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REVIEW ARTICLE

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Role of nutrition in gastroenterological surgery

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Abstract

Nutrition plays important roles in recovery after gastroenterological surgery. Severe surgical stress increases muscle breakdown and lipolysis, thereby accelerating wound healing and enhancing host defense against microbes. Malnourished patients have insufficient amounts of muscle and body fat. Therefore, they may not appropriately respond to surgical stress. Perioperative nutritional therapy maintaining nutritional status reduces postoperative complications and accelerates recovery after surgery, particularly for malnourished patients. In addition, perioperative oral or enteral nutrition is now recommended for preserving host defense mechanisms against microbes. Lack of enteral nutrition impairs gut and hepatic immunity, systemic mucosal defense and peritoneal host defense, even when nutrient amounts supplied by parenteral nutrition are adequate. Thus, surgeons should avoid no oral or enteral nutrition periods. Supplemental administration of specific nutrients such as glutamine, arginine and ω-3 fatty acids is termed "immunonutrition", and is expected to reduce the morbidity of infectious complications and length of hospital stay. Nutritional therapy is important even after discharge to maintain body weight and compensate for abnormalities in the digestion and absorption of nutrients. Understanding the significance of nutrition in gastroenterological patients leads to better outcomes.

KEYWORDS
enteral nutrition, gut immunity, immunonutrition, nutritional status, parenteral nutrition

1 | INTRODUCTION

Gastroenterological surgeons do their best to cure disease and/or to relieve the symptoms of patients by applying the best available surgical techniques. Regardless of the types of surgical procedures, it is hoped that the patients will recover as rapidly as possible without suffering from postoperative complications. Patients are also recommended to return to normal daily activities after discharge. However, because gastroenterological surgery involves direct manipulation of the gastrointestinal (GI) tract and/or hepatobiliary and pancreatic organs, patients may not be able to ingest adequate amounts of food after surgery. In some cases, restarting oral food intake is postponed until day 7. In the worst scenario, anastomotic leakage or a surgical site infection develops, such that patients cannot ingest food for several weeks. Moreover, due to gastrointestinal symptoms, patients sometimes cannot ingest appropriate amounts of food, leading to malnutrition before surgery. Thus, gastroenterological surgery is accompanied by a risk of malnutrition during the perioperative period. Even after discharge, some surgical procedures may cause prolonged nutritional disorders.

In this review, the following items are addressed and the results summarized: (a) significance of nutritional status; (b) nutritional aspect of enhanced recovery after surgery (ERAS®) program; (c) special

nutritional formulas for preventing postoperative complications; and (d) nutritional therapy after discharge.

2 | SIGNIFICANCE OF NUTRITIONAL STATUS

Nutritional status has been demonstrated to have a major impact on the morbidity of postoperative complications and the length of hospital stay.[1] Modern options for surgical procedures are often minimally invasive. Such procedures can be chosen on condition that patients will likely benefit, as well as extended procedures in terms of curability. However, minimally invasive procedures do not provide beneficial effects in terms of patient recovery if surgeons do not take systemic conditions, such as nutritional status, into account.

Why is nutritional status so important? The human body needs adenosine triphosphate (ATP) for all of life's activities. ATP is produced via sophisticated chemical reactions in cells using carbohydrates, lipids and proteins (amino acids). Because we do not continuously receive nutrition from the external environment, we consume nutrients stored in our bodies when not ingesting food. Thus, patients may survive even severe surgical insults without any nutritional therapy if they are well nourished and no severe complications occur. Unfortunately, many patients undergoing gastroenterological surgery may be malnourished before the operation due to cancer cachexia and/or GI tract symptoms. Thus, appropriate nutritional management must be mandatory for malnourished patients beginning with the preoperative period.

Nutrition is, of course, important not only as an energy source but also for regeneration of tissue and proliferation of cells. It is reasonable that wound healing is delayed and appropriate host defense against microbial invasion does not function in states of malnutrition.

Under stress-free conditions, simple starvation lowers human metabolic rate and the primary energy source changes from glucose to fat, thereby preventing catabolism of muscle protein. This metabolic alteration is reflected by reduced nitrogen excretion into urine. However, surgical stress activates host responses aimed at preventing hostile microbial invasion, accelerating wound healing and providing energy and amino acids to vital organs (Figure 1). Otherwise, patients could not survive these insults. The human body provides energy and materials for the enhanced host response by breaking down muscle protein in addition to fat. If external nutrition provision is inadequate or absent, patients instantly lose large amounts of muscle, delaying restoration of daily activities and/or increasing the risk of respiratory complications.

2.1 | Pitfalls of nutritional assessment

Given the importance of nutrition in surgery, one of the first steps in evaluating the tolerability of an operation for patients is nutritional screening and assessment. Many evaluation methods have been developed and used in clinical settings (Table 1).[2] Yet, the optimal method has yet to be determined. Subjective global assessment is a simple and reliable method of assessing nutritional status, for which no special instruments or measurements are needed. Basic anthropometric measurements including body mass index, muscle mass of the extremities, subcutaneous fat, body weight change, the presence of GI tract symptoms, and food intake changes are determinants of nutritional status. However, the accuracy may depend on evaluators' experiences and competence.

Serum albumin levels have been favorably used as a screening tool for nutritional status in Japan. However, we should recognize that serum albumin level is a marker of systemic inflammation and is not a good reflection of nutritional screening results.[3] The reasons are that, first, the half-life is long (3 weeks), second, production is reduced while excretion is enhanced, in association with liver dysfunction and renal insufficiency, and finally, redistribution occurs under increased vascular permeability which is often observed under stressful conditions. Thus, albumin should not be used for nutritional screening and assessment in patients with acute diseases.

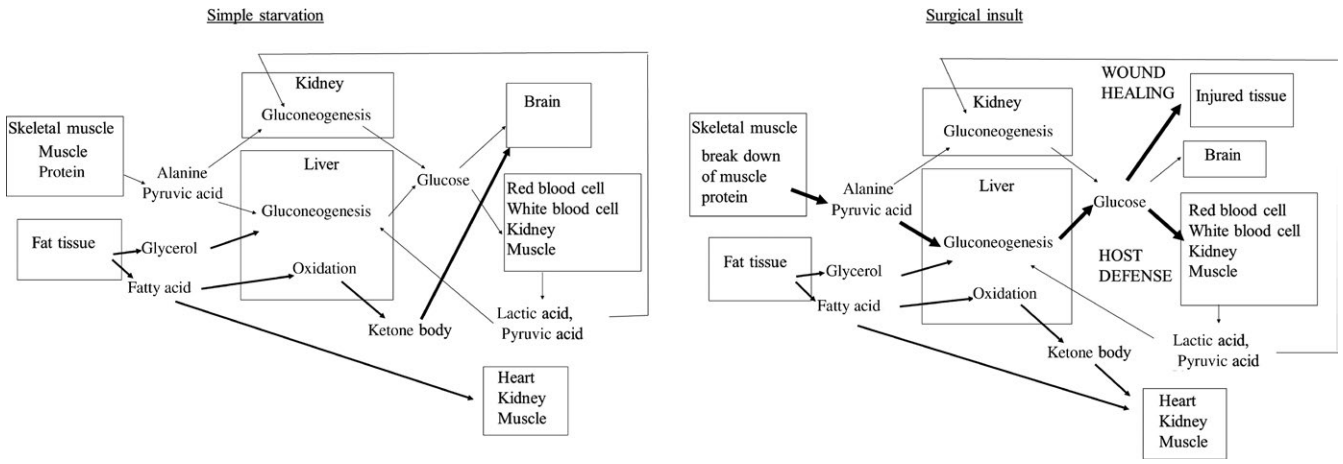

FIGURE 1 Metabolism under simple starvation and surgical insult. Under simple starvation, muscle protein breakdown is spared; however, stress markedly increases its breakdown

TABLE 1 Nutritional assessment tool and prognostic nutritional index

Nutritional assessment tool
SGA: Subjective global assessment
MUST: Malnutrition universal screening tool
NRS-2002: Nutritional risk score
MNA: Mini-nutritional assessment
CONUT: Controlling nutritional status
Prognostic nutritional index
Onodera's prognostic nutritional index
PINI: Prognostic inflammatory and nutritional index

3 | NUTRITIONAL ASPECT OF ENHANCED RECOVERY AFTER SURGERY (ERAS®) PROGRAM

The European Society for Clinical Nutrition and Metabolism (ESPEN) has established a new concept of perioperative management for early recovery after surgery. So-called ERAS® is an abbreviation of enhanced recovery after surgery and a collection of protocols which have been separately proposed and utilized for the management of patients during the perioperative period.[4] This concept is now prevalent worldwide. ERAS® was initially applied to colonic surgery and has recently been extended to upper GI tract surgery and hepatobiliary pancreatic operations.[5,6] According to clinical reports, ERAS® markedly shortens hospital stays without increasing the morbidity of postoperative complications or the readmission rate.

Table 2 demonstrates the main protocols involved in ERAS®.[4] It is not necessary to apply all of these items in order to introduce ERAS®. As shown in the figure, protocols aimed at minimizing the period of no-intake-of-food by mouth are an important part of ERAS®. The reasons why lack of enteral or oral nutrition should be avoided in surgical patients are detailed below.

3.1 | Significance of oral/enteral nutrition

Before establishment of total parenteral nutrition (TPN), increased metabolic demand after major surgery could not be compensated by peripherally administered solutions. Many patients who received major surgery developed malnutrition and their outcomes were poor. TPN has enabled us to provide patients with sufficient amounts of nutrients even when the GI tract is not available for nutrition provision. Consequently, surgeons have options for preventing the progression of malnutrition. There is no question as to the value of the contributions of TPN to gastroenterological surgery.

However, aggressive basic and clinical research has revealed that lack of enteral nutrition, even when an appropriate amount of nutrition is provided parenterally, causes various impairments of host defense mechanisms against pathogens.[7–10] Table 3

TABLE 2 ERAS® protocols

Nutrition-associated items
Perioperative oral nutrition
Stimulation of gut motility
Prevention of nausea and vomiting
No bowel preparation
Fluid and carbohydrate loading/no fasting
Preoperative management-associated items
Pre-admission counseling
No nasogastric tube
No premedication
Intraoperative management-associated items
Mild-thoracic epidural anesthesia/analgesia
Short-acting anesthetic agent
Warm air body, heating in theater
Short incisions, no drains
Avoidance of sodium/fluid overload
Postoperative management-associated items
Non-opiate oral analgesics/non-steroidal anti-inflammatory drugs
Early removal of catheters
Routine mobilization care pathway
Audit of compliance/outcome

TABLE 3 Influences of nutrition routes on host defense mechanism

	Enteral	Parenteral
Gut immunity		
Gut-associated lymphoid tissue cell number	Preserved	Reduced
Gut cytokine milieu	Th2 dominant	Th1 dominant
Gut immunoglobulin A (IgA) level	Preserved	Reduced
Systemic mucosal immunity		
Respiratory tract IgA level	Preserved	Reduced
Resistance against viruses and bacteria	Good	Bad
Hepatic immunity		
Hepatic mononuclear cell number	Preserved	Reduced
Intracellular signaling activation	Responsive	Blunted
Cytokine production	Responsive	Blunted
Survival in portal bacteremia	Good	Bad
Peritoneal host defense		
Resident macrophage number	Preserved	Reduced
Exudative neutrophil number	Preserved	Reduced
Nuclear factor-κB activation	Responsive	Blunted
Cytokine production	Responsive	Blunted
Survival in bacterial peritonitis	Good	Bad

summarizes the influences of nutrition routes on host defense mechanisms.

3.2 | Gut barrier system

The gut lumen harbors tremendous numbers of microbes and toxins. Only one layer of gut epithelial cells forms the borderland of the sterile gut submucosal space and the non-sterile gut lumen. Tight junctions between the epithelial cells, and the epithelial cells themselves, form a physiological barrier to luminal microbes and toxins. A rat feeding model clarified that 15% of total energy supply through the enteral route can maintain gut morphology to the level of that in fully enterally fed animals.[11] Gastric acid, gut motility and mucin secreted by goblet cells are also very important factors preventing luminal bacteria from reaching and attaching to the gut mucosal surface.

The gut has another essential mucosal barrier system, i.e. the immunological barrier.[7] The gut functions not only in the digestion and absorption of nutrients, but also acts as an immune organ. Gut-associated lymphoid tissue (GALT), including Peyer patches, intraepithelial lymphocytes and lamina propria lymphocytes, contributes to the largest immune organs in the body. Intraluminal antigens are sampled by M cells and processed by mature dendritic cells within the Peyer patches. The dendritic cells interact with naïve lymphocytes which migrate from the capillaries. Sensitized lymphocytes, then, move to mesenteric lymph nodes, where they undergo maturation and proliferation, and finally return to the systemic circulation via the thoracic duct. Some lymphocytes are home to the GALT effector sites (intraepithelial spaces and lamina propria), while others migrate to extraintestinal mucosal sites such as the respiratory tract and the genitourinary tract, where they function in mucosal protection. Intraepithelial lymphocytes produce various cytokines and remove injured mucosal cells, thereby protecting mucosal integrity. Plasma cells in the lamina propria transform into immunoglobulin A (IgA)-producing cells. IgA secreted into the mucosal lumen neutralizes pathogens and toxins without inducing inflammation.

3.3 | Enteral nutrition and gut immunity

Murine feeding models have clarified that enteral nutrition preserves GALT cell numbers and IgA levels in the gut lumen as compared to parenteral nutrition, thereby maintaining the gut immunological barrier.[7] Complex enteral diet was demonstrated to preserve the gut barrier as effectively as normal diets, while intragastric administration of TPN solution only achieved gut barrier preservation midway between that of a complex enteral diet and parenterally administered TPN solution. Thus, routes and types of nutrition dramatically affect the gut immunological barrier. Enteral nutrition also preserved respiratory tract IgA levels and strengthened antiviral and antibacterial functions, via the common mucosal immune system mechanisms detailed above, as compared to parenteral nutrition. Evidence of enteral nutrition superiority in terms of gut immunity in humans is minimal. However, our laboratory has recently demonstrated that terminal ileum tissues resected from patients fed orally before surgery contain more T cells, IgA-producing cells and mature dendritic cells than those from parenterally fed patients, suggesting that nutrition routes have similar impacts on gut immunity in animal models and humans.[10]

3.4 | Dietary restriction and gut immunity

Even when oral feeding was provided in an animal study, reduced energy and protein intakes were found to lead to significant decreases in GALT cell numbers. Interestingly, GALT cell numbers were not normalized when the total energy requirement was supplied in small percentages through an enteral route. The higher were the percentages of total energy that mice were given enterally, the greater was the restoration of GALT cell numbers.[12]

3.5 | Hepatic immunity and enteral nutrition

The liver is the central organ for metabolism and also acts as an immune organ based on the presence of abundant mononuclear cells (MNCs) eliminating pathogens and toxins from the blood stream. Representative immune cells in the liver are Kupffer cells. These cells are activated through lipopolysaccharide (LPS) binding to Toll-like receptor-4 and intracellular signaling. Our murine feeding model revealed that, as compared to enteral nutrition, parenteral nutrition decreased hepatic MNC numbers without changing their phenotypes, and blunted activation of extracellular signal-regulated kinase phosphorylation (an important intracellular signal pathway) as well as both pro-inflammatory and anti-inflammatory cytokine productions in the MNCs.[8] These changes resulted in poorer survival in a bacteremia model induced by intraportal injection of live *Pseudomonas*. Changes in hepatic MNCs might be a mechanism underlying increased morbidity of blood stream infection in parenteral-only fed patients.

3.6 | Dietary restriction and hepatic immunity

Basic research using mice has also revealed that hepatic MNC numbers and functions are impaired, whenever the amount of oral feeding is reduced.[13] Effects of supplemental parenteral nutrition in addition to oral feeding require further study.

3.7 | Peritoneal host defense mechanism and enteral nutrition

Resident macrophages exist in the sterile peritoneal cavity. Once a cavity is contaminated by pathogens, the macrophages are activated and produce chemokines and cytokines, which in turn cause further activation of macrophages and massive exudation of polymorphonuclear neutrophils (PMNs) from the blood stream. The PMNs phagocytize and kill pathogens through reactive oxygen species and proteases.

When mice were fed parenterally, the resident peritoneal macrophage number was markedly reduced and translocation of nuclear factor (NF)-κB from the cytoplasm to the nucleus was blunted during

in vitro culture with LPS, as compared to enteral nutrition.[9] According to these changes, a rapid increase in pro- and anti-inflammatory cytokines in the peritoneal cavity and the following PMN exudation were both inhibited in the parenteral nutrition group. Thus, similar to the phenomena observed in the liver, the numbers and functions of immune cells playing important roles in peritoneal defense against hostile microbes are influenced by nutritional route.

3.8 | Surgical stress and host defense mechanism

Various surgical stresses may impair host defense mechanisms. Perioperative hyperglycemia is a reasonable response to stress, delivering more glucose to injured tissue, red blood cells and immune cells, which are necessary for surviving the stress. However, excessive hyperglycemia under conditions of increased insulin resistance causes dysfunction of immune cells, vascular endothelial cells, neurons and the kidneys, leading to increased postoperative complications. Thus, blood glucose control during the perioperative period is very important. Intensive insulin therapy aimed at achieving a blood glucose level of 80-110 mg/dL was demonstrated to reduce mortality and morbidity in patients admitted to the surgical intensive care unit (ICU) who were receiving mechanical ventilation.[14] Nevertheless, many clinicians and researchers have challenged the efficacy of what they consider to be excessively strict control and, in fact, randomized controlled trials (RCTs) have revealed poorer outcomes in association with hypoglycemia in patients with strict blood glucose control.[15] At present, based on clinical experience and research, a blood glucose level of 110-160 mg/dL is recommended. Particularly, in patients without diabetes who undergo gastroenterological surgery, a target blood glucose of ≤150 mg/dL is recommended by Takesue et al.[16]

Surgical stress which causes severe gut ischemia reperfusion and/or endotoxemia may cause impairment of gut and hepatic immunity, although these data were obtained in animal studies.[17] Prolonged loss of hepatic MNC and GALT cell numbers has been observed.[18] Moreover, truncal vagotomy, a surgical procedure performed for lymph node dissection in upper GI tract malignancy operations, worsens the resistance to gut ischemia reperfusion and impairs gut immunity.[19,20]

Thus, clinicians should recognize that severe surgical stress may trigger deterioration of host defense mechanisms against various pathogens, placing patients at risk for developing postoperative complications. Appropriate nutritional therapy may reduce this risk, while lack of attention to nutrition may aggravate the stress-induced impairment of host defense systems.

3.9 | Speed of immune cell changes by nutritional routes

Clear evidence as to how rapidly immune defects occur in the absence of enteral feeding in clinical settings is still lacking. Data obtained from animal studies are not directly applicable to humans due to the marked differences in life span, body size, nutritional stores and metabolic rate. However, GALT and hepatic MNC changes occur only in a few days after starting parenteral nutrition and these changes are reversed, resulting in normalization, within a few days after restarting oral feeding. These findings suggest that clinicians should minimize the period without enteral nutrition to the extent possible.[7,21] In mice, just 12 hours of starvation causes significant loss of GALT cell numbers and gut morphological atrophy.[22] These changes are moderately normalized by a small amount of 12.5% carbohydrate liquid gavage at 2 hours before sacrifice, indicating that oral carbohydrate loading is effective not only for elimination of thirst and anxiety, as well as prevention of insulin resistance, but also for preservation of gut immunity. Taken together, these observations suggest that ERAS® protocols support host defense mechanisms against infection to reasonably functional levels by reducing the period of nothing-by-mouth intake.

3.10 | Possible adverse effects of early enteral nutrition

Early enteral nutrition is not always safe after surgery. Shock, severe gut ischemia reperfusion, massive GI tract bleeding and anastomotic leakage are contraindications for enteral feeding. If patients have these conditions, early enteral nutrition should be withheld. Of course, if enteral nutrition is given to the distal site of the anastomotic leakage site, enteral nutrition is rather recommended for early recovery. However, well controlled anesthesia and improved surgical techniques have reduced the risks of these severe postoperative complications, especially in patients undergoing elective surgery.

ERAS® programs have been successfully applied for promoting rapid functional recovery after gastrectomy, pancreatic resections, pelvic surgery, hysterectomy, and gynecologic oncology procedures.[1] Balzano et al[23] retrospectively demonstrated early recovery protocols, wherein clear liquid started on day 3 and solid food intake on day 4 after pancreaticoduodenectomy (PD), to reduce delayed gastric emptying and hospital stay. Braga et al[24] started clear liquid (from day 3 to day 2) and solid food (from day 4 to day 3) even earlier, with no adverse effects. The ERAS pathway significantly shortened the length of hospital stay in patients with uneventful postoperative courses and those with minor complications. Combining enteral nutrition delivered via a nasojejunal or needle catheter jejunostomy and parenteral nutrition started immediately after transfer to the ICU was found to be safe and to adequately meet nutritional demands without causing adverse effects. However, a recent RCT demonstrated early nasojejunal enteral feeding (starting at day 1) increased morbidity of overall postoperative complications and more severe pancreatic fistula development. The authors advocated avoiding early nasojejunal feeding.[25] The soft pancreas rate was higher in the enteral nutrition group, which might be the mechanism underlying the increased fistula formation rate, but the precise reason remains unknown. Thus, whether or not early enteral feeding is safe in patients with a soft pancreas undergoing PD is still controversial.

3.11 | Pitfalls of nutritional therapy

Early restart of oral feeding does not always mean no need of supplemental enteral or parenteral nutrition. Advantages of enteral nutrition over parenteral nutrition do not mean that parenteral nutrition is ill-advised and should be withheld when enteral nutrition is not tolerable or indicated. According to the results of the EPaNIC study, full coverage of energy expenditure during the first several days after surgery might be detrimental in terms of the infectious complication rates and length of ICU stay.[26] However, avoidance of prolonged nutritional debt is important. Early nutritional management including parenteral nutrition should be started for patients who suffer preoperatively from malnutrition and/or are expected not to resume full oral intake of food until day 7.[27]

Because serum albumin levels can still serve as a marker of nutritional status, some surgeons may prescribe an albumin solution to asymptomatic patients with low serum albumin levels. Indeed, hypertonic albumin (20%-25%) is recommended for the treatment of refractory ascites and pleural effusion in patients with decompensated liver cirrhosis. However, low albuminemia without any clinical symptoms is not a condition that merits administration of an albumin solution. Recent clinical research clarified that albumin synthesis is markedly increased even after major surgery.[28] Because approximately 15 g of albumin are synthesized daily in the functioning liver per 1 day, appropriate nutritional provision including amino acids and/or proteins (1-2 g/kg/d) should be considered first as a strategy for increasing serum albumin levels. On the other hand, an albumin solution should not be given as nutritional therapy, since albumin is not a substrate for protein synthesis.

4 | SPECIAL NUTRITIONAL FORMULAS FOR PREVENTING POSTOPERATIVE COMPLICATIONS

During the last several decades, the roles of specific nutrients such as glutamine, arginine, ω-3 fatty acids and nucleotides have been intensively investigated. The concept of immunonutrition, a new nutritional therapy using specific nutrients (immunonutrients) which have beneficial effects on host response and immunity, has now finally been established and tested in many clinical trials. Although one meta-analysis found no difference in clinical efficacy between standard formulas and immunonutrition formulas, many meta-analyses have confirmed the advantages of immunonutrition over standard therapy in terms of decreased postoperative infectious complication rates and length of hospital stay.[29,30] Use of immunonutrition during the perioperative period in gastroenterological surgery reportedly reduces the risk of infectious complications by 50%. Although WHO and Centers for Disease Control and Prevention guidelines for prevention of surgical site infection did not refer to the significance of nutrition therapy in previous versions, the 2016 WHO guidelines listed immunonutrition as a method contributing to the prevention of surgical site infection.[31] The guidelines recommend multiple nutrient-enhanced nutritional formulas containing any combination of arginine, glutamine, ω-3 fatty acids and nucleotides. However, patients who would likely benefit from immunonutrition must be carefully selected. The reason is that the cost of such formulas is generally higher than that of standard formulas and that the beneficial effects might be obscured by perioperative factors associated with very low morbidity of severe complications.

5 | POSSIBLE EFFECTS OF INDIVIDUAL IMMUNONUTRIENTS ON HOST RESPONSE

5.1 | Glutamine

Glutamine is a conditionally essential amino acid. Under conditions of severe surgical stress, glutamine production may not achieve the amount needed, leading to glutamine deficiency. Glutamine is an energy substrate of rapidly proliferating cells such as gut mucosal cells, lymphocytes and PMNs, serving as a material for synthesis of glutathione, a potent intrinsic antioxidant, and enhances heat shock protein expression. Previously, we clarified that glutamine dose-dependently increases the production of reactive oxygen intermediates production from human PMNs and that a parenteral nutrition formula containing glutamine reverses lack of enteral nutrition-induced GALT atrophy in mice.[32]

Because standard parenteral nutrition formulas do not contain glutamine due to its instability in solutions, new formulas containing glutamine-dipeptide have been developed. Such products are available for clinical use in Western countries and China, but not in Japan.

Beneficial effects of additive glutamine have been demonstrated in basic and clinical studies, i.e. prevention of diarrhea and preservation of gut morphology and immunity. Another RCT, the REDOX study, was conducted to confirm the beneficial effects of glutamine supplementation on patients in the ICU; however, conversely, mortality was worse than in the control groups.[33] Consequently, the authors cautioned against glutamine use in ICU patients. However, their study has been criticized for prescribing excessive doses of glutamine. The total amount of supplemental glutamine administered parenterally and enterally to the study group was too large (50 g for a patient weighing 60 kg) and exceeded the doses recommended in clinical guidelines.

5.2 | Arginine

Arginine is also a conditionally essential amino acid. Arginine stimulates growth hormone secretion, is metabolized to polyamine and enhances collagen production, thereby accelerating wound healing. Arginine is also a substrate of nitric oxide, a free radical, maintaining the microcirculation and killing microbes. Arginine increases NFκB

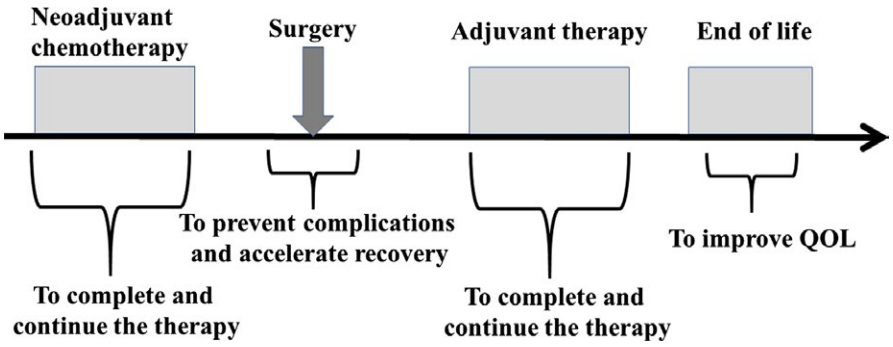

FIGURE 2 Role of nutritional therapy in gastroenterological surgery. Nutrition is important not only during perioperative period but also during neoadjuvant chemotherapy and after discharge. QOL, quality of life

translocation and reinforces the functions of immune cells, thereby enhancing host immunity.[34] Thus, arginine is essential for host responses to surgical stress. However, excessive production of nitric oxide by inducible nitric oxide synthase is known to cause refractory hypotension and tissue injury. Moreover, arginine supplementation given to patients with severe inflammation may exacerbate inflammatory responses. Appropriate timing and patient conditions for supplementation are the keys to the clinical use of arginine. Excessive doses should be avoided in patients with inflammatory status.

5.3 | ω-3 fatty acids

ω-3 fatty acids are metabolized to less inflammatory and less immunosuppressive eicosanoids than ω-6 fatty acids. Since ω-3 and ω-6 fatty acids are metabolized by the same enzymes, ω-3 fatty acids are expected to prevent excessive inflammatory responses and immunosuppression through competition for enzyme use. ω-3 fatty acids are also metabolized to anti-inflammatory mediators, i.e. resolvins and protectins, which rapidly terminate inflammation by modulating PMN and macrophage functions in the inflammatory site (PMN: inhibited migration and increased apoptosis; macrophage: increased migration).

Fish oil emulsion enriched with ω-3 fatty acids has been demonstrated to normalize TPN-induced hepatic MNC dysfunction in animal models.[35] Clinically, fish oil emulsions are used to treat TPN-induced liver dysfunction. Enteral formulas enriched with ω-3 fatty acids were demonstrated to prevent lung injury and improve survival as compared with other fat-rich formulas. Thus, clinical guidelines recommended the use of ω-3 fatty acid-rich enteral formulas as nutrition therapy for patients with lung injury. Yet, a recent large RCT denied the beneficial effects of ω-3 fatty acids in patients with lung injury.[36] Moreover, Ida et al found no differences in either surgical morbidity or body weight loss at 1 and 3 months after total gastrectomy for gastric cancer between a standard diet group and a standard diet + oral supplementation with an eicosapentaenoic acid (EPA)-enriched enteral formula (7 days preoperatively and 21 days postoperatively, 600 kcal with 2.2 g EPA).[37] The recommendation level appears to be reduced in recent guidelines.

5.4 | Cystine and theanine

In addition to glutamine and arginine, cystine and theanine might be newly identified immunonutrients. Oral administration of cystine and theanine during the perioperative period reportedly lowered postoperative plasma interleukin-6 levels, C-reactive protein levels, PMN counts and body temperature in cancer patients undergoing distal gastrectomy. Moreover, this combination has been demonstrated to attenuate adverse events of S-1 adjuvant chemotherapy in GI cancer patients.[38] A possible mechanism might involve enhancement of glutathione metabolism by cystine and theanine.[39]

6 | NUTRITIONAL THERAPY AFTER DISCHARGE

Because gastroenterological surgery may impair normal GI tract function for long periods, even permanently, after an operation, special attention should be paid to the nutritional care provided to patients. Upper GI tract surgery, particularly gastrectomy, is known to cause marked body weight loss due to reduced oral intake, and deficiencies of iron, vitamin B_{12}, vitamin D, and calcium due to malabsorption.

Hatao et al[40] demonstrated that weight loss in an oral nutritional supplement group (12-week administration of 400 kcal/d of a standard enteral formula after discharge) after total gastrectomy was significantly less than that in a control group (no supplements). The reason for the discrepancy between the two studies (Ida study: no effect of an EPA-enriched enteral formula; Hatao study: positive effect of a standard formula) is not clear.[37,40] The difference between the periods of the supplementation may have affected the results (Ida study: 28 days; Hatao study: 84 days). Thus, long-term oral nutritional supplementation after total gastrectomy may mitigate body weight loss. Deficiencies of vitamins and minerals should also be corrected.

7 | CONCLUSIONS

Nutritional treatment is an essential element supporting and improving the outcomes of gastroenterological surgery not only during the

perioperative period but also during neoadjuvant chemotherapy and until the end of life (Figure 2). Surgeons consistently strive to improve surgical outcomes. Understanding the importance of nutrition will help surgeons and patients achieve good outcomes.

DISCLOSURE

Conflict of Interest: The author declares no conflict of interests for this article.

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