervous system; FDA, U.S. Food and Drug Administration; hERG, human ether-à-go-go-related gene; QTc, corrected QT interval.

gestive tract, are crucial in stimulating gastric emptying [5]. Macrolide antibiotics, used as motilin receptor agonists, are especially focused on their effects in the stomach [43]. Erythromycin, the most extensively studied agent in this class, enhances gastric emptying and transiently improves gastroparesis symptoms by stimulating fundic and antral contractions while inhibiting pyloric activity [51,52]. However, its widespread clinical use is limited by side effects such as abdominal cramps, nausea, diarrhea, QTc prolongation, and tachyphylaxis [5,43,51]. In clinical practice, hospitalized patients typically receive erythromycin via intravenous infusion at a dose of 1.5–3 mg/kg over 45 minutes every 6–8 hours, whereas outpatients are managed with 125 mg twice daily in an oral liquid formulation, which improves drug absorption in cases of markedly DGE [43]. Caution is advised when erythromycin is used in combination with agents that interfere with CYP3A4 metabolism (e.g., diltiazem, verapamil, domperidone) due to an increased cardiac risk [53].

Relamorelin, a synthetic pentapeptide ghrelin receptor agonist, is 15–130 times more potent than natural ghrelin [43,54]. Administered subcutaneously at a dose of 100 μg, it has been shown to accelerate gastric emptying in patients with type 1 or type 2 diabetes mellitus experiencing DGE [43,55]. Unlike erythromycin, relamorelin increases distal antral contraction frequency without impairing gastric accommodation or altering postprandial satiation in healthy individuals [43,56]. However, because patients who have undergone distal subtotal gastrectomy lack an antrum, further research is needed to determine whether relamorelin is effective in this population based on its proposed mechanism of action.

Cholinesterase inhibitors also promote gastrointestinal motility and are particularly useful for managing various intestinal motor disorders such as postoperative ileus, constipation, and chronic intestinal pseudo-obstruction [5]. Acotiamide, a newer cholinesterase inhibitor, additionally inhibits presynaptic muscarinic autoreceptors, thereby enhancing gastric contractility and accommodation to alleviate dyspeptic symptoms associated with gastroparesis. However, it is less effective for treating epigastric pain and burning sensations [5,58].

Levosulpiride, a sulpiride derivative, enhances gastrointestinal motility through dual mechanisms: antagonism of D_2 dopamine receptors and agonism of serotonin 5-HT_4 receptors, which together facilitate cholinergic activity [5,59].

Neurokinin-1 receptor antagonists show promise as a potential therapeutic option by improving multiple symptoms of gastroparesis, although they are not yet approved for the treatment of nausea and vomiting associated with this condition [43,60,61]. Preliminary results from a phase 2 trial of tradipitant, an NK1 receptor antagonist, were encouraging; however, its approval for gastroparesis management depends on the outcomes of phase 3 trials and further analyses [60,61].

Conclusion

Postoperative DGE remains a significant challenge following distal gastrectomy, resulting in reduced quality of life, prolonged hospital stays, and an increased psychological burden. This narrative review has examined the multifactorial etiology of DGE, including disruptions in vagal innervation, impaired smooth muscle and ICC function, and gut microbial dysbiosis. A comprehensive understanding of these pathophysiological mechanisms is essential for developing effective prevention and management strategies. Proactively identifying key risk factors may help optimize postoperative outcomes and improve quality of life. Furthermore, emerging therapeutic approaches, such as gut microbiota modulation and advanced pharmacological interventions, offer promising avenues for future management. Given the substantial influence of surgical techniques and perioperative factors on DGE incidence, further research is warranted to elucidate the underlying mechanisms and refine surgical strategies to mitigate its occurrence. Overall, this review underscores the importance of a comprehensive and personalized approach to DGE to minimize its impact on recovery and increase the overall success of gastrectomy in patients with gastric cancer.

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Authors' contribution

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Review

Perioperative nutritional management to improve long-term outcomes in critically ill perioperative organ transplant patients: a narrative review

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Abstract

Purpose: This review examines the significance of perioperative nutritional management in organ transplantation, with a particular focus on liver transplantation. Organ transplant recipients often experience malnutrition and sarcopenia due to nutritional and metabolic abnormalities associated with organ dysfunction. Because transplantation is a highly invasive procedure, optimizing perioperative nutritional care is critical for improving short-term outcomes and reducing postoperative infection-related mortality.

Current concept: Recent clinical investigations have shown that liver transplant recipients, who are frequently afflicted with end-stage liver disease and uncompensated cirrhosis, are particularly vulnerable to protein-energy malnutrition and secondary sarcopenia. Our analysis identified low pre-transplant nutritional status and the absence of preoperative branched-chain amino acid supplementation as independent risk factors for post-transplant sepsis. In response, we developed a customized nutritional therapy protocol that incorporates precise body composition analysis, serial measurements of biochemical markers (including prealbumin, zinc, and the branched-chain amino acid/tyrosine ratio), and targeted supplementation with branched-chain amino acids, zinc acetate, and synbiotics. Early initiation of enteral nutrition coupled with postoperative rehabilitative interventions resulted in improved outcomes. In addition, stratified body composition parameters correlated with survival differences and informed revised transplantation criteria.

Conclusion: Tailored perioperative nutritional management and rehabilitative strategies are essential for improving early postoperative outcomes in liver transplantation. These findings underscore the need for proactive nutritional assessment and intervention, which may represent a breakthrough in transplant prognosis. Future research should refine nutritional protocols and integrate novel biomarkers, while education and interdisciplinary collaboration remain crucial for enhancing transplant outcomes and reducing complications.

Keywords: Enteral nutrition; Liver transplantation; Nutrition assessment; Protein-energy malnutrition; Sarcopenia

Introduction

Background

Organ transplantation encompasses procedures involving the heart, lung, liver, pancreas, kidney, and small intestine. Consequently, organ transplant recipients frequently experience malnutrition and sarcopenia due to nutritional and metabolic abnormalities associated with organ dysfunction. Additionally, because organ transplantation is a highly invasive surgical procedure, effective perioperative nutritional

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management is critical for patients to tolerate the surgery. Thus, perioperative nutritional management is essential for improving short-term prognosis in organ transplant patients.

Objectives

In this article, I discuss the significance of perioperative nutritional management in organ transplantation and its role in improving prognosis, using liver transplantation—my specialty—as an illustrative example drawn from my own experience.

Ethics statement

This is a literature-based study. Institutional Review Board approval was not required, as the study did not involve human subjects research.

Necessity of perioperative nutritional management in liver transplantation

Liver transplant recipients suffer from end-stage liver diseases that cannot be managed by internal medicine or alternative surgical methods. These conditions include biliary atresia, biliary stasis, various hepatocellular diseases (e.g., viral or alcoholic cirrhosis), hepatocellular carcinoma complicated by liver cirrhosis, and acute liver failure. The progression of these diseases to decompensated cirrhosis often results in protein-energy deprivation. Moreover, many liver transplant recipients develop secondary sarcopenia. In addition, liver transplantation is considered a high-risk procedure because the immunosuppressive drugs used postoperatively increase the risk of infection.

I became involved in liver transplantation in 2007. At that time, I observed a steep decline in the post-transplant survival curve during the early postoperative period, indicating a high early post-transplant mortality rate. Consequently, I concluded that reducing early post-transplant mortality was essential to improve outcomes and to understand the causes of early post-transplant death. Our analysis revealed that more than 60% of deaths were due to infectious diseases such as pneumonia and bacteremia [1]. We identified low pre-transplant nutritional status (as measured by low body cell volume) and the absence of preoperative branched-chain amino acid supplementation as independent risk factors for post-transplant sepsis and infection-related mortality [2]. Furthermore, we observed that the preoperative nutritional status of liver transplant recipients ranged from relatively well-nourished patients to those with markedly reduced muscle mass and nutritional deficiency. Thus, we developed a treatment strategy emphasizing customized perioperative nutritional intervention, infection control, and improved short-term post-transplant outcomes.

Establishment of tailor-made perioperative nutritional therapy

Accurate nutritional assessment and appropriate nutritional therapy are the two cornerstones of effective nutritional management. However, common assessment parameters such as body mass index, brachial circumference, and serum albumin are inadequate for evaluating liver transplant patients with cirrhosis and edema. Therefore, we implemented body composition analysis using a specialized analyzer to accurately assess the nutritional status of liver transplant recipients. This evaluation revealed that preoperative hyponutrition, as indicated by low somatic cell volume, is an independent risk factor for early post-transplant mortality due to infection [2].

In addition, we measured blood biochemical nutritional parameters over time, including prealbumin (transthyretin), a rapidly turning over protein, zinc, and the branched-chain amino acid/tyrosine ratio. The findings indicated that levels of prealbumin, zinc, and the branched-chain amino acid/tyrosine ratio were markedly decreased at admission [3]. Zinc, in particular, demonstrated a significant positive correlation with prealbumin and a negative correlation with ammonia [3]. Hypozincemia is linked to delayed wound healing, stomatitis, decreased appetite, hypoproteinemia, and hyperammonemia, all of which impede early postoperative recovery. Liver transplantation requires anastomosis of blood vessels and bile ducts, and hypozincemia occurs in the early postoperative period when wound healing is most important and appetite should be improved [4]. Therefore, we measured serum zinc levels and considered perioperative zinc supplementation to be necessary if zinc levels were low.

Based on these findings, we established a customized liver transplant perioperative nutritional rehabilitation therapy (hereafter referred to as "rehabilitation"), which includes nutritional assessment on admission and tailored interventions based on each patient's nutritional status (Fig. 1) [5]. The following outlines the perioperative nutritional management protocol.

First, because the lack of preoperative branched-chain amino acids is an independent risk factor for post-transplant sepsis, oral amino acid products formulated for liver failure and enriched with branched-chain amino acids are administered between meals in the afternoon and before bedtime (late evening snack) from the time of admission. One week before surgery, immunomodulating nutritional supplements

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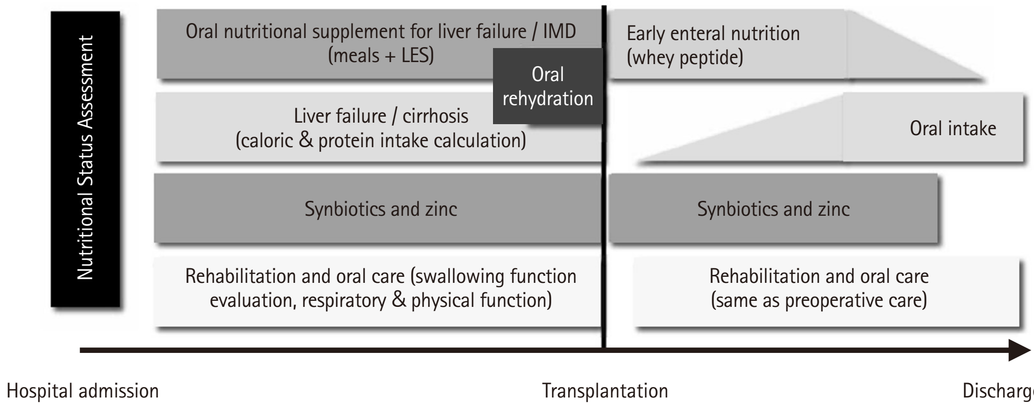

Fig. 1. Customized perioperative nutritional rehabilitation therapy for liver transplant patients. IMD, immunomodulatory nutritional supplement; LES, late evening snack.

replace the standard oral amino acid formula for liver failure. The diet is then adjusted by a dietitian to avoid excessive calories and protein [2].

Second, zinc supplementation should be initiated for patients with hypozincemia. While conventional zinc preparations do not rapidly increase blood zinc levels, administering a zinc acetate preparation containing a high concentration of zinc has been shown to significantly elevate blood zinc concentrations [6].

Third, patients with decompensated cirrhosis are susceptible to disturbances in intestinal mucosal integrity due to portal hypertension. To prevent bacterial translocation, synbiotics—a combination of probiotics and prebiotics—are administered from the time of admission, as they have been shown to enhance intestinal immunity and reduce the incidence of post-transplant infections [7].

Fourth, historically, patients were required to abstain from food and solids until dinner on the day before surgery and from liquids until lights out (approximately 10:00 pm). Currently, patients are permitted to consume solid foods until midnight on the day before surgery and fluids (such as oral rehydration solutions, water, or tea) until 6:00 am on the day of surgery. These preoperative nutritional interventions have significantly mitigated the decline in lymphocyte count and rise in C-reactive protein, while also significantly increasing prealbumin and zinc levels [8].

Fifth, early initiation of enteral nutrition is central to postoperative management. At Kyoto University, an enterostomy tube was placed through the upper jejunum during liver transplantation, and enteral nutrition commenced within 24 hours after surgery. This regimen includes immunomodulating supplements containing whey peptides [9], which possess anti-inflammatory and antioxidant properties. Notably, the incidence of postoperative bacteremia was significantly lower in the whey peptide immunomodulating nutrition group compared to the conventional digestive-form nutrition group [5,10].

Sixth, liver transplant recipients are susceptible to intestinal edema and paralysis resulting from factors such as portal hypertension, hypoalbuminemia, prolonged surgery, and extensive intraoperative fluid infusion. Consequently, the initiation of oral or enteral nutrition may be delayed or insufficient. We conducted a multicenter, double-blind, randomized, comparative study at 14 major liver transplant centers in Japan to assess the efficacy of postoperative Daiken-Chutou in enhancing gastrointestinal motility [11]. Based on these findings, Daiken-chu-tang (15 g, minimum three doses) is administered via an enteral tube, particularly for patients experiencing intestinal dysmotility.

Seventh, postoperatively, patients continue to receive enteral or oral synbiotics until they can maintain adequate oral intake. Additionally, if serum zinc levels remain low, zinc acetate supplementation is administered.

Significance of sarcopenia in liver transplantation

Sarcopenia, defined as "loss of muscle mass, muscle strength, or physical function [12,13]," is classified into primary and secondary forms. Primary sarcopenia is related to aging, while secondary sarcopenia is associated with factors such as reduced physical activity (disuse), poor nutrition, organ failure, invasive procedures, tumors, and other diseases. Liver transplant recipients typically experience secondary sarcopenia due to decreased activity resulting from edema and ascites as well as poor nutritional status and liver failure.

Skeletal muscle mass can be assessed through whole-body or limb/trunk analysis, or via cross-sectional measurements of the trunk (often at the level of the third lumbar vertebra) using computed tomography (CT) or magnetic resonance imaging. We investigated the correlation between skeletal muscle mass determined by CT and that obtained by body composition analysis before liver transplantation in both donors and recipients. We found a strong correlation for donors (r=0.737) and recipients (r=0.682) [14]. Given the high correlation between these two methods, the choice of measurement should depend on the availability of CT and body composition analysis equipment at each institution.

In our study, 38% of liver transplant recipients exhibited sarcopenia (low skeletal muscle mass), and post-transplant survival was significantly worse in patients with preoperative sarcopenia compared to those with higher skeletal muscle mass [15]. Preoperative sarcopenia was identified as an independent risk factor for post-transplant mortality. Additionally, we examined the relationship between preoperative respiratory function and skeletal muscle mass, finding that lower muscle mass was associated with poorer respiratory function, including reduced lung capacity and lower expiratory volumes [16]. We believe that preoperative rehabilitation is crucial for early postoperative recovery; accordingly, we have actively implemented preoperative rehabilitation programs that include respiratory muscle training, resistance exercises, and aerobic exercise using an ergometer alongside nutritional therapy [17]. Thus, the combination of preoperative rehabilitation and nutritional therapy is vital in liver transplantation.

Beyond muscle mass, we also examined muscle quality and visceral fat obesity. We were the first to report that poor muscle quality and visceral fat obesity are independent adverse prognostic factors following liver transplantation [18,19].

Significance of perioperative nutritional therapy in liver transplantation

We examined the impact of perioperative nutritional therapy in patients with differing preoperative skeletal muscle mass. In patients with low skeletal muscle mass, postoperative survival was significantly improved by perioperative nutritional therapy (P=0.009) (Fig. 2A) [15]. In contrast, among patients with high skeletal muscle mass, the benefits of nutritional therapy on survival were minimal (Fig. 2B) [16]. Considering limited manpower and resources, we developed a treatment strategy focused on nutritional assessment at admission—including body composition analysis—with targeted nutritional intervention for patients with sarcopenia to improve short-term outcomes, further enhanced by preoperative rehabilitative intervention.

New indications for liver transplantation based on body composition

We investigated the prognostic impact of body composition (including skeletal muscle mass, muscle quality, and the visceral fat/subcutaneous fat ratio) in 277 patients who underwent living donor liver transplantation at Kyoto University between 2008 and July 2016. Preoperative simple CT at the L3 level was used to assess body composition. Using cutoff values derived from living liver transplant donors, we examined the prognostic significance of low skeletal muscle mass, poor muscle quality, and visceral fat obesity. We found that each abnormality was associated with poor prognosis and served as an independent risk factor [20]. Subsequently, we evaluated the impact of the number of abnormal factors on post-transplant survival. The 1-year survival rates were dis-

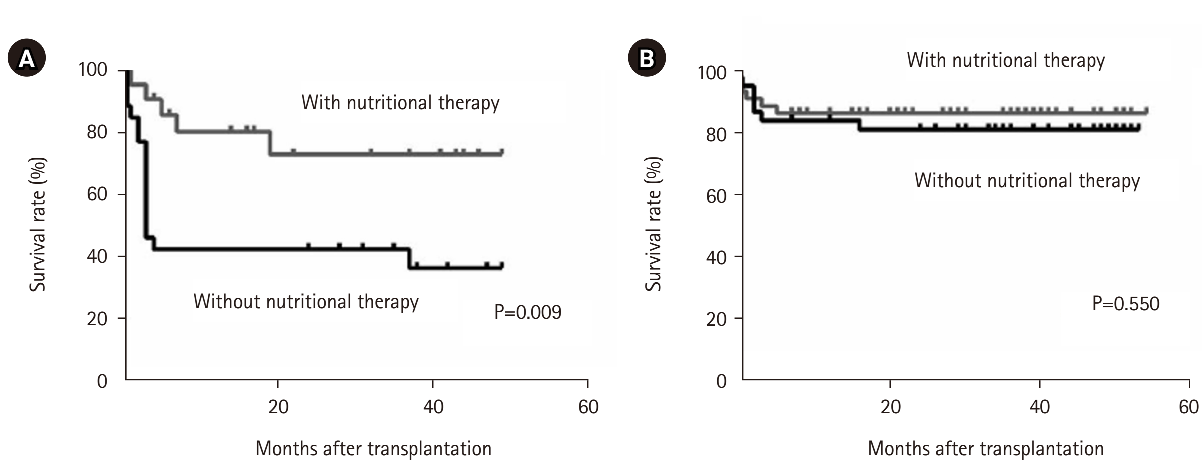

Fig. 2. Survival rate after liver transplantation with and without perioperative nutritional therapy in patients with low preoperative skeletal muscle mass (A) and high skeletal muscle mass (B) (log-rank test).

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tinctly stratified according to the number of abnormalities: 98% with no abnormal factors, 78% with one, 60% with two, and 41% with three (P<0.001) (Fig. 3) [20]. To further elucidate these findings, we examined the relationship between the number of abnormal body composition factors and the incidence of postoperative bacteremia. We discovered that the incidence of bacteremia increased significantly with the number of abnormal factors [21]. Moreover, the mortality rate for patients who developed bacteremia was 12% in the group with no abnormalities, escalating to 87% in the group with three abnormalities. In summary, preoperative abnormalities in body composition in living donor liver transplant recipients not only heighten the risk of postoperative bacteremia but also correlate with a high mortality rate once bacteremia develops. This suggests that preoperative body composition is closely linked to infectious complications, possibly due to decreased myokine production and increased adipokine levels that reduce immunocompetence.

Based on these results, since October 2016 we have recommended that patients with one or two abnormal body composition factors undergo aggressive perioperative nutritional rehabilitation to improve short-term outcomes after transplantation. Conversely, patients with three abnormal factors are advised to consider brain-dead liver transplantation with a larger liver and to receive nutritional rehabilitation during the waiting period, as they are deemed difficult to rescue with living donor liver transplantation. We established a new indication for living donor liver transplantation. We established a new indication for living donor liver transplantation and initiated its implementation. The 1-year survival rates of patients with 0, 1, 2, and 3 abnormalities were significantly stratified at 98%, 78%, 60%, and 41%, respectively (P<0.001) (Fig. 3) [20]. To clarify these results, we compared the 1-year survival rates in patients with body composition abnormalities to those with hepatic abnormalities. Further analysis revealed that the incidence of postoperative bacteremia increased significantly with the number of abnormal body composition factors [21]. Furthermore, the mortality rate among patients with bacteremia was 12% in the group with no abnormalities, rising to 87% in those with three abnormalities. In other words, preoperative body composition abnormalities in living donor liver transplant recipients not only heighten the risk of postoperative bacteremia but also lead to a high mortality rate once bacteremia develops. Therefore, preoperative body composition and infection are closely interrelated.

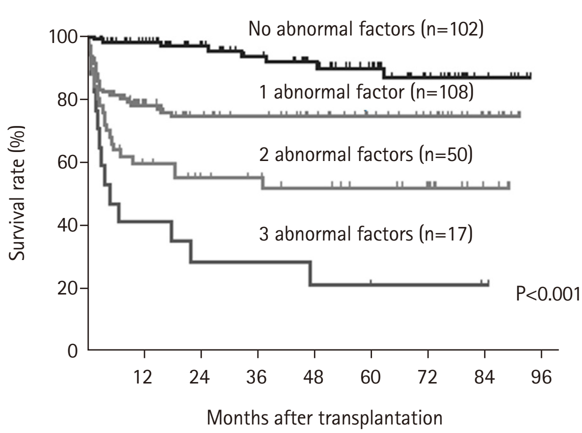

Fig. 3. Number of factors contributing to abnormal preoperative body composition (skeletal muscle mass, muscle quality, visceral fat obesity) and survival rate after liver transplantation (log-rank test).

As a result of these comprehensive interventions, an exceptional 1-year survival rate of 99% was achieved after liver transplantation [22]. Advances in perioperative management, including nutritional management, and the introduction of new surgical techniques [23,24] contributed to the improvement of transplantation outcomes.

Conclusion

Numerous clinical studies were initiated in response to needs identified in clinical practice. Based on these findings, we established a policy of "new indications for liver transplantation and perioperative nutrition and rehabilitation intervention based on body composition" and prospectively validated its effectiveness. Consequently, we achieved an outstanding 1-year survival rate of 99% after liver transplantation. The importance of perioperative nutritional management is now being recognized in other organ transplants, and this study represents a breakthrough in improving transplantation outcomes.

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Authors' contribution

All work was done by Toshimi Kaido.

Conflict of interest

The author of this manuscript has no conflicts of interest to disclose.

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Data availability

Not applicable.

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Supplementary materials

None.

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Original Article

Development of a pre- and re-habilitation protocol for gastrointestinal cancer surgery

Eun Young Kim[1], Jung Hoon Bae[2], Jiseon Kim[3], Eun Joo Yang[4,*], Sang-Jae Park[5], In Kyu Lee[2], on behalf of the Task Force Team for Development and Trial Application of Pre/Rehabilitation Protocol in GI Cancer Surgery

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Abstract

Purpose: Surgical resection is the primary curative treatment for gastrointestinal (GI) cancer; however, it is associated with high postoperative complication rates and impaired recovery. Frailty, malnutrition, and sarcopenia increase morbidity and mortality, underscoring the need for perioperative rehabilitation programs. Standardized rehabilitation protocols during the perioperative period are currently lacking in Korea. We aimed to develop an evidence-based rehabilitation protocol for GI cancer patients to enhance postoperative outcomes and facilitate clinical implementation.
Methods: A multidisciplinary task force team comprising experts in surgery, clinical nutrition, and rehabilitation medicine conducted a systematic literature search and comprehensive review from 2012 to 2022 to develop a standardized pre- and re-habilitation protocol for GI cancer surgery. The protocol underwent external validation and subsequent refinements before being finalized through expert consensus.
Results: The protocol development process was organized into four consecutive phases: keyword selection, literature review and case report form development, initial protocol drafting, and external validation leading to the final version of the protocol. The final version of the rehabilitation protocol is presented in the main text and included as Supplements.
Conclusion: This protocol provides a standardized clinical guideline based on the latest evidence-based pre- and re-habilitation strategies and is designed for seamless integration into routine clinical practice. By facilitating proactive rehabilitation interventions, it aims to improve outcomes in GI cancer patients who are at high risk of postoperative complications, functional decline, and malnutrition.

Keywords: Consensus; Frailty; Gastrointestinal tract; Neoplasms; Perioperative period

Introduction

Background

For patients diagnosed with gastrointestinal (GI) cancer, curative surgical resection is generally the only opportunity for long-term survival [1,2]. However, it is associated with a high rate of postoperative complications, reported in 40% to 50% of cases [3-7]. These complications significantly prolong

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hospitalization and lead to serious functional impairments [8-10]. In particular, patients who develop complications may experience delays or an inability to receive subsequent adjuvant therapy, which negatively impacts long-term oncologic outcomes [11-13]. Therefore, identifying risk factors for postoperative complications and implementing proactive interventions to mitigate these risks is crucial. Notably, preoperative frailty and malnutrition have been identified as key predictors of poor outcomes and reduced survival in patients undergoing surgery for GI cancers [14-17].

Frailty is characterized by an age-related decline in physical, functional, and cognitive capacities, resulting in impaired physical function and contributing to the development of malnutrition [18-20]. Malnutrition is common in GI cancer patients, with a reported prevalence ranging from 20% to 70% [21]. Similarly, sarcopenia has been reported as an independent risk factor for postoperative complications and poor survival in GI cancers [22,23]. Studies have shown that frail patients face a 2- to 4-fold increased risk of postoperative morbidity and mortality [24-26]. Given these risks, various interventions aimed at improving preoperative conditions have been explored. The systematic implementation of pre- and re-habilitation programs—including nutritional supplementation and strength training—has been shown to improve quality of life, enhance functional recovery, and reduce major postoperative complications [27]. Furthermore, the interplay of preexisting frailty or malnutrition, the physiological stress of surgery, and postoperative bed rest with reduced physical activity further impairs physical function and cardiopulmonary capacity, thereby increasing the risk of complications [28]. Therefore, beyond preoperative interventions, subsequent rehabilitation during postoperative recovery is essential for improving outcomes. Despite this need, no standardized protocols for pre- and re-habilitation in GI cancer surgery currently exist in Korea, and many hospitals continue to rely on individually developed protocols or administer rehabilitation therapy without a formal framework.

Objectives

In this context, our study aimed to systematically develop a standardized protocol for pre- and re-habilitation therapy for GI cancer surgery. Ideally, rehabilitation therapy should be delivered through the coordinated efforts of a multidisciplinary team involving various healthcare professionals. To ensure that the protocol was comprehensive and widely accepted, we engaged experts from multiple disciplines—surgeons, physiatrists, and dietitians—in the protocol development process [29]. Our aim is to provide clinical practice guidelines and fundamental resources that will enable healthcare professionals to implement standardized, high-quality pre- and re-habilitation therapy for GI cancer patients, whether they are preparing for surgery or recovering postoperatively.

Methods

Ethics statement

This study was exempt from IRB approval since it does not involve a human population.

Setting

To develop a pre- and re-habilitation protocol for patients undergoing GI cancer surgery, a multidisciplinary task force team (TFT) was established under the leadership of the Korean Society of Surgical Metabolism and Nutrition, with recommendations from the Korean Society of Clinical Nutrition and the Korean Society of Cancer Rehabilitation. The TFT comprised ten board-certified surgeons, five physiatrists, and four clinical dietitians from university hospitals and tertiary referral centers in Korea. The protocol development process was divided into four sequential phases to ensure a systematic and comprehensive approach from 2012 to 2022 (Fig. 1).

Phase I

For the development of a comprehensive pre- and re-habilitation protocol, the TFT was subdivided into two specialized subgroups—the Nutrition Division and the Exercise

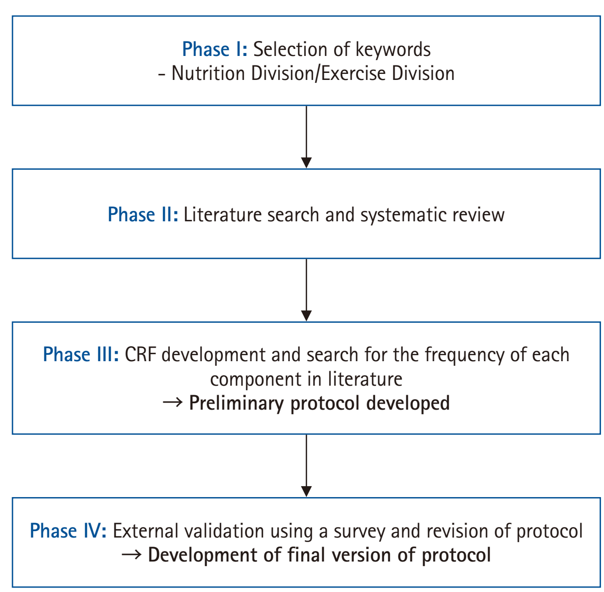

Fig. 1. The protocol development process. CRF, case report form.

Division—based on each member's expertise. Each subgroup conducted discussions to identify primary key terms related to nutritional and exercise implementation for rehabilitation therapy. These initial key terms were then presented to all TFT members, and consensus was reached to finalize the key terms for the Phase II literature review.

Phase II

A systematic literature review was conducted using the final set of selected keywords. The search covered articles published between October 2012 and October 2022 in online databases, including PubMed, Web of Science, and the Library of Congress. The inclusion criteria were as follows: studies reporting the effectiveness of rehabilitation therapy for adult cancer patients, articles written in English, full-text availability, and studies categorized as randomized controlled trials or quasi-experimental studies. During the initial abstract screening, articles were excluded if they were in a non-English language, lacked full-text availability, involved a pediatric patient population, employed a non-randomized or non-quasi-experimental design, or were duplicate records. Subsequently, full-text reviews were conducted, and studies were further excluded if their research objectives were not aligned with the purpose of the review or if they did not meet the required study design criteria.

Phase III

In Phase III, the studies selected from the systematic literature review were analyzed and categorized into diagnostic and assessment tools, nutritional rehabilitation, and exercise rehabilitation. Based on these categories, a case report form (CRF) was developed and distributed among TFT members, who conducted a secondary literature review and evaluated the frequency of each item. This process led to the development of the preliminary draft of the pre- and re-habilitation protocol.

Phase IV

To externally validate the preliminary draft of the protocol, feedback was sought from experts affiliated with relevant professional organizations and societies, including the Korean Society of Surgical Metabolism and Nutrition, the Korean Surgical Society, the Korean Society of Cancer Rehabilitation, and the Korean Society of Clinical Nutrition. Additionally, a public hearing was held at the 40th Congress of the KSSMN in October 2024, where feedback and validation were obtained from attending surgeons to ensure the protocol's clinical relevance and feasibility.

Each question in the preliminary draft of the pre- and rehabilitation protocol was presented with four answer options, allowing respondents to select only one; multiple responses were not permitted. Options were scored as follows: A, strongly agree (4 points); B, somewhat agree (3 points); C, somewhat disagree (2 points); and D, strongly disagree (1 point). The content validity index (CVI) was subsequently calculated for each item using the method proposed by Lynn [26]. An item was considered to have achieved significant agreement if a consensus rate of 78% or higher was reached, and it was then selected as a valid recommendation. Additionally, the average item-level CVI (I-CVI) was calculated, and if it exceeded 0.8, the entire scale was deemed to have acceptable content validity. Respondents were encouraged to provide additional comments or opposing opinions. If any item required modification, feedback on suggested revisions was collected, and opinions were sought regarding the need for new items and overall comments on the protocol. All feedback was further discussed by TFT members to determine whether to revise or supplement each question.

Based on the survey results, the initial protocol draft was revised, and a final version was developed in accordance with the consensus on the recommendations. Ultimately, a comprehensive pre- and re-habilitation protocol for the perioperative care of GI cancer surgery was created to serve as a practical guideline and to be considered for future updates in clinical practice guidelines.

Results

Phase I

In the Nutrition Division, the first subgroup discussion categorized keywords into four main domains: disease, procedure, nutrition, and outcome. In the disease category, three keywords were selected: cancer, malignancy, and sarcopenia. For the procedure category, five keywords were chosen: surgery, operative, surgical procedures, prehabilitation, and rehabilitation. In the nutrition category, six keywords were selected: nutrition, nutritional assessment, nutritional screening, nutritional intervention, nutritional support, and nutritional therapy. For the outcome category, no specific keywords were included to avoid restricting the search results. The initial set of 14 keywords selected during the first discussion was subsequently refined through a second round of discussions with all TFT members, resulting in a final selection of nine keywords (Table 1).

In the Exercise Division, the subgroup discussion categorized keywords into three main domains: subject, evaluation, and therapy. During the first discussion, five keywords were selected for the subject category: surgical procedures, opera-

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Table 1. Selected keywords for literature review and protocol development

Division	Category	Initially selected keywords	Finally selected keywords
Nutrition Division	Disease	Cancer, malignancy, and sarcopenia	Cancer
	Procedure	Surgery, operative, surgical procedures, prehabilitation, and rehabilitation	Malignancy
	Nutrition	Nutrition, nutritional assessment, nutritional screening, nutritional intervention, nutritional support, and nutritional therapy	Surgery
			Operative
	Outcome	-[a]	Surgical procedures
			Nutrition assessment
			Nutrition therapy
			Prehabilitation
			Rehabilitation
Exercise Division	Subject	Surgical procedures, operative, digestive system, surgical procedures, and neoplasm	Cancer
			Malignancy
	Evaluation	Sarcopenia, muscle weakness, frailty, body constitution, walking speed, muscle strength, and physical fitness	Sarcopenia
			Muscle weakness
	Therapy	Preoperative exercise, rehabilitation, physical therapy, exercise, and physical therapy modalities	Frailty
			Body composition
			Walking speed
			Muscle strength
			Physical fitness
			Preoperative exercise
			Physical therapy modalities
			Exercise
			Rehabilitation

[a]For the outcome category, no specific keywords were included to avoid restricting the search results.

tive, digestive system, surgical procedures, and neoplasm. For the evaluation category, seven keywords were chosen: sarcopenia, muscle weakness, frailty, body constitution, walking speed, muscle strength, and physical fitness. In the therapy category, five keywords were selected: preoperative exercise, rehabilitation, physical therapy, exercise, and physical therapy modalities. Out of the 17 keywords identified during the initial discussion, the second round of discussions with all TFT members refined the list, resulting in a final selection of 13 keywords (Table 1).

Phase II

A systematic literature review was conducted using the final set of selected keywords. For the Nutrition Division team, the search terms included: ("gastrointestinal" OR "stomach" OR "colorectal" OR "colon" OR "liver" OR "hepatobiliary" OR "pancreas" OR "pancreatobiliary") AND ("cancer" OR "malignancy") AND ("surgery" OR "operative" OR "surgical procedures") AND ("nutrition assessment" OR "nutrition therapy") AND ("prehabilitation" OR "rehabilitation"). For the Exercise Division team, the search terms included: ("gastrointestinal" OR "stomach" OR "colorectal" OR "colon" OR "liver" OR "hepatobiliary" OR "pancreas" OR "pancreatobiliary") AND ("cancer" OR "malignancy") AND ("sarcopenia" OR "muscle weakness" OR "frailty" OR "body composition" OR "walking speed" OR "muscle strength" OR "physical fitness") AND ("preoperative exercise" OR "physical therapy modalities" OR "exercise") AND ("rehabilitation"). In total, 93,316 articles were retrieved from the search results, with 71,736 articles related to exercise therapy and 21,580 articles related to nutrition therapy. These articles were distributed among the TFT members for review and screening. After applying the inclusion criteria, a total of 45 articles (22 on nutrition therapy and 23 on exercise therapy) were finally selected for the study.

Phase III

The CRF was developed based on the 45 final selected studies and categorized into six main sections: diagnostic criteria, nutritional assessment tool, muscle status evaluation (including sarcopenia assessment), nutritional intervention, exercise intervention, and outcome assessment tool. For each section, all assessment tools and intervention methods presented in the selected studies were thoroughly reviewed and classified into corresponding subcategories to create a comprehensive CRF. Based on these results, the most frequently occurring items were selected, and the preliminary draft of a pre- and re-habilitation protocol for GI cancer patients undergoing surgery was developed. This draft includes a summary organized into three sections: diagnostic exam and assessment tools; nutritional rehabilitation in the perioperative period; and exercise rehabilitation in the perioperative period. The diagnostic criteria and assessment tools for the protocol were defined as follows. The exclusion criteria for GI cancer patients included illiteracy, dementia, cognitive impairment, inability to perform physical activity or consume oral intake, and cases with distant metastases where surgical resection was not feasible. For nutritional assessment, the Nutrition Risk Screening (NRS) and Patient-Generated Subjective Global Assessment (PG-SGA) were utilized. Nutritional status was classified as malnutrition if the NRS score was ≥3 and the PG-SGA category was B or C. In such cases, nutritional intervention was implemented according to the pre-rehabilitation protocol. In addition to these tools, laboratory tests, body weight changes, and anthropometric measures such as body mass index were also recommended. Nutritional assessments were advised both preoperatively and postoperatively.

For the diagnosis of sarcopenia, body composition analysis was performed and handgrip strength testing was used to assess muscle strength. To evaluate muscle mass, the use of at least one of the following tools was recommended: dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or computed tomography scan. The criteria for sarcopenia diagnosis followed the Asian Sarcopenia Guidelines [30]. Although surveys such as the 36-Item Short Form (SF-36) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) were considered for sarcopenia assessment, they were not designated as mandatory components of the protocol.

The perioperative nutritional rehabilitation treatment recommends providing 25–30 kcal/kg/day of energy and 1.0–1.5 g/kg/day of protein for adults preparing for surgery, with adjustments made according to the patient's clinical condition. For patients diagnosed with malnutrition or sarcopenia, the use of oral nutritional supplements (ONS) should be considered both preoperatively and postoperatively, with a recommendation to provide at least 400 kcal/day divided into two or more servings. In cases where oral intake is insufficient, parenteral nutrition supplementation may be considered, along with personalized nutritional management through counseling and education.

For perioperative exercise rehabilitation treatment, 150 minutes of moderate-intensity or 75 minutes of high-intensity aerobic exercise per week, combined with resistance training twice a week, was recommended. Breathing exercises were encouraged as part of the pre- and re-habilitation program. The type and intensity of exercise should be modified according to the patient's medical condition. It was emphasized that patients with stomas, lymphedema, severe sarcopenia, frailty, or malnutrition must undergo a safety evaluation by medical professionals before initiating exercise therapy. The frequency analysis results of each CRF item for the development of the preliminary draft of the pre- and re-habilitation protocol are presented in Supplement 1.

Phase IV

To collect feedback and validate the preliminary draft of the protocol, a questionnaire was developed to assess agreement on each component. The survey was conducted during public hearings and expert meetings to gather additional opinions and gauge consensus. The survey results, including the I-CVI, are presented in Table 2. Among the 23 items, 21 (91.3%) achieved an I-CVI of 0.78 or higher, indicating that they were considered valid recommendations. The average I-CVI across all items was 0.918, confirming that the overall scale demonstrated an acceptable level of content validity.

During the survey and discussion process, two items (8.7%) received additional comments or opposing opinions from experts. One notable example was item 1-9, which concerned the selection of diagnostic tools for physical function tests in sarcopenia assessment. The recommendation was to use the 6-minute walk test (6MWT) as the primary evaluation tool, with cardiopulmonary exercise testing performed when feasible. However, this item received an I-CVI of 0.61, with 39% of respondents expressing disagreement (18% somewhat disagree and 21% strongly disagree). A counterargument to item 1-9 suggested that, since multiple methods exist for conducting functional tests, the assessment should not be limited solely to the 6MWT. Additionally, some institutions noted practical limitations in performing tests such as the 6MWT. Based on TFT discussions, it was determined that both the Short Physical Performance Battery—which includes the standing balance test, gait velocity test, and repeated chair stands—and the 6MWT should be included as diagnostic tools for physical function assessment in sarcopenia evaluation of GI cancer patients. When feasible, cardiopulmonary exercise testing was recommended as a supplementary assessment to further evaluate cardiopulmonary capacity and functional status.

Regarding item 2-3, which recommended that the determination and evaluation of insufficient oral intake be left to the clinical judgment of healthcare professionals or clinical dietitians, the I-CVI was 0.68, with 32% of respondents expressing disagreement (19% somewhat disagree and 13% strongly disagree). A comment suggested changing the phrase "based on the judgment of medical staff or clinical dietitians" to "based on the judgment of medical staff, including clinical dietitians," since clinical dietitians are also part of the medical staff. Consequently, the wording of this item was revised according

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Table 2. Results of the questionnaire for validation of the pre- and re-habilitation protocol in gastrointestinal cancer patients

Item of protocol		Score, No. (%)				Total score	No. of total respondents	I-CVI[b]
		4[a]	3[a]	2[a]	1[a]			
I. Diagnostic exam and assessment tool for pre- and postoperative rehabilitation	1-1	19 (59)	8 (25)	5 (16)	0	110	32	0.84
	1-2	13 (42)	14 (45)	3 (10)	1 (3)	101	31	0.87
	1-3	18 (56)	10 (31)	4 (13)	0	110	32	0.87
	1-4	21 (66)	10 (31)	1 (3)	0	116	32	0.97
	1-5	29 (91)	2 (6)	1 (3)	0	124	32	0.97
	1-6	7 (21)	23 (70)	3 (9)	0	103	33	0.91
	1-7	23 (72)	4 (12)	5 (16)	0	114	32	0.84
	1-8	25 (78)	4 (13)	2 (6)	1 (3)	117	32	0.91
	1-9	3 (9)	17 (52)	6 (18)	7 (21)	82	33	0.61
	1-10	14 (42)	17 (52)	2 (6)	0	111	33	0.94
II. Nutritional rehabilitation program in pre- and postoperative period	2-1	20 (69)	9 (31)	0	0	107	29	1.00
	2-2	22 (71)	8 (26)	1 (3)	0	114	31	0.97
	2-3	7 (23)	14 (45)	6 (19)	4 (13)	86	31	0.68
	2-4	21 (68)	9 (29)	1 (3)	0	113	31	0.97
	2-5	12 (39)	18 (58)	1 (3)	0	104	31	0.97
	2-6	16 (52)	13 (42)	2 (6)	0	107	31	0.94
	2-7	18 (58)	12 (39)	0	1 (3)	109	31	0.97
	2-8	27 (87)	3 (10)	0	1 (3)	118	31	0.97
	2-9	24 (78)	5 (16)	2 (6)	0	115	31	0.94
III. Exercise rehabilitation program in pre- and postoperative period	3-1	8 (30)	18 (66)	1 (4)	0	88	27	0.96
	3-2	24 (89)	3 (11)	0	0	105	27	1.00
	3-3	24 (89)	3 (11)	0	0	105	27	1.00
	3-4	21 (78)	6 (22)	0	0	102	27	1.00

[a]Score for each option (A, B, C, D, respectively).
[b]Item-level content validity index (I-CVI), the I-CVI is computed for each item individually to determine its validity. This value indicates the degree of consensus on the relevance of that specific item. The CVI is calculated by determining the proportion of experts who rate each item as 3 ("somewhat agree") or 4 ("strongly agree").

to the suggested feedback. Additionally, some respondents raised concerns about whether all clinical dietitians could reliably perform the PG-SGA assessment (item 1-2, I-CVI 0.87, with four respondents expressing some or strong disagreement). However, consensus was reached that this would not pose a significant issue. For item 1-6 concerning the timing of nutritional pre- and re-habilitation interventions, some concerns were raised that "if necessary, preoperative nutritional therapy should last at least 2 weeks, so starting it only 1 week prior is too late" (I-CVI 0.91, with three respondents somewhat disagreeing). Nevertheless, it was agreed that setting a minimum standard based on realistic institutional circumstances was more appropriate, and the current recommendation was maintained.

After the revision process based on expert discussions and survey results, all modified items were reviewed until complete consensus was reached among TFT members. The final version of the pre- and re-habilitation protocol for GI cancer surgery was then developed (Appendices 1, 2, Supplement 2).

Discussion

We have systematically developed a structured pre- and re-habilitation protocol for patients undergoing GI tract cancer surgery to ensure effective implementation in clinical practice. This process involved a comprehensive review of international guidelines and the latest evidence from the literature. To enhance its clinical applicability, the protocol was designed to be highly specific and sequentially structured, covering key aspects such as patient assessment, nutritional and exercise therapy, and outcome evaluation. It was meticulously formulated to enable immediate use in clinical settings. Furthermore, the protocol underwent a rigorous review and approval process by a multidisciplinary team of experts and healthcare professionals to facilitate its adoption into routine practice. To our knowledge, this is the first standardized protocol systematically compiled to guide clinical decision-making in the pre- and re-habilitation management of GI tract cancer surgery in Korea.

Most cancer patients experience not only physical and functional decline but also systemic inflammatory changes and frailty. Additionally, individuals aged 65 years or older constitute the majority of cancer patients undergoing surgery [31]. Among these patients, approximately 40% are reported to be frail, and nearly 20% of frail older adults develop new postoperative disabilities that impair their ability to perform daily activities [32]. Frailty is characterized by a decline in physiological and physical reserves, leading to reduced adaptability to external stressors and increased vulnerability to disease [33-35]. It is also associated with more than a twofold increase in postoperative complication rates, mortality, and the likelihood of discharge to long-term care facilities compared to non-frail patients. With the acceleration of population aging, the number of frail older adults undergoing surgery is expected to rise, further increasing the risk of postoperative adverse events. Pre- and re-habilitation aims to enhance physiological and functional reserves before surgery, thereby mitigating postoperative functional decline and facilitating a faster return to preoperative performance levels. The role of rehabilitation in improving surgical outcomes for frail patients is increasingly emphasized, as it has been recognized as a key strategy for reducing postoperative complications and promoting functional recovery. Therefore, the standardized protocol developed in this study should be regarded as an essential therapeutic intervention rather than merely an adjunctive treatment. It is intended for active implementation in patients who are particularly vulnerable to physiological changes and surgical stress, and it is expected that postoperative outcomes and long-term prognoses will improve in high-risk populations, while also supporting preoperative functional recovery. However, some previously published studies on frail older adults have failed to demonstrate significant improvements in postoperative function or complication rates following perioperative rehabilitation, often reporting an average protocol adherence rate below 60%. In contrast, when analyses were restricted to participants who completed at least 80% of the rehabilitation protocol, significant reductions in complication rates and improved recovery of pre-rehabilitation functional levels were observed [36]. Therefore, to confirm the clinical efficacy of pre- and re-habilitation protocols, efforts should be made to maintain an optimal adherence rate of at least 80%. This goal necessitates continuous investigation and intervention to identify and address factors that may hinder protocol adherence, ultimately ensuring the effective implementation of these programs.

This protocol was developed based on the latest research findings and international guidelines. However, certain details remain subject to ongoing discussion, as some principles are not yet firmly established or may require individualized application depending on specific clinical conditions. Therefore, ongoing refinement through further research and revisions may be necessary. For example, the recommended energy intake (25–30 kcal/kg/day) and protein intake (1.0–1.5 g/kg/day) in items 1-1 and 1-2 of the Nutritional Rehabilitation Program were determined based on the American Society for Parenteral and Enteral Nutrition [37] and European Society for Clinical Nutrition and Metabolism guidelines [38], with approval from the committee and external experts. Nonetheless, in patients with specific risk factors such as advanced age or sarcopenia, as well as those with underlying conditions like renal or hepatic failure, individualized targets should be considered. Given that this protocol primarily aims to establish standardized clinical guidelines for pre- and re-habilitation in GI tract cancer surgery, it does not include detailed specifications for every individual parameter.

Enteral immunonutrition using ONS containing omega-3 fatty acids, glutamine, arginine, and nucleotides has recently attracted growing interest for perioperative nutritional support in cancer patients. However, despite its theoretical advantages, meta-analyses have produced inconclusive results. The heterogeneity of the studies—resulting from variations in cancer types, surgical factors, and individual nutritional statuses—has made it difficult to draw definitive conclusions. As a result, major nutritional guidelines present varying recommendations for preoperative ONS and immunonutrition. For example, the ASPEN guidelines recommend that preoperative ONS for 5–7 days may benefit malnourished patients prior to surgery [37]. In contrast, the ESPEN guidelines endorse preoperative ONS but highlight the lack of clear evidence favoring immunomodulating ONS formulations (e.g., those containing arginine, omega-3 fatty acids, and nucleotides) over standard ONS [38]. Although immunonutrition may be considered, the guidelines do not offer a standardized recommendation due to insufficient evidence. In our protocol, perioperative ONS use (items 2-5 to 2-7) is recommended, with a minimum daily intake of 400 kcal split into at least two doses. The use of immunomodulating ONS containing omega-3 fatty acids and arginine is suggested only when deemed necessary. Future updates and revisions of this protocol should include more detailed specifications of certain nutritional therapy items to enhance clinical applicability.

The exercise program outlined in this protocol recommends high-intensity aerobic and resistance exercises for all cancer patients who are capable of participating in pre- and re-habilitation, regardless of age, while also incorporating respiratory rehabilitation to account for surgical characteristics (item 3-1). Resistance exercise directly stimulates protein synthesis in skeletal muscle, with synthesis rates increasing in proportion to exercise intensity. Aerobic exercise training improves maximal oxygen uptake, mitochondrial oxidative enzyme activity, and insulin sensitivity. When combined with resistance exercise, it can further enhance protein synthesis. Moreover, regular physical exercise induces anti-inflammatory cytokines and helps mitigate muscle wasting associated with cancer-related inflammation, benefiting patients recovering from major surgery who often exhibit systemic inflammatory responses postoperatively. Despite these advantages, concerns may arise regarding the safety of implementing exercise pre- and re-habilitation for high-risk cancer patients, such as those who are elderly or malnourished. However, recent studies support the feasibility and safety of exercise even in high-risk older patients. For example, Chia et al. [39] conducted a perioperative exercise rehabilitation program in colorectal cancer patients with a mean age of 79 years who had preoperative frailty and reported an adherence rate exceeding 80%. Similarly, Karlsson et al. [40] investigated preoperative exercise rehabilitation in colorectal cancer patients with a mean age of 83.5 years, observing a compliance rate of 97% with no critical complications. These findings suggest that, when tailored appropriately in terms of intensity and frequency to each patient's characteristics, exercise pre- and re-habilitation—including both resistance and aerobic components—can be safely implemented in elderly, high-risk patients. Therefore, as highlighted in items 3-2 and 3-3, individualized exercise programs should be administered under the supervision of rehabilitation specialists within a multidisciplinary team. Further refinements should be made to specify detailed considerations based on patients' underlying conditions and frailty levels.

This protocol has some limitations. It was developed with the primary objective of establishing comprehensive guidelines for a diverse population of patients with GI cancer. However, due to the limited number of well-established randomized controlled trials specifically targeting GI surgery patients, this protocol was formulated based on a systematic literature review, integrating the frequency of individual components and expert consensus. This approach may represent a methodological limitation. Furthermore, this study did not create cancer type–specific protocols or differentiate detailed subcategories according to patients' comorbidities, disease staging, or clinical conditions. Future research should therefore focus on developing more specialized and stratified sub-protocols that account for variations in cancer types, comorbidities, and pathological characteristics. Additionally, this protocol does not offer a framework for evaluating the feasibility and effectiveness of implementing pre- and rehabilitation strategies in clinical practice. Objective assessment of clinical outcomes and guideline adherence is essential to ensure successful protocol execution and to optimize its impact. Consequently, future studies should establish standardized criteria and assessment tools to measure both the appropriateness of implementation and the clinical efficacy of each component of the protocol.

Conclusion

Upon completion, the final version of this protocol received official endorsement from the Korean Society of Surgical Metabolism and Nutrition. To promote its adoption in clinical practice, the protocol will be disseminated via email and official websites to medical professionals affiliated with relevant academic societies, including the Korean Society of Surgical Metabolism and Nutrition, the Korean Surgical Society, the Korean Society of Cancer Rehabilitation, and the Korean Society of Clinical Nutrition. By providing the latest evidence on perioperative rehabilitation and a standardized clinical guideline that can be easily integrated into routine practice, this protocol is expected to facilitate proactive pre- and re-habilitation interventions for GI tract cancer patients at high risk of postoperative complications, functional decline, and malnutrition. Consequently, it may contribute to improved postoperative outcomes and better long-term prognoses for these patients.

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Conceptualization: IKL, EYK. Methodology: IKL, EYK, JHB. Formal analysis/validation: JK, EJY, GYK, DHK, JAK, JSK, KEN, SUB, JHP, SYA, EYK, JHB. Project administration: SJP, SYO, SJY, SHJ, NJC, JHH. Funding acquisition: IKL. Writing – original draft: EYK. Writing – review & editing: EYK, IKL. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there are no potential conflicts of interest.

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Data availability

The research data, including the case report form, are available on request from the corresponding author.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.15747/ACNM.25.0001

Supplement 1. The frequency analysis results of each case report form item for the development of the preliminary draft of the pre- and re-habilitation protocol.
Supplement 2. Summary of the pre- and re-habilitation protocol for gastrointestinal cancer patients. (Korean version)

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Appendix 1. The final version of the pre- and re-habilitation protocol for gastrointestinal cancer patients

I. Diagnostic Exam and Assessment Tool for Pre- and Postoperative Rehabilitation

1-1. Exclusion Criteria

The following patients should be excluded from this prehabilitation protocol if they meet any of the criteria below.

A. Illiteracy/Dementia/Cognitive impairment

B. Inability to ambulate or perform physical activity

C. Inability to consume food orally

D. Presence of distant metastases unsuitable for surgical resection

1-2. Nutrition Screening & Assessment

A. Nutrition screening should be performed using NRS (Nutritional Risk Screening), and patients scoring 3 or higher are recommended to refer to a clinical dietitian.

B. The clinical dietitian evaluates nutritional status using the PG-SGA (Patient-Generated Subjective Global Assessment) and considers nutritional intervention.

C. Based on nutritional status:

- If the patient has adequate nutrition (NRS ≥3, PG-SGA A), they are recommended to receive Standard Care.
- If the patient is malnourished (NRS ≥3, PG-SGA B or C), they are recommended to follow the Nutrition Intervention Care under the pre-rehabilitation protocol.

1-3. Nutritional Assessment (Food Intake Record)

A. Pre- and postoperatively, a 3-day food record or 24-hour dietary recall can be used to evaluate the patient's usual intake to assess the effects of nutritional intervention and set management goals.

B. However, this is optional and may be omitted if necessary.

1-4. Nutritional Assessment (Laboratory Tool)

A. Pre- and postoperative blood tests should be performed, including albumin, pre-albumin, hemoglobin, and C-reactive protein.

B. If feasible, measure TLC (total lymphocyte count), transferrin, and vitamin D as well.

1-5. Nutritional Assessment (Anthropometric)

A. Pre- and postoperatively, assess weight changes and BMI (body mass index) as indicators of nutritional status.

B. Body composition analysis for sarcopenia diagnosis is essential. If possible, assess fat mass (FM) and lean body mass (LBM).

1-6. Nutritional Assessment (Timing)

A. Nutritional assessments should be performed both pre- and postoperatively.

B. It is recommended that preoperative assessments be conducted at least one week before surgery along with the diagnosis.

C. It is recommended that postoperative assessments be done before discharge or on the 7th postoperative day. For patients who underwent nutritional intervention due to malnutrition, reassessment should be conducted 2 months after surgery.

1-7. Sarcopenia Evaluation (Muscle Strength Test)

A. Muscle strength for sarcopenia evaluation is recommended to be assessed using the Handgrip Strength Test.

B. Measure three times and calculate the average value for evaluation.

C. Cutoff values: male <28 kg, female <18 kg (Asian Sarcopenia Guidelines).

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1-8. Sarcopenia Evaluation (Muscle Mass)

A. Muscle mass for sarcopenia evaluation is recommended to be measured using DEXA, BIA, or CT scans.

B. Cutoff values (Asian Sarcopenia Guidelines):

- DEXA: SMI; Male <7.0 kg/m^2, Female <5.4 kg/m^2
- BIA: Male <7.0 kg/m^2, Female <5.7 kg/m^2

1-9. Sarcopenia Evaluation (Physical Function Test)

A. Physical function for sarcopenia evaluation is recommended to be assessed using both the Short Physical Performance Battery (SPPB)—comprising the standing balance test, gait velocity test, and repeated chair stands—and the 6-Minute Walk Test.

B. CPET (Cardiopulmonary Exercise Test) may be performed if available, as it provides comprehensive evaluation of exercise capacity and cardiopulmonary function.

1-10. Sarcopenia Evaluation (Questionnaire)

A. Quality of life assessment for sarcopenia evaluation can consider using SF-36 or EORTC QLQ-C30, but it is not mandatory.

II. Nutritional Rehabilitation Program in Pre- and Postoperative Period

2-1. Energy requirements should be determined considering the patient's physical condition, metabolic status, and disease impact. For adults undergoing surgery, 25–30 kcal/kg/day of energy is recommended. For elderly patients, providing more than 30 kcal/kg/day is recommended. However, this requirement may be adjusted according to the patient's condition.

2-2. Protein is essential for maintaining and restoring muscle mass after surgery. Generally, 1.0–1.5 g/kg/day of protein is recommended. For elderly patients or those at risk of sarcopenia, at least 1.2 g/kg/day of protein should be provided.
Answer: A. Strongly Agree B. Somewhat Agree C. Somewhat Disagree D. Strongly Disagree

2-3. The evaluation of insufficient oral intake should be based on the judgment of medical staff, including clinical dietitians.

2-4. If malnutrition or sarcopenia is present, the use of oral nutritional supplements (ONS) should be considered in the pre- and postoperative periods.

2-5. Oral nutritional supplements (ONS) should provide at least 400 kcal/day.

2-6. Oral nutritional supplements (ONS) should be administered in two or more divided doses per day.

2-7. If necessary, select oral nutritional supplements containing Omega-3 or Arginine.

2-8. In cases of insufficient oral intake in the pre- and postoperative periods, parenteral nutrition (PN) should be applied as needed.

2-9. If necessary, refer to a clinical dietitian for personalized nutritional counseling and education for tailored nutrition management

III. Exercise Rehabilitation Program in Pre- and Postoperative Period

3-1. For healthy cancer patients, it is recommended that the exercise prescription include 150 minutes of moderate-intensity aerobic exercise or 75 minutes of high-intensity aerobic exercise per week (3–5 days per week), along with resistance exercises twice a week involving 8–10 muscle groups with 8–10 repetitions for at least 2 sets. Breathing exercises are also recommended to reduce postoperative complications.

3-2. Patients with a low risk of exercise-related complications may transition from a hospital-based exercise program to a home-based exercise program. However, for patients with a high risk of exercise-related complications, a supervised exercise program is required.

3-3. For elderly patients or those with sarcopenia, a comprehensive assessment of the patient's medical condition should be conducted, and a structured exercise program tailored to the individual's physical status—including the type and intensity of exercises—should be provided.

3-4. For patients with comorbidities, stomas, lymphedema, severe sarcopenia (frailty), or severe malnutrition, a medical pre-evaluation must be conducted. Exercise should only be initiated after medical safety confirmation by healthcare providers and performed under the supervision of rehabilitation specialists.

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Appendix 2. Summary of the pre- and re-habilitation protocol for gastrointestinal cancer patients

I. Enrollment Criteria and Assessment of Malnutrition and Sarcopenia

1. Inclusion and Exclusion
   1. This protocol targets patients diagnosed with gastrointestinal cancer (stomach cancer, colon cancer, liver cancer, bile duct cancer, and pancreatic cancer) who have undergone surgery.
   2. Patients who meet any of the following criteria will be excluded:
      - Illiterate / Dementia / Cognitive impairment
      - Unable to move / Unable to exercise
      - Unable to intake food
      - Presence of distant metastasis that cannot be surgically resected

2. Malnutrition Assessment
   1. Nutrition Risk Screening (NRS) is used as a nutrition screening tool, and if the score is 3 or higher, the patient is referred to a clinical nutritionist.
   2. The clinical nutritionist assesses the nutritional status using Patient-Generated Subjective Global Assessment (PG-SGA) and considers nutritional interventions.
   3. Depending on the nutritional status, if the patient is in good nutritional condition (NRS<3, PG-SGA A), standard care will be implemented. If the patient is in a malnourished state (NRS≥3, PG-SGA B or C), the pre-rehabilitation protocol under Nutrition Intervention Care will be followed.
   4. Dietary intake records can be made using a 3-day food diary or a 24-hour recall method, though it is not mandatory.
   5. Pre- and post-surgery, blood tests (albumin, pre-albumin, hemoglobin, CRP) are performed.
   6. If possible, TLC, transferrin, and vitamin D should also be measured.
   7. Pre- and post-surgery, weight changes and body mass index (BMI) are assessed as indicators of nutritional status.
   8. Nutritional assessment is performed both before and after surgery.
   9. The pre-surgery assessment should be conducted at least 1 week before surgery, along with the diagnosis.
   10. Post-surgery, the assessment is conducted either before discharge or within 1 week. For patients who underwent intervention due to malnutrition, the assessment is done 2 months after surgery.

3. Sarcopenia Assessment
   1. The muscle strength evaluation for sarcopenia assessment is conducted using the handgrip test.
      - A total of 3 measurements are taken, and the average value is calculated for assessment.
      - Reference values: Men <28 kg, Women <18 kg (Asian Sarcopenia Guideline)
   2. The muscle mass evaluation for sarcopenia assessment is conducted using one of the following methods: DEXA, BIA, or CT scan.
      - DEXA: SMI; Men <7.0 kg/m^2, Women <5.4 kg/m^2
      - BIA: SMI; Men <7.0 kg/m^2, Women <5.7 kg/m^2
   3. The physical function evaluation for sarcopenia assessment is conducted using the 6-minute walk test or SPPB.
   4. CPET, which allows comprehensive evaluation of exercise capacity and cardiopulmonary function, should be performed if possible.
   5. As a quality of life-related survey for sarcopenia assessment, SF-36 and EORTC QLQ-C30 may be considered, but they are

not mandatory.

II. Summary of Nutrition Pre- and Re-habilitation: Assessment and Intervention

1. Nutrition assessment

Nutrition Rehabilitation Program (Pre, Post- op period)		Age	<65, ≥65			
		Nutrition status	Malnutrition(+)	Malnutrition(+)	Malnutrition(-)	Malnutrition(-)
		Sarcopenia status	Sarcopenia(+)	Sarcopenia(-)	Sarcopenia(+)	Sarcopenia(-)
Indicator	Criterion	Sub-items	+ / +	+ / -	- / +	- / -
Screening	O (NRS-2002)	Weight loss, reduced intake, disease	O	O	O	O
Assessment	O (PG-SGA)	Weight loss, reduced intake, disease, ECOG, Physical exam, disease, metabolic status etc.	O	O	-	-
Food Intake	O (If needed)	24-hour recall, 3 days record	(If needed)	(If needed)	(If needed)	-
Laboratory	O	Albumin, Hemoglobin, CRP, WBC, TLC	O	O	O	-
Anthropometry	O	Weight loss %, BMI, LBM, FM	O	O	O	O

2. Nutrition intervention

Nutrition Rehabilitation Program (Pre, Post- op period)		Age	<65, ≥65			
		Nutrition status	Malnutrition(+)	Malnutrition(+)	Malnutrition(-)	Malnutrition(-)
		Sarcopenia status	Sarcopenia(+)	Sarcopenia(-)	Sarcopenia(+)	Sarcopenia(-)
Indicator	Criterion	Sub-items	+ / +	+ / -	- / +	- / -
Energy	O	25-30 kcal/kg/day REE (Physical factor, injury factor)	O	O	O	-
Protein	O	1.2~1.5g/kg/day (~2g/kg/day)	O	O	O	-
Timing	O	Preoperative: Conducted at least 1 week prior, along with the diagnosis Postoperative: - Conducted either before discharge or within 1 week - Re-evaluated 2 months after surgery if nutritional support was provided	O	O	O	-
Supplement 1	(If needed)	Oral Nutrition Supplement	(If needed)	(If needed)	(If needed)	-
Supplement 2	(If needed)	Omega-3, arginine, calcium, vitamin D etc..	(If needed)	(If needed)	(If needed)	-
Support(EN/PN)	(If needed)	Oral intake insufficient	(If needed)	(If needed)	(If needed)	-
Dietary counseling	O	Individual counseling, Diet advice	O	O	O	(If needed)

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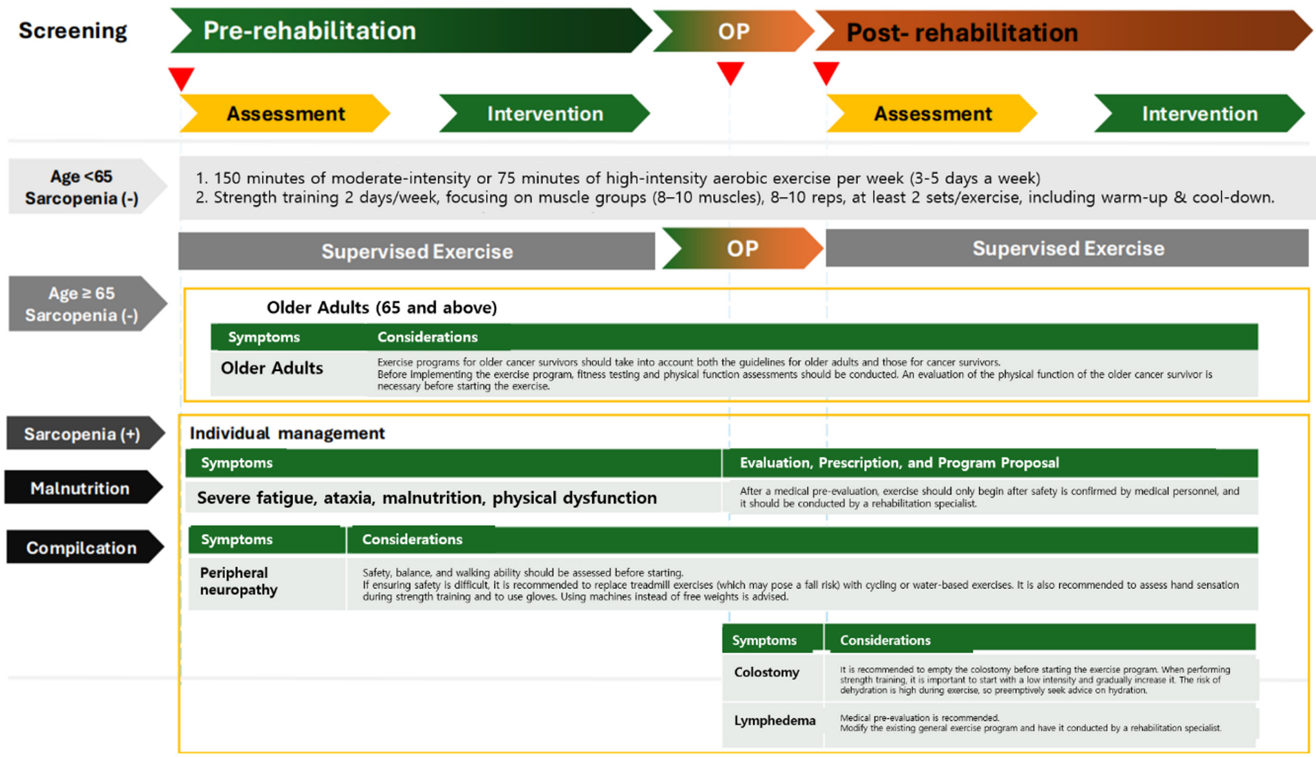
III. Summary of Exercise Pre- and Re-habilitation: Assessment and Intervention



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Original Article

Comparison of efficacy of enteral versus parenteral nutrition in patients after esophagectomy in Malaysia: a prospective cohort study

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Abstract

Purpose: This study aims to assess the effectiveness of enteral versus parenteral feeding in patients after esophagectomy.
Methods: This a prospective cohort study of post-esophagectomy intensive care unit (ICU) patients over 12 months in the National Cancer Institute, Malaysia. Early enteral feeding followed the Enhanced Recovery After Surgery protocol, and parenteral nutrition (PN) was considered if there was a risk for conduit ischemia. It compared the effectiveness of enteral versus PN following esophagectomy, and assessed the correlations between biochemical nutritional markers and hospital lengths of stay or ventilation days.
Results: It included two cohorts receiving PN (n=11) or enteral nutrition (EN) (n=11) following elective esophagectomy. Preoperative weight, body mass index, and Subjective Global Assessment were higher in the EN group (P=0.033, P=0.021, P=0.031, respectively). Nutritional interruption occurred more frequently in the EN group (63.7%) compared to the PN group (P=0.001). Mean levels of energy and protein received were 93.1 kcal/kg and 1.4 g/kg for PN versus 92.4 kcal/kg and 1.2 g/kg for EN (P=0.893 and P=0.036). The median lengths of ICU stay (P=0.688) and postoperative stay (P=0.947) between groups showed no significant difference. In addition, 30-day mortality (P=0.214) and other postoperative complications (P>0.05) were comparable in the two groups.
Conclusion: Early initiation of supplementary PN due to significant interruption in EN led to higher protein intake compared to the EN group. However, there were no significant differences in postoperative outcomes, including 30-day mortality, ICU length of stay, and ventilation days. PN ensures adequate nutritional intake, especially in terms of protein delivery, without adversely affecting postoperative recovery and clinical outcomes.

Keywords: Complications; Enhanced recovery after surgery; Enteral nutrition; Esophagectomy; Parenteral nutrition

Introduction

Background

Malnutrition affects up to 78.9% of oesophageal cancer patients, leading to higher postoperative complications and mortality [1,2]. Nutritional support, particularly enteral nutrition (EN), is crucial for better outcomes due to its lower complication rates and costs compared to parenteral nutrition (PN) [3]. While early oral feeding post-esophagectomy may shorten hospital stays and improve recovery, concerns about anastomotic leaks remain [4].

In Asia, meta-analysis study in China by Peng et al. [5] found that only 37% of patients post-esophagectomy met nutritional goals via EN alone, necessitating supplemental PN. Another study in China by Yu et al. [6] reported greater infection rates in PN patients compared to those on EN

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after esophagectomy. It was noted that PN group exhibited higher, the rate of systemic inflammatory response than the EN group. Although EN group is generally preferred, PN is essential in certain situation where the gastrointestinal tract unable to support enteral feeding, lowering complications and aspiration risks in specific conditions [7].

Studies have compared the effectiveness of EN and PN in achieving nutritional goals after esophagectomy, with conflicting outcomes. Worthington et al. [8] noted that PN is essential when intestinal issues prevent adequate oral or EN and can reduce mortality. Fell et al. [9] found worse nutritional outcomes when PN is delayed in critically ill infants and children. Conversely, Mudge et al. [10] reported no significant differences in energy and protein delivery between EN and PN groups. These conflicting results may be due to variations in surgical techniques, postoperative care, and patient characteristics across centres.

A systematic review and meta-analysis by Chow et al. [11] found no significant differences in overall complication rates, anastomotic leaks, or respiratory complications between EN and PN groups. The researchers emphasize that there is no observed superiority between PN and EN regarding nutrition support complications, major adverse events, and mortality outcomes. A study by Weijs et al. [12] found no significant difference in hospital stay or ventilation days between the EN and PN groups. Martinez-Ortega et al. [13] recommend a combination of EN and PN if caloric and nutrient needs cannot be adequately met through oral and enteral means alone (less than 50% of the caloric requirement) after 7 days. In cases where nutrition therapy is necessary and EN is contraindicated, such as instances of intestinal obstruction, prompt initiation of PN is advised.

While not directly related to clinical outcomes, cost-effectiveness has also been compared [14]. Studies show EN to be more cost-efficient than PN due to lower costs of enteral feeding formulations and administration [15-17].

Objectives

This study aims to compare the efficacy of EN and PN in Malaysian patients after esophagectomy by evaluating nutritional adequacy, complications, hospital stay length, and mechanical ventilation duration. Furthermore, correlation between length of stay (LOS) or ventilation duration and biochemical markers, including albumin and C-reactive protein (CRP) level, were analysed. These results will be basic data to guide optimal nutritional management in patients after esophagectomy.

Methods

Ethics statement

Institutional review board approval was obtained from National Cancer Institute, Malaysia for this study (No. 800-5/3/1), and informed consent was provided by all participants.

Study design

It was a prospective cohort study and described according to the STROBE statement available at https://www.strobe-statement.org/.

Setting

This study was done at the intensive care unit (ICU) of the National Cancer Institute, Putrajaya, Malaysia, from May 31, 2023, to May 31, 2024. Early enteral tube feeding was initiated in all post-esophagectomy patients according to the Enhanced Recovery After Surgery protocol within 24 hours of surgery [12,18]. However, in cases with risk of conduit ischemia, PN will be initiated to ensure targeted calorie and protein provision by postoperative day 5.

Participants

The study included all patients who underwent esophagectomy and were admitted to the ICU postoperatively (Fig. 1).

Variables

The primary outcomes are calories and protein level of patient following esophagectomy postoperative day 5. The secondary outcomes are biochemical nutritional markers, complications, ICU and hospital lengths of stay, ventilation days, and overall postoperative complications according to Clavien-Dindo classification.

Data sources/measurement

Demographic and clinical data were obtained from patients' medical records. Nutritional intake was monitored daily, with energy and protein intakes calculated using standard formulas. Complications were classified according to the Clavien-Dindo system [19,20].

Bias

There was no selection bias reportable.

Study size

Sample size estimation was not done since the entire target population was subjected to it.

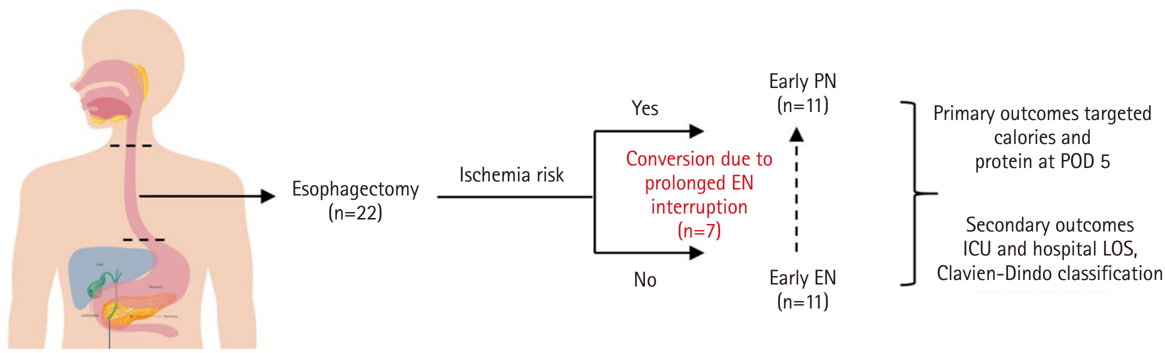

Fig. 1. Comparison enteral nutrition (EN) versus parenteral nutrition (PN) on clinical outcome in esophagectomy patients. POD, postoperative day; ICU, intensive care unit; LOS, length of stay.

Statistical methods

Statistical analysis was conducted using IBM SPSS version 26 [21]. Continuous variables were reported as mean±standard deviation (SD) or median (interquartile range), while categorical variables were presented as frequency and percentage. The Student t-test or Mann-Whitney U test was used to compare continuous variables between the EN and PN groups, and the chi-square test or Fisher exact test was used for categorical variables. A P-value <0.05 was considered statistically significant [22-24].

Results

Participants

Participants' sociodemographic characteristics are presented in Table 1. The mean ages were 60.9 years (PN) and 55.1 years (EN). The EN group had better preoperative weight, body mass index, and Subjective Global Assessment scores (P<0.05). Nutritional interruptions occurred more frequently in the EN group (63.7%), with seven patients converted to PN due to prolonged intestinal failure type I. Mean energy and protein intakes were similar between groups: PN (93.1 kcal/day, 1.4 g/kg) and EN (92.4 kcal/day, 1.2 g/kg) with P-values of 0.893 and 0.036, respectively. ICU and postoperative hospital stays, 30-day mortality, and postoperative complications did not differ significantly between groups.

Nutritional parameters and clinical outcomes between EN and PN groups are presented in Table 2. The caloric intake for both groups did not show significant differences across the days measured, as in Table 2. This pattern continued through day 7, where the mean caloric intake was 92.8 kcal (SD=11.35) for all patients, with no significant differences between groups (P=0.893). In contrast to caloric intake, total protein intake showed significant differences, particularly from day 2 onward. On day 2, the PN group had a mean protein intake of 0.9 g (SD=0.70) compared to 0.5 g (SD=0.25) for the EN group, with a significant P-value of 0.001. Levels of biochemical markers, specifically albumin and CRP, were also evaluated. While there were no significant differences in albumin levels across the days measured, value on day 3 (P=0.055) suggested a potential impact of nutritional strategy on protein status.

Postoperative complications of EN and PN groups measured according to the Clavien-Dindo system were presented in Table 3. The overall incidence of complications was similar between the EN and PN groups, with no significant differences in rates of complications (P=0.574), as in Table 3. The most common complications were of grade IIIb, occurring in 36.4% of all patients, with a higher rate in the PN group (45.4%) compared to the EN group (27.2%). As expected, the PN group experienced risk of conduit ischemia.

Albumin and CRP levels between pneumonia and non-pneumonia groups were presented in Table 4. Albumin levels did not show significant differences (P=0.302), whereas CRP levels were significantly higher in the pneumonia group (243.5 mg/L, SD=82.69) compared to the non-pneumonia group (137.4 mg/L, SD=96.58), with a P-value of 0.012, as in Table 4.

Correlation between LOS or ventilation duration and biochemical markers, including albumin and CRP level, were presented in Table 5. There is no significant correlation of LOS or ventilation days with albumin levels (P>0.05), as in Table 5.

Discussion

Key results

EN group had significantly better preoperative weight, body mass index, and Subjective Global Assessment scores but experienced more nutritional interruptions (63.7%) with

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Table 1. Sociodemographic characteristic comparison between PN and EN groups

Characteristic	All (n=22)	PN (n=11)	EN (n=11)	P-value
Age (yr), mean±SD	58.0±12.79	60.9±10.63	55.1±14.55	0.297[a]
Sex, No. (%)				0.647[b]
Male	15 (68.2)	7 (63.6)	8 (72.7)	
Female	7 (31.8)	4 (36.4)	3 (27.3)	
ASA, No. (%)				0.540[b]
I	7 (31.8)	3 (27.3)	4 (36.4)	
II	11 (50.0)	5 (45.5)	6 (54.5)	
III	4 (18.2)	3 (27.3)	1 (9.1)	
ECOG, No. (%)				0.078[b]
0	12 (54.5)	4 (36.4)	8 (72.7)	
1	9 (40.9)	7 (63.6)	2 (18.2)	
2	1 (4.5)	0	1 (9.1)	
SGA, No. (%)				0.031[b]
A	10 (45.4)	2 (18.2)	8 (72.7)	
B	6 (27.3)	5 (45.5)	1 (9.1)	
C	6 (27.3)	4 (36.4)	2 (18.2)	
Stage, No. (%)				0.189[b]
II	2 (9.1)	0	2 (18.2)	
III	14 (63.7)	9 (81.8)	5 (45.5)	
III	1 (4.5)	0 (0.0)	1 (9.1)	
IV	1 (4.5)	1 (9.1)	0	
NA	4 (18.2)	1 (9.1)	2 (27.3)	
Weight (kg), mean±SD	62.1±12.33	56.6±10.88	67.8±11.60	0.033[a]
BMI (kg/m2), mean±SD	23.3±3.97	21.4±2.73	25.2±4.21	0.021[a]
ICU stay (day), median (IQR)	3.0 (2.00–9.50)	3.0 (2.00–14.00)	2.00 (2.00–5.00)	0.688[c]
Hospital stay (day), median (IQR)	29.0 (15.00–43.50)	30.0 (15.00–41.00)	20.0 (15.00–61.00)	0.947[c]
Postoperative complication, No. (%)				
30-day mortality	3 (13.6)	3 (27.3)	0	0.214[c]
Morbidity	11 (50.0)	6 (54.5)	5 (45.5)	0.670[b]
Pneumonia	12 (54.5)	6 (54.5)	6 (54.5)	>0.999[c]
Prolonged ventilation	1 (4.5)	0	1 (9.1)	>0.999[c]
Re-admission to ICU	7 (31.8)	3 (27.3)	4 (36.4)	>0.999[c]
SSI	1 (4.5)	1 (9.1)	0	>0.999[c]
Change in strategy, No. (%)				
Interruption and change of feeding route	-	0	7 (63.7)	0.001[b]

PN, parenteral nutrition; EN, enteral nutrition; SD, standard deviation; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; SGA, Subjective Global Assessment; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; SSI, surgical site infection.
[a]Independent t-test was applied, significant P-value was set at 0.05.
[b]Chi-square test was applied, significant P-value was set at 0.05.
[c]Fisher test was applied, significant P-value was set at 0.05.

seven conversions to PN. Both groups achieved similar energy intake, yet PN provided significantly higher protein intake from day 2 onward. ICU and hospital stays, 30-day mortality, and overall complications were comparable, except for a higher grade IIIb complication rate in PN. Elevated CRP levels were clearly associated with pneumonia and positively correlated with longer hospital stays.

Interpretation

Caloric intake trend continued through day 7, where the PN group maintained higher protein intake, indicating that PN may be more effective in meeting protein requirements in critically ill patients [25-29]. CRP levels did not differ significantly between groups, indicating similar inflammatory responses throughout the study period [12,29-31]. Fluid bal-

Table 2. Comparison of nutritional parameters and clinical PN and EN groups

Characteristic	All (n=22)	PN (n=11)	EN (n=11)	P-value[a]
Calorie and protein targets in ICU				
Calorie intake (kcal/kg), mean±SD				
D1	29.9±18.70	33.5±15.53	26.2±21.56	0.379
D2	41.9±13.00	45.7±9.34	38.1±15.35	0.174
D3	54.0±12.97	56.6±14.10	51.5±11.82	0.362
D5	77.9±17.08	82.1±12.79	73.7±20.27	0.261
D7	92.8±11.35	93.1±8.86	92.4±14.10	0.893
Total protein (g/kg), mean±SD				
D1	0.5±0.35	0.6±0.38	0.4±0.37	0.121
D2	0.7±0.31	0.9±0.70	0.5±0.25	0.001
D3	0.9±0.31	1.0±0.27	0.7±0.26	0.008
D5	1.1±0.29	1.3±0.28	1.0±0.24	0.034
D7	1.3±0.21	1.4±0.20	1.2±0.18	0.036
Biochemical parameters				
Albumin (g/L), mean±SD				
D1	29.2±4.03	28.4±4.50	30.1±3.51	0.327
D3	27.0±3.48	25.5±3.01	28.4±3.47	0.055
D5	28.5±3.02	28.1±2.17	29.0±3.74	0.494
D7	28.9±5.31	27.3±3.90	30.5±6.17	0.153
CRP (mg/L), mean±SD				
D1	102.3±59.37	121.5±70.2	83.2±40.66	0.134
D3	200.0±102.22	221.7±108.40	178.3±95.67	0.331
D5	195.3±102.48	225.2±66.61	165.4±125.09	0.182
D7	163.0±98.52	182.0±70.83	144.0±120.70	0.380
Fluid balance (mL), median (IQR)				
D1	1,438 (854.3 to 1,961)	997.0 (566.0 to1,948)	1,599 (1,200 to 2,000)	0.158
D3	439.5 (−218.0 to 798.5)	292.0 (−199.0 to 576.0)	742.0 (−674.0 to 830.0)	0.577
D5	354.0 (−56.0 to 605.5)	580.0 (−8.0 to 900.0)	67.0 (−74.0 to 400.0)	0.061
D7	338.0 (−30.3 to 761.5)	520.0 (194.0 to 859.0)	190.0 (−46.0 to 729.0)	0.375[b]

PN, parenteral nutrition; EN, enteral nutrition; ICU, intensive care unit; SD, standard deviation; CRP, C-reactive protein; IQR, interquartile range.
[a]Independent t-test, significant P-value was set at 0.05.
[b]Mann Whitney U test was applied, significant P-value was set at 0.05.

Table 3. Postoperative complications (Clavien-Dindo system)

Grade	No. (%)			P-value
	All (n=22)	PN (n=11)	EN (n=11)	
0	8 (36.4)	4 (36.4)	4 (36.4)	0.574
I	0	0	0	
II	3 (13.7)	1 (9.1)	2 (18.2)	
IIIa	1 (4.5)	0	1 (9.1)	
IIIb	8 (36.4)	5 (45.4)	3 (27.2)	
IVb	1 (4.5)	0	1 (9.1)	
V	1 (4.5)	1 (9.1)	0	

PN, parenteral nutrition; EN, enteral nutrition.

ance, as measured by median values and interquartile ranges, showed no significant differences between the groups, with P-values ranging from 0.061 to 0.577, suggesting comparable fluid management strategies.

Although there was no significant correlation between LOS or ventilation days with albumin level, a significant positive correlation was found between LOS and CRP levels (P=0.049), indicating that longer hospital stays are associated with higher inflammatory markers. This suggests that monitoring CRP levels may be crucial in managing patients' nutritional needs and overall recovery [32,33].

Even though the ICU guidelines highlight early enteral feeding in the ICU among the esophagectomy cohort, this can be difficult. The challenges in managing potential gut intolerance after major surgery position such patients at risk of not achieving targeted calorie and protein goals. Potential conduit ischemia is another issue that may hinder EN tolerance [24]. If there are no major issues after surgery, especially

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Table 4. Comparison of albumin and CRP levels between pneumonia and non-pneumonia groups

Biochemical parameter	Mean±SD		t-test (df)	P-value[a]
	Non-pneumonia (n=10)	Pneumonia (n=12)		
Albumin (g/L)	27.8±2.62	29.2±3.30	−1.06 (20)	0.302
CRP (mg/L)	137.4±96.58	243.5±82.69	−2.77 (20)	0.012

CRP, C-reactive protein; SD, standard deviation; df, degree of freedom.
[a]Independent t-test was applied, significant P-value was set at 0.05.

Table 5. Correlations of LOS, ventilation duration, and biochemical markers with albumin and CRP

Correlation	Correlation coefficient	P-value[a]
LOS vs. albumin	−0.256	0.250
LOS vs. CRP	0.424	0.049
Ventilation days vs. albumin	−0.190	0.397
Ventilation days vs. CRP	0.276	0.213

LOS, length of stay; CRP, C-reactive protein.
[a]Pearson correlation was applied, significant P-value was set at 0.05.

esophagectomy, EN is acceptable, as demonstrated herein; by day 7, the EN group had achieved 92.4% of the caloric target. The PN group achieved higher protein levels throughout the observation period, with significantly higher levels from day 2 (0.9 g/kg/day vs. 0.5 g/kg/day, P=0.001) through day 7 (1.4 g/kg/day vs. 1.2 g/kg/day, P=0.036). Complication rates were similar between groups, with Clavien-Dindo grade IIIb complications observed in 45.4% of PN patients versus 27.2% of EN patients (P>0.05). This aligns with previous findings on the safety of supplementary PN [34-36]. However, 63.6% of EN patients needed modifications to their feeding strategy, compared to none in the PN group (P=0.006), indicating that supplementary PN delivers nutrition more reliably [37].

The findings of this study also support key aspects of the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline implementation especially in supplementary PN timing. Significant nutritional gaps in the first 3–5 days post-surgery validate ESPEN's recommendation for supplementary PN when EN provides <50% of nutritional needs by days 3–5. This shows the importance of early assessment of EN adequacy. By consistently evaluating whether patients are meeting their nutritional targets, healthcare providers can promptly identify those at risk of nutritional deficiencies. It also highlighted the importance of achieving the protein targets, which is a common issue among ICU patients receiving EN only [33,38-40].

It is important to adopt a flexible approach to nutritional support that is tailored to individual patient characteristics. Such an approach requires healthcare providers to consider a range of patient-specific factors, including age, underlying health conditions, treatment goals, and personal preferences. Such an individualized strategy ensures that nutritional interventions are effective and aligned with the patient's overall care plan. The implementation of these recommendations can significantly improve the quality of nutritional support provided to patients, fostering better clinical outcomes and enhancing the overall effectiveness of nutritional management in various healthcare settings. By prioritizing early assessments, focusing on protein delivery, monitoring inflammatory markers, and personalizing care, clinicians can make substantial strides in addressing the nutritional needs of their patients.

The study confirms that EN and PN are equally important for early nutritional support among ICU patients, especially those recovering from major surgery. There is no significant difference in outcomes with these two methods, but an early change to PN in patients who cannot tolerate EN will support achievement of calorie and protein targets for optimal recovery. Supplementary PN and/or conversion to total PN is acceptable for patients expected to not tolerate EN well. Both of these methods demonstrate the importance of focus on nutritional support with the aims of calorie and protein targets to support patient recovery.

The results of this study provide robust empirical support for the ESPEN guidelines, which advocate for the use of supplementary PN in post-esophagectomy patients within intensive care settings. While EN remains the preferred primary strategy, the data indicate that supplementary PN is crucial in enhancing nutritional intake, particularly in terms of protein, without increasing the risk of complications. By day 7, patients receiving PN consistently achieved higher protein intake than those in the EN group, further reinforcing the effect of ESPEN on early nutritional intervention and the critical significance of adequate protein levels for recovery [28,29].

Despite similar energy intake between the two groups, the superior protein delivery in the PN group underscores the necessity of supplementary PN when EN alone fails to meet nutritional targets. This finding is especially pertinent for patients who experience interruptions in EN or are at higher nutritional risk, as evidenced by the substantial percentage of EN patients who required a transition to PN during recovery.

The study also highlights the safety and efficacy of supplementary PN, with postoperative outcomes such as ICU stay, ventilation duration, and complication rates showing no significant differences between the groups. Furthermore, the correlation between elevated CRP levels and prolonged hospital stays suggests that effective nutritional support, including supplementary PN, may mitigate inflammatory responses and enhance recovery [18].

Integrating supplementary PN in accordance with ESPEN guidelines provides a reliable method to ensure comprehensive nutritional support during the early postoperative period following esophagectomy. By addressing the nutritional deficiencies that often occur with EN alone, clinicians can potentially improve patient outcomes, including reduced complications, expedited recovery times, and improved overall clinical results. These findings enhance the body of evidence supporting a flexible and individualized approach to postoperative nutrition, positioning supplementary PN as a valuable component of patient care after esophagectomy [27].

Limitations

First, the relatively small sample size (n=22) may compromise the statistical power of the findings, potentially affecting the robustness of the conclusions. This limitation can hinder the generalizability of the results and is consistent with concerns raised in related studies. Furthermore, the non-randomized nature of the research introduces a risk of selection bias, which may affect the validity of the comparisons and outcomes. This issue has been acknowledged in previous research as well, emphasizing the need for caution when interpreting results derived from non-randomized designs. Additionally, the higher baseline nutritional risk observed in the PN group may confound the comparisons between groups. This variability in initial risk levels could potentially skew the outcome assessments, as noted in the literature. Such confounding factors must be addressed in future research to provide clearer insights into the efficacy of nutritional interventions.

Suggestion for further studies

Several avenues for future research emerge from these limitations. Large-scale, randomized controlled trials specifically focused on supplementary PN will be crucial. These studies would enhance statistical power and allow more definitive conclusions regarding the efficacy of PN in various clinical contexts. Second, the development of precise criteria for initiating supplementary PN is essential. Clear guidelines will help clinicians make informed decisions regarding patient nutrition, improving patient outcomes. Finally, further investigation into the optimal protein-to-energy ratios in supplementary PN formulations is warranted. Understanding the ideal nutritional composition can significantly impact patient recovery and overall health. By exploring these areas, future research can contribute to a more nuanced understanding of nutritional support and its role in clinical practice, ultimately leading to improved patient care.

Implications

An unexpected detail is the high calorie intake (up to 93 kcal/kg/day by day 7), which is unusually high compared to typical ICU targets (25–30 kcal/kg/day). This may reflect aggressive nutritional support in this cohort, potentially due to increased metabolic demands post-esophagectomy. The significant correlation between CRP and LOS adds a new layer, suggesting that inflammation management could be key to reducing hospital stays.

Conclusion

While EN remains the preferred initial approach, supplementary PN proves essential when EN falls short, particularly in achieving protein targets without increasing complications. It also reveals no significant differences between EN and PN groups in hospital stay, ventilation duration, or complication rates. These findings advocate for a flexible, patient-tailored nutritional strategy that aligns with ESPEN guidelines to optimize outcomes and emphasize the need for early nutritional assessment.

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Authors' contribution

Conceptualization: all authors. Data curation; Formal analysis: RMS, KCK. Project administration: all authors. Funding acquisition: Not applicable. Writing – original draft: RMS. Writing – review & editing: TSC, MSJ. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Contact the corresponding author for data availability.

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Supplementary materials

None.

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Original Article

Impact of postoperative nutritional status on the patients' clinical outcomes and knee biomechanics following total knee arthroplasty in Japan: a prospective cohort study

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Abstract

Purpose: The impact of postoperative nutritional status on clinical outcomes and biomechanics following total knee arthroplasty remains largely unknown. This study aimed to assess this question using the prognostic nutritional index to evaluate the nutritional status of orthopedic participants.

Methods: Patients with knee osteoarthritis who underwent total knee arthroplasty (n=49) in Japan were divided into two groups based on their 1-week postoperative prognostic nutritional index. Group L patients had a prognostic nutritional index <40, whereas Group H comprised patients with a prognostic nutritional index ≥40. Postoperative improvements in Knee Injury and Osteoarthritis Outcome Score were evaluated. The patients performed squats under single-fluoroscopic surveillance in the sagittal plane for biomechanical evaluation. A two-dimensional/three-dimensional registration technique was employed to measure the tibiofemoral kinematics. The axial rotation of the femoral component relative to the tibial component and the anteroposterior translation of the medial and lateral femorotibial contact points were measured.

Results: Group H showed significantly higher pain scores than Group L at 12 and 36 months postoperatively and a significantly higher symptom score at 36 months postoperatively. The kinematic comparison revealed that the axial external rotation in Group L was larger than that in Group H from 70° to 80° with flexion. Moreover, in the medial anteroposterior translation, Group L was more anteriorly located than Group H, with flexion beyond 30°.

Conclusion: The results suggest that a high postoperative nutritional status significantly improved pain and other symptoms and was associated with better knee biomechanics following total knee arthroplasty.

Keywords: Biomechanical phenomena; Japan; Knee osteoarthritis; Knee replacement arthroplasty; Nutrition assessment

Introduction

Background/rationale

Malnutrition induces postoperative complications in total knee arthroplasty (TKA) and leads to sarcopenia. Resistance exercises such as squats are recommended to improve sarcopenia [1,2]. Moreover, combining resistance exercise with proper nutrition provides greater improvement in patients

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with sarcopenia [1,2]. In TKA, the force of the leg muscles, such as the quadriceps, plays a significant role in predicting postoperative functional prognosis and patient satisfaction [3]. Resistance exercises are effective in rehabilitation following TKA [4]; therefore, it is important to evaluate both the nutritional status and resistance exercises to determine the impact on postoperative outcomes following TKA. Recent studies have reported that TKA kinematics are related to clinical outcomes, such as patient-reported outcome measures (PROMs) [5-7]. However, the impact of postoperative nutritional status on clinical outcomes and biomechanics remains largely unknown.

There are various methods for evaluating the nutritional status [8-11]; Onodera's prognostic nutritional index (PNI) can be easily calculated using simple, low-cost blood tests [8,12]. The PNI is a strong prognostic indicator after surgery [12,13]. In orthopedic surgeries such as TKA, most patients exhibit early recovery postoperatively. Therefore, simple blood tests are typically performed. Thus, the PNI serves as a useful evaluation tool after orthopedic surgery.

Objectives

This study was designed to evaluate the effects of postoperative nutritional status on clinical outcomes and biomechanics after TKA using PNI. We hypothesized that the postoperative nutritional status affects the improvement of PROMs and knee biomechanics.

Methods

Ethics statement

This study was approved by the University of Tokyo Institutional Ethics Review Board (number: 10462-(1)), and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants included in the study. The patients provided informed consent for publication of their data and photographs.

Study design

It was a prospective cohort study. It was described according to the STOBE statement, which is available at: https://www.strobe-statement.org/.

Setting

All patients in this study were evaluated at The University of Tokyo Hospital between October 2015 and December 2019.

Participants

Patients (n=49) with knee osteoarthritis who underwent TKA using the Journey II BCS system (Smith & Nephew) were recruited for the study. Patients were divided into two groups based on their 1-week postoperative PNI to exclude the effects of fasting and supplementation.

Variables

Dependent variables were Knee Injury and Osteoarthritis Outcome Score (KOOS) as a clinical outcome and knee biomechanics values. Independent variable was Onodera's PNI as a postoperative nutritional status.

Bias

There was no selection bias since all target patients were recruited.

Data sources

Data were from the patient's medical records, measurement score, and X-ray images

Measurements

The PNI was calculated from the serum albumin level and lymphocyte count as described previously: 10×albumin (g/dL)+0.005×total lymphocyte count (/mm^3) [8,13]. PNI scores lower than 40 are associated with poor postoperative longevity [8]. Therefore, patients were divided according to PNI with a threshold of 40. Group L (n=20) had a PNI <40, while Group H (n=29) had a PNI ≥40. The mean PNI in Groups L and H were 36.4±1.9 and 43.1±2.2, respectively. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the total neutrophil count (/mm^3)/total lymphocyte count (/mm^3) [12,14].

A medial parapatellar surgical approach in which the patella was not everted was used. The distal femur and proximal tibia were incised using a navigation system (Precision N; Stryker Orthopedics). The femur was aligned at 90° to the mechanical axis in the frontal plane with 4° flexion in the sagittal plane, and the tibia was aligned at 90° to the mechanical axis in the frontal plane with a posterior slope of 3° in the sagittal plane. The femoral rotation was determined using the average rotational axis of the transepicondylar axis and the axis perpendicular to the Whiteside axis, whereas the tibial rotation was determined using the range of motion technique [15,16].

The postoperative improvement in PROMs using the KOOS was evaluated. The KOOS is a self-reported questionnaire with 42 items comprising five separately analyzed subscales of pain; symptoms; and activities of daily living (ADL) for

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physical function, sport/recreation function, and knee-related quality of life (QOL). Each of the five scores is calculated as the sum of the items included, and the scores are then transformed to a 0- to 100-point scale, with 0 points representing extreme knee problems and 100 points representing no knee problems [17]. KOOS was measured at 3, 6, 12, 24, and 36 months after TKA (Table 1).

Patients who could safely perform deep-standing squats after surgery were evaluated (Fig. 1). Each patient was asked to perform deep-standing squats at a natural pace under single-fluoroscopic surveillance in the sagittal plane. The squats were performed from full extension to maximum flexion. The participants practiced the motion several times before being recorded as sequential digital radiographic images (1024×1024×12 bits/pixel, 7.5-Hz serial spot images in a DICOM file) using a 17-inch flat panel detector system (ZEXIRA DREX-ZX80; Toshiba). All images were processed using dynamic-range compression for edge enhancement.

To estimate the spatial position and orientation of the femoral and tibial components, a 2D-to-3D registration technique was used [18,19]. This technique is designed on a contour-based registration algorithm that uses single-view fluoroscopic images and 3D computer-aided design models. The margin of error of the estimated relative motion between the metal components was ≤0.5° for rotation and ≤0.4° for translation. The following variables were measured: knee range of motion, varus-valgus alignment, axial rotation of the femoral component relative to the tibial component, and anteroposterior (AP) translation of the medial and lateral femorotibial contact points. A local coordinate system for the femoral component was used according to previously described methods [18,20]. Knee flexion and rotation angles were described using the joint rotational convention method described by Grood and Suntay [21]. Flexion and external rotation of the femoral component relative to the tibial component are denoted as positive values. Positive and negative AP translation values are defined as those anterior and posterior to the axes of the tibial component, respectively. The femorotibial contact point is defined as the region on the insertion surface where the proximity of the component surfaces is less than the 0.5-mm threshold.

Table 1. Knee Injury and Osteoarthritis Outcome Score (KOOS)

Detailed information
The KOOS uses data on five knee-specific patient-centered outcomes: (1) Pain (2) Other symptoms such as swelling, restricted range of motion, and mechanical symptoms (3) Disability at the level of activities of daily living (ADL) (4) Disability at a level physically more demanding than ADL (5) Mental and social aspects such as awareness and lifestyle changes
The KOOS is self-administered and filled out by the patient: (1) The five patient-relevant subscales of KOOS are scored separately: Pain (9 items); Symptoms (7 items); ADL (17 items); Sport and Recreation (5 items); Quality of Life (4 items). (2) A Likert scale is used, and all items have five possible answers scored from 0 (no problems) to 4 (extreme problems); each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems.

Study size

The primary endpoint of this study was the comparison of knee biomechanics between Group H and Group L. Since all target participants had been recruited prior to the study, a prospective sample size calculation was not feasible. Therefore, a post-hoc power analysis was conducted using G*Power to evaluate the statistical power for detecting differences in knee biomechanics between the groups. Based on a two-tailed test, an effect size of 0.375, sample sizes of 20 in Group

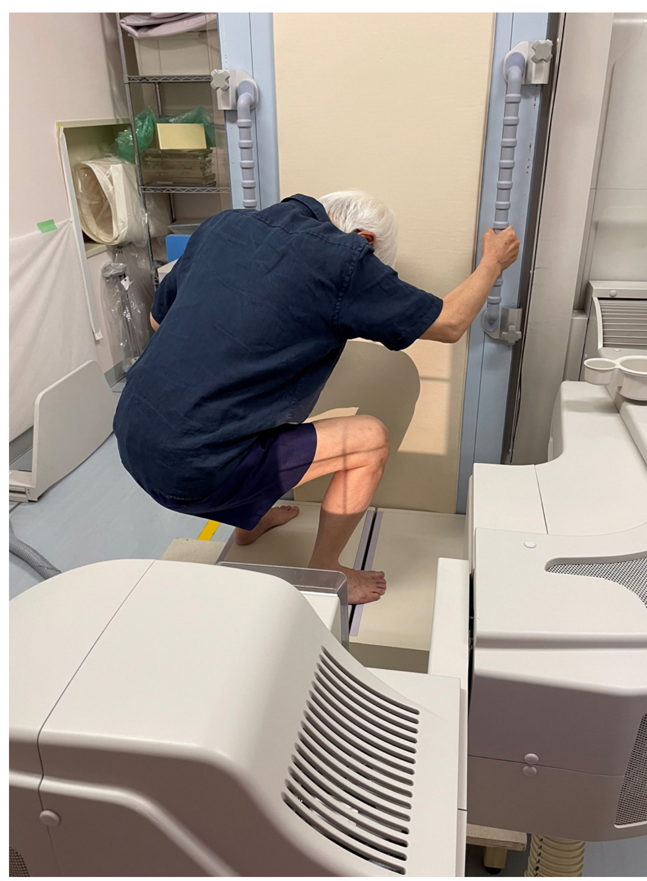

Fig. 1. Patient who could safely perform deep-standing squats after surgery for fluoroscopic analysis.

H and 29 in Group L, and a correlation of 0.72 among repeated measures [22], the calculated statistical power (1–β error probability) was 0.941.

Statistical methods

Statistical analyses were conducted using SPSS version 25 (IBM Corp.). For correlated observations, such as PROMs and knee biomechanics, repeated-measures analysis of variance was applied. The model included time as a within-subjects factor and group (Groups H and L) as a between-subjects factor, followed by Bonferroni correction for multiple comparisons. Only inter-group effects were evaluated. The Mann–Whitney U test was used to compare white blood cell count, C-reactive protein (CRP) levels, NLR, age, body mass index, fluoroscopic follow-up distance, and sex ratio between Groups H and L. A P-value of <0.05 was considered statistically significant. Data are presented as means±standard deviations.

Results

Participants

The patients' demographic findings and clinical characteristics are presented in Table 2. The postoperative white blood cell count, CRP level, and NLR are shown. CRP levels and NLR in Group L were significantly higher than those in Group H. There were no significant differences between the groups regarding age, body mass index, fluoroscopic follow-up distance, or sex ratio.

Patient-reported outcome measures

The KOOS scores gradually improved in both groups. However, the KOOS-pain score in Group H was significantly higher than in Group L at 12 and 36 months. Additionally, the KOOS-symptoms score was significantly higher in Group H than that in Group L at 36 months. There were no significant differences between the two groups in terms of KOOS-ADL, sports/recreation, or QOL (Fig. 2, Supplement 1).

Kinematic comparison

The axial external rotation in Group L was greater than that in Group H from 70° to 80° with flexion (Fig. 3, Supplement 2). In medial AP translation, Group L was located more anteriorly than Group H, beyond 30° with flexion. In contrast, there was no significant difference in the lateral AP translation between the two groups (Fig. 4, Supplement 3).

Discussion

Key results

The most important finding of this study was that high nutritional status can improve PROMs and knee kinematics after TKA. The KOOS-pain and KOOS-symptoms scores in Group H were significantly higher compared to those in Group L. In particular, improvements were seen beyond 1 year after surgery.

Interpretation/comparison with previous studies

This finding suggests that the perioperative nutritional status affects midterm clinical outcomes. Several studies have reported that appropriate nutrition has anti-inflammatory effects and improves pain [23,24]. Therefore, early nutritional improvement may provide postoperative pain relief.

In this study, femoral external rotation in Group L was larger than that in Group H at mid-flexion. In addition, the medial AP translation in Group L was more anteriorly located than that in Group H beyond early flexion. A previous study reported that, after TKA, the low PROMs groups exhibited excessive femoral external rotation [6]. Patients with malnutrition such as those in Group L could easily perform external femoral rotation according to the implant's guided motion design. In addition, excessive femoral external rotation can lead to iliotibial band traction syndrome, which causes poor clinical outcomes [25]. Another study reported that, after TKA, the low PROMs group displayed medial anterior translation with flexion [5]. These findings suggest that a high postoperative nutritional status might improve knee biomechanics. Several studies have demonstrated that a combination of nutrition and resistance exercise results in greater improvement in patients with sarcopenia [1,2]. Moreover, muscle-loaded stability reflects knee stability af-

Table 2. Patient characteristics of the two groups

Variable	Group L (n=20)	Group H (n=29)	P-value
Age (yr)	76.6±6.2	74.6±6.4	0.27
Body mass index (kg/m^2)	26.7±3.4	26.7±4.3	0.81
Fluoroscopic follow-up time (mo)	15.0±7.8	12.4±7.5	0.06
Sex (female:male)	16:4	25:4	0.71
WBC (/µL)	6,830±1,661	6,424±1,367	0.42
CRP (mg/L)	5.7±3.2	3.8±3.7	0.01
NLR	4.3±2.1	2.7±1.1	<0.01

Values are presented as mean ±standard deviation. Group L had a prognostic nutritional index (PNI) <40, while Group H had a PNI ≥40.
WBC, white blood cell count; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio.

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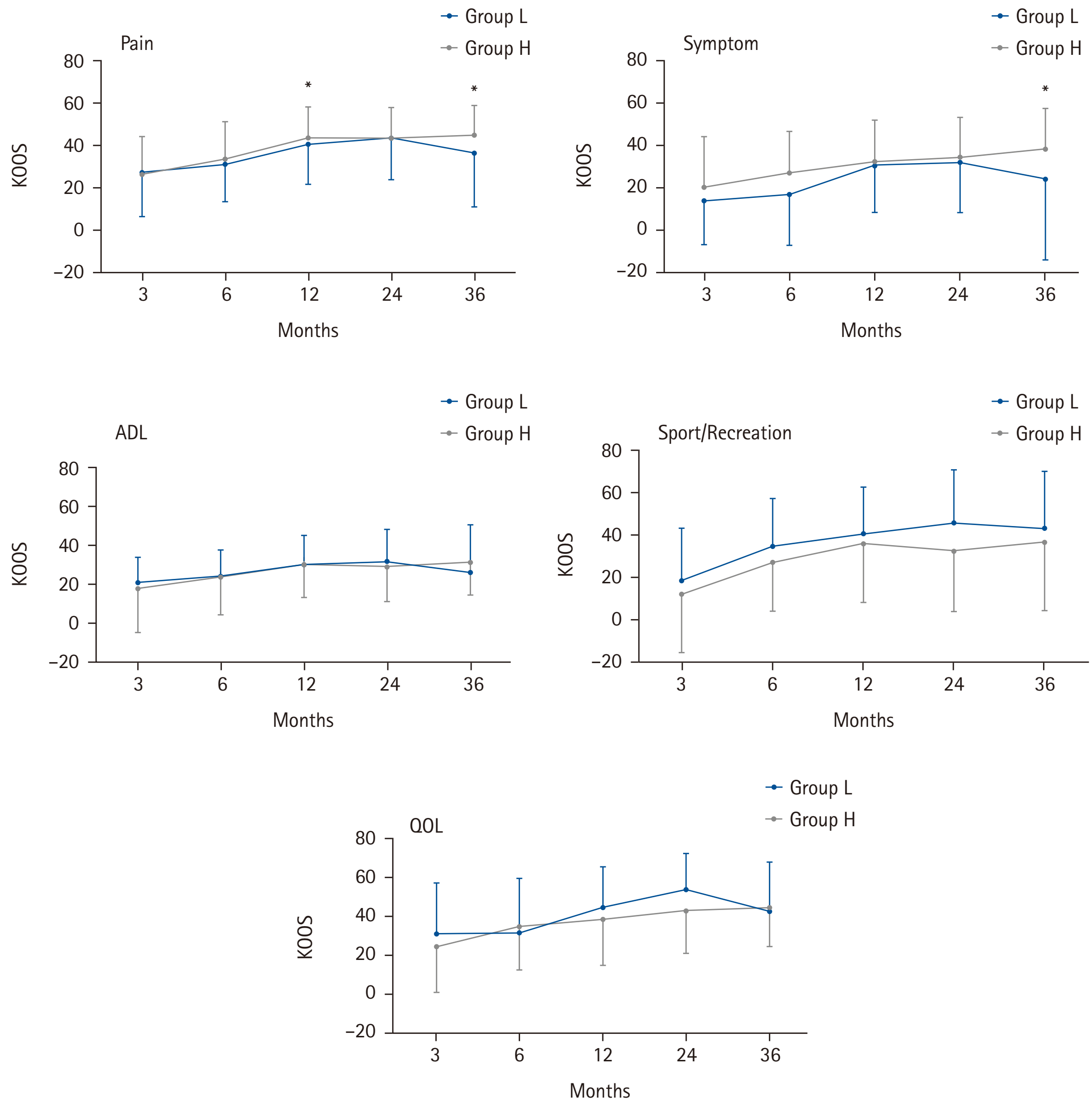

Fig. 2. Comparison of patient-reported outcome measures (Knee Injury and Osteoarthritis Outcome Score, KOOS) between Groups L and H. Group L had a Prognostic Nutritional Index (PNI) <40, while Group H had a PNI ≥40. The five graphs show the subscales of KOOS. The KOOS-pain score in Group H was significantly higher than that in Group L at 12 and 36 months. Additionally, the KOOS-symptoms score was significantly higher in Group H than that in Group L at 36 months. *Significant difference between Group L and Group H (P<0.05). ADL, activities of daily living; QOL, quality of life.

ter TKA [26-29]. Therefore, not only patients with sarcopenia but general patients after TKA might require a combination of nutrition and resistance exercises, such as squats, to improve postoperative clinical outcomes.

The postoperative (1 week after surgery) CRP level and NLR were significantly higher in Group L than those in Group H. A high postoperative NLR is associated with poor prognosis after surgery [30,31]. These findings suggest that prolonged postoperative inflammation may result in poor clinical outcomes and knee kinematics.

Limitations

First, we evaluated only the perioperative nutritional status. Further studies are required to assess the nutritional status during long-term follow-up. Second, only one type of implant was evaluated, and other implants may exhibit different biomechanical properties. Third, we did not analyze the kinematics preoperatively to minimize X-ray exposure. Therefore, this study did not directly compare the pre- and postoperative kinematics. Hence, we cannot rule out the possibility that the preoperative knee kinematics affected the postoperative kinematics. Additionally, for variables 10°, 20°,

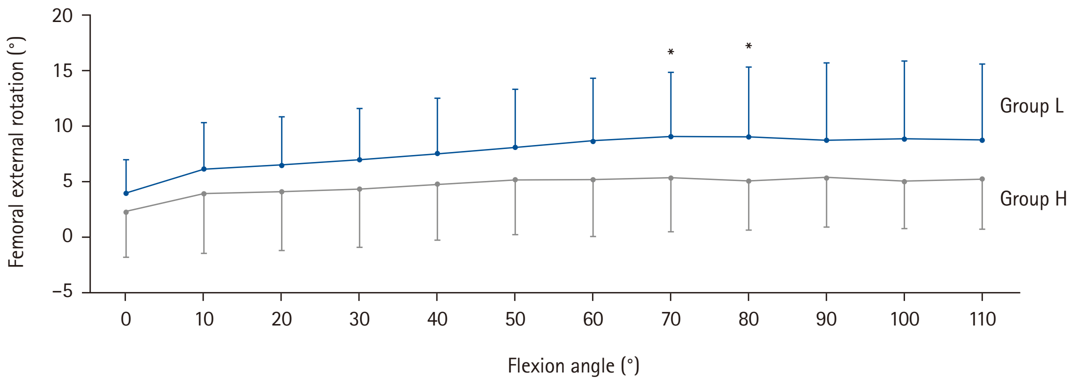

Fig. 3. Kinematic comparison between Groups L and H with respect to axial rotation. Group L had a Prognostic Nutritional Index (PNI) <40, while Group H had a PNI ≥40. *P<0.05.

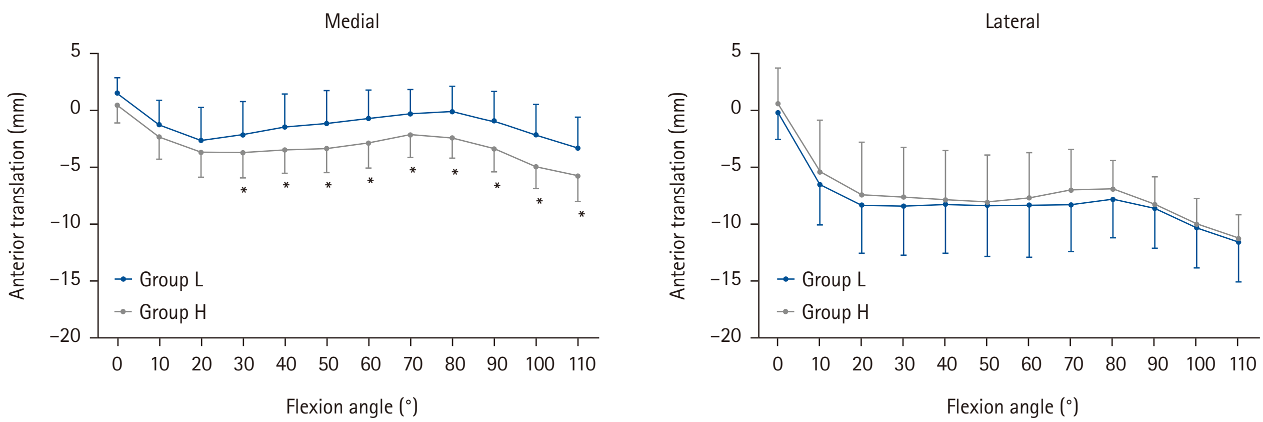

Fig. 4. Kinematic comparison between Groups L and H regarding medial and lateral anteroposterior translation. Group L had a Prognostic Nutritional Index (PNI) <40, while Group H had a PNI ≥40. *Significant difference between Groups L and H (P<0.05).

and 30°, the sample size was insufficient; therefore, future studies focusing specifically on the variables with low power would need larger sample sizes to achieve adequate statistical power.

Conclusion

This study demonstrated that postoperative nutritional status significantly influences clinical outcomes and knee biomechanics following TKA. Patients with higher prognostic nutritional indices experienced superior pain relief, symptom improvement, and more favorable knee kinematics than patients with low indices. These findings stress the importance of optimizing nutritional status, potentially in combination with resistance exercises, to enhance recovery.

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Research data are available from the corresponding author upon reasonable request.

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Supplementary materials

Supplement 1. Data for figure 2 in Excel format.
Supplement 2. Data for figure 3 in Excel format.
Supplement 3. Data for figure 4 in Excel format.

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Original Article

The enteral feeding tube access route in esophageal cancer surgery in Japan: a retrospective cohort study

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Abstract

Purpose: Feeding catheter jejunostomy is a useful access route for early enteral nutrition during esophageal cancer surgery. However, it may lead to postoperative bowel obstruction associated with feeding jejunostomy (BOFJ). To prevent BOFJ, we introduced feeding catheter duodenostomy via the round ligament in 2018. This study aimed to compare the incidence of BOFJ and postoperative body weight changes between feeding catheter jejunostomy and duodenostomy.
Methods: A total of 109 patients who underwent thoracoscopic esophagectomy and gastric tube reconstruction for esophageal cancer at Kochi Medical School Hospital between March 2013 and November 2020 were included. Preoperative patient characteristics (age, sex, preoperative weight, body mass index, cancer stage, and preoperative treatment), surgical outcomes (operative time, blood loss, and postoperative complications [wound infection, pneumonia, anastomotic leakage, BOFJ]), and body weight changes at 1, 3, 6, and 12 months post-surgery were compared between the jejunostomy (J) and duodenostomy (D) groups.
Results: The D group consisted of 35 patients. No significant differences were observed between the groups regarding age, sex, weight, body mass index, cancer stage, operative time, postoperative complications, or duration of tube placement. However, the D group had a significantly lower rate of preoperative chemotherapy (45.7% vs. 78.4%, P=0.001) and lower operative blood loss (120 mL vs. 150 mL, P=0.046) than the J group. All 12 cases of BOFJ occurred in the J group. Furthermore, the D group experienced a significantly lower weight loss ratio at 1 month postoperatively (93.9% vs. 91.8%, P=0.039).
Conclusion: In thoracoscopic esophagectomy, feeding duodenostomy may prevent bowel obstruction and reduce early postoperative weight loss without increasing operative time compared with feeding catheter jejunostomy.

Keywords: Duodenostomy; Enteral nutrition; Esophageal cancer; Esophagectomy; Jejunostomy

Introduction

Background

Esophagectomy for esophageal cancer is a highly invasive procedure that involves lymph node dissection in the cervical, thoracic, and abdominal regions. Although minimally invasive thoracoscopic surgery has become more common in recent years [1], the complication rate remains high [2]. Notably, anastomotic leakage necessitates prolonged fasting and nutritional management. Even in the absence of anastomotic leakage, patients may require enteral nutrition at home because of nutritional deficiencies and weight loss resulting

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from decreased food intake [3,4]. Feeding jejunostomy is a valuable method for providing early enteral nutrition during the perioperative period for esophageal cancer [5]. However, bowel obstruction associated with feeding jejunostomy (BOFJ), which results from bending, adhesion, or torsion of the intestinal tract around the catheter, is a common complication [6]. To address this issue, we introduced feeding duodenostomy in 2018, in which a feeding tube is inserted through the duodenum via the round ligament.

Objectives

We compared the effects of jejunostomy and duodenostomy on the incidence of BOFJ and postoperative weight changes in esophageal cancer surgery.

Methods

Ethics statement

This study was approved by the Institutional Review Board of Kochi Medical School Hospital (No. ERB-104180). The requirement for informed consent was waived.

Study design

This retrospective cohort study compared the effects of two interventions—feeding tube insertion into the jejunum versus the duodenum—on the incidence of BOFJ during the perioperative period of esophageal cancer.

Setting

This study was conducted between March 2013 and November 2020. Tube became the standard method after August 2018. The feeding tube was placed under direct vision following gastric tube reconstruction. For jejunostomy, a 9-Fr tube was inserted 30 cm into the jejunum using a Seldinger kit approximately 25–30 cm from the Treitz ligament; the puncture site was secured with one purse-string suture and three Witzel stitches (Fig. 1A). The tube was then guided out of the abdominal wall using a Seldinger kit (Fig. 1B), and the abdominal wall along with the puncture site was fixed with four stitches. The jejunum on the anorectal side was sutured to the abdominal wall so that it formed a long axis of approximately 4 cm (Fig. 1C).

For duodenostomy, following Kocher mobilization, a tube was inserted into the descending portion of the duodenum in a manner similar to the jejunostomy technique (Fig. 2A), and the puncture site was buried. The round ligament of the liver was ligated and trimmed at the umbilicus, and the tube was guided out through the fatty tissue of the round ligament using a Seldinger kit (Fig. 2B). Finally, the abdominal wall and the area around the duodenal puncture site were sutured and secured using the round ligament (Fig. 2C). Continuous enteral nutrition was initiated at 20 mL/hr on the day following surgery, gradually increasing to 40–80 mL/hr until oral intake commenced. Once oral intake began, patients were instructed to self-administer 200 mL of nutritional supplements intermittently three times a day over 2 to 3 hours, continuing at

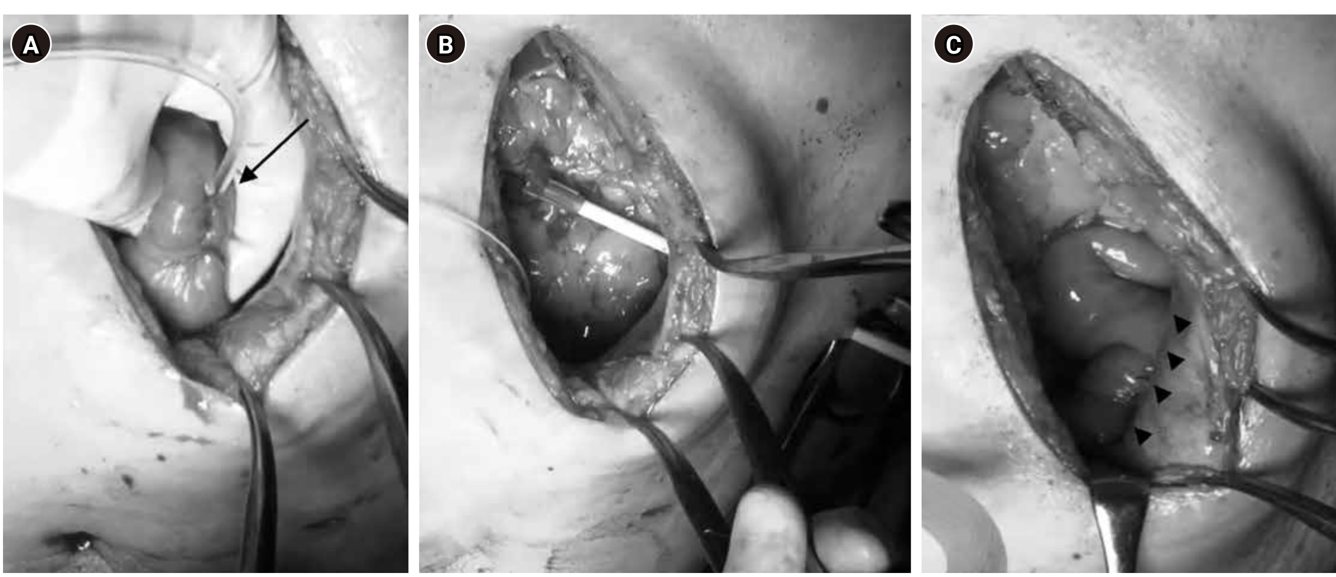

Fig. 1. Surgical technique for jejunostomy. (A) The jejunal puncture site for the 9-Fr tube (arrow) was secured with one drawstring suture and three Witzel sutures. (B) The tube was guided out of the abdominal wall. (C) The anorectal portion of the jejunum was fixed to the abdominal wall over a length of approximately 4 cm (arrowheads).

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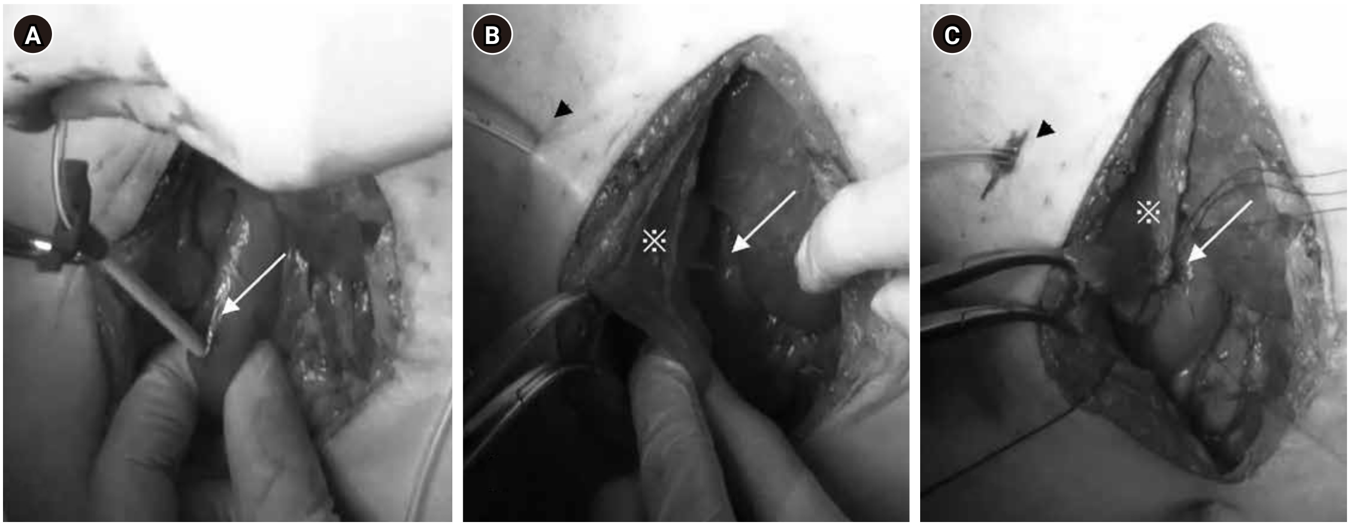

Fig. 2. Surgical technique for tube duodenostomy. (A) The tube was inserted into the descending duodenal leg (arrow) and implanted. (B) After guiding the tube out of the abdominal wall (arrowhead), the hepatic round ligament (*) was trimmed to reach the duodenal entry point of the tube (arrow). (C) The hepatic round ligament (*), the abdominal wall (arrowhead), and the area around the duodenal entry site (arrow) were sutured and fixed.

home after discharge.

Participants

A total of 109 patients who underwent thoracoscopic esophagectomy and gastric tube reconstruction for esophageal cancer between March 2013 and November 2020 were included.

Variables

Preoperative baseline characteristics included age, sex, weight, body mass index, cancer stage, and preoperative treatment. Outcome variables comprised surgical outcomes (operative time and blood loss), postoperative complications (wound infection, pneumonia, anastomotic leakage, and BOFJ), and body weight at 1, 3, 6, and 12 months after surgery.

Data sources/measurement

Patients' food intake was assessed during outpatient interviews 1 month or more after surgery. The feeding tube was removed once patients could consume sufficient food or nutritional supplements orally. Body weight was recorded at 1, 3, 6, and 12 months postoperatively, and these outcome variables were compared between the two groups.

Bias

As all eligible patients from a single institution during the study period were included, selection bias was not an issue.

Study size

No sample size estimation was performed because the study encompassed the entire target population.

Statistical methods

The chi-square test and Mann-Whitney test were employed for statistical analysis, with $P<0.05$ considered statistically significant.

Results

Participants

The median age was 68 years, with 74 patients in the jejunostomy (J) group and 35 patients in the duodenostomy (D) group (Table 1). Among comorbidities, 17 patients (15.6%) had diabetes mellitus, 47 (43.1%) had hypertension, and 24 (22.0%) had cardiovascular disease. Posterior mediastinal route reconstruction was performed in 110 patients, and pneumonia and anastomotic leakage were observed in 15 patients (13.0%) each. Trends in nutritional doses up to 21 days postoperatively are presented in Fig. 3.

Main results

Until May 2018, high-calorie infusions were administered via a postoperative central venous catheter; as a result, the J group tended to receive more intravenous nutrition for up to 10 days postoperatively and less enteral nutrition after 8 days compared with the D group. The median preoperative

Table 1. Characteristics of the 109 patients who underwent thoracoscopic esophagectomy for esophageal cancer

Characteristic	Number (%)
Male sex	84 (77.1)
Age (yr), median (range)	68 (43–91)
cT 1/2/3/4	41/12/49/7
cN 0/1/2/3	40/43/15/11
cM 0/1	94/15
cStage I/II/III/IV	39/18/29/23
Diabetes mellites	17 (15.6)
Hypertension	47 (43.1)
Cardiovascular disease	24 (22.0)
Preoperative body weight (kg), median (range)	55.0 (30.7–78.0)
Preoperative body mass index (kg/m^2), median (range)	21.3 (14.0–30.0)
Neoadjuvant chemotherapy	74 (67.9)
History of radiation therapy	12 (11.0)
Operative time (min), median (range)	607 (379–859)
Blood loss (mL), median (range)	150 (10–1,600)
Postoperative complications	
Pneumonia	14 (12.8)
Anastomotic leakage	15 (13.8)
Wound infection	23 (21.1)
Hospital stay (day), median (range)	21 (10–201)
Type of feeding tube, duodenostomy/jejunostomy	35/74
Duration until feeding catheter removal (day), median (range)	78 (6–376)
Surgery for bowel obstruction associated with feeding tube	12 (11.0)

weight was 55.0 kg, which decreased to 50.0 kg at 3 months postoperatively, with only slight further decreases at 6 and 12 months (Fig. 4).

The median duration of feeding tube placement was 78 days. The shortest duration was 6 days postoperatively, observed in a patient who required emergency surgery for strangulated bowel obstruction. The longest duration was 376 days, as one patient requested extended use due to dysphagia and aspiration following head and neck cancer surgery. There were 12 cases (11.0%) of BOFJ, all occurring exclusively in the J group. The median time to BOFJ onset was 211 days post-surgery, with the longest interval being 1,450 days. Additionally, one patient in the D group developed a peri-pancreatic abscess with a pancreatic fistula, as indicated by a high amylase level in the drainage.

Comparisons between the groups revealed no significant differences in age, gender, weight, body mass index, cancer stage, operative time, postoperative complications, or duration of tube placement. However, the D group had significantly less preoperative chemotherapy (45.7% vs. 78.4%, P=0.001) and lower operative blood loss (120 mL vs. 150 mL, P=0.046) compared with the J group (Table 2). Regarding the postoperative weight-to-preoperative weight ratio (set at 100%) (Fig. 5), the D group exhibited a significantly lower weight loss rate at 1 month postoperatively (93.9% vs. 91.8%, P=0.039). Although the rate remained lower at 3 months (90.0% vs. 87.3%, P=0.077), no difference was observed after 6 months. When excluding patients with BOFJ, there was no significant difference in the weight loss rate at 1 month (93.9% vs. 93.1%, P=0.244). At 3 months, a trend toward a lower weight loss rate in the D group persisted (90.0% vs. 88.6%, P=0.056).

There was no significant difference in serum albumin levels between the two groups; however, the total lymphocyte count was higher in the D group (Fig. 6). Additionally, the incidence of BOFJ did not differ significantly between patients who received preoperative chemotherapy and those who did not (9.5% vs. 14.3%, P=0.517).

Discussion

Key results

The present study suggests that tube duodenostomy can prevent BOFJ and weight loss in the early postoperative period, without prolonging the operative time compared to jejunostomy.

Interpretation/comparison with previous studies

Early postoperative rehabilitation and enteral nutrition, as advocated by the Enhanced Recovery After Surgery protocol, are recommended during the perioperative period for esophageal cancer [7]. However, clear guidelines regarding the optimal access route for enteral nutrition remain lacking. With jejunostomy, it is recommended that the catheter be fixed to the abdominal wall to prevent bending of the intestinal tract around the catheter—a factor that may lead to obstruction due to bending, adhesion, or torsion. In some cases, the intestinal tract on the anorectal side may fall into the space above the abdominal wall fixation site, further predisposing it to torsion [8].

We also secured the jejunum along its long axis on the anorectal side of the tube. Despite this, we encountered cases where the fixation thread dislodged when using absorbable sutures, as well as instances of torsion even with non-absorbable threads. In addition, inadequate abdominal wall fixation on the oral side of the tube insertion site may have contributed to tube bending. A previous study reported that a tube entry site located near the midline of the abdominal wall was correlated with BOFJ [6]. This association may be due to the

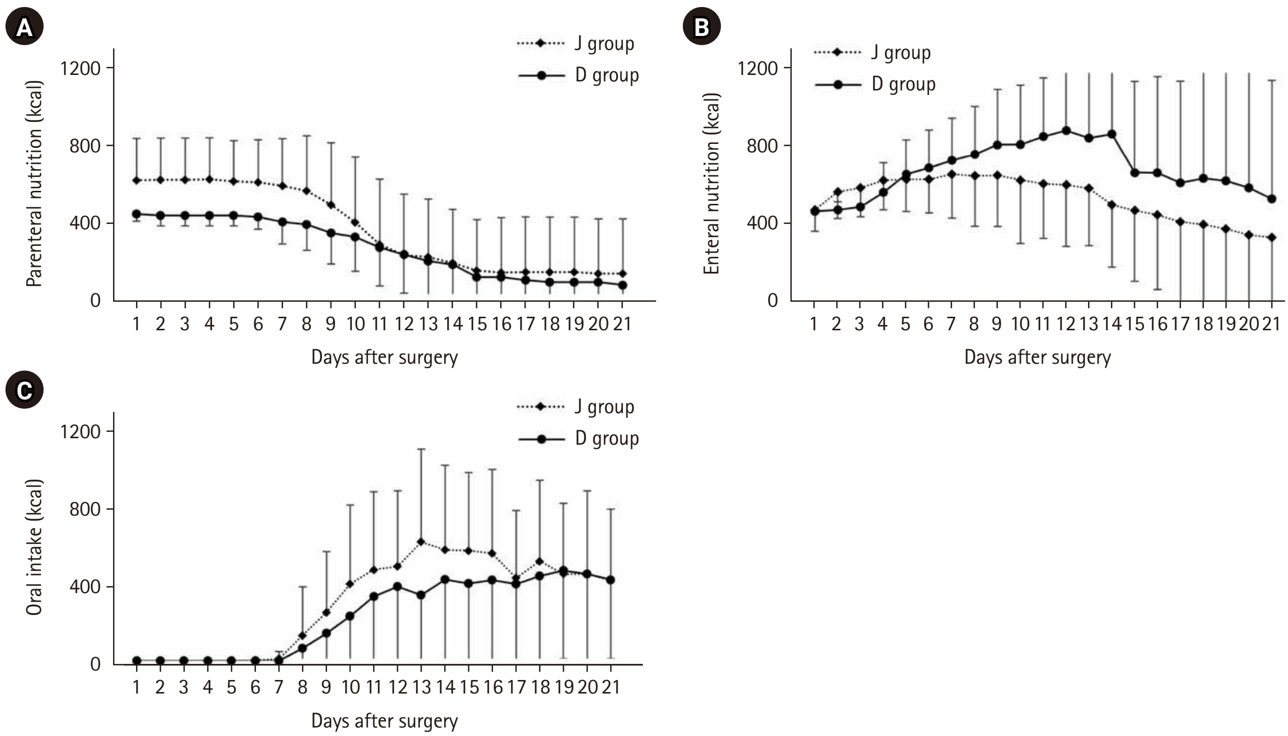

Fig. 3. Changes in the amount of energy administered for postoperative nutrition. (A) Intravenous nutrition, (B) enteral nutrition, and (C) oral intake. J group, jejunostomy group; D group, duodenostomy group.

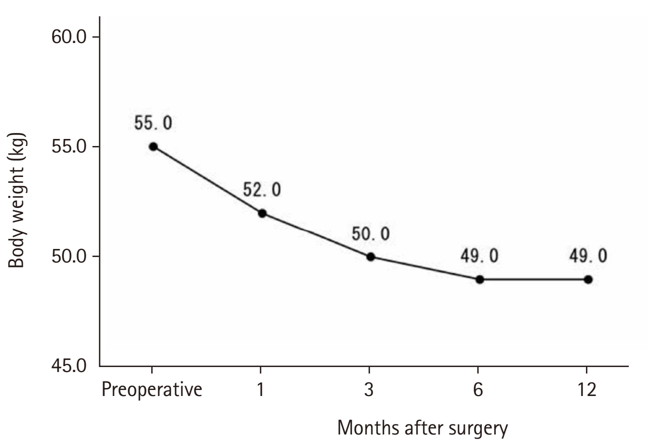

Fig. 4. Preoperative and postoperative weight change (kg).

laparoscopic abdominal lymph node dissection followed by gastric tube creation and jejunostomy through a small incision, which positions the tube entry site near the midline and creates a non-adherent space on the left side into which the jejunum on the anal side can herniate, mimicking an internal hernia.

Kamada et al. [9] performed a button-type jejunostomy in the jejunum 20 cm distal to the Treitz ligament and measured the distance from the button to the umbilicus via computed tomography. They found that a longer vertical distance was associated with intestinal obstruction compared with cases without obstruction.

Their procedure, which involved hand-assisted laparoscopic surgery with a small incision just below the xiphoid process, suggested that placing the jejunostomy in the upper abdomen increases the angle from the Treitz ligament to the jejunostomy, leading to flexion. Based on these findings, the optimal jejunostomy site should be as far left lateral as possible at the level of the umbilicus and secured to the abdominal wall with non-absorbable sutures along the long axis of the anal jejunum to prevent internal hernia. Employing a laparoscopic approach to position the jejunostomy on the left lateral side may be more suitable than direct visualization through a small laparotomy—a topic warranting further investigation.

Duodenostomy, which involves inserting a tube through the antrum of the stomach via the round ligament of the liver, is less likely to result in internal hernia or torsion than jejunostomy. This is because the space above the abdominal wall is shielded by the liver, and the horizontal portion of the duodenum is fixed to the retroperitoneum, thereby preventing torsion or internal herniation of the distal intestine [10-12].

Table 2. Comparison of the outcomes between the two groups

Variable	Duodenostomy (n=35)	Jejunostomy (n=74)	P-value
Male sex	25 (71.4)	59 (79.7)	0.336
Age (yr), median (range)	70 (49–91)	67 (43–82)	0.250
cT 1/2/3/4	16/4/11/4	25/8/38/3	0.117
cN 0/1/2/3	20/7/6/2	20/36/9/9	0.007
cM 0/1	29/6	65/9	0.481
Stage I/II/III/IV	16/5/7/7	23/13/22/16	0.462
Diabetes mellites	4 (11.4)	13 (17.6)	0.574
Hypertensions	18 (51.4)	29 (39.2)	0.228
Cardiovascular disease	9 (25.7)	15 (20.3)	0.522
Preoperative body weight (kg), median (range)	52.9 (30.7–77.4)	55.3 (39.9–78.0)	0.525
Preoperative body mass index (kg/m^2), median (range)	21.9 (14.0–27.7)	21.2 (14.1–30.0)	0.987
Neoadjuvant chemotherapy	16 (45.7)	58 (78.4)	0.001
History of radiation therapy	5 (14.3)	7 (9.5)	0.517
Operative time (min), median (range)	593 (379–694)	611 (456–859)	0.115
Blood loss (mL), median (range)	120 (30–950)	150 (10–1,600)	0.046
Postoperative complications			
Pneumonia	4 (11.4)	10 (13.5)	1.000
Anastomotic leakage	6 (17.1)	9 (12.2)	0.555
Wound infection	7 (20.0)	16 (21.6)	0.846
Hospital stay (day), median (range)	27 (13–144)	20 (10–201)	0.008
Duration until feeding catheter removal (day), median (range)	67 (46–376)	78 (6–316)	0.379
Surgery for bowel obstruction associated with feeding tube	0	12 (16.2)	0.009

Values are presented as number (%) unless otherwise indicated.

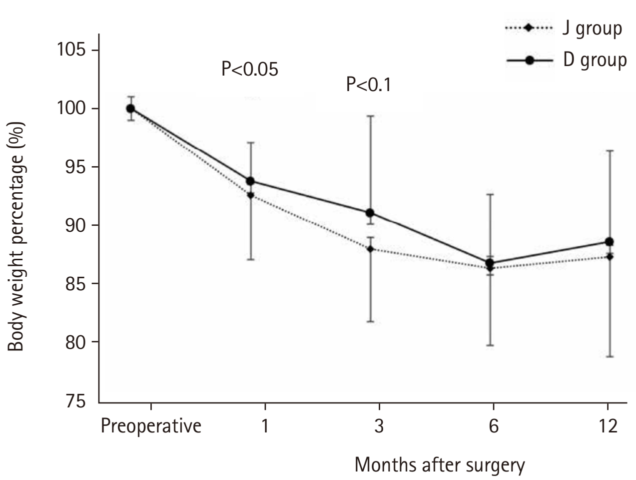

Fig. 5. Preoperative and postoperative body weight ratio (%). J group, jejunostomy group; D group, duodenostomy group.

In our study, no cases of BOFJ were observed in the D group, and the rate of weight loss at 1 to 3 months postoperatively was lower compared to the J group. These findings suggest that duodenostomy may reduce flexion and torsion, facilitating smoother food passage.

Oya et al. [10] inserted a tube through the duodenum just below the pyloric ring, whereas Kawai et al. [11] and Huang et al. [12] placed the tube through the antrum of the reconstructed gastric tube. In our practice, we generally employed the posterior mediastinal route; however, because the antrum of the elevated gastric tube was located near the esophageal hiatus, it was challenging to insert the tube and secure the round ligament. Consequently, we performed Kocher's mobilization of the duodenum and inserted the tube through its descending portion. In this configuration, the distance between the abdominal wall and the duodenum is longer than that in posterior sternal route reconstruction, which may predispose patients with minimal fat tissue around the round ligament to leakage of intestinal fluid. Additionally, if edema develops in the descending portion of the duodenum due to Kocher's mobilization, duodenal puncture, or suturing, it may lead to inflammation at the puncture site or edema of the Vater's papilla. Therefore, inserting the tube through the antrum of the gastric tube via the posterior sternal route might be a better option.

There is ongoing debate regarding the necessity of a feeding tube for all patients. Akiyama et al. [13] found no significant differences in infectious complications or hospital stay

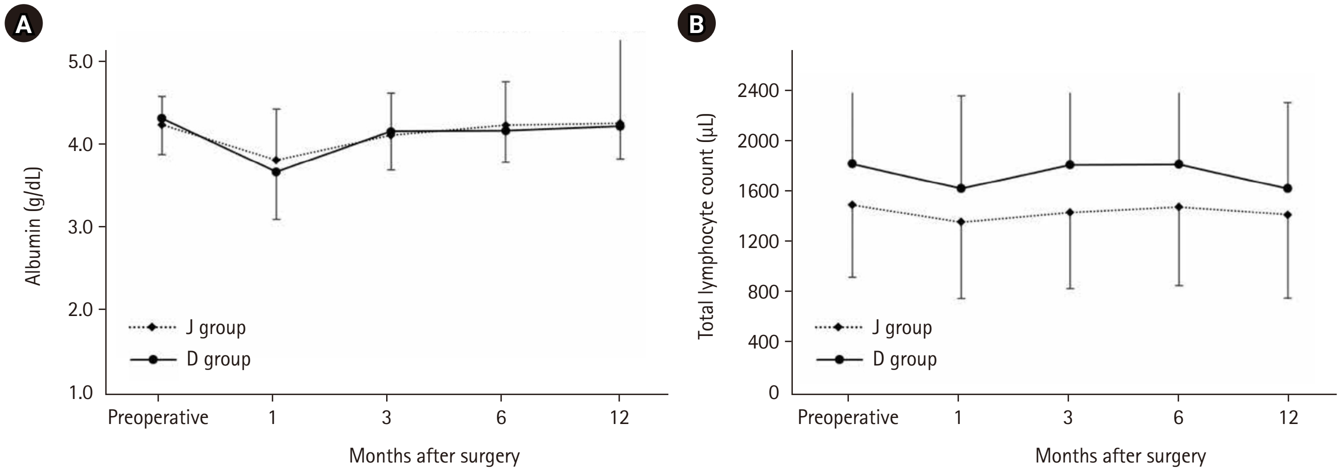

Fig. 6. Serum albumin and total lymphocyte count. J group, jejunostomy group; D group, duodenostomy group.

duration between patients receiving parenteral nutrition combined with jejunostomy and those receiving PPN alone. Similarly, Koterazawa et al. [14] reported no difference in weight loss at 3 months post-surgery based on the presence or absence of jejunostomy; however, 11% of patients in the J group experienced intestinal obstruction. Their multivariate analysis identified age 75 years or older, preoperative treatment, anastomotic leakage, and pneumonia as factors associated with the need for long-term jejunostomy. In our study, 48 patients (41.7%) were aged 70 years or older, and many were on antihypertensive or antithrombotic medications, suggesting that early postoperative administration of these drugs via jejunostomy may offer an advantage.

Limitations/suggestions for further studies

This retrospective study involved a small number of cases, and the perioperative nutritional doses varied among patients. Furthermore, the exact amount and duration of enteral nutrition were not strictly defined, making it difficult to quantify the nutritional benefits. Future prospective studies with standardized nutritional dosing and duration are needed to more accurately assess the benefits of duodenostomy versus jejunostomy.

Conclusion

Patients who underwent duodenostomy experienced no bowel obstruction and demonstrated reduced early postoperative weight loss without an increase in operative time. These results suggest that feeding duodenostomy is a safer option for enteral nutrition in patients undergoing esophagectomy. Despite the limitations of a retrospective design and variability in nutritional dosing, our findings support further prospective investigations to validate these results and refine feeding strategies for improved outcomes in esophageal cancer surgery.

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Authors' contribution

Conceptualization: KH. Data curation: HK. Methodology/formal analysis/validation: HK, KY, TN, KH. Project administration: KH. Funding acquisition: Not applicable. Writing–original draft: HK. Writing–review & editing: HK, KY, TN, KH. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Contact the corresponding author for data availability.

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Supplementary materials

None.

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Original Article

Perioperative outcomes of older adult patients with pancreatic cancer based on nutritional status: a retrospective cohorat study

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Abstract

Purpose: This study investigated the effects of preoperative nutritional status on postoperative outcomes in older adult patients with pancreatic adenocarcinoma.

Methods: The background and perioperative factors of patients who underwent pancreatectomy for pancreatic adenocarcinoma between 2007 and 2020 were retrospectively analyzed.

Results: Patients aged 75 years or over (older adults) were significantly associated with hypertension, upfront surgery, and lower prognostic nutritional index. In addition, these patients had a significantly lower rate of portal vein resection, less blood loss, and shorter operation time than patients aged less than 75 years (non-older adults). During the postoperative course, older adult patients had a higher rate of pneumonia and lower overall survival than younger patients, although recurrence-free survival was comparable. In addition, older adult patients showed preoperative malnutrition as a risk factor for postoperative in-hospital death.

Conclusion: Surgical treatment for pancreatic cancer in older adult patients was performed safely. However, preoperative malnutrition is a risk factor for in-hospital death and such patients require nutritional support and less-invasive surgery.

Keywords: Aged; Nutritional status; Pancreatectomy; Pancreatic neoplasm; Prognosis

Introduction

Background

Japan has entered a full-fledged aging society with a declining birthrate. The late-stage older adult population accounted for 17.48 million, or 13.8% of the total population, in fiscal year 2009 [1]. The incidence of pancreatic cancer and biliary tract cancer has been increasing in recent years, and it is not uncommon to perform difficult hepatobiliary and pancreatic surgery on older adult patients. Although the application of highly invasive hepatobiliary and pancreatic surgery requires sufficient verification, there is no clear indicator to determine the indication for surgery in older adult patients, which is currently left to the attending physician or each institution.

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The context of this article was summarized and presented in the 57th Annual Meeting of the Japanese Surgical Metabolism and Nutrition held in 2020.

Objectives

The CONUT value [2] and Onodera's prognostic nutritional index (PNI) [3] are nutritional indices that can be calculated from daily blood sampling data, are easy to use, and can be performed at general facilities. We selected these two indicators and investigated their usefulness as perioperative risk assessment factors for the nutritional status of older adult (≥75 years) and non-older adult (<75 years) patients with pancreatic cancer.

Methods

Ethics statement

This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2020-1-322) as a "Study of clinicopathologically relevant factors and treatment outcomes in pancreatic diseases." The written informed consent was waived because this design is a retrospective study.

Study design

It is a retrospective cohort study. It was described according to the STOBE statement available at: https://www.strobe-statement.org/.

Setting

This study was done at Tohoku University Hospital between January 2007 and June 2020. Surgical procedure for pancreatic cancer patients were as follows:

The standard pancreaticoduodenectomy (PD) for pancreatic cancer in our department is a subtotal stomach-sparing PD in which the stomach is orally dissected 2-4 cm from the pyloric ring and standard lymph node dissection. The modified Child method is used for reconstruction, and the Blumgart method is mainly used for pancreaticojejunostomy since 2016, although the two-layer pancreaticojejunostomy was used until 2015 [4]. An enteral feeding tube is also implanted and postoperative enteral nutrition is used. Distal pancreatectomy (DP) with standard lymph node dissection, dividing the pancreas just above the portal vein, is the basic approach for pancreatic cancer. In open DP, the main pancreatic duct is double ligated and the pancreatic stump is closed in a fish-mouth fashion; however, in laparoscopic surgery, the stump is closed with an automatic suturing device.

Participants

We included 549 patients with pancreatic cancer who underwent resection in the Department of General Surgery, Tohoku University Hospital between January 2007 and June 2020. A total of 122 patients (22.2%) were aged 75 years or older (older adult group) with the remaining 427 patients (77.8%) aged less than 75 years (non-older adult group).

Variables

The following background factors, intraoperative factors, and postoperative outcomes of the older adult and non-older adult groups were reviewed in the medical records and our department database for retrospective evaluation. Background factors included age, sex, comorbidities (hypertension, diabetes), preoperative chemotherapy, stage of disease, and preoperative nutritional indices such as PNI and CONUT values. Intraoperative factors included surgical technique, portal vein resection, operative time, blood loss, and R0 resection. The postoperative outcome measures included all complications, major complications, hospital mortality, postoperative pancreatic fistula, surgical site infection (SSI), organ space SSI, pneumonia, sepsis, thrombosis, postoperative hospital stay, readmission within 30 days, overall survival, and recurrence-free survival. Severe complications were defined as IIIa or higher of the Clavien-Dindo classification [5], and postoperative pancreatic fistula was defined according to the criteria of the revised International Study Group on Pancreatic Surgery [6]. Staging was described in accordance with the 7th edition of the General Rules for the Study of Pancreatic Cancer [7]. Patients were followed up every 3 months after surgery as outpatients, and the presence or absence of recurrence was confirmed mainly by imaging tests. Overall survival and recurrence-free survival were defined as the period from the date of surgery to the date of death, the date of recurrence confirmation, or the date of the last outpatient visit, with the date of recurrence confirmation being the date when recurrence was confirmed by imaging tests. Recurrence-free survival was terminated in the case of death without recurrence.

Bias

There was no selection bias reportable.

Data sources

Data were from the patient's medical records.

Measurements

We compared the background, intraoperative, and postoperative factors between the older adult and non-older adult patients, and confirmed the background and perioperative characteristics of older adult patients undergoing pancreatic cancer resection. The PNI and CONUT values were calculated using the following formula, and patients with PNI less than 40 were classified as malnourished.

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PNI=10×(albumin value)+0.005×(total lymphocyte count), CONUT values [2] were calculated as shown in Fig. 1.

A score of 0 to 1 is normal, 2 to 4 is mildly abnormal, 5 to 8 is moderately abnormal, and 9 or more is severely abnormal. In this study, patients with moderate or severe abnormalities with a CONUT value of 5 or higher were defined as malnourished.

Study size

Since all target patients were recruited and included according to the selection criteria, no sample size estimation was done.

Statistical methods

Continuous variables are presented as the mean±standard deviation if they followed a normal distribution, or as the median and range if they did not. For nominal variables, either the chi-square test or the Fisher direct probability calculation method was used. Survival rates were statistically analyzed using the log-rank test with the Kaplan-Meier method. A P-value of less than 0.05 was defined as statistically significant.

Results

Characteristics of resected pancreatic cancer cases in older adult patients

A comparison of background factors showed that 80 (65.5%, P<0.001) of the patients in the older adult group had coexisting hypertension, and the number of patients who received pre-operative chemotherapy was significantly lower (P<0.001) (Table 1). Preoperative CONUT values were not significantly different between the two groups, but preoperative PNI was 43.0±5.7 in the older adult group, which was significantly lower (P=0.032). There was no difference in stage between the two groups. On the other hand, DP was performed significantly higher in the older adult group than in the non-older adult group (P=0.007), with total pancreatectomy (TP) being less common in the older adult group. In addition, 33 patients underwent combined portal vein resection (27.1%, P<0.001), and operative time and blood loss were also significantly lower than patients in the non-older adult group (P<0.001 for each).

When examining the postoperative course, there was no difference in overall postoperative complications or major complications, and postoperative pancreatic fistula tended to be more common in the older adults, but with no significant difference (P=0.058) (Table 2).

Postoperative pneumonia occurred in 13 patients in the older adult group (10.6%), which was significantly higher than that in the non-older adult group (P=0.02). Long-term prognosis showed that overall survival was significantly lower in the older adult group than in the non-older adult (P=0.002) (Fig. 2A). However, there was no significant difference in recurrence-free survival (Fig. 2B).

Perioperative outcomes based on nutritional indices

Nutritional disorders were defined in 36 (29.5%) of the 122 older adult patients using PNI, and 31 (25.4%) were identified by CONUT values. Comparing the cases of pancreatic cancer resection in the older adult group between PNI 40 or less and the other groups, there was no difference in background factors, but there were seven cases of preoperative chemotherapy in the PNI 40 or less group (19.4%), which was significantly less (P=0.022) (Table 3). Although postoperative outcomes were similar, mortality after pancreatectomy was significantly higher in the PNI 40 or less group, with three (8.3%) deaths in the hospital (P=0.042) (Table 4).

On the other hand, in the CONUT classification, the group with nutritional disorders did not differ from the group without nutritional disorders in terms of background factors (Table 5). However, as with the PNI classification, postoperative mortality was significantly higher in patients with nutritional disorder (P<0.001) (Table 6). The four deaths among old-

Albumin level (mg/dL)	≥3.50 (0 points)	3.00–3.49 (1 point)	2.50–2.99 (2 points)	<2.50 (3 points)
Total lymphocyte count (/μL)	≥1,600 (0 points)	1,200–1,599 (1 point)	800–1,199 (2 points)	<800 (3 points)
Total cholesterol (mg/dL)	≥180 (0 points)	140–179 (1 points)	100–139 (2 points)	<100 (3 points)

Nutrition levels	Normal	Slight anomaly	Moderate anomaly	Anomalous anomaly
CONUT value (total score)	0–1 points	2–4 points	5–8 points	9–12 points

Fig. 1. CONUT value calculation table.

Table 1. Comparison of the background and intraoperative factors between the older adult and non-older patients

		<75 yr	≥75 yr	P-value
Sex (male:female)		253:174	69:53	0.594
Preoperative CONUT value		2 (0–11)	3 (0–9)	0.260
Preoperative PNI		44.3±6.0	43.0±5.7	0.032[a]
Diabetes mellitus		220 (51.5)	61 (50.0)	0.837
Hypertension		199 (46.6)	80 (65.5)	<0.001[a]
Preoperative chemotherapy		230 (53.8)	43 (35.3)	<0.001[a]
Stage of an illness	0	3 (0.7)	2 (1.6)	0.070
	IA	29 (6.8)	8 (6.6)	
	IB	7 (1.6)	1 (0.8)	
	IIA	98 (22.9)	43 (35.2)	
	IIB	233 (54.6)	60 (49.2)	
	III	5 (1.2)	0	
	IV	52 (12.2)	8 (6.6)	
Operative procedure	PD	248 (58.1)	61 (50.0)	
	DP	118 (27.6)	51 (41.8)	0.007[a]
	TP	61 (14.3)	10 (8.2)	
Combined portal vein resection		172 (40.3)	33 (27.1)	0.008[a]
Operation time (min)		534 (150–1,160)	481 (182–851)	<0.001[a]
Amount of blood loss (mL)		1,179 (22–7,250)	906 (63–9,695)	<0.001[a]
R0 resection		358 (83.8)	100 (82.0)	0.597

Values are presented as median (range), mean±SD, or number (%).
PNI, prognostic nutritional index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; SD, standard deviation.
[a]Statistically significant differences.

Table 2. Comparison of postoperative results between resected pancreatic cancer cases in older adult and non-older patients

	<75 yr	≥75 yr	P-value
Postoperative hospital stay (day)	24 (5–193)	25 (3–415)	0.858
Total complications	328 (76.8)	87 (71.3)	0.232
Serious complications	121 (28.3)	36 (29.5)	0.820
Death in hospital	11 (2.5)	4 (3.2)	0.752
Readmission within 30 day	19 (15.5)	54 (12.6)	0.613
SSI	106 (24.8)	36 (29.5)	0.294
Organ space SSI	71 (16.6)	24 (19.6)	0.419
Postoperative pancreatic fistula	56 (13.1)	25 (20.4)	0.058
Postoperative pneumonia	21 (4.9)	13 (10.6)	0.020[a]
Septicemia	26 (6.0)	6 (4.9)	0.826
Thrombosis	22 (5.7)	7 (5.1)	0.818

Values are presented as median (range) or number (%).
SSI, surgical site infection.
[a]Statistically significant differences.

er adult patients were all due to infectious complications, except for one death due to primary disease, but no other trends were observed (Table 7). In these patients, there were one case of high intraoperative blood loss due to invasive surgery including portal vein and celiac axis resection, and two cases of postoperative pancreatic fistula, which resulted in infectious complications.

Discussion

Key results

Older adult patients with pancreatic cancer after resection had more hypertension (65.5%) and received less preoperative chemotherapy than non-older adult patients. Preoperative PNI was lower (43.0±5.7), but CONUT values were

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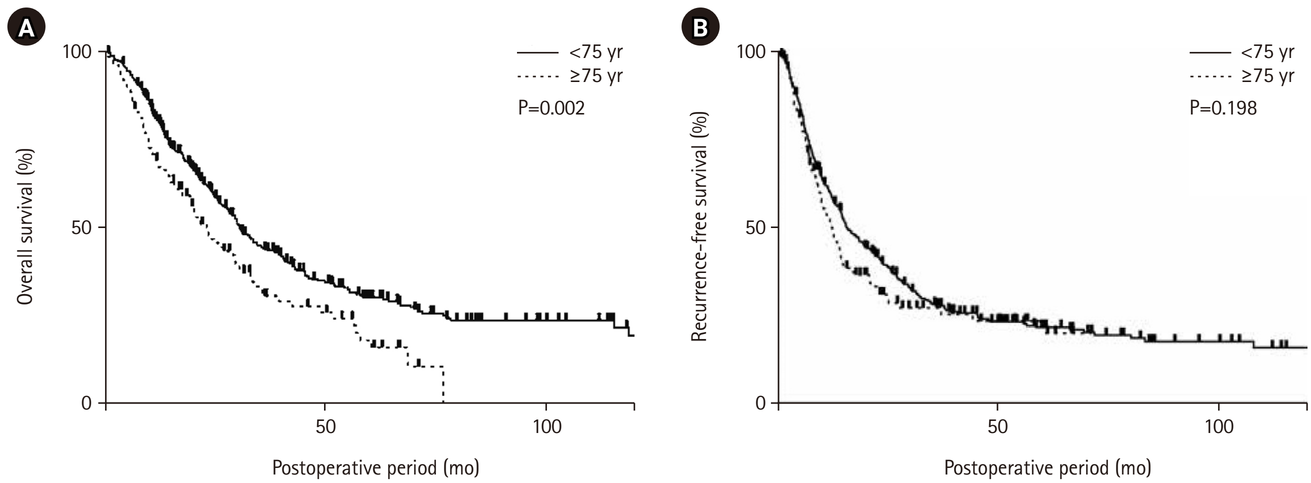

Fig. 2. Long-term outcomes after pancreatic cancer resection in older adult (≥75 yeasr) and non-older (<75 years) patients. Comparing patients aged ≥75 years with those aged <75 years, the overall survival rate was significantly better in patients aged <75 years (P=0.002) (A). However, the two groups had no significant difference in recurrence-free survival (P=0.198) (B).

Table 3. Background and intraoperative factors of late-stage elderly pancreatic cancer cases grouped by PNI40

		PNI≤40	PNI>40	P-value
Sex (male:female)		24:12	45:41	0.165
Hypertension		26 (72.2)	54 (62.8)	0.404
Diabetes mellitus		19 (52.8)	42 (48.8)	0.842
Preoperative chemotherapy		7 (19.4)	36 (41.8)	0.022[a]
Operative procedure	PD	21 (58.3)	40 (46.5)	0.536
	DP	14 (38.9)	37 (43.0)	
	TP	1 (2.8)	9 (10.5)	
Combined portal vein resection		12 (33.3)	21 (24.4)	0.372
Operation time (min)		502 (182–851)	470 (202–845)	0.306
Amount of blood loss (mL)		1,222 (82–9,639)	834 (63–9,695)	0.149
R0 resection		28 (77.8)	72 (83.7)	0.529

Values are presented as number (%) or median (range).
PNI, prognostic nutritional index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.
[a]Statistically significant differences.

Table 4. Postoperative outcomes of older adult patients with pancreatic cancer grouped by PNI40

	PNI≤40	PNI>40	P-value
Postoperative hospital stay (day)	27.5 (3–163)	24 (10–415)	0.355
Total complications	28 (77.8)	59 (68.6)	0.382
Serious complications	14 (38.9)	22 (25.6)	0.191
Death in hospital	3 (8.3)	1 (1.2)	0.042[a]
Readmission within 30 day	3 (8.3)	16 (18.6)	0.181
SSI	12 (33.3)	24 (27.9)	0.663
Organ space SSI	8 (22.2)	16 (18.6)	0.627
Postoperative pancreatic fistula	7 (19.4)	18 (20.9)	0.852
Postoperative pneumonia	6 (16.1)	7 (8.1)	0.200
Septicemia	1 (2.7)	5 (5.8)	0.669
Thrombosis	4 (11.1)	3 (3.5)	0.193

Values are presented as median (range) or number (%).
PNI, prognostic nutritional index; SSI, surgical site infection.
[a]Statistically significant differences.

Table 5. Background and intraoperative factors of older adult patients with pancreatic cancer grouped by CONUT values

		No nutritional disorders	Nutritional disorders	P-value
Sex (male:female)		48:43	21:10	0.207
Hypertension		21 (67.7)	59 (64.8)	0.829
Diabetes mellitus		17 (54.8)	44 (48.3)	0.677
Preoperative chemotherapy		35 (38.5)	8 (25.8)	0.276
Operative procedure	PD	43 (47.2)	18 (58.1)	0.388
	DP	39 (42.9)	12 (38.7)	
	TP	9 (9.9)	1 (3.2)	
Combined portal vein resection		24 (26.4)	9 (29.0)	0.816
Operation time (min)		471 (202–845)	498 (182–851)	0.462
Amount of blood loss (mL)		870 (63–9,695)	1,145 (82–9,639)	0.432
R0 resection		76 (83.5)	24 (77.4)	0.565

Values are presented as number (%) or median (range).
PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

Table 6. Postoperative outcomes of older adult patients with pancreatic cancer grouped by CONUT value

	No nutritional disorders	Nutritional disorders	P-value
Postoperative hospital stay (day)	24 (10–415)	28 (3–100)	0.085
Total complications	61 (67.0)	26 (83.8)	0.106
Serious complications	25 (27.5)	11 (35.5)	0.494
Death in hospital	0	4 (12.9)	<0.001[a]
Readmission within 30 day	17 (18.7)	2 (6.5)	0.151
SSI	25 (27.4)	11 (35.5)	0.494
Organ space SSI	18 (19.8)	6 (19.4)	0.958
Postoperative pancreatic fistula	20 (21.9)	5 (16.1)	0.799
Postoperative pneumonia	8 (8.8)	5 (16.1)	0.312
Septicemia	4 (4.4)	2 (6.4)	0.643
Thrombosis	5 (5.5)	2 (6.5)	0.845

Values are presented as median (range) or number (%).
SSI, surgical site infection.
[a]Statistically significant differences.

Table 7. Pancreatic cancer in-hospital deaths in older adult patients

	Age	Sex	Technique	PVR	Blood loss (mL)	Operation time (min)	Postoperative pancreatic fistula	PNI	CONUT	Cause of death
1	76	Male	DP	None	9,639	453	Yes	37.1	5	Renal failure, pneumonia
2	75	Male	DP-CAR	None	350	535	None	41.4	5	Pancreatic cancer liver metastasis
3	79	Women	SSPPD	None	545	531	Yes	29.7	8	Sepsis
4	82	Male	SSPPD, right colon resection	Yes	1,483	529	None	36.7	6	Sepsis, ARDS

PVR, portal vein combined resection; PNI, prognostic nutritional index; DP, distal pancreatectomy; DP-CAR, distal pancreatectomy with celiac axis resection; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; ARDS, acute respiratory distress syndrome.

similar. Surgeries were less extensive, with shorter duration and less blood loss. Postoperative pneumonia incidence and overall mortality were significantly higher among older adult patients, though recurrence-free survival was similar. Nutritional disorders, defined by low PNI or CONUT values, significantly correlated with increased postoperative mortality, primarily due to infectious complications, including pancreatic fistula.

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Interpretation/comparison with previous studies

Pancreatectomy, including PD and TP, is a difficult and highly invasive procedure that requires careful management in older adult patients. The risk of pancreatic fistula is particularly high in PD, and the incidence of postoperative complications and mortality rates are reported to be 41.6% and 2.8%, respectively, even with the improvement of surgical techniques and the development of perioperative management [8]. However, there are an increasing number of reports in recent years showing that PD for the older adult has comparable postoperative outcomes to those for younger patients [9,10]. In this study, we compared the postoperative results between older adult and non-older adult patients, and found that pancreatectomy can be performed safely in older adult patients as in previous reports. However, the older adult patients had lower preoperative PNI, more nutritional problems, and more preoperative comorbidities. On the other hand, the perioperative results showed that the postoperative outcome of the older adult patients was relatively good, even if they had preoperative nutritional problems. Although the influence of preoperative patient selection is undeniable, it is also possible that the incidence of postoperative complications was reduced by shifting to less invasive procedures and by efforts to reduce blood loss and operation time. Even so, not all complications were controlled, and postoperative pneumonia was more common in the older adult group.

The incidence of postoperative pneumonia in the older adult was significantly higher than that in the non-older adult group. Prevention of postoperative pneumonia in the older adult requires not only reduction of surgical invasiveness but also more multifaceted medical care. The effectiveness of oral care in reducing postoperative infectious complications after PD surgery [11] and the introduction of a perioperative management team in preventing pneumonia [12] have been reported, suggesting that there is room for further improvement in the prevention of postoperative pneumonia in older adult patients with pancreatic cancer.

In a study of long-term prognosis in older adult patients with pancreatic cancer, overall survival was significantly lower than that in non-older adult patients, but recurrence-free survival was similar. Although it is difficult to make a generalized statement because the study did not match the surgical technique and stage, the overall survival rate was probably influenced by the median age (78 years) and comorbidities in the older adult group. On the other hand, there was no difference in recurrence-free survival or R0 resection rate, suggesting that surgical resection for pancreatic cancer in the older adult is comparable to that in the non-older adults. In addition, it is interesting to note that preoperative chemotherapy was administered at a significantly lower rate in older adult patients with pancreatic cancer. Currently, the standard treatment for resectable pancreatic cancer is pre-operative chemotherapy with gemcitabine plus S1 and surgical resection, but the PREP-02/JSAP-05 trial, on which this standard is based, did not enroll patients aged 80 or older [13]. Although the long-term prognosis was not examined in our study, 39 (31.9%) of the patients in the late-stage older adult group were aged 80 years or older.

Considering that the outcomes of resected patients are similar, it is possible that preoperative chemotherapy is unnecessary for patients over 80 years of age. The necessity of preoperative treatment for pancreatic cancer patients over 80 years of age should also be considered in the future. In addition, among resected pancreatic cancer patients in the older adults, significantly more patients with a PNI of 40 or less did not receive preoperative chemotherapy. Although our institution does not conduct nutritional assessment as a preoperative treatment criterion for pancreatic cancer, it is possible that patients were selected a priori based on nutritional assessment. In this sense, the significance of nutritional evaluation as a requirement for preoperative treatment of pancreatic cancer in the older adults may be significant.

In older adult patients with pancreatic cancer, preoperative nutritional disorders were considered a risk factor for post-operative hospital mortality, although they did not affect other complications. Ishida et al. [14] compared preoperative nutritional status and postoperative complications in PD and reported that postoperative complications were significantly more frequent in patients with preoperative nutritional problems than in normal patients when the effect of pancreatic fistula was excluded. Older adult patients have a decline in immune function associated with aging, and aging has been cited as a poor prognostic factor in patients with sepsis [1]. Yanagawa et al. [15] also studied gastric cancer patients with pyloric stenosis, and reported that poor preoperative nutrition was associated with a high risk of postoperative infectious complications. In this report, three out of four patients who died in the hospital also had infectious complications, suggesting that older adult patients with preoperative malnutrition who underwent pancreatic cancer resection are more prone to infectious complications and more likely to develop serious complications.

It is also interesting to note that in this comparison between older adult and non-older adult patients, the older adult patients had significantly lower PNI, whereas no difference was observed in CONUT scores. Although both PNI and CONUT included albumin and total lymphocyte counts as calculation factors, total cholesterol, which is considered an indicator of lipid metabolism, was included only in CONUT. Nutritional improvement has been reported by administering pancrelipase to patients with pancreatic exocrine insufficiency [16], and the effect on pancreatic cancer patients may be equivalent to that of pancrelipase. Early administration of pancrelipase in pancreatic cancer patients may improve preoperative nutritional status and postoperative outcomes.

Limitations

It was a single-center, retrospective study and that surgical treatment was likely to have been performed only in selected patients with older adult disease. In addition, we did not include any nutritional indices such as muscle mass, performance status, hypertension, and diabetes mellitus in this study. However, it is also true that a simpler and more objective evaluation index is required in daily clinical practice, and the development of a more versatile index is expected in the future.

Conclusion

We examined cases of pancreatic cancer resection in the older adults, and found that surgical treatment was safe and less invasive, although many patients with pancreatic cancer in the older adults were accompanied by nutritional disorders. However, preoperative malnutrition is a risk factor for in-hospital mortality, and it is necessary to take measures such as improving malnutrition and avoiding over-invasive surgery.

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Authors' contribution

Conceptualization: TM. Data curation: TM, MI. Formal analysis: TM, MI. Investigation: TM, MI. Methodology: TM, MI. Project administration: TM. Supervision: MU. Funding acquisition: Not applicable. Writing – original draft: TM. Writing – review & editing: MI, MM, KN, TK, MU. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

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Supplementary materials

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Original Article

Association between decreased dietary intake during hospitalization and long-term weight loss in postoperative gastric cancer patients over 75 years of age: a retrospective cohort study

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Abstract

Purpose: Weight loss following gastrectomy is a significant concern, and maintaining adequate nutrition is necessary, especially given the growing number of older adult patients. This study examined the relationship between postoperative food intake and long-term weight loss in postgastrectomy patients aged ≥75 years.
Methods: Out of 88 patients who underwent gastrectomy for gastric cancer at our institute, 46 were aged ≥75 years. These patients were divided into two groups: one with an average energy intake exceeding 50% of the basal metabolic rate and one with an intake below 50% of the basal metabolic rate. The percentage change in body weight up to 6 months post-surgery was compared between the groups.
Results: In the group with higher dietary intake, the rate of weight change at 3 and 6 months postoperatively was lower, and fewer patients received postoperative adjuvant chemotherapy.
Conclusion: Poor postoperative food intake may serve as a predictor of weight loss up to 3 months following surgery in postgastrectomy patients aged ≥75 years.

Keywords: Basal metabolism; Energy intake; Gastrectomy; Stomach neoplasms; Weight loss

Introduction

Background

Weight loss is a critical issue in the continuation of cancer treatment. In gastric cancer specifically, postoperative weight loss has been linked to both the continuation of adjuvant chemotherapy and the rate of postoperative recurrence [1,2]. Therefore, implementing nutritional therapy to control weight loss is crucial during the postoperative period of gastric cancer.

Despite the importance of maintaining nutritional intake after gastric cancer surgery, patients often experience reduced food consumption. Reports indicate that food intake in postoperative gastric cancer patients decreases by 8.9% after pyloric gastrectomy and by 15.6% after total gastrectomy compared to preoperative levels at 1 month after surgery

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[3]. Furthermore, surgical indications for older adults are expanding due to an aging patient population and advances in perioperative management, resulting in an increasing percentage of patients aged ≥75 years undergoing gastric cancer surgery [4]. It has been reported, however, that gastric cancer patients ≥80 years of age experience greater loss of lean body mass compared to those under 80 [5], underscoring the need for more intensive nutritional therapy in older adult patients.

In terms of nutritional therapy, studies have shown that administering nutritional supplements after gastric cancer surgery can effectively mitigate postoperative weight loss [6]. On the other hand, there are few studies investigating the relationship between energy intake during postoperative hospitalization and long-term weight changes in gastric cancer patients, particularly in older adults. In clinical practice, many older adult patients experience a sustained decrease in food intake during postoperative hospitalization, which often leads to continued weight loss after discharge. As the number of gastric cancer patients aged ≥75 years increases, the ability to predict long-term postoperative weight loss based on early declines in energy intake during hospitalization could facilitate the implementation of early and intensive nutritional therapy.

Objectives

We conducted a study to clarify the association between reduced energy intake during postoperative hospitalization and long-term weight loss in older adult gastric cancer patients.

Methods

Ethics statement

This study received approval from the Ethics Committee of Chikamori Hospital (Approval No. 473, issued on November 24, 2021).

Study design

This study was a retrospective cohort study. It was described according to the STROBE statement, which is available at https://www.strobe-statement.org/.

Setting

The study was conducted at Chikamori Hospital using patient records from January 2017 to December 2020. Nutritional management followed the clinical pathway (Fig. 1). On the second postoperative day, patients were allowed drinking water; on the third day, they were given a liquid diet (divided meals); on the fourth day, a semi-solid diet (divided meals); on the sixth day, a porridge diet (divided meals); and on the seventh day, a normal diet (divided meals). The energy and protein content of each meal type are shown in Table 1. From postoperative day 1 to day 5, patients received extracellular fluid replacement and a hypotonic electrolyte solution. If oral

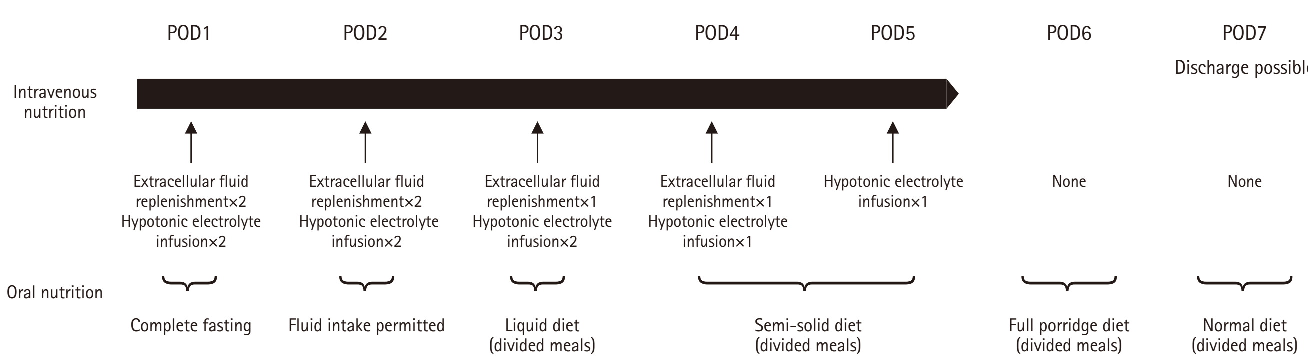

Fig. 1. Flow of nutritional management in the clinical pathway of postoperative management. POD, postoperative day.

Table 1. Nutritional composition of each meal type provided after gastrectomy

	Liquid diet (divided meals)	Semi-solid diet (divided meals)	Full porridge diet (divided meals)	Regular diet (divided meals)
Energy (kcal)	600	750	1,400	1,600
Protein (g)	20	48	60	70

intake could not be initiated by postoperative day 5, a 7.5% glucose-sweetened amino acid solution was administered, as depicted in Fig. 1.

Participants

Out of 88 patients who underwent gastrectomy for gastric cancer at Chikamori Hospital between January 2017 and December 2020, 84 patients (aged 50–96 years) were included. One patient who died in the hospital and three patients whose weight measurement conditions could not be standardized due to maintenance dialysis were excluded. For intergroup comparisons, these 84 subjects were initially divided into two groups: patients aged ≥75 years and those <75 years. Then, among the 46 patients aged ≥75 years, we subdivided them into a "sufficient" group (22 patients) with an average energy intake during hospitalization of at least 50% of the basal energy expenditure (BEE), and a "insufficient" group (24 patients) with an intake below 50% of BEE.

Variables

Outcome variables are detailed in the Measurement section below. In the regression analysis, the dependent variable was the percentage change in body weight at 3 and 6 months postoperatively, while the explanatory variables included energy sufficiency relative to BEE and the surgical technique, which reflects differences in the extent of resection.

Bias

Since all target subjects were included, there was no selection bias.

Data sources

Medical records were collected using Nippon Electric Company's MegaOakHR.

Measurement

Patient background

Data on patient age, sex, preoperative body mass index (BMI), skeletal mass index (SMI), and sarcopenia were collected. SMI was measured using the Inbody S10, and sarcopenia was diagnosed based on the criteria established by the Asian Working Group for Sarcopenia 2019 [7].

Blood test findings

Blood tests, conducted by SRL Inc., assessed preoperative serum albumin (Alb), total lymphocyte count, and C-reactive protein (CRP).

Surgical findings and postoperative course

The surgical technique and approach (laparoscopic or open) were documented. Postoperative complications were classified as grade II or higher according to the Clavien-Dindo system.

Nutritional evaluation

Based on preoperative blood test results, we investigated the Prognostic Nutritional Index (PNI) developed by Onodera et al. [8] and the Glasgow Prognostic Scale with cutoff values of 1.0 mg/dL for serum CRP and 3.5 g/dL for serum Alb, according to Elahi et al. [9].

Weight change

Patients were weighed by a nurse 2 to 3 hours after breakfast, either in their room or in the outpatient examination area. The rate of weight change was calculated using the preoperative weight as the baseline and comparing it to the weight at discharge and at 1, 3, and 6 months post-surgery.

BEE calculation method and energy intake sufficiency ratio

BEE was calculated using the Harris-Benedict equation. Nurses recorded the energy intake from each meal, and the energy values of the main meal and side dishes were determined from these records. The cumulative energy intake from the start of meals until the day before discharge was calculated. This value, combined with the energy intake from intravenous nutrition administered after surgery, was divided by the length of hospital stay (from the first postoperative day to the day before discharge) to derive the sufficiency ratio relative to BEE.

Others

We also examined the incidence and completion rate of postoperative adjuvant chemotherapy following discharge, as well as the rate of patient readmission.

Study size

As all eligible patients were included based on the selection criteria, no formal sample size estimation was performed.

Statistical methods

Continuous variables are presented as mean±standard deviation. The Mann-Whitney U test, unpaired t-test, and chi-square test were used for comparisons between groups. Multiple regression analysis was performed to identify factors associated with the rate of weight change at 3 and 6 months postoperatively, with energy sufficiency relative to BEE, surgical technique, pathological stage (pStage), and the presence of postoperative adjuvant chemotherapy as independent variables. The analyses were performed using SPSS version 28.0.0.1 (IBM Corp.), and statistical significance was defined as P<0.05.

Results

Participants

The subjects and procedures of this study are shown in Fig. 2.

Main results

In Study 1, 84 patients were compared, with patients ≥75 years of age versus patients <75 years of age. The older group exhibited a 37% higher prevalence of sarcopenia than the younger group (P=0.061). There were no significant differences in preoperative BMI, PNI, or postoperative dietary intake between the groups. However, at 3 months postoperatively, the older group of patients had lower PNI (P=0.019) and serum Alb levels (P=0.013) (Tables 2, 3).

The weight change was significantly lower in the adults ≥75 years of age (−4.1%±4.7%) than in the younger group (−6.4%±5.0%) at discharge (P=0.029). However, there were no significant differences in the weight change at 1, 3, and 6 months postoperatively (Fig. 3), or in the rate of weight change at 1, 3, and 6 months postoperatively (Fig. 3).

In Study 2, 46 patients aged ≥75 years were divided into a sufficient group (22 patients) and an insufficient group (24 patients). There were no significant differences in patient

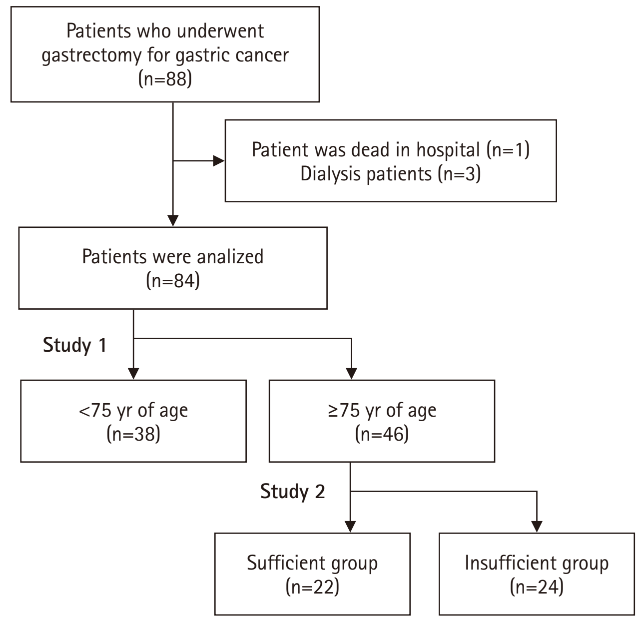

Fig. 2. Analysis of subjects and procedures in this study.

Table 2. Comparison of patient backgrounds between adults ≥75 and <75 years of age

Variable	All (n=84)	<75 yr (n=38)	≥75 yr (n=46)	P-value
Male sex	70 (83)	34 (89)	36 (78)	0.864
Preoperative BMI (kg/m^2)	22.9±3.3	22.7±3.4	23.1±3.3	0.645
Preoperative SMI (kg/m^2)	6.9±1.1	7.1±1.2	6.8±1.1	0.229
Sarcopenia (present)	24 (29)	7 (19)	17 (37)	0.061
Preoperative CRP (mg/dL)	0.5±1.1	0.4±0.7	0.5±1.3	0.924
Preoperative Alb (g/dL)	4.0±0.5	4.0±0.5	4.0±0.5	0.622
Preoperative TLC (10^3/μL)	1.7±0.5	1.7±0.5	1.6±0.6	0.687
Preoperative GPS (0/1/2)	69/11/4	31/7/0	38/4/4	0.090
Preoperative PNI	48.4±5.5	48.8±5.3	48.1±5.8	0.540
pStage (I/II/III/IV)	40/18/18/8	17/8/9/4	24/10/9/3	0.848
Laparoscopic surgery	44 (52)	18 (47)	26 (57)	0.511
Surgical procedure (DG/PG/TG/others)	36/7/39/2	15/5/18/0	21/2/21/2	0.206
Postoperative hospital stay (day)	170±18.4	185±18.8	155±18.2	0.657
Complications	40 (48)	17 (45)	23 (50)	0.631
Energy intake (kcal)	657±208	682±240	637±168	0.660
BEE (kcal)	1,302±188	1,354±199	1,259±169	0.021[a]
Fulfillment rate relative to BEE (%)	51.2±17.1	51.6±21.0	50.8±13.4	0.615

Values are presented as number (%) or mean±standard deviation.
BMI, body mass index; SMI, skeletal muscle index; CRP, C-reactive protein; Alb, albumin; TLC, total lymphocyte count; GPS, Glasgow Prognostic Score; PNI, Prognostic Nutritional Index; pStage, pathological stage; DG, distal gastrectomy; PG, proximal gastrectomy, TG, total gastrectomy; BEE, basal energy expenditure.
[a]t-test without correspondence; P<0.05.

Table 3. Trends in postoperative PNI and Alb in adults ≥75 and <75 years of age

	All (n=84)	<75 yr (n=38)	≥75 yr (n=46)	P-value
PNI at discharge	36.6±4.5	36.4±4.6	36.4±4.5	0.314
PNI at 1 mo post-surgery	45.8±4.5	46.4±5.1	45.4±4.0	0.370
PNI at 3 mo post-surgery	47.5±5.6	49.0±5.2	46.2±5.7	0.031[a]
PNI at 6 mo post-surgery	48.1±5.0	48.7±5.6	47.7±4.5	0.391
Alb at discharge (g/dL)	3.0±0.4	3.1±0.4	3.0±0.4	0.328
Alb at 1 mo post-surgery (g/dL)	3.8±0.4	3.8±0.4	3.8±0.4	0.411
Alb at 3 mo post-surgery (g/dL)	3.9±0.4	4.0±0.4	3.8±0.5	0.015[a]
Alb at 6 mo post-surgery (g/dL)	4.0±0.4	4.1±0.4	4.0±0.4	0.290

Values are presented as mean±standard deviation.
PNI, Prognostic Nutritional Index; Alb, albumin.
[a]P<0.05, t-test without correspondence.

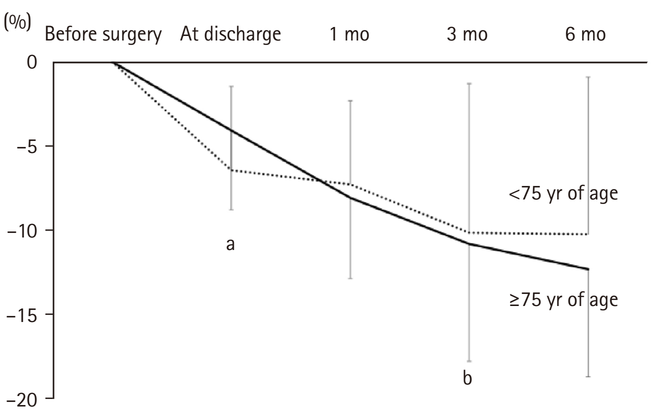

Fig. 3. Trends and comparison of weight loss rates between adults ≥75 and <75 years of age. In the older group, the weight loss rate at discharge was significantly lower, but no difference was observed thereafter compared to the younger group. [a]Mann-Whitney U test: <0.05; [b]t-test without correspondence: <0.05.

background, surgical technique, or postoperative course between the groups, although the insufficient group showed a trend toward a higher percentage of advanced cancer (P=0.075) (Table 4).

The mean energy intake in the sufficient group was 769±146 kcal, whereas it was 517±106 kcal in the insufficient group (P<0.001). There was no difference in the duration of intravenous nutrition or the percentage of patients who received nutritional solutions (Table 5).

Preoperative PNI did not differ between the groups; however, at 3 months postoperatively, the insufficient group showed a tendency toward lower PNI (44.9±7.2) compared with the secure group (47.6±3.1, P=0.064). Additionally, serum Alb at 3 months postoperatively was significantly lower in the insufficient group (3.7±0.5 g/dL) than in the secure group (4.0±0.3 g/dL, P=0.013) (Table 6).

There was no significant difference in postoperative weight change between the two groups at discharge and at 1 month. However, at 3 months postoperatively, the insufficient group experienced significantly greater weight loss (−12.9%±7.4%) compared to the secure group (−8.3%±5.7%, P=0.032). Similarly, at 6 months postoperatively, weight loss was −9.5%±6.2% in the secure group versus −14.5%±5.8% in the insufficient group (P=0.018) (Fig. 4).

The number of patients receiving postoperative adjuvant chemotherapy after discharge was significantly higher in the insufficient group (P=0.035), with three patients in the secure group and 10 in the insufficient group. Moreover, 0 (0%) patients in the secure group and three (30%) in the insufficient group completed chemotherapy. Additionally, the readmission rate after discharge was significantly higher in the insufficient group, with 14 patients (58%) compared to six patients (27%) in the secure group (P=0.023).

Multiple regression analysis, with the rate of weight change at 3 and 6 months postoperatively as the dependent variable and energy sufficiency relative to BEE, surgical technique, pStage, and the presence of postoperative adjuvant chemotherapy as independent variables, identified postoperative adjuvant chemotherapy as an independent predictor of weight loss at 6 months postoperatively (Table 7).

Discussion

Key results

In Study 1, patients ≥75 years of age exhibited a 37% higher prevalence of sarcopenia (P=0.061) than those <75 years of age and had lower PNI (P=0.019) and serum Alb levels (P=0.013) at 3 months post-surgery. Although weight loss at discharge was lower in the older group (−4.1%±4.7%) than in the younger group (−6.4%±5.0%, P=0.029), weight loss rates became similar thereafter. In Study 2, among older adult patients (≥75 years) divided into sufficient (n=22) and insuf-

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Table 4. Comparison of patient background and postoperative course between the sufficient group and the insufficient group in patients aged ≥75 years after gastrectomy

Variable	Sufficient group (n=22)	Insufficient group (n=24)	P-value
Age (yr)	81.0±5.6	80.2±3.9	0.825
Male sex	19 (86)	17 (71)	0.821
Preoperative BMI (kg/m^2)	23.4±2.9	22.8±3.7	0.312
Preoperative SMI (kg/m^2)	6.7±1.1	6.8±1.1	0.927
Weight (kg)	8 (36)	17 (38)	0.936
Preoperative CRP (mg/dL)	0.6±1.5	0.5±1.2	0.947
Preoperative Alb (g/dL)	4.0±0.5	4.0±0.4	0.625
Preoperative TLC (10^3/μL)	1.6±0.5	1.7±0.6	0.625
Preoperative GPS (0/1/2)	18/1/3	20/3/1	0.364
Preoperative PNI	48.2±6.0	47.9±5.7	0.538
pStage (I/II/III/IV) (%)[a]	13/2/6/1	8/8/4/4	0.075
Laparoscopic surgery (present)	15 (68)	11 (46)	0.149
Surgical procedure (DG/PG/TG/other)	12/2/10/0	9/0/11/2	0.222
Postoperative hospital stay (day)	190±25.4	123±6.0	0.657
Postoperative fasting days (day)	4.1±6.2	3.5±1.9	0.299
Complications (present)	17 (45)	23 (50)	0.631

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; SMI, skeletal muscle index; CRP, C-reactive protein; Alb, albumin; TLC, total lymphocyte count; GPS, Glasgow Prognostic Score; PNI, Prognostic Nutritional Index; pStage, pathological stage; DG, distal gastrectomy; PG, proximal gastrectomy, TG, total gastrectomy.
[a]Mann-Whitney U test: <0.05.

Table 5. Energy intake, sufficiency rate relative to basal energy expenditure, duration of intravenous nutrition administration, and proportion of patients receiving nutritional infusion in patients aged 75 years and older after gastrectomy

	Sufficient group (n=22)	Insufficient group (n=24)	P-value
Energy intake (kcal/day)	769±146	517±106	<0.001[a]
Protein intake (g/day)	30±7	19±7	<0.001[a]
Basal energy expenditure (kcal)	1,248±176	1,270±166	0.821
Duration of intravenous nutrition administration (day)	7.2±6.3	7.1±4.4	0.738
Number of patients who received nutritional infusion	5 (23)	6 (25)	0.857

Values are presented as mean±standard deviation or number (%).
[a]Mann-Whitney U test: <0.05.

Table 6. Postoperative trends in PNI and Alb in the sufficient and insufficient group

	Sufficient group (n=22)	Insufficient group (n=24)	P-value
PNI at discharge	35.7±4.4	37.0±4.6	0.397
PNI at 1 mo post-surgery	45.7±2.9	45.3±4.8	0.951
PNI at 3 mo post-surgery	47.6±3.1	44.9±7.2	0.064
PNI at 6 mo post-surgery	47.7±3.2	48.6±5.7	0.934
Alb at discharge (g/dL)	2.9±0.4	3.1±0.3	0.439
Alb at 1 mo post-surgery (g/dL)	3.8±0.3	3.7±0.4	0.481
Alb at 3 mo post-surgery (g/dL)	4.0±0.3	3.7±0.5	0.013[a]
Alb at 6 mo post-surgery (g/dL)	4.0±0.3	4.0±0.4	0.770

Values are presented as mean±standard deviation.
PNI, Prognostic Nutritional Index; Alb, albumin.
[a]t-test without correspondence: <0.05.

ficient (n=24) groups, there were no baseline differences, although a trend toward more advanced cancer was observed in the insufficient group (P=0.075). The sufficient group had a higher energy intake (769±146 kcal) than the insufficient group (517±106 kcal, P<0.001). At 3 months postoperatively, the insufficient group had lower serum Alb (P=0.013) and greater weight loss (P=0.032), with these differences persisting at 6 months (P=0.018). Additionally, both adjuvant chemotherapy and readmission rates were higher in the insufficient group (P=0.035 and P=0.023, respectively). Notably, postoperative adjuvant chemotherapy emerged as a predictor of weight loss at 6 months.

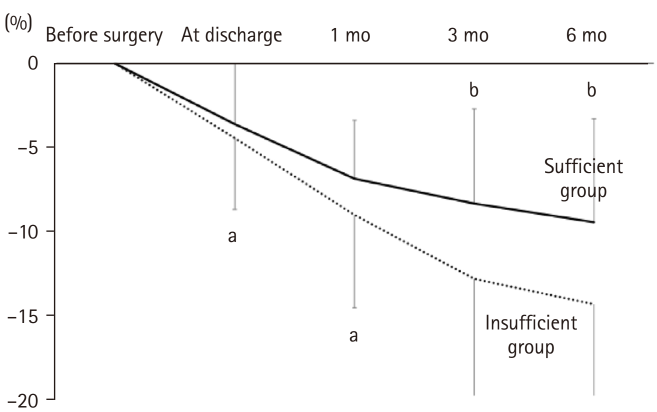

Fig. 4. Weight change rates in patients ≥75 years of age after gastrectomy: sufficient group versus insufficient group. In the insufficient group, the weight loss rates at 3 and 6 months post-surgery were significantly greater. [a]Mann-Whitney U test: <0.05; [b]t-test without correspondence: <0.05.

Interpretation/comparison with previous studies

First, no significant difference was observed in the percentage of postoperative inpatient energy intake relative to BEE between patients ≥75 and <75 years of age following gastrectomy. Although the rate of weight change at hospital discharge was lower in the older group, the weight change rates at 1, 3, and 6 months postoperatively did not differ between the groups. Moreover, there were no differences in disease background or preoperative nutritional status between the two age groups.

Similarly, the postoperative course was comparable, indicating no significant difference in energy intake or BEE sufficiency. Nevertheless, the rate of weight change at hospital discharge was lower in the older group. This may be attributed to the fact that the actual energy consumption in older adults is lower than the BEE calculated by the Harris-Benedict equation, due to reduced lean body mass and activity levels [10,11].

The study found that the prevalence of sarcopenia was higher among adults ≥75 years of age, who are likely to have diminished physical function and reduced activity levels. This discrepancy between the calculated BEE and actual energy consumption may have contributed to the suppressed weight change rate at hospital discharge. Furthermore, both PNI and serum Alb at 3 months postoperatively were lower in older adults. Previous studies have reported that older patients exhibit less recovery in food intake after an initial decline compared to younger patients [12], and that dietary intake decreases by 5%–10% within 1 to 3 months following gastrectomy, a decline that correlates with weight loss [3]. This finding suggests that it is difficult for late-stage

Table 7. Predictive factors of body weight change rate at 3 and 6 months post-surgery

	Univariate analysis			Multivariate analysis		
	Correlation coefficient	95% CI	P-value	Correlation coefficient	95% CI	P-value
Weight change rate at 3 mo post-surgery (%)						
Surgical procedure (TG/DG/PG/other)	−0.23	−0.50 to 0.08	0.140	−0.22	−3.38 to 0.53	0.148
Cancer stage (pStage)	−0.20	−0.47 to 0.11	0.196	−0.06	−2.39 to 1.61	0.695
Sufficiency rate relative to BEE (%)	0.40	0.11 to 0.62	0.009*	0.37	0.03 to 0.35	0.025*
Presence or absence of postoperative adjuvant chemotherapy	0.19	−0.19 to 7.45	0.232	0.30	−4.29 to 5.10	0.862
Weight change rate at 6 mo post-surgery (%)						
Surgical procedure (TG/DG/PG/other)	−0.26	−0.54 to 0.08	0.128	−0.23	−3.11 to 0.28	0.118
Cancer stage (pStage)	−0.18	−0.45 to 0.15	0.279	−0.04	−2.26 to 1.64	0.780
Sufficiency rate relative to BEE (%)	0.34	0.01 to 0.60	0.042*	0.18	−0.07 to 0.34	0.250
Presence or absence of postoperative adjuvant chemotherapy	0.54	3.52 to 11.49	<0.001*	0.45	2.04 to 10.52	0.005*

CI, confidecne interval; TG, total gastrectomy; DG, distal gastrectomy; PG, proximal gastrectomy; pStage, pathological stage; BEE, basal energy expenditure.
*P<0.05.

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older adult patients to improve their food intake once it has decreased. Weight change was suppressed at the time of discharge, but may have become more prevalent thereafter, leading to a delay in improving nutritional status.

In patients aged ≥75 years who underwent gastrectomy, the rate of weight change from discharge to 1 month postoperatively did not differ between the secure and insufficient groups. However, at 3 and 6 months postoperatively, the secure group exhibited a significantly lower rate of weight change. The lack of difference in early postoperative weight change rates may be explained by observations in colorectal cancer surgery, where early postoperative weight change does not correlate with energy intake [13]. Similar trends were observed in this study. Previous reports indicate that nutritional management using intravenous nutrition can reduce early postoperative weight change in gastric cancer patients when the average energy intake exceeds 1,500 kcal/day [14]. In contrast, the sufficient group in the present study had an average energy intake of 769±146 kcal/day, which is considerably lower, suggesting a minimal effect on the rate of weight change at discharge and at 1 month postoperatively.

Conversely, at 3 and 6 months postoperatively, the secure group exhibited a significantly lower rate of weight change. The predictors identified for weight change at 3 and 6 months were the proportion of energy intake during hospitalization relative to BEE and the presence of postoperative adjuvant chemotherapy, respectively. Older patients often experience a prolonged decline in food intake [12], which may compound the effects of gastrectomy and impact long-term weight change.

Previous studies have reported that early administration of nutritional supplements in the postoperative period can suppress weight change 6 to 8 weeks after gastrectomy [6]. Therefore, focusing on achieving a sufficient energy intake during hospitalization may help mitigate long-term weight loss. In this study, the presence of postoperative adjuvant chemotherapy was identified as a predictor of weight loss at 6 months. It has been previously documented that adjuvant chemotherapy can contribute to postoperative weight loss and low body weight [15,16]. The higher frequency of adjuvant chemotherapy in the group with low dietary intake may have influenced the 6-month weight change rate. Given that adjuvant chemotherapy after gastric cancer surgery is typically recommended for 6 months to 1 year [17], weight change at 6 months postoperatively may be linked to whether patients receive chemotherapy.

At 3 months postoperatively, the sufficient group had higher serum Alb levels; however, no significant difference was observed at 6 months. The lower rate of weight change in the sufficient group up to 3 months postoperatively indicates improved nutritional status. Conversely, between 3 and 6 months postoperatively, the rate of weight change did not differ significantly between the maintenance group (–2.1%±3.8%) and the shortage group (–1.0%±5.5%, P=0.347), suggesting that the nutritional status in the insufficient group may have improved over time, leading to an eventual increase in serum Alb levels at 6 months.

The readmission rate after discharge was lower in the secure group. The differences in post-discharge weight change between the secure and insufficient groups may have contributed to the overall differences in outcomes [18].

Although no difference was found in energy intake during hospitalization or in long-term weight change between younger (<75 years) and older (≥75 years) patients, the percentage of energy intake sufficiency relative to BEE during hospitalization was associated with long-term weight change in older adults. Previous studies have demonstrated that intravenous nutrition and oral nutritional supplements after gastrectomy can reduce early postoperative weight change [6,14]. Furthermore, weight changes within the first month post-gastrectomy have been shown to affect weight changes up to 6 months postoperatively [19], underscoring the importance of early nutritional management, such as prompt initiation of enteral nutrition. Based on our findings, early intervention to optimize energy intake during hospitalization may positively impact long-term weight outcomes in post-gastrectomy patients aged ≥75 years.

Limitations

This study was a single-center, retrospective analysis with a limited patient population. The accuracy of oral energy intake measurements was constrained because nutrition was not strictly enforced, and nutritional intake after discharge was not assessed. Future prospective studies with larger cohorts, standardized nutritional assessments, and interventions both during hospitalization and post-discharge are warranted. Although no significant difference in hospital stay was observed among postgastrectomy patients aged ≥75 years, the group receiving sufficient nutritional support tended to have a longer hospital stay (19.0±25.4 days) compared to the group with insufficient support (12.3±6.0 days). This difference in hospital stay may have influenced weight change rates, as appropriate nutritional management is provided during hospitalization. Nonetheless, our study found a negative correlation between the length of hospital stay and weight change rate at discharge (correlation coefficient, –0.62; P<0.001), with no significant correlation at 1, 3, or 6 months postoperatively. Additionally, previous studies have reported that hospital stay is not associated with weight change at 1 or 6 months postoperatively after gastrectomy [19], suggesting that the effect of hospital stay on long-term weight change is minimal.

Conclusion

Energy intake during postoperative hospitalization did not differ between patients <75 years of age and those ≥75 years of age undergoing gastrectomy. However, in patients aged ≥75 years, the adequacy of energy intake relative to BEE during hospitalization was a predictor of weight change at 3 months postoperatively.

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Authors' contribution

Conceptualization: AT. Methodology/Formal analysis/validation: DT, IM, AT. Project administration: AT. Funding acquisition: Not applicable. Writing – original draft: DT. Writing – review and editing: DT, IM, AT. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Contact the corresponding author for data availability.

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Supplementary materials

None.

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Original Article

Effects of enteral nutrition formulas with varying carbohydrate amounts on glycemic control in diabetic mice

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Abstract

Purpose: This study evaluated the effects of an 8-week liquid diets with different carbohydrate contents–64% energy in HINE E-Gel (ST) and 50% energy in HINE E-Gel LC (LC)–on glycemic control and nutritional status in a mouse model of type 2 diabetes mellitus (db/db mice). The objective was to determine whether reducing carbohydrate intake within the Dietary Reference Intakes for Japanese people improves glycemic control indices, addressing the evidence gap in regarding the long-term safety and efficacy of low-carbohydrate enteral nutrition in patients with diabetes.

Methods: db/db mice (n=10 per group) and non-diabetic db/m mice (n=4) as controls were fed ST, LC, or AIN-93G diets ad libitum for 8 weeks. The diets primarily differed in carbohydrate content (64% in ST vs. 50% in LC). Blood glucose and glycated hemoglobin (HbA1c), plasma glucose and glycoalbumin, organ weights, and renal function markers were measured weekly or at 4 and 8 weeks. Histopathological examinations of the liver and kidneys were performed at 8 weeks.

Results: At 8 weeks, the LC group showed significantly lower plasma glucose (P=0.0051) and glycoalbumin (P=0.0013) levels compared to the ST group, with a trend toward lower HbA1c (P=0.0514). Although body weight was significantly higher in the LC group (P=0.0038), there were no significant differences between the ST and LC groups in caloric intake, renal function, or histopathological findings.

Conclusion: Reducing carbohydrate intake to 50% of total energy within dietary guidelines may improve glycemic control in diabetic mice, suggesting the need for further long-term evaluation for clinical applications.

Keywords: Blood glucose; Glycated hemoglobin; Liquid diet; Low-carbohydrate diet; Recommended dietary allowances

Introduction

Background

In nutritional management utilizing enteral nutrition formulas, products with reduced carbohydrate content compared to the standard range (45%–60% energy) may be employed as needed to attenuate post-administration blood glucose spikes [1]. Enteral nutrition products with a lower carbohydrate content (32.4% energy) have been reported to mitigate blood glucose elevations and reduce insulin usage in critically ill patients receiving early enteral nutritional management [2], as well as improve glycemic control in perioperative enteral nutrition patients [3].

The Dietary Reference Intakes for Japanese 2020 were

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established for healthy individuals and populations, with a target carbohydrate level of 50%–65% energy [4]. Accordingly, standard enteral nutrition products are formulated to meet this target for long-term nutritional management. However, insufficient evidence supports the prognosis and safety of long-term use of enteral nutrition products containing carbohydrates below this target [5]. Moreover, a meta-analysis comparing low-carbohydrate and low-fat diets on cardiovascular risk factors found that low-carbohydrate diets resulted in weight loss and triglyceride reduction, while low-density lipoprotein cholesterol levels increased [6].

A consensus statement by the Japan Diabetes Society indicates that no definitive evidence exists for an optimal energy-producing nutrient ratio for the prevention and management of diabetes; thus, individualized and flexible approaches are recommended. As a general guideline, however, carbohydrate energy should comprise 50%–60% (150 g/day or more), protein should account for 20% or less, and the remaining energy should be derived from lipids. If the fat energy ratio exceeds 25%, it becomes crucial to consider the fatty acid composition and adjust by increasing the proportion of polyunsaturated fats [7].

Because prolonged hyperglycemia can lead to various forms of organ damage [8], effective glycemic control is paramount. Consequently, it is important to investigate the effects of long-term administration of standard enteral nutrition formulas in patients requiring stringent glycemic control.

Objectives

This study investigated the effects of an 8-week administration of enteral nutrition formulas, with varying carbohydrate amounts within the target range of the Dietary Reference Intakes for Japanese people, on glycemic control indices and nutritional status in a mouse model of type 2 diabetes mellitus. The test diets were HINE E-Gel (ST) and HINE E-Gel LC (LC), containing 64% and 50% carbohydrate energy, respectively, while being similar in overall composition. A preliminary study (unpublished) in normal animals indicated that a single oral administration of LC produced a significantly lower early-phase increase in blood glucose levels compared to ST.

Methods

Ethics statement

This study was conducted in accordance with the animal experiment guidelines of Otsuka Pharmaceutical Factory, Inc. and was approved by the Otsuka Pharmaceutical Factory Animal Experiment Committee (approval number: OPF-CAE-20-143).

Test diets

The test diets used were HINE E-Gel (ST) and HINE E-Gel LC (LC), which contain 64% and 50% carbohydrate energy, respectively, while being similar in overall composition except for carbohydrate content. Both ST and LC were lyophilized and provided to the animals as powdered diets. For comparison, a standard purified feed, AIN-93G (Oriental Yeast Co., Ltd.), was also used. AIN-93G has an energy ratio of 19.3% protein, 16.7% fat, and 64.0% carbohydrate [9]. In contrast, ST contained 16.0% protein, 19.8% fat, and 64.3% carbohydrate, while LC contained 16.0% protein, 34.0% fat, and 50.0% carbohydrate. The detailed nutrient composition of ST, LC, and AIN-93G [9] is presented in Table 1.

Experimental animals and study design

Six-week-old male BKS.Cg-+ Lepr ^{db}/+ Lepr ^{db}/Jcl mice (db/db mice) (CLEA Japan, Inc.) were used as experimental animals. db/db mice are commonly used as model animals for type 2 diabetes mellitus because they spontaneously develop symptoms of diabetes, such as obesity, overeating, and hyperinsulinemia [10]. BKS.Cg-m+/+Lepr ^{db}/Jcl mice (db/m mice) (CLEA Japan, Inc.), which are closely related to db/db mice but do not develop diabetes, were served as control animals. The mice were maintained at a temperature of 23±3 °C, 55%±15% humidity, and a 12-hour light-dark cycle (light period: 07:00–19:00). During the acclimation period, the mice were fed AIN-93G.

After 12 days of acclimation, the 8-week-old db/db mice were fasted overnight, and glucose was administered orally at 1.0 g/kg body weight. Tail-vein blood glucose levels were measured immediately before administration and at 15, 30, 60, and 90 minutes post-administration using a glucose analyzer (Glutest Mint, Sanwa Kagaku Kenkyusho Co., Ltd.). The area under the curve (AUC) for blood glucose levels was calculated with time on the horizontal axis and blood glucose on the vertical axis. Based on the AUC values, mice were assigned to three groups via stratified randomization using the equal-width method with the statistical analysis software EXSUS Ver. 10 (EP Croit Co., Ltd.): db/db mice fed AIN-93G (DM group, n=4), db/db mice fed the test diet ST (ST group, n=10), and db/db mice fed the test diet LC (LC group, n=10). The grouping results are presented in Tables 2 and 3.

There were no significant differences between groups, confirming that stratified randomization was effective. Similarly aged db/m mice were fed AIN-93G as the CT group (n=4). All animals were provided with the prescribed test diet and water ad libitum for 8 weeks. Food intake was measured before administration and at 4 and 8 weeks after administration. Boby weight and tail-vein blood glucose levels were

Table 1. Nutritional components of test foods

Component	Test food (per 100 kcal)		
	ST	LC	AIN-93G
Protein (g)	4.0	4.0	4.7
Lipid (g)	2.2	3.78	1.86
Saturated fatty acids (g)	0.85	1.33	0.29
MCT (g)	0.64	1.11	-
Monounsaturated fatty acids (g)	0.6	1.4	0.4
n-6 fatty acids (g)	0.39	0.53	-
n-3 fatty acids (g)	0.14	0.25	-
Carbohydrates (g)	16.76	13.25	17.09
Sugars (g)	15.38	11.75	-
Dietary fiber (g)	1.38	1.50	-
Vitamin			
Vitamin B_1 (mg)	0.225	0.225	0.133
Vitamin B_2 (mg)	0.238	0.238	0.159
Niacin (mgNE)	2.25	2.25	-
Vitamin B_6 (mg)	0.30	0.30	0.16
Folic acid (μg)	30	30	53
Vitamin B_{12} (μg)	0.30	0.50	0.66
Biotin (μg)	4.25	4.25	5.31
Pantothenic acid (mg)	1.25	1.25	-
Vitamin C (mg)	52.5	52.5	-
Vitamin A (μg RE)	67.5	67.5	-
Vitamin A (IU)	225	225	106
Vitamin E (mg)	2.38	2.38	1.99
Vitamin D (μg)	1.25	1.25	-
Vitamin D (IU)	50.0	50.0	26.6
Vitamin K (μg)	6.25	6.25	23.9
Mineral			
Sodium (mg)	166.3	166.3	27.6
Sodium (mEq)	7.2	7.2	
Salt equivalent (g)	0.422	0.422	0.070
Chloride (mg)	151.3	194.4	43.3
Chloride (mEq)	4.3	5.5	-
Potassium (mg)	156.3	156.3	95.6
Potassium (mEq)	4.0	4.0	-
Magnesium (mg)	22.5	22.5	13.6
Magnesium (mmol)	0.9	0.9	-
Calcium (mg)	58.8, 1.47	58.8, 1.47	132.8
Calcium (mmol)	1.47	1.47	-
Phosphorus (mg)	82.5	82.5	79.7
Phosphorus (mmol)	2.6	2.7	-
Chromium (μg)	2.88	2.88	26.55
Molybdenum (μg)	5.0	5.0	4.0
Manganese (mg)	0.325	0.325	0.266
Iron (mg)	0.588	0.588	1.195
Copper (mg)	0.080	0.080	0.159
Zinc (mg)	1.20	1.20	1.01
Selenium (μg)	3.25	3.25	4.78
Iodine (μg)	13.8	13.8	5.31
L-carnitine (mg)	-	25	-

ST, HINE E-Gel; LC, HINE E-Gel LC; MCT, medium-chain triglyceride.

measured weekly during the study period. Tail-vein blood and 24-hour urine samples were collected before administration and at 4 and 8 weeks after administration. Following the 8-week collection, the animals were sacrificed by exsanguination after blood collection from the posterior vena cava under isoflurane anesthesia, and necropsy was performed. Tissues including the liver, kidneys, lower limb skeletal muscles, and epididymal fat were collected.

Blood and urine analysis

At baseline, 4, and 8 weeks after administration, a small incision was made in the tail vein with a scalpel, and the exuded blood was used to determine blood glucose levels. The remaining blood was collected into heparin-filled microcentrifuge tubes for glycated hemoglobin (HbA1c) measurement (DCA Vantage, Siemens Healthcare Diagnostics Inc.). Plasma was separated from the necropsy blood. All plasma and urine samples were stored at –80 °C until analysis. Plasma glucose, glycoalbumin, urea nitrogen, total protein, albumin, total cholesterol, triglycerides, as well as urinary albumin and N-acetylglucosaminidase, were measured using an automatic analyzer 7180 (Hitachi High-Tech Corporation).

Histopathological examination

Tissue samples were weighed using a precision balance, and the liver and kidneys were fixed in a 10% neutral buffered formalin solution (pH 7.4). The hematoxylin- and eosin-stained liver and kidney specimens were subsequently examined pathologically. Note that one kidney specimen from the LC group was missing due to technical issues. Hepatocyte lipidosis, glomerulonephritis, and mesangial cell proliferation were graded as "very slight" when 0%–25% of the evaluation area was affected, and as "slight" when 25%–50% was affected.

Statistical analysis

Data are presented as the mean±standard deviation. Repeated measures analysis of variance was employed to compare blood glucose, HbA1c, and body weight at different time points between the ST and LC groups, with group and time point as the two factors. Fisher test was used to analyze histopathological differences in incidence, while the Wilcoxon rank-sum test (a non-parametric test) was used for other comparisons. The CT and DM groups were served as reference groups. A significance level of 5% was used. Statistical analyses were performed using EXSUS Ver. 10 (EP Croit Co., Ltd.) and Bell Curve Ver. 4.00 (Social Survey Research Information Co., Ltd.) for histopathological examinations.

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Table 2. Grouping based on AUC

Group[a]	AUC mean	SD	SE	Median
DM (mg·min/dL) (n=4)	52,170	4,887	2,444	53,505
ST (mg·min/dL) (n=10)	52,289	5,441	1,721	52,395
LC (mg·min/dL) (n=10)	52,099	6,036	1,909	52,384

AUC, area under the curve; SD, standard deviation; SE, standard error; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).
[a]Tolerance range: 2,691.

Table 3. Tukey-type multiple comparison test of AUC

Reference group[a]	Comparison group	t-statistic	P-value	Significance
DM	ST	0.0358	0.9993	NS
DM	LC	−0.0214	0.9997	NS
ST	LC	−0.0756	0.9969	NS

AUC, area under the curve; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC); NS, no significant difference.
[a]Tolerance range: 2,691.

Table 4. Daily calorie intake

Measurement time	CT (n=4)	DM (n=4)	ST (n=10)	P-value	LC (n=10)
Before administration (kcal/day)	13.59±2.64	21.85±2.18	20.79±5.92	0.6484	18.96±8.27
4 wk administration (kcal/day)	15.20±1.91	23.85±1.50	17.55±3.50	0.6229	16.86±1.75
8 wk administration (kcal/day)	14.63±2.16	21.57±2.35	18.03±1.75	0.0533	16.25±2.15

Values are presented as mean±standard deviation.
CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).

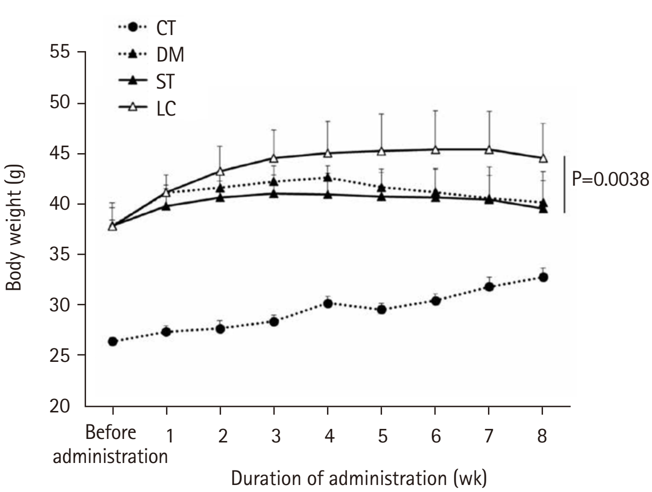

Fig. 1. Weight transition. Vales are presented as mean±standard deviation; ST versus LC (repeated measurement variance analysis). CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).

Results

Caloric intake, body weight, and organ weights

There were no significant differences in daily caloric intake between the ST and LC groups at baseline, 4 weeks, or 8 weeks after administration (Table 4). However, body weight was significantly higher in the LC group compared to the ST group (P=0.0038) (Fig. 1). When organ weights were normalized to body weight, differences were observed between the ST and LC groups in the liver and tibialis anterior muscles, but not in the epididymal fat, kidneys, gastrocnemius, or soleus muscles (Table 5).

Blood glucose control index

At 8 weeks, plasma glucose and glycoalbumin levels were significantly lower in the LC group than in the ST group (P=0.0051 and P=0.0013, respectively) (Table 6). Although HbA1c tended to be lower in the LC group than in the ST group (P=0.0514), no differences in overall blood glucose levels were observed between the two groups (Fig. 2).

Table 5. Tissue weights at 8 weeks after administration

	CT (n=4)	DM (n=4)	ST (n=10)	P-value	LC (n=10)
Tissue weights per body weight (g/kg)					
Epididymal adipose tissue	14.66±1.19	28.56±2.12	27.60±3.06	0.7337	27.40±3.87
Liver	33.19±3.43	49.01±2.80	70.32±4.52	0.0010	61.56±4.21
Kidney	6.72±0.26	6.51±0.58	5.37±0.64	0.9698	5.39±0.68
Gastrocnemius muscle	3.96±0.16	1.71±0.19	1.62±0.26	0.4274	1.49±0.13
Soleus muscle	0.16±0.03	0.12±0.03	0.11±0.02	0.4727	0.11±0.03
Tibialis anterior muscle	1.50±0.05	0.64±0.09	0.63±0.05	0.0091	0.56±0.04
Absolute tissue weights (g)					
Epididymal adipose tissue	0.465±0.036	1.102±0.055	1.077±0.159	0.0640	1.193±0.151
Liver	1.056±0.141	1.900±0.218	2.731±0.136	0.6232	2.693±0.307
Kidney	0.213±0.014	0.251±0.011	0.208±0.018	0.0140	0.235±0.025
Gastrocnemius muscle	0.126±0.003	0.066±0.009	0.063±0.009	0.6232	0.065±0.005
Soleus muscle	0.005±0.001	0.004±0.001	0.004±0.001	0.3840	0.005±0.001
Tibialis anterior muscle	0.047±0.003	0.025±0.002	0.025±0.002	0.7052	0.025±0.002

Values are presented as mean±standard deviation.
CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).
ST versus LC (Wilcoxon two-group comparison test).

Table 6. Blood glucose control indicators

	Measurement time	CT (n=4)	DM (n=4)	ST (n=10)	P-value	LC (n=10)
Plasma glucose (mg/dL)	8-wk administration	287.8±27.4	870.0±89.1	1,034±167.3	0.0051	857.8±69.0
Plasma glycoalbumin (%)	8-wk administration	3.2±0.3	11.6±0.9	12.1±1.5	0.0013	9.4±0.9
HbA1c (%)	Before administration	4.18±0.05	6.88±0.21	6.67±0.31	0.0514	6.60±0.34
	4-wk administration	4.33±0.10	13.48±0.56	12.72±0.95		12.13±1.47
	8-wk administration	4.25±0.13	13.53±0.66	13.06±0.83		11.83±1.08

Values are presented as mean±standard deviation.
CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC); HbA1c, glycated hemoglobin.
ST versus LC (Wilcoxon two-group comparison test).

Renal function-related indices

Urinary albumin and N-acetylglucosaminidase levels showed no significant differences between the ST and LC groups at 8 weeks after administration (Table 7).

Blood biochemistry

At 8 weeks, no significant differences were observed between the ST and LC groups in total protein, albumin, or triglycerides. However, blood urea nitrogen was significantly higher in the ST group than in the LC group (P=0.0058), and total cholesterol was significantly higher in the LC group than in the ST group (P=0.0125) (Table 8).

Histopathological examination

In the liver, lobular-centered, very slight hepatocyte lipidosis was observed in all four mice in the DM group, in nine of 10 mice in the ST group, and in seven of 10 mice in the LC group; additionally, slight lipidosis was observed in three of 10 mice in the LC group. Very slight glomerulonephritis and mesangial cell proliferation in the kidneys were observed in two of four mice in the DM group, three of 10 mice in the ST group, and three of nine mice in the LC group. The incidences of hepatocyte lipidosis, as well as very slight glomerulonephritis and mesangial cell proliferation in the kidneys, did not differ significantly between the ST and LC groups.

Discussion

Interpretation/comparison with previous studies

The comparison between the CT and DM groups, established to confirm that the groups accurately represent the disease state of diabetes mellitus, demonstrated that the DM group consistently exhibited higher blood glucose and HbA1c levels than the CT group throughout the evaluation period, confirming the onset of diabetes mellitus. There was no significant difference in caloric intake between the ST and LC groups at any time point (before administration and at 4 and 8 weeks post-administration). Similarly, no significant differences in blood glucose levels were observed between the ST and LC groups at these time points; however, HbA1c tended to be lower in the LC group (P=0.0514). Glycoalbumin—a potentially more useful marker than HbA1c for assessing whether blood glucose levels remain within a target range, as it reflects variations in postprandial blood glucose in addition to mean levels [11]—was significantly lower in the LC group than in the ST group at 8 weeks post-administration. Plasma glucose was also significantly lower in the LC group. In our preliminary study comparing blood glucose levels in normal animals after a single oral administration of ST and LC, blood glucose levels were significantly lower in the LC group than in the ST group during the early phase of administration (unpublished). In this study, blood glucose levels were measured at fixed intervals after feeding, suggesting that variations in the degree of blood glucose elevation during feeding accumulated over time and were reflected in the differences observed in HbA1c and glycoalbumin levels.

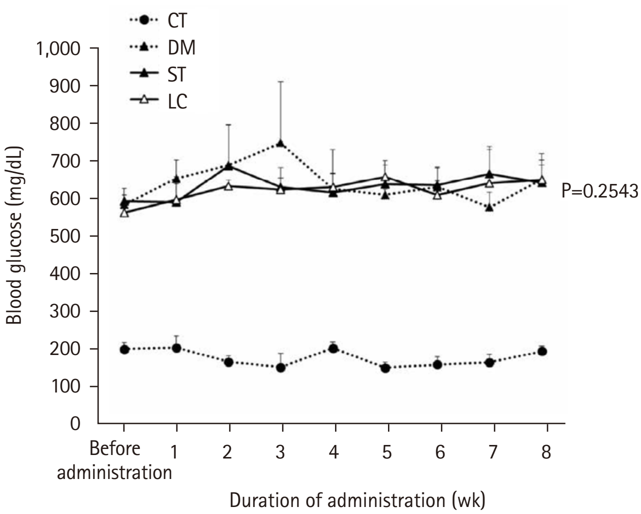

Fig. 2. Changes in blood sugar levels from time to time. Vales are presented as mean±standard deviation. CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).

A study using diabetic mice observed differences in HbA1c after feeding diabetic model mice (Akita mice) diets with widely varying carbohydrate contents (68% vs. 16% energy ratio) for 8 weeks [12]. Furthermore, STZ-induced diabetic model mice were fed diets with carbohydrate energy ratios of 75, 20, 15, and 1% for 14 weeks. Lower carbohydrate ener-

Table 7. Renal function tests

	Measurement point	CT (n=4)	DM (n=4)	ST (n=10)	P-value	LC (n=10)
U-ALB (μg/kg)	Before administration	922±279	12,640±3,763	13,650±6,413	0.6776	13,174±3,926
	4-wk administration	512±229	10,970±2,544	6,360±1,463	0.3447	7,142±1,697
	8-wk administration	458±210	13,908±4,173	6,934±2,087	0.7337	7,282±2,113
U-NAG (IU/kg)	Before administration	2.59±0.93	2.93±0.42	2.96±0.56	0.5205	2.78±0.68
	4-wk administration	3.05±0.47	2.63±0.50	1.07±0.25	0.1859	1.15±0.15
	8-wk administration	3.23±1.08	2.65±0.46	1.06±0.21	0.4727	1.15±0.26

Values are presented as mean±standard deviation.
CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC); U-ALB, urinary albumin; U-NAG, urinary N-acetylglucosaminidase.
ST versus LC (Wilcoxon two-group comparison test).

Table 8. Blood biochemistry tests (after 8 weeks of administration)

Variable	CT (n=4)	DM (n=4)	ST (n=10)	P-value	LC (n=10)
Total protein (g/dL)	4.95±0.17	6.00±0.39	6.05±0.29	0.0848	6.29±0.27
Albumin (g/dL)	3.10±0.08	3.68±0.19	3.93±0.18	0.2769	3.91±0.29
Blood urea nitrogen (mg/dL)	18.0±2.2	23.4±2.3	29.2±6.2	0.0058	22.2±3.7
Total cholesterol (mg/dL)	107.5±13.1	146.0±11.5	129.1±16.3	0.0125	155.2±26.6
Triglycerides (mg/dL)	37.3±13.2	121.5±51.2	155.5±61.8	0.6232	148.0±71.7

Values are presented as mean±standard deviation.
CT group, control group; DM group, db/db mice fed AIN-93G; ST group, db/db mice fed the test diet ST (HINE E-Gel); LC group, db/db mice fed the test diet LC (HINE E-Gel LC).
ST versus LC (Wilcoxon two-group comparison test).

gy ratios were associated with reduced postprandial blood glucose levels, and the glucose AUC during the glucose tolerance test was also lower. Additionally, significant differences were noted between the groups with the lower carbohydrate energy ratios (20% and 15%) [13]. In a human study, it was reported that over 14 days, diets with widely different carbohydrate contents (approximately 10% vs. 75% energy) resulted in higher blood glucose levels and poorer glucose tolerance in the high-carbohydrate group [14]. Thus, the difference in carbohydrate energy ratio between ST and LC (64% vs. 50%) in this study may have affected glucose tolerance, leading to the observed differences in plasma glucose and glycoalbumin levels.

The present results suggest that even a modest difference in carbohydrate content in enteral nutrition formulas, such as a 64% versus 50% energy ratio, can produce measurable differences in plasma glucose and glycoalbumin, which are key indicators of glucose control, after a period of management. Recently, cases of ketoacidosis have been reported in patients who are on extremely low-carbohydrate diets and are taking SGLT2 inhibitors [15]. We hypothesize that reducing carbohydrate intake within the dietary reference intakes could be beneficial for preventing ketoacidosis and controlling blood glucose in these patients.

Long-term nutritional management requires attention not only to glycemic control indices but also to other nutritional parameters. Plasma total protein and albumin, which are standard nutritional indices, did not differ between the ST and LC groups, suggesting that whole-body protein metabolism was similar in both groups. The body weight of the LC group was significantly higher than that of the ST group, despite similar daily caloric intakes between the two groups at all time points (before, 4 weeks, and 8 weeks post-administration). When normalized to body weight, organ weights showed no differences in epididymal fat and lower limb skeletal muscle, except for the tibialis anterior muscle, between the ST and LC groups. Body weight is maintained when caloric intake equals caloric expenditure. Although the ST and LC groups had similar caloric intakes, carbohydrates require more energy for diet-induced thermogenesis compared to fats. This may explain why the LC group, with its lower carbohydrate intake, exhibited a higher body weight than the ST group. However, this difference in body weight may not have been sufficient to produce differences in organ weights normalized to body weight. Body weight and composition are as critical as blood glucose levels in managing diabetes mellitus; therefore, future studies should examine changes in these parameters in detail.

In this study, differences in carbohydrate content among the test diets were balanced by adjusting the fat content; thus, the effects of fat intake must be considered in long-term management. Liver histopathology revealed no evidence of accelerated hepatocyte lipogenesis in the LC group, suggesting that the impact of increased fat content on liver fat accumulation was minimal. Liver weight normalized to body weight was significantly higher in the ST group than in the LC group, likely attributable to weight loss in the ST group. Plasma total cholesterol levels were significantly higher in the LC group compared to the ST group; however, these levels were similar to those in the DM group, and no differences in triglyceride levels were observed between the two groups. In the LC group, the fat content was primarily composed of medium-chain fatty acids and monounsaturated fatty acids. Since monounsaturated fatty acids are known to improve lipid metabolism [16], the impact of fat content on these parameters is likely minor.

Since hyperglycemia can damage various organs [8], renal function was evaluated, and renal histopathological examinations were performed. The mouse models of diabetes mellitus used in this study exhibit pathologies similar to progressive diabetic kidney disease, including increased urinary albumin and mesangial substrate [10], paralleling human pathology, where urinary albumin excretion further increases as the disease progresses [17]. The DM group, serving as the reference, was used to evaluate both renal function and histopathological changes. As expected, the DM reference group exhibited significantly higher levels of urinary albumin and N-acetylglucosaminidase compared to the ST and LC groups. The low urinary albumin levels in the ST and LC groups suggest a milder disease progression. Because restricted feeding is known to improve renal parameters [18], the reduced caloric intake or variations in the composition of the test diets likely contributed to mitigating the symptoms. The LC group exhibited urinary albumin and N-acetylglucosaminidase levels comparable to those of the ST group. Moreover, no significant differences were observed in renal histopathology between the ST and LC groups, suggesting that the test diets exerted a similar impact on the kidneys. However, the long-term progression of diabetic nephropathy remains unclear and warrants further investigation. The protein sources for the test diets were soybean peptide and collagen peptide in the ST and LC groups, and casein (AIN-93G) in the DM group. Soybean peptide has been reported to improve glucose metabolism by increasing GLUT4 expression in skeletal muscle more effectively than casein [19]. Additionally, one report suggests that protein quality is more critical than quantity in preserving renal function, noting a reduced risk of end-stage renal failure when the protein source was switched

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to soy [20]. Therefore, it is important to consider both carbohydrate content and protein source when evaluating the effects of diet on glycemic control and renal function in diabetes mellitus.

Limitations

The limitations of this study include the 8-week evaluation period and the potential effects of the test diets on caloric intake. For applications beyond the study period, careful administration is necessary, and a longer-term evaluation is required to clarify the effects on glycemic control, nutritional status, and renal disorders. Further studies involving both young and aged animals, which are not pathological models, are necessary for clinical translation. ST and LC are enteral nutrition formulas developed for humans; in this study, they were powdered and used as test foods. Consequently, it is possible that mice disliked the taste and odor of these test diets, which may have affected caloric intake during ad libitum feeding. Since no differences in caloric intake were observed between the ST and LC groups at any time point (before, 4 weeks, and 8 weeks post-administration), comparisons between the two groups are considered valid. However, for a more rigorous nutritional assessment, equalizing the caloric intake between the three groups (DM, ST, LC) is necessary in a mouse model of type 2 diabetes mellitus.

Conclusion

This study demonstrated that reducing carbohydrate intake within the range of the Dietary Reference Intakes for Japanese people may lower plasma glucose and glycoalbumin levels—key indices of glycemic control—in diabetic mice. Further long-term evaluations are needed.

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Authors' contribution

Conceptualization: KH. Methodology: YM, KH. Formal analysis/validation: YM, KH. Project administration: KH. Funding acquisition: Not applicable. Writing – original draft: YM. Writing – review and editing: YM, KH. All authors read and approved the final manuscript.

Conflict of interest

YM and KH are employees of Otsuka Pharmaceutical Factory, Inc. Except for that, no potential conflict of interest relevant to this article was reported.

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Data availability

Research data are available from the corresponding author upon reasonable request.

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Supplementary materials

None.

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Abbreviations should be avoided as much as possible. One word should not be expressed through an abbreviation, although more than two words may be expressed through an abbreviation. The full term for which the abbreviation stands should be used at its first occurrence in the text. Abbreviations should not be present in the title. Common abbreviations, however, may be used, such as DNA.

Units
The use of International Standardized (SI) units is encouraged. These are available at NIST (https://physics.nist.gov/cuu/Units/index.html). Arabic numbers should be used, and all units use SI units (International System of Units). Use a comma after thousands (e.g., 10,000).

Machines and equipments
When the use of reagents or devices is reported in the text, the name of the manufacturer should be indicated. Regarding devices, reagents, and medicine, information on the manufacturing company should be provided in parentheses.

Statistics
Statistical methods must be described, and the program used for data analysis and its source should be stated.

Original articles

The manuscripts for original articles should be organized in the following order: Title page, Abstract, Main text, References, Tables, Figure legends, and Figures.

Title page
- The title page must include the article title, the authors' names (including ORCID), affiliations, corresponding authors' names and contact information, running title, and declarations.
- Authors and affiliations: First, middle, and last names should be included for each author. For authors with different affiliations, the authors should be marked "1," "2," "3," and so forth in Arabic numerals, which should appear in superscript at the top-right-hand corner of the author's name and before the affiliation.
- ORCID: We recommend that the ORCIDs of all authors be provided. To have an ORCID, authors should register on the ORCID website (https://orcid.org). Registration is free to every researcher in the world.
- Corresponding author: The corresponding author's name and e-mail address should be included.
- Running title: A running title of less than 50 characters, including letters and spaces, should be included in English. If the included running title is inappropriate, the Editorial Board may revise it.
- Article information:
  - Conflict of interest: If there are any conflicts of interest,

authors should disclose them in the manuscript. Disclosures allow editors, reviewers, and readers to approach the manuscript with an understanding of the situation and background of the completed research. Please consult the COPE Guidance (https://publicationethics.org/) on conflict of interest. If there are no conflicts of interest, authors should include the following sentence: "The authors of this manuscript have no conflicts of interest to disclose."

- Funding: Funding for the research should be provided here. Providing a FundRef ID is suggested, including the name of the funding agency, the country, and, if available, the number of grants provided by the funding agency. If the funding agency does not have a FundRef ID, please ask the agency to contact the FundRef registry (fundref.registry@crossref.org). A detailed description of the FundRef policy can be found on the Crossref website (https://www.crossref.org/services/funder-registry/).
- Authors' contribution: The journal uses the CRediT taxonomy to define authors' contribution. Each author on a paper may have one or more CRediT contribution roles. CRediT author contribution statements should be provided during the submission. More details on CRediT are available at https://credit.niso.org/

  [Examples of CRediT author statement]
  Conceptualization: OOO, OOO. Data curation: OOO, OOO. Formal analysis: OOO, OOO. Funding acquisition: OOO, OOO. Investigation: OOO, OOO. Methodology: OOO, OOO. Project administration: OOO, OOO. Resources: OOO, OOO. Software: OOO, OOO. Supervision: OOO, OOO. Validation: OOO, OOO. Visualization: OOO, OOO. Writing–original draft: OOO, OOO. Writing–review & editing: OOO, OOO. (OOO: initial of author)

- Acknowledgments: Persons or institutes that contributed to the paper but did not meet the criteria for authorship are acknowledged here.
- If any sections are irrelevant to the manuscript, please include the heading and write "Not applicable." for that section.

Abstract

All manuscripts should contain a structured abstract. Abstracts should have the following headings: Purpose, Methods, Results, and Conclusion. Reference quotations must not be included in the abstract. A maximum of 5 keywords should be listed immediately after the abstract in alphabetical order. These words should be drawn from the Medical Subject Heading (MeSH) terminology in the United States National Library of Medicine's (NLM) (https://www.nlm.nih.gov/oet/ed/mesh/meshondemand.html). The first letter of the keyword should be capitalized, and the remaining letters should be lowercase; a semi-colon should separate them without a period at the end of the last word.

Main text

The main text of the original article should include Introduction, Methods, Results, and Discussion sections.

- Introduction should provide a brief background and aims of the study.
- Methods should provide your selection of the observational or experimental participants, including eligibility and exclusion criteria and a description of the source population in the case of clinical research. In addition, it should provide statistical methods and references and brief descriptions of methods that have been published. Give reasons for using new or modified methods. Clinical trial studies should be presented with the approval of the Institutional Review Board (IRB) and informed consent from patients enrolled in that trial. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.
- Results are listed according to the order of figures and tables presenting the study results. Do not repeat all data in the figures or tables in the text of the results section and emphasize the critical results briefly.
- Discussion should be limited to essential aspects of the study that follow from them. Do not detail the data or previously given information in the Results section. Avoid content unrelated to the results. In the Discussion section, the conclusion should be presented in a clear and concise manner and help the reader understand why your research should matter to them after they have finished reading the paper. A conclusion is not merely a summary of your points or a restatement of your research problem but a synthesis of key points.

References

- References should be numbered consecutively in the order in which they are first mentioned in the text.
- References should be identified in text with full-size Arabic numerals on the line and in square brackets [ ].

- Up to six authors may be listed. References with seven or more authors should list only the first six followed by "et al." Names should be separated by a comma and one space.
- Journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/). Journal titles that are not listed in the NLM Journal Catalog should follow the ISO abbreviation as described in Access to the LTWA (List of Title Word Abbreviations; https://www.issn.org/services/online-services/access-to-the-ltwa).
- If not specified below, the references should follow the ICMJE reference style (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

[Examples of reference style]

- Journal
  Lim CS, Kim H, Han IW, Yun WG, Go E, Lee J, et al. Incidence and risk factors of nonalcoholic fatty liver disease after pancreaticoduodenectomy in Korea: a multicenter retrospective cohort study. Ann Clin Nutr Metab 2024;16:125-33.
- Book
  DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. Vol 2. 4th ed. Lippincott; 1998.
- Chapter in book
  Ginberg RJ, Kris MG, Armstrong JG. Cancer of the lung. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. Vol 2. 4th ed. Lippincott; 1993. 673-758.
- Electronic format
  Ang SW, Liew J, Dharmaratnam VM, Yik VY, Kok S, Aftab S, et al. Diagnostic performance of various radiological modalities in the detection of sarcopenia within Asian populations: a systematic review. Ann Coloproctol 2024 Dec 20 [Epub].
  https://doi.org/10.3393/ac.2024.00080.0011
- Web sites
  Sage Terapeutics. A study with SAGE-547 for super-refractory status epilepticus [Internet]. U.S. National Library of Medicine; 2022 [cited 2024 Nov 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT02477618?term=NCT02477618&rank=1

Tables and figures

ACNM publishes in full color and encourages authors to use color to increase the clarity of figures. An individual should not be recognizable in photographs or X-ray films provided at the time of submission. Authors must submit figures and illustrations as electronic files. Images must be provided in PPT, JPG, TIF, or PDF format. Each figure must be of good quality, have a resolution higher than 600 dpi, and have good contrast and sharpness. Submit files of figures and photographs separately from the text of the paper. Number figures as "Figure Arabic numeral" in the order of their citation (e.g., Fig. 1). If a figure is divided into more than two images, mark each figure with Arabic numerals and a capital letter (e.g., Fig. 1A, Fig. 1B). Authors should submit line drawings in black and white. Figures should be explained briefly in the titles. Explain all nonstandard abbreviations in footnotes, and use the following symbols in sequence: a, b, c, d (e.g., Rad, radiation; Chemo, chemotherapy; NS, not significant. *P<0.001). The brief title of tables and figures should be described as the verse or phrase in the above line of tables and the section of figure legends, respectively. Only the first character of the title should be capitalized. The first character of each cell in tables is also capitalized. Figure legends must describe all abbreviations and acronyms used in the figure. This section should be typed on a separate page.

Case reports

Case reports describe unique and instructive cases that make an important teaching point or scientific observation, novel techniques, use of new equipment, or new information on diseases that are important to clinical nutrition and metabolism. The manuscripts for case reports should be organized in the following order: Introduction, Case report, Conclusion, and References.

Guidelines

The clinical practice guidelines are usually invited. Clinical practice guidelines are systematically developed statements or recommendations intended to help clinicians and patients make decisions about appropriate healthcare in specific clinical circumstances. A structured abstract is required. The main text is recommended to be described according to the AGREE statement at https://www.agreetrust.org/.

Reviews

Reviews are usually requested by the Editor in Chief. However, unrequested reviews could be considered after contacting the Editor in Chief by e-mail to determine the appropriateness of the review to ACNM. The abstract must have the following headings: Purpose, Current concept, and Conclusion. The main text comprises the Introduction, Main body, and Conclusion sections. Otherwise, it keeps the style and format of the original articles, but the details may be more flexible depending on the contents.

Interesting images

The "Interesting images" section presents clinically interesting or informative images regarding nutrition or metabolism. The section is intended to share experiences and relevant commentary rather than report a specific case or study. The section should include the title, authors' names and affiliations, main text, images, image legends, keywords, and references.

Editorials

Editorials provide invited perspectives on an area of clinical nutrition and metabolism, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required, and a brief unstructured text should be prepared. Although editorials are usually invited or written by an Editor, unsolicited editorials may be submitted.

Letter to the editor

Letters to the Editor should include brief constructive comments concerning a published article, a short, freestanding opinion, or a short, interesting case. Letters to the Editor should be submitted no more than 1 year after the relevant paper has been published. Responses from the author of the relevant paper may be provided. The responses should have the same format as Letters to the Editor.

Table 1 summarizes each publication type's key features and word count limit. The length of each article is negotiable with the editor-in-chief.

Table 1. Key features and word count limits of publication type

Type of article	Abstract (words)	Text (words)[a]	References	Tables and figures
Original article	Structured, 250	3,000	40	10
Review article	Structured, 250	5,000	50	10
Case report	200	1,500	20	10
Guidelines	Structured, 250	5,000	100	15
Interesting images	NR	800	10	5
Editorial	NR	1,500	10	5
Letter to the editor	NR	1,000	10	5

NR, not required.
[a]The length of each article is negotiable with the editor-in-chief.

Reporting guidelines

Authors should follow the relevant reporting guidelines for specific study designs, such as randomized controlled trials, diagnostic accuracy studies, meta-analyses, observational studies, and non-randomized studies. Recommended sources include the EQUATOR Network (https://www.equator-network.org/) and the National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html).

Annals of Clinical Nutrition and Metabolism requires compliance with the reporting guidelines summarized in Table 2 for the listed article types. For other study design and reporting guidelines, contact the editorial office at https://e-acnm.org/about/contact.php.

Table 2. Reporting guidelines for specific study designs

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	https://www.equator-network.org/reporting-guidelines/consort/
TREND	Non-randomized controlled study	https://www.cdc.gov/trendstatement/index.html
STROBE	Observational studies	https://www.equator-network.org/reporting-guidelines/strobe/
STARD	Diagnostic/prognostic studies	https://www.equator-network.org/reporting-guidelines/stard/
PRISMA	Systematic reviews and meta-analyses	https://www.equator-network.org/reporting-guidelines/prisma/
CARE	Case reports	https://www.equator-network.org/reporting-guidelines/care/
AGREE	Clinical practice guidelines	https://www.equator-network.org/reporting-guidelines/the-agree-reporting-checklist-a-tool-to-improve-reporting-of-clinical-practice-guidelines/

PEER REVIEW AND EDITORIAL PROCESS OF ACCEPTED MANUSCRIPTS

It is available at: https://e-acnm.org/policy/publish_policy.php#1

ARTICLE PROCESSING CHARGE

It is available at https://e-acnm.org/authors/processing_charge.php.

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