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Review

Targeted nutritional strategies in postoperative care

Hye Jin Ham[1] and Jeongmin Kim[2,3]

[1]Department of Nutrition Care, Severance Hospital, [2]Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, [3]Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author
Jeongmin Kim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-2420
Fax: 82-2-312-7185
E-mail: anesjeongmin@yuhs.ac

Immunonutrition, which uses specific nutrients to modulate the immune response, has emerged as a vital adjunct to perioperative care. Surgery-induced stress triggers immune responses that can lead to complications, such as infections and delayed wound healing. Traditional nutritional support often overlooks the immunological needs of surgical patients. Immunonutrition addresses this oversight by providing key nutrients, such as arginine, omega-3 fatty acids, glutamine, nucleotides, and antioxidants (vitamins C and E) to enhance immune function and support tissue repair. This review examined the efficacy and safety of immunonutrition in surgical settings, guided by the recommendations of the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. Both organizations recommend immunonutrition for high-risk or malnourished patients undergoing major surgery and support its use in reducing complications and improving recovery. The key nutrients in immunonutrition aim to improve immune cell function, reduce inflammation, and enhance wound healing. Clinical studies and meta-analyses have demonstrated that immunonutrition lowers the infection rate, shortens the length of hospital stay, and accelerates recovery. Challenges hindering the clinical application of immunonutrition include cost, logistics, and a lack of standardized and personalized protocols. Future studies should focus on biomarker-driven approaches, pharmacogenomics, and innovative nutrient formulations. Addressing these issues will help to integrate immunonutrition into clinical practice, ultimately improving surgical outcomes and patient recovery.

Keywords: Arginine; Enhanced recovery after surgery; Immune response; Immunonutrition; Omega-3 fatty acids; Vitamin C; Vitamin E.

INTRODUCTION

Immunonutrition, a specialized dietary approach aimed at modulating the immune response, has emerged as a promising adjunctive therapy in perioperative care [1,2]. Physiological stress induced by surgery elicits a cascade of immune responses, predisposing patients to complications, such as infections and delayed wound healing [3]. Although traditional nutritional support strategies predominantly focus on caloric requirements, they often neglect the specific immunological needs of surgical patients.

Understanding the intricate interplay between nutrition and immune functions is crucial for anesthesiologists in postoperative care units and operating rooms. Immunonutrition offers a tailored approach by providing key nutrients that modulate immune responses and support tissue repair. Immunonutrients, such as amino acids (arginine and glutamine), omega-3 fatty acids (FAs), nucleotides, and antioxidants play pivotal roles in these processes. These nutrients are instrumental in modulating inflammatory responses, boosting immune function, and promoting effective tissue repair, thereby improving perioperative outcomes [4,5].

This review aimed to evaluate the efficacy and safety of immunonutrition in surgical settings, offering insights relevant to anesthesiologists involved in all stages of patient care. Drawing from guidelines established by the American Society for

Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), this review aimed to provide a comprehensive overview of the current state of immunonutrition in perioperative care. The ASPEN guidelines emphasize the importance of perioperative nutrition in reducing complications and improving recovery. They recommend considering immunonutrition in patients undergoing major surgery, particularly those at a high risk of complications or those with preexisting malnutrition [6]. Similarly, the ESPEN guidelines highlight the role of immunonutrition in modulating the inflammatory response to surgery and promoting wound healing. These guidelines provide valuable recommendations for clinical practice in Europe and other regions [7].

Considering the increasing recognition of the importance of immune modulation in surgical patients, understanding the role of immunonutrition is essential for anesthesiologists. By addressing the specific immunological needs of surgical patients, immunonutrition can potentially improve outcomes and reduce the burden of postoperative complications.

STUDY DESIGN

This study aimed to evaluate the effects of immunonutrition on perioperative outcomes. A comprehensive literature search was conducted using the ScienceDirect and PubMed databases to identify relevant studies and references for this review. To draft and refine this manuscript, we used ChatGPT, a language model developed by OpenAI, to generate and edit the text.

LITERATURE REVIEW

History and development of immunonutrition

Immunonutrition, the practice of modulating the immune system through specific nutritional interventions, has significantly evolved over the past few decades. The concept emerged from the realization that malnutrition and nutrient deficiency severely compromise immune functions, increase susceptibility to infections, and lead to poor clinical outcomes [1,6]. Research in the 1980s and the 1990s identified key nutrients that could enhance immune responses and improve patient outcomes, particularly in patients with critical illnesses and those undergoing surgery [8,9].

The development of immunonutrition has gained momentum with the introduction of specialized nutritional formulations designed to support immune function. These formulas typically include nutrients, such as arginine, omega-3 FAs, nucleotides, and glutamine. Clinical trials conducted in the 2000s provided evidence that immunonutrition can reduce infection rates, decrease the length of hospital stay, and improve recovery in surgical and critically ill patients [10-12]. Consequently, immunonutrition has become an integral part of surgical protocols that aim at optimizing perioperative care and outcomes [1].

Basic concepts and mechanisms of immunonutrition

Immunonutrition is based on the principle that specific nutrients can modulate the function of the immune system, enhance its ability to combat infections, reduce inflammation, and promote healing. Fig. 1 shows that the underlying mechanism of immunonutrition is multifaceted and involves several biological processes.

Key nutrients in immunonutrition

1. Arginine

Arginine is a semi-essential amino acid whose requirements increase significantly under stress-inducing conditions such as surgery or trauma. Arginine is critical for immune function, particularly as a key substrate for T lymphocytes. Its availability directly influences T lymphocyte proliferation and reduces the risk of infection [13]. Arginine is a precursor of nitric oxide (NO), which is synthesized by nitric oxide synthase (NOS). NO activates soluble guanylate cyclase in smooth muscle cells, leading to the conversion of guanosine triphosphate to cyclic guanosine monophosphate. This process activates protein kinase G, which decreases intracellular calcium concentrations and induces smooth muscle relaxation through various signaling pathways, resulting in vasodilation. The resulting increase in blood flow enhances tissue oxygenation and vascular per-

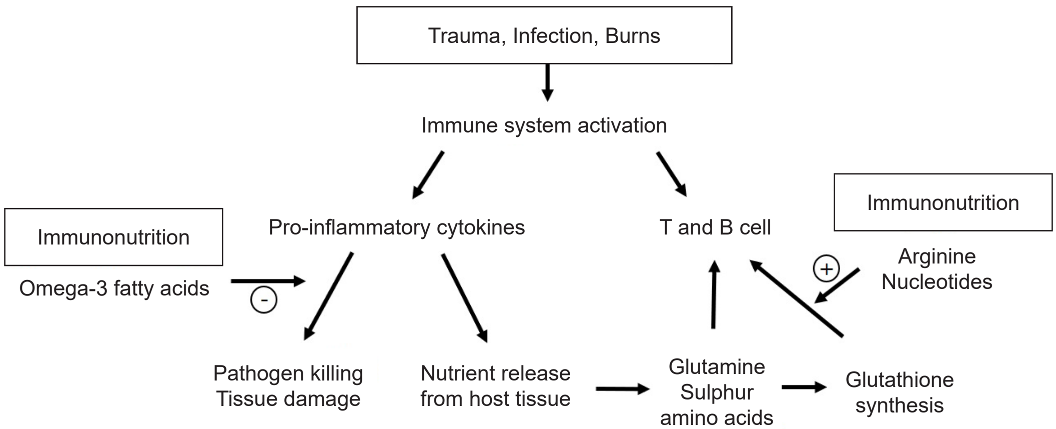

Fig. 1. Immune system activation and immunonutrition in response to injury and infection. Adapted from the article of Grimble (E Spen Eur E J Clin Nutr Metab 2009; 4: e10-e3.) [87] with original copyright holder's permission.

meability [14]. The vasodilatory effects of NO also facilitate greater oxygen delivery, promote leukocyte infiltration, and enhance the microbicidal activity of macrophages [15,16]. In addition to its role in immune functions, arginine is a precursor of proline. Proline is crucial for the synthesis of hydroxyproline, a major component of collagen, essential for proper wound healing. Arginine is metabolized by arginase-1 in the kidneys to produce ornithine and urea, which are subsequently converted to proline, which in turn, undergoes hydroxylation to form hydroxyproline [17-19]. Deficiency in arginine, and consequently NO production, has been implicated in delayed wound healing [20]. Furthermore, arginine deficiency is associated with impaired microperfusion, decreased immune function, and a higher risk of ischemia due to endothelial dysfunction [21].

2. Omega-3 FAs

Omega-3 FAs are polyunsaturated FAs (PUFAs), including alpha-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Omega-3 FAs are essential FAs that cannot be synthesized endogenously and must be acquired from dietary sources, predominantly from cold-water fatty fish. They are key components of cell membranes and act as precursors to bioactive molecules, such as prostaglandins, thromboxanes, and leukotrienes, which contribute to immune regulation and exhibit significant anti-inflammatory properties [22-24]. In particular, EPA and DHA attenuate the production of proinflammatory cytokines and eicosanoids derived from arachidonic acid, an omega-6 FA. Additionally, they enhance the synthesis of resolvins and protectins, which are involved in resolving inflammation, and thus, contribute to wound-healing processes [25-27]. Omega-3 FAs also possess antithrombotic properties, help maintain tissue microperfusion, and stimulate the production of prostaglandin E2. These contribute to preventing immunosuppression at the cellular level [28]. Consequently, omega-3 FA supplementation is recommended for conditions characterized by heightened inflammatory responses, such as surgical procedures [29,30].

3. Nucleotides

Nucleotides, which are fundamental components of deoxyribonucleic acid and ribonucleic acid, are nitrogen-based molecules involved in nearly all intracellular processes [31]. Although nucleotides are synthesized endogenously, they are also obtained through dietary intake of proteins found in animal and plant cells [32]. Nucleotides play a critical role in enhancing immune function by supporting the differentiation and proliferation of T lymphocytes. These processes are particularly important during surgery or infection when the demand for immune cell production and tissue regeneration increases [31,33]. Thus, the nucleotide requirement is markedly increased during surgery or infection [34].

4. Glutamine

Glutamine is a conditionally essential amino acid and the most abundant amino acid in the body, accounting for the highest concentration of all amino acids in the plasma [35]. Under catabolic conditions induced by stress, trauma, or surgery, the demand for glutamine increases, because it serves as the primary energy source for the kidneys, intestinal mucosa, and immune cells [36]. Previous studies have reported that plasma glutamine levels significantly decline in patients with burns, major surgeries, trauma, or critical illness [37,38]. In these patients, glutamine depletion leads to impaired intestinal cell function and a subsequent decline in immune function.

5. Antioxidants (vitamins C and E)

Antioxidants, such as vitamins C and E, are vital for protecting immune cells from oxidative stress. Vitamin C is a water-soluble vitamin that functions as an antioxidant by neutralizing reactive oxygen species and inhibiting oxidative stress, thereby protecting cellular tissues from damage [39,40]. Vitamin E, the most potent lipid-soluble antioxidant, plays a key role in maintaining cell membrane stability by preventing free radical-induced oxidation of PUFAs within the cell membrane [41,42]. Oxidative stress is a significant issue in postoperative patients because excessive production of free radicals can lead to tissue damage and impede healing [43]. These antioxidant supplements have been shown to reduce organ failure and the length of intensive care unit (ICU) stay, thereby improving recovery outcomes in critically ill patients who have undergone surgery [44].

CLINICAL STUDIES AND EVIDENCE

Review of major clinical studies: results from meta-analyses and systematic reviews

1. Omega-3 FAs

A meta-analysis reported that continuous administration of omega-3 FAs during both the preoperative and postoperative periods in patients undergoing liver surgery was significantly more effective in reducing postoperative infection rates than the administration of omega-3 FAs during either the preoperative or postoperative period alone. However, no benefits were observed concerning mortality or ileus [45]. A randomized controlled trial (RCT) investigating patients undergoing hepatectomy found that the administration of omega-3 FAs was associated with the amelioration of complications and shortening of the length of hospital stay [46]. In contrast, a systematic review found insufficient evidence to support the preoperative use of omega-3 FAs in patients undergoing major gastrointestinal surgery [47]. Various meta-analyses have reported that the doses of omega-3 FAs provided through enteral or parenteral routes ranged from 2.0–6.5 g per day, which yields a reduction in inflammation-related markers. However, when omega-3 FAs were administered preoperatively to patients undergoing abdominal surgery, no significant effects on inflammatory markers were observed. This outcome may be attributed to the small number of studies, limiting result interpretations [48]. According to another systematic review and meta-analysis, immunomodulatory supplementation of omega-3 and omega-6 FAs, along with antioxidants delivered through enteral nutrition (EN), in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) elicited no significant differences in ICU length of stay (LOS), organ failure, or hospital stay compared with patients administered the standard formula [49,50].

2. Nucleotides

Although studies focusing solely on nucleotide supplementation in humans are limited, animal studies have demonstrated that long-term feeding of a nucleotide-free diet leads to a reduced antibody response to T cell-dependent antigens in rodents. Restoration of nucleotides in the diet results in a rapid improvement in immune function [51,52]. Animal studies have demonstrated that nucleotide supplementation increases jejunal villus height. In human infant models, nucleotide-enriched formulas were found to improve intestinal blood flow, potentially contributing to the preservation of gut barrier integrity [53-55]. However, most studies have combined nucleotides with other immunonutrients such as omega-3 FAs and arginine, resulting in positive outcomes such as reduced infection rates. Therefore, it is difficult to attribute these results solely to the effects of nucleotides [56].

3. Glutamine

Previous small-scale studies in critically ill patients have suggested that glutamine supplementation exerts positive effects by improving immune function and suppressing inflammatory responses [57]. Research in this field has increased substantially over the past decade. While some single-center studies have reported positive outcomes, multicenter trials have demonstrated the negative effects of glutamine supplementation [58]. In one of the largest studies, the Scottish Intensive Care Glutamine or SeleNium Evaluative Trial, a double-blind RCT involving 502 critically ill patients, 20.2 g/day of glutamine was administered via parenteral nutrition (PN). The study revealed that glutamine did not have a significant effect on infection incidence or mortality rate [59]. Similarly, the Reducing Deaths due to Oxidative Stress trial (REDOX), a randomized, blinded trial involving 1,223 patients with multi-organ failure across 40 ICUs in Canada, the United States, and Europe, found that glutamine supplementation was associated with increased mortality without other clinical benefits. It is important to note that the patient population in the REDOX trial consisted of critically ill individuals with multiorgan failure, many of whom received less than 50% of their nutritional requirements via enteral feeding. This limitation affected the interpretation of the findings [60]. Although this was a large-scale study, the condition of the patient population and inadequate nutritional support impeded definitive conclusions. Therefore, additional studies and meta-analyses have been conducted. Although the evidence remains limited, glutamine supplementation has shown some benefits in reducing infection rates and hospital LOS, albeit without any effect on mortality. PN appears to yield more favorable outcomes; however, the optimal dosage and duration of supplementation have yet to be clearly established [61].

A meta-analysis of studies evaluating formulas containing various immunonutrients, including arginine and fish oil, administered to high-risk patients undergoing elective surgery during the preoperative and postoperative periods found a significant reduction in infection rates and LOS, albeit without a difference in mortality [62]. Another meta-analysis of patients undergoing elective gastrointestinal surgery demonstrated that the use of immunomodulatory formulae during the perioperative and postoperative periods led to a reduction in infectious complications, shortened hospital LOS, and decreased overall complications [63]. These findings suggest potential benefits for reducing overall morbidity.

Role of immunonutrition in perioperative recovery

Surgical stress amplifies postoperative inflammatory responses, which can compromise immune function and increase the susceptibility to infections. This stress may also accelerate the depletion of critical nutrients involved in immune regulation, potentially leading to deficiencies [64]. In a prospective randomized study, perioperative immunonutrition was administered to patients undergoing pancreaticoduodenectomy, which yielded positive effects on key immunological parameters, including T helper type 1 (Th1), Th2 cells, and interleukin (IL)-17-producing CD4(+) helper T (Th17) cells. Additionally, reductions in postoperative infectious complications and immunosuppression were observed [65]. Another study focusing on patients with a low skeletal muscle index undergoing pancreaticoduodenectomy found that preoperative immunonutritional supplementation suppressed IL-6 levels, which correlated with a reduction in postoperative complications [66]. A meta-analysis of patients undergoing pancreaticoduodenectomy demonstrated that perioperative immunonutrition, provided both before and after surgery, was more effective in reducing infectious complications than immunonutrition provided either preoperatively or postoperatively [67]. A meta-analysis of seven RCTs that enrolled patients undergoing gastrointestinal surgery revealed that preoperative immunonutrition reduced the rate of infectious complications by nearly 50% compared with that in the control group. Additionally, the average length of hospital stay was significantly shortened, from 15.3 days in the control group to 13.6 days in the immunonutrition group [68].

A meta-analysis of 24 studies involving patients undergoing head and neck or gastrointestinal cancer surgery further confirmed that immunonutrition significantly ameliorated all postoperative complications [69]. Meta-analyses of multiple RCTs investigating patients with gastric and colorectal cancers demonstrated a reduction in infectious complications with the use of immunonutrition [70,71].

An observational, retrospective cohort study of patients undergoing gastrectomy who received nutritional support for an average of 10 days pre- and postoperatively also showed that immunonutrition significantly shortened the hospital stay by 34% and reduced infectious complications by 70.1% [72]. Although variations in study scale and outcome measures hinder the drawing of definitive conclusions on perioperative immunonutrition, it can be inferred that immunonutrition plays a crucial role in alleviating surgery-induced inflammatory responses and immune suppression, potentially reducing infectious complications and shortening the length of hospital stay.

PRACTICAL APPLICATIONS AND RECOMMENDATIONS

Guidelines for the use of immunonutritional supplements

Although arginine has been shown to positively influence immune function and wound healing, its supplementation remains controversial, and caution is advised when administering it to patients with septic shock [6]. Inflammatory stimuli can activate inducible NOS, an intracellular enzyme that converts arginine to NO, leading to vasodilation. This can result in hemodynamic instability and tissue damage, necessitating careful consideration when administering arginine to this patient population [21].

Glutamine supplementation is not recommended for all patients except those with trauma or burns. In critically ill patients with complex conditions, especially those with liver or renal failure, the use of glutamine via PN is not advised [73].

The SCCM/ASPEN guidelines do not recommend routine administration of formulas containing omega-3 FAs in patients with ALI or ARDS, as shown in Table 1. However, immunomodulatory formulas containing arginine and fish oil are recommended postoperatively for patients admitted to the surgical ICU [6].

Pre- and postoperative immunonutrition management protocols

The ESPEN guidelines recommend the use of immunonutrients (arginine, omega-3 FAs, and nucleotides) during the perioperative period, or at least in the postoperative period, for malnourished patients scheduled for major surgery [7]. In contrast, the American Society for Enhanced Recovery guidelines recommend high-protein oral supplements before major surgery and suggest immunonutritional use [74]. However, evidence supporting the use of immunonutrition remains ambiguous, necessitating large-scale multicenter clinical trials to establish clear guidelines. The current lack of robust evidence hinders the development of standardized protocols, resulting in challenges for consistent implementation in clinical practice.

Clinical application

1. Arginine

The recommended dose of arginine for healthy individuals ranges from 5 to 30 g/day. Commercially available enteral formulas used for immune support in critically ill patients typically contain arginine at concentrations ranging from 0 and 18.7 g/L. In contrast, domestic enteral formulas contain significantly lower arginine levels ranging from 0 to 5 g/L. International clinical studies have reported that critically ill patients who achieve their target nutritional intake via enteral feeding receive an average arginine dose of 10–30 g/day [75]. For perioperative or critically ill patients, determining the exact dose can be challenging because of metabolic instability and inflammatory states. However, arginine supplementation should remain within the 10–30 g/day range, be-

Table 1. Recommendations for Immunonutrition Supplements in Critically Ill Patients: ASPEN (2016) and ESPEN (2023) Guidelines

Formula and nutrient type	Routine use	Not for routine use
ASPEN (2016) [6]		
IMF	SICU, TBI, perioperative, postoperative patient	MICU, severe sepsis
IMF (+ arginine, fish oil)	Severe trauma +	-
IMF (+ arginine)	TBI	-
standard formula (+ EPA, DHA supplement)		
Enteral nutrition, glutamine	-	O
ESPEN (2023) [86]		
Glutamine	Burns (> 20% BSA)	ICU patient, additional EN glutamine (except burns and trauma patient) should not be administered.
	EN glutamine 0.3–0.5 g/kg/day, administered for 10–15 days.	Unstable ICU patient, liver, renal failure, PN glutamine dipeptide shall not be administered.
	Critically ill trauma patient, first 5 days EN, additional EN dose glutamine (0.2–0.3 g/kg/day)	
Omega-3 FAs	Omega-3 FA-enriched EN (within the nutritional dose)	High doses of omega-3-enriched EN should not be given via bolus administration.
	PN containing EPA+DHA (fish oil dose 0.1–0.2 g/kg/day) is available.	

IMF: immunomodulating formula, SICU: surgical intensive care unit, MICU: medical intensive care unit, ICU: intensive care unit, TBI: traumatic brain injury, BSA: body surface area, EN: enteral nutrition, PN: parenteral nutrition, FA: fatty acid, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, ASPEN: American Society for Parenteral and Enteral Nutrition, ESPEN: European Society for Clinical Nutrition and Metabolism.

cause higher doses may increase the risk of adverse effects [6,15].

2. Omega-3

While it remains challenging to accurately delineate the therapeutic effect and no specific recommended dosage has been established, the omega-3 FA content in currently available enteral formulas in South Korea ranges from 0.8 to 1.7 g/L. Commercially available 20% lipid emulsion solutions contain approximately 3 g of fish oil per 100 ml, accounting for approximately 15% of the total volume. In lipid-based PN formulations, the composition of FAs varies according to the manufacturer; however, fish oil-based preparations typically comprise 15–20% of the total lipid content. According to the Dietary Guidelines for Americans 2015–2020, the recommended daily intake of omega-3 FAs to maintain optimal physiological function is 450–500 mg/day [76]. According to the Dietary Reference Intakes for Koreans 2020, the adequate intake of omega-3 FAs for adults aged 50–64 years is set at 500 mg/day for men and 240 mg/day for women [77].

3. Nucleotides

The exact nucleotide content of individual food items has not been officially established; however, it is estimated that healthy individuals consume approximately 1–2 g/day through their diet. Some commercially available enteral formulas from international sources contain between 1.2 and 2.8 g/L of nucleotides [56]. However, the nucleotide content of domestic Korean products is yet to be determined.

4. Glutamine

The recent ESPEN guidelines recommend the administration of glutamine via EN for trauma patients at a dose of 0.2–0.3 g/kg/day for the first 5 days of initiating EN. In cases of complicated wound healing, glutamine should be administered for more than 10–15 days, and for patients with burns with body surface area involvement exceeding 20%, the recommended dosage is 0.3– 0.5 g/kg/day for 10–15 days. Glutamine supplementation is not recommended in patients other than those with trauma or burns. Additionally, for critically ill patients with complex conditions, particularly those with liver or renal failure, the use of glutamine via PN is not advised [73].

5. Vitamin C and E

The 2020 Korean Dietary Reference Intake guideline recommends a daily intake of 100 mg vitamin C, a water-soluble vitamin, while the adequate intake for vitamin E, a fat-soluble vitamin, is 12 mg α-TE per day [77]. Among the commercial EN products available in Korea, the vitamin C content ranges from 140 mg to 500 mg per 1,000 kcal, and the vitamin E content ranges from 10 mg to 50 mg α-TE per 1,000 kcal.

As shown in Table 2, none of the domestically available EN formulas contain glutamine or nucleotides. Moreover,

Table 2. Nutritional Content of Commercial Enteral Formulas Available in Korea (per 1 L)

Formulas (Manufacturer)	Types	Arginine (g)	Omega-3 FAs (mg) (DHA + EPA)	Vitamin C (mg)	Vitamin E (mg alpha-TE)
Nucare® (Daesang Wellife)	Standard	1.7	-	140–200	10–24
	High protein	-	-	150	38–50
	Immune modulating	-	800–2,400	500	44
	1.5 Concentrated	3.3	-	230–260	26–45
Greenbia® (Dr.Chung's Food Co., Ltd.)	Standard	-	-	100–200	10–24
	High protein	-	-	200	24
	Immune modulating	-	3300	200	24
	1.5 Concentrated	-	-	150	15
Mediwell® (Maeil Dairies Co., Ltd.)	Standard	3.5–3.8	-	150	30
	High protein	3.5	-	150	30
	1.5 Concentrated	5	-	230	45
	Immune modulating formulas not available				
Medifood® (Korea Medical Foods)	Standard	-	-	150	28
	High protein, immune modulating, 1.5 concentrated formulas not available				

FA: fatty acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid.

glutamine is only available as an intravenous preparation. Currently, the EN formulas available in Korea do not provide all immunonutrients in a single product. Among the formulations commonly used for the immune support of critically ill patients, some include omega-3 FAs, such as DHA and EPA. However, arginine, which should be restricted in cases of sepsis, is not included [6].

Challenges and considerations

The clinical application of faces several significant hurdles. Identifying and addressing the various obstacles that hinder the widespread application of immunonutrition is crucial. One of the primary concerns is the substantial cost of immunonutritional supplements. These costs may limit access for some patients and healthcare facilities, particularly those operating under tight budget constraints [78].

Logistical constraints pose significant challenges. Ensuring the timely and appropriate delivery of immunonutritional supplements is a complex task, especially in busy clinical settings. This complexity is compounded by a lack of standardized protocols, which leads to variability in the administration and effectiveness of immunonutrition. In the absence of clear guidelines, healthcare providers may struggle to implement these strategies consistently and effectively [1].

Personalized approaches to immunonutrition are essential for optimizing patient outcomes. Individual patient characteristics, such as nutritional status, comorbidities, and specific types of surgery should inform tailored nutritional interventions [79]. Standardized protocols alone cannot address the unique needs of each patient, highlighting the importance of personalized nutritional plans.

In summary, although immunonutrition holds great promise for improving surgical outcomes, its implementation is challenging. Addressing cost and logistic issues, developing standardized protocols, and emphasizing personalized approaches based on patient characteristics and surgical procedures are critical steps toward overcoming these obstacles and realizing the full potential of immunonutrition in clinical practice.

FUTURE DIRECTIONS

Immunonutrition use in surgical patients is poised for significant advancements driven by emerging research and technological innovations. A promising research area is the development of biomarker-driven approaches. By identifying specific biomarkers associated with nutritional status and the immune response, clinicians can tailor immunonutritional interventions to the individual needs of patients, thereby enhancing their efficacy and outcomes [80,81]. These biomarkers can help predict patients who are most likely to benefit from specific nutrients, thereby enabling more personalized and effective treatment plans.

Pharmacogenomics, the study of how genes affect an individual's response to drugs, offers exciting possibilities for immunonutrition. By understanding the genetic variations that influence nutrient metabolism and immune function, personalized nutrition plans can be developed to optimize the immune modulations and recovery of each individual surgical patient [80,82,83]. This approach ensures that patients receive the most suitable nutrients in the correct amounts based on their genetic profiles, thus, potentially improving surgical outcomes and reducing complications.

Innovations in the formulation and delivery of immuno-nutritional supplements constitute another key area for future research. Novel formulations that enhance the bioavailability and stability of key nutrients could improve their effectiveness. Moreover, advanced delivery methods, such as encapsulation technologies and targeted delivery systems, can ensure that nutrients are delivered precisely where they are needed, maximizing their therapeutic potential [84,85].

To fully realize the potential of immunonutrition, it is essential to conduct multicenter RCTs with standardized protocols. These trials can provide robust evidence of the efficacy of immunonutrition in various surgical populations and help clarify the role of specific nutrients in improving surgical outcomes. Additionally, standardized protocols are needed to ensure consistency and reliability in administering immunonutritional interventions and may facilitate better comparisons of results across different studies.

By integrating these advancements, the field of immunonutrition can move towards more personalized, effective, and evidence-based practices, ultimately enhancing the recovery and overall health of surgical patients.

CONCLUSION

Immunonutrition plays a crucial role in optimizing surgical outcomes by enhancing immune functions, reducing inflammation, and promoting wound healing. Despite its potential, the implementation of immunonutrition faces significant challenges including cost, logistical constraints, and the lack of standardized protocols. Further research is essential to overcome these obstacles and validate the efficacy of tailored nutritional interventions. Continued efforts to refine immunonutritional strategies are necessary to improve perioperative care and optimize patient recovery following surgery. By addressing these challenges, the full potential of immunonutrition may be realized, ultimately benefiting the patient's health and surgical success.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Writing - original draft: Jeongmin Kim. Writing - review & editing: Hye Jin Ham, Jeongmin Kim. Conceptualization: Jeongmin Kim. Formal analysis: Jeongmin Kim. Methodology: Jeongmin Kim. Visualization: Jeongmin Kim. Investigation:Jeongmin Kim. Validation: Jeongmin Kim.

ORCID

Hye Jin Ham, https://orcid.org/0009-0001-3686-1588
Jeongmin Kim, https://orcid.org/0000-0002-0468-8012

REFERENCES

1. Gupta R, Senagore A. Immunonutrition within enhanced recovery after surgery (ERAS): an unresolved matter. Perioper Med (Lond) 2017; 6: 24.
2. Bharadwaj S, Trivax B, Tandon P, Alkam B, Hanouneh I, Steiger E. Should perioperative immunonutrition for elective surgery be the current standard of care? Gastroenterol Rep (Oxf) 2016; 4: 87-95.
3. Tang F, Tie Y, Tu C, Wei X. Surgical trauma-induced immunosuppression in cancer: Recent advances and the potential therapies. Clin Transl Med 2020; 10: 199-223.
4. He M, Fan Q, Zhu Y, Liu D, Liu X, Xu S, et al. The need for nutritional assessment and interventions based on the prognostic nutritional index for patients with femoral fractures: a retrospective study. Perioper Med (Lond) 2021; 10: 61.
5. Wang Y, Jiang Y, Luo Y, Lin X, Song M, Li J, et al. Prognostic nutritional index with postoperative complications and 2-year mortality in hip fracture patients: an observational cohort study. Int J Surg 2023; 109: 3395-406.
6. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016; 40: 159-211.
7. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN practical guideline: Clinical nutrition in surgery. Clin Nutr 2021; 40: 4745-61.
8. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, et al. Immune and metabolic effects of arginine in the surgical patient. Ann Surg 1988; 208: 512-23.
9. Jian ZM, Cao JD, Zhu XG, Zhao WX, Yu JC, Ma EL, et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. JPEN J Parenter Enteral Nutr 1999; 23(5 Suppl): S62-6.
10. Radrizzani D, Bertolini G, Facchini R, Simini B, Bruzzone P, Zanforlin G, et al. Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: a randomized clinical trial. Intensive Care Med 2006; 32: 1191-8.
11. Briassoulis G, Filippou O, Hatzi E, Papassotiriou I, Hatzis T. Early enteral administration of immunonutrition in critically ill children: results of a blinded randomized controlled clinical trial. Nutrition 2005; 21: 799-807.
12. Beale RJ, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, et al. Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. Crit Care Med 2008; 36: 131-44.
13. Zhu X, Herrera G, Ochoa JB. Immunosupression and infection after major surgery: a nutritional deficiency. Crit Care Clin 2010 26: 491-500, ix.
14. Wink DA, Hines HB, Cheng RYS, Switzer CH, Flores-Santana

W, Vitek MP, et al. Nitric oxide and redox mechanisms in the immune response. J Leukoc Biol 2011; 89: 873-91.
15. Patel JJ, Miller KR, Rosenthal C, Rosenthal MD. When is it appropriate to use arginine in critical illness? Nutr Clin Pract 2016; 31: 438-44.
16. Grimble RF. Nutritional modulation of immune function. Proc Nutr Soc 2001; 60: 389-97.
17. Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, et al. Arginine metabolism and nutrition in growth, health and disease. Amino Acids 2009; 37: 153-68.
18. Witte MB, Barbul A. Arginine physiology and its implication for wound healing. Wound Repair Regen 2003; 11: 419-23.
19. Stechmiller JK, Childress B, Cowan L. Arginine supplementation and wound healing. Nutr Clin Pract 2005; 20: 52-61.
20. Ochoa JB, Makarenkova V, Bansal V. A rational use of immune enhancing diets: when should we use dietary arginine supplementation? Nutr Clin Pract 2004; 19: 216-25.
21. Visser M, Vermeulen MAR, Richir MC, Teerlink T, Houdijk APJ, Kostense PJ, et al. Imbalance of arginine and asymmetric dimethylarginine is associated with markers of circulatory failure, organ failure and mortality in shock patients. Br J Nutr 2012; 107: 1458-65.
22. Chan EJ, Cho L. What can we expect from omega-3 fatty acids? Cleve Clin J Med 2009; 76: 245-51.
23. Calder PC. Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases. Mol Nutr Food Res 2008; 52: 885-97.
24. Calder PC. Immunonutrition in surgical and critically ill patients. Br J Nutr 2007; 98 Suppl 1: S133-9.
25. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients 2010; 2: 355-74.
26. Żebrowska A, Hall B, Stolecka-Warzecha A, Stanula A, Sadowska-Krępa E. The effect of omega-3 fatty acid supplementation on serum adipocytokines, lipid profile and biochemical markers of inflammation in recreational runners. Nutrients 2021; 13: 456.
27. Shaikh SR, Jolly CA, Chapkin RS. n-3 Polyunsaturated fatty acids exert immunomodulatory effects on lymphocytes by targeting plasma membrane molecular organization. Mol Aspects Med 2012; 33: 46-54.
28. Calder PC. Very long-chain n-3 fatty acids and human health: fact, fiction and the future. Proc Nutr Soc 2018; 77: 52-72.
29. Yu J, Liu L, Zhang Y, Wei J, Yang F. Effects of omega-3 fatty acids on patients undergoing surgery for gastrointestinal malignancy: a systematic review and meta-analysis. BMC Cancer 2017; 17: 271.
30. Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis. Clin Nutr 2017; 36: 737-46.
31. Hess JR, Greenberg NA. The role of nucleotides in the immune and gastrointestinal systems: potential clinical applications. Nutr Clin Pract 2012; 27: 281-94.
32. Schloerb PR. Immune-enhancing diets: products, components, and their rationales. JPEN J Parenter Enteral Nutr 2001; 25(2 Suppl): S3-7.
33. Gil A. Modulation of the immune response mediated by dietary nucleotides. Eur J Clin Nutr 2002; 56 Suppl 3: S1-4.
34. Iwasa M, Iwasa Y, Ohmori Y, Ogoshi S. Effect of administration of nucleosides and nucleotides on protein turnover and the hypoxic myocardium. J Gastroenterol 2000; 35 Suppl 12: 25-8.
35. Coëffier M, Déchelotte P. The role of glutamine in intensive care unit patients: mechanisms of action and clinical outcome. Nutr Rev 2005; 63: 65-9.
36. Andrews FJ, Griffiths RD. Glutamine: essential for immune nutrition in the critically ill. Br J Nutr 2002; 87 Suppl 1: S3-8.
37. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997; 13: 295-302.
38. Parry-Billings M, Evans J, Calder PC, Newsholme EA. Does glutamine contribute to immunosuppression after major burns? Lancet 1990; 336: 523-5.
39. Papoulidis P, Ananiadou O, Chalvatzoulis E, Ampatzidou F, Koutsogiannidis C, Karaiskos T, et al. The role of ascorbic acid in the prevention of atrial fibrillation after elective on-pump myocardial revascularization surgery: a single-center experience–a pilot study. Interact Cardiovasc Thorac Surg 2011; 12: 121-4.
40. Rodrigo R, Gutiérrez R, Fernández R, Guzmán P. Ageing improves the antioxidant response against postoperative atrial fibrillation: a randomized controlled trial. Interact Cardiovasc Thorac Surg 2012; 15: 209-14.
41. Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med 2007; 43: 4-15.
42. Lassnigg A, Punz A, Barker R, Keznickl P, Manhart N, Roth E, et al. Influence of intravenous vitamin E supplementation in cardiac surgery on oxidative stress: a double-blinded, randomized, controlled study. Br J Anaesth 2003; 90: 148-54.
43. Stevens JL, Feelisch M, Martin DS. Perioperative oxidative stress: the unseen enemy. Anesth Analg 2019; 129: 1749-60.
44. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 2002; 236: 814-22.
45. Xiao F, Han W, Yue Q, Ke J, Jia B, Fu X. Perioperative omega-3

fatty acids for liver surgery: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2021; 100: e25743.
46. Gong Y, Liu Z, Liao Y, Mai C, Chen T, Tang H, et al. Effectiveness of ω-3 polyunsaturated fatty acids based lipid emulsions for treatment of patients after hepatectomy: a prospective clinical trial. Nutrients 2016; 8: 357.
47. George J, White D, Fielding B, Scott M, Rockall T, Whyte MB. Systematic review of preoperative n-3 fatty acids in major gastrointestinal surgery. BMJ Surg Interv Health Technol 2023; 5: e000172.
48. Mohsen G, Stroemer A, Mayr A, Kunsorg A, Stoppe C, Wittmann M, et al. Effects of omega-3 fatty acids on postoperative inflammatory response: a systematic review and meta-analysis. Nutrients 2023; 15: 3414.
49. Li C, Bo L, Liu W, Lu X, Jin F. Enteral immunomodulatory diet (omega-3 fatty acid, γ-linolenic acid and antioxidant supplementation) for acute lung injury and acute respiratory distress syndrome: an updated systematic review and meta-analysis. Nutrients 2015; 7: 5572-85.
50. Dushianthan A, Cusack R, Burgess VA, Grocott MP, Calder PC. Immunonutrition for acute respiratory distress syndrome (ARDS) in adults. Cochrane Database Syst Rev 2019; 1: Cd012041.
51. Ogoshi S, Iwasa M, Kitagawa S, Ohmori Y, Mizobuchi S, Iwasa Y, et al. Effects of total parenteral nutrition with nucleoside and nucleotide mixture on D-galactosamine-induced liver injury in rats. JPEN J Parenter Enteral Nutr 1988; 12: 53-7.
52. Adjei AA, Takamine F, Yokoyama H, Shiokawa K, Matsumoto Y, Asato L, et al. The effects of oral RNA and intraperitoneal nucleoside-nucleotide administration on methicillin-resistant Staphylococcus aureus infection in mice. JPEN J Parenter Enteral Nutr 1993; 17: 148-52.
53. Holen E, Jonsson R. Dietary nucleotides and intestinal cell lines: I. Modulation of growth. Nutrition Research 2004; 24: 197-207.
54. Evans ME, Tian J, Gu LH, Jones DP, Ziegler TR. Dietary supplementation with orotate and uracil increases adaptive growth of jejunal mucosa after massive small bowel resection in rats. JPEN J Parenter Enteral Nutr 2005 29: 315-20; discussion 320-1.
55. Carver JD, Saste M, Sosa R, Zaritt J, Kuchan M, Barness LA. The effects of dietary nucleotides on intestinal blood flow in preterm infants. Pediatr Res 2002; 52: 425-9.
56. Suchner U, Kuhn KS, Fürst P. The scientific basis of immunonutrition. Proc Nutr Soc 2000; 59: 553-63.
57. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med 2002; 30: 2022-9.
58. Pasin L, Landoni G, Zangrillo A. Glutamine and antioxidants in critically ill patients. N Engl J Med 2013; 369: 482-4.
59. Andrews PJ, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. Bmj 2011; 342: d1542.
60. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013; 368: 1489-97.
61. Apostolopoulou A, Haidich AB, Kofina K, Manzanares W, Bouras E, Tsaousi G, et al. Effects of glutamine supplementation on critically ill patients: Focus on efficacy and safety. An overview of systematic reviews. Nutrition 2020; 78: 110960.
62. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg 2011; 212: 385-99, 399.e1.
63. Osland E, Hossain MB, Khan S, Memon MA. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. JPEN J Parenter Enteral Nutr 2014; 38: 53-69.
64. Jabłońska B, Mrowiec S. The role of immunonutrition in patients undergoing pancreaticoduodenectomy. Nutrients 2020; 12: 2547.
65. Suzuki D, Furukawa K, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, et al. Effects of perioperative immunonutrition on cell-mediated immunity, T helper type 1 (Th1)/Th2 differentiation, and Th17 response after pancreaticoduodenectomy. Surgery 2010; 148: 573-81.
66. Furukawa A, Furukawa K, Suzuki D, Yoshitomi H, Takayashiki T, Kuboki S, et al. Effect of immunonutrition on infectious complications in low skeletal muscle mass patients after pancreaticoduodenectomy. Clin Nutr 2021; 40: 103-9.
67. Wang SY, Hung YL, Hsu CC, Hu CH, Huang RY, Sung CM, et al. Optimal perioperative nutrition therapy for patients undergoing pancreaticoduodenectomy: a systematic review with a component network meta-analysis. Nutrients 2021; 13: 4049.
68. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev 2012; 11: CD008879.
69. Matsui R, Sagawa M, Sano A, Sakai M, Hiraoka SI, Tabei I, et al. Impact of perioperative immunonutrition on postoperative outcomes for patients undergoing head and neck or gastrointestinal cancer surgeries: a systematic review and meta-analysis of randomized controlled trials. Ann Surg 2024; 279: 419-28.
70. Song GM, Liu XL, Bian W, Wu J, Deng YH, Zhang H, et al. Sys-

tematic review with network meta-analysis: comparative efficacy of different enteral immunonutrition formulas in patients underwent gastrectomy. Oncotarget 2017; 8: 23376-88.
71. Xu J, Sun X, Xin Q, Cheng Y, Zhan Z, Zhang J, et al. Effect of immunonutrition on colorectal cancer patients undergoing surgery: a meta-analysis. Int J Colorectal Dis 2018; 33: 273-83.
72. Martinez Gonzalez A, Llopiz Castedo J, Rodeiro Escobar P, Gonzalez Nunes M, Fernandez Lopez B, Garcia Cardoner MLA, et al. [Effectiveness of immunonutrition in the perioperative nutritional management of gastric cancer]. Nutr Hosp 2024; 41: 330-7. Spanish.
73. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019; 38: 48-79.
74. Wischmeyer PE, Carli F, Evans DC, Guilbert S, Kozar R, Pryor A, et al. AAmerican society for enhanced recovery and perioperative quality initiative joint consensus statement on nutrition screening and therapy within a surgical enhanced recovery pathway. Anesth Analg 2018; 126: 1883-95.
75. Rosenthal MD, Carrott PW, Patel J, Kiraly L, Martindale RG. Parenteral or enteral arginine supplementation safety and efficacy. J Nutr 2016; 146: 2594S-600S.
76. Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: dietary fatty acids for healthy adults. J Acad Nutr Diet 2014; 114: 136-53.
77. Hwang JY, Kim Y, Lee HS, Park EJ, Kim J, Shin S, et al. The development of resources for the application of 2020 Dietary Reference Intakes for Koreans. J Nutr Health 2022; 55: 21-35.
78. Reis AM, Kabke GB, Fruchtenicht AV, Barreiro TD, Moreira LF. Cost-effectiveness of perioperative immunonutrition in gastrointestinal oncologic surgery: a systematic review. Arq Bras Cir Dig 2016; 29: 121-5.
79. Loon MM, Goshe M, Rashid M, Shehryar A, Rehman A, Abdallah S, et al. Impact of preoperative nutritional support on surgical outcomes in gastrointestinal surgeries: a systematic review. Cureus 2024; 16: e56416.
80. Serelli-Lee V, Ito K, Koibuchi A, Tanigawa T, Ueno T, Matsushima N, et al. A state-of-the-art roadmap for biomarker-driven drug development in the era of personalized therapies. J Pers Med 2022; 12: 669.
81. Fountzilas E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. Genome Med 2022; 14: 101.
82. Wang F, Zheng J, Cheng J, Zou H, Li M, Deng B, et al. Personalized nutrition: A review of genotype-based nutritional supplementation. Front Nutr 2022; 9: 992986.
83. Hesketh J. Personalised nutrition: how far has nutrigenomics progressed? Eur J Clin Nutr 2013; 67: 430-5.
84. Kumari S, Goyal A, Sonmez Gurer E, Algin Yapar E, Garg M, Sood M, et al. Bioactive loaded novel nano-formulations for targeted drug delivery and their therapeutic potential. Pharmaceutics 2022; 14: 1091.
85. Manocha S, Dhiman S, Grewal AS, Guarve K. Nanotechnology: An approach to overcome bioavailability challenges of nutraceuticals. J Drug Deliv Sci Technol 2022; 72: 103418.
86. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clin Nutr 2023; 42: 1671-89.
87. Grimble RF. Basics in clinical nutrition: Immunonutrition – Nutrients which influence immunity: Effect and mechanism of action. E Spen Eur E J Clin Nutr Metab 2009; 4: e10-e3.