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Pharmaconutrition: Which substrates?

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ABSTRACT

With the term "pharmaconutrition" or "immunonutrition" is intended the use of specific nutritional substrates having the ability of modulating specific mechanisms involved in several immune and inflammatory pathways. To achieve these goals, these substrates have to be administered with over physiologic dose.

Glutamine and omega-3 polyunsaturated fatty acids, used as single substrate, did not show clear clinical advantages on solid endpoints such as postoperative complications.

Despite several multiple substrate enteral feeds are available on the market, very few of them have been tested in randomized clinical trial to prove efficacy. The most extensive investigated formulation is a combination of arginine, omega-3 fatty acids, ribonucleic acid with or without glutamine. Several meta-analyses of randomized clinical trials have been conducted to compare the effects of enteral immunonutrition with control diets on post-surgical morbidity. The results consistently showed that the use of enteral multiple substrate formulas significantly reduced infectious complications and duration of hospitalization.

In a more contemporary view, pharmaconutrition should be tested more accurately in the contest of enhanced recovery programs, during neoadjuvant chemotherapy, and in the prehabilitation setting.

1. Introduction

In oncologic surgical patients, the traditional rationale behind the use of nutritional support was the attempt to prevent or correct malnutrition and, consequently, the malnutrition-associated risk of postoperative morbidity. Beyond the risk of poor nutritional status, it is well-recognized that the tissue trauma induced by major surgery and general anesthesia, generates immunosuppression, generalized inflammation, and gut dysfunction. Therefore, the above concepts, targeted on the simple maintenance of nutritional and metabolic homeostasis, evolved and the preservation of a trophic gut mucosa through enteral nutrition, the boost of the immune response, and the restrain of the hyperiflammation become priority. This paradigmatic change has been attempted through the administration of specialized nutrients. With the term of pharmaconutrition or immunonutrition is intended the use of specific nutritional substrates having the ability of modulating specific mechanisms involved in several immune and inflammatory pathways. To achieve these goals, these substrates have to be administered with over physiologic dose. As such they may also induce undesirable side effects. Moreover, the expected effects may be obtained even if given with no aim of calorie and nitrogen support. Thus, the provision of these specific nutrients may achieve effects that should be ascribed more to pharmacological activity than to nutritional repletion [1]. This phenomenon is defined as "effect of nutrients dissociated from nutrition" and as such the benefits should be observed also in patients without nutritional derangements.

2. Glutamine

The administration of glutamine, alone or in combination, showed historically high interest in the surgical community for the intrinsic characteristics of this amino acid. Indeed, glutamine (Gln)

Abbreviations: Gln, glutamine; omega-3 PUFA, omega-3 polyunsaturated fatty acids; NAT, neoadjuvant treatments; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; ERAS, Enhanced recovery after surgery; EIN, enteral immunonutrition.

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is involved in a variety of biological processes, such as anabolic functions, acid-base regulation in the kidney, and ammonium and nitrogen metabolism [2]. The importance of Gln in maintaining the body metabolic homeostasis becomes evident during periods of stress, when it becomes a conditionally essential amino acid. Depletion in Gln storage during stressful events such as sepsis, burn, and injury has been indeed reported [3,4]. Moreover, the excessive needs of Gln during catabolic states such as an advanced malignant disease are supplied from muscle stores, and this might lead to a massive depletion of this amino acid in the skeletal muscle. Gln starvation results in energy depletion, decreased immune defense, and stimulated apoptosis [5].

Skeletal muscle is not only the main source of glutamine, but it also synthesizes, stores, and releases Gln to be used by several tissues and cells, such as lymphoid organs and leukocytes [6]. The decrease in plasma glutamine availability has been reported to contribute to the impaired immune function in several clinical conditions. In fact, glutamine depletion reduces lymphocyte proliferation, impairs expression of surface activation proteins on and production of cytokines, and induces apoptosis in these cells [5]. Depletion of Gln storage has been indeed associated with unfavorable outcomes in several medical settings. In critically ill patients, low levels of Gln are associated with increased morbidity and mortality [7–10].

The supplementation with Gln, either oral, enteral or parenteral increases the response against bacterial infections, and parenteral Gln has been reported to be beneficial for patients after surgery, radiation treatment, bone marrow transplantation, or injury [11,12]. The administration of glutamine before the onset of stressful events may prevent unfavorable outcomes related to the deficiency of this amino acid [13]. Evidence suggested that an exogenous Gln supplementation is associated with improved protein synthesis, preservation of gut barrier, enhancement of wound healing, reduction of oxidative stress, negative nitrogen balance, improvement of glucose metabolism, and modulation of the immune system [14–17]. A recent meta-analysis on more than 1,000 acute pancreatitis patients demonstrated that Gln-supplemented nutrition, either enteral or parenteral, significantly reduced mortality, complications and duration of hospitalization. Moreover, parenteral Gln improved restoration of liver, kidney and immune function [18]. Conversely, in a large RCT including severely burn-injured patients the administration of enteral Gln did not show any benefit in terms of survival, major adverse events, nor time to discharge from hospital [19].

The effect of Gln supplementation on the increase amount of lean mass in cancer patients has been broadly observed [20]. In gastric and esophageal cancer patients, supplementation with parenteral Gln given in the perioperative had a positive dose-dependent impact on the recovery of serum albumin levels [21]. However, whether this recognized positive effect on surrogate endpoints translates into a clear protection of the occurrence of surgical-related complications remains unclear. Some underpowered RCTs analyzing clinical outcomes following elective abdominal surgery reported contrasting results on the effects of Gln supplementation [22–26]. However, the largest and adequately powered randomized, multicenter trial, carried out in 428 subjects who were candidates for elective major gastrointestinal surgery, clarified the role Gln supplementation [27]. Patients, with documented gastrointestinal cancer and weight loss <10%, received either intravenous infusion of Gln (n = 212), or no supplementation (control group, n = 216). Glutamine infusion began the day before operation and continued postoperatively for at least 5 days. No postoperative artificial nutrition was allowed unless patients could not adequately eat by day 7. Patients were homogenous for baseline and surgical characteristics. The mean percent of weight loss was 1.4 (2.7) in controls and 1.4 (2.4) in Gln group. The overall postoperative complication rate was 34.9% (74/212) in Gln group and 32.9% (71/216) in control group (P = 0.65). Infectious morbidity was 19.3% (41/212) in Gln group and 17.1% (37/216) in controls (P = 0.55). The rate of major complications was 7.5% (16/212) in Gln group and 7.9% (17/216) in controls (P = 0.90). Mean duration of hospitalization was 10.2 days in Gln group versus 9.9 days in controls (P = 0.90).

Contrasting results had also been confirmed by several meta-analyses [28–32]. Inconsistency in terms of clinical outcomes may be conditioned by several features such as study design, type of patients, baseline disease and nutritional status, concomitants treatments, route, and dose of administration.

Given those evidence, no standard parenteral Gln supplementation should be routinely given to patients undergoing surgery for gastrointestinal malignancy. Current guidelines recommend considering parenteral glutamine supplementation in selecting cases, namely those who cannot be fed adequately enterally and need exclusive parenteral nutrition. The extent to which parenteral glutamine administration in combination with oral nutrition/EN may have a positive effect, cannot be clarified at present due to lack of available data. Furthermore, no clear recommendation can be given regarding the supplementation of oral glutamine, as no clinical benefit has been provided so far, and data regarding oral glutamine supplementation as a single substance are limited [33].

3. Omega-3 polyunsaturated fatty acids

The omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, have been shown in a number of preclinical studies [34] to exert anti-inflammatory and immunomodulatory effects through the effect on eicosanoid metabolism, with potential beneficial consequences on surgical outcome and recovery. This constituted the rationale for omega-3 fatty acids supplementation in surgical patients.

The preoperative period represents an ideal setting for providing substrates with the aim to reach adequate tissue levels of substrates at the time of surgery and eventually, to modulate the postoperative inflammation.

In the last two decades, several randomized trials [35–46] investigated the effects of preoperative omega-3 fatty acid supplementation in major abdominal surgery. The available trials are heterogeneous in terms of surgical procedures, nutritional status, and route and schedule of administration of omega-3 fatty acids supplementation, as described in Table 1.

n-3 PUFAs were provided as EPA or a combination of EPA and DHA, through intravenous infusion or oral/enteral administration. Preoperative supplementation was continued postoperatively in seven clinical trials (Table 1). Non-oncologic patients were also included in one trial [44] and most of the surgical procedures were performed as open surgery.

3.1. Biologic and inflammatory results

The effects of the nutritional intervention, in terms of serum fatty-acids levels and the subsequent membrane modification of leukocytes, have been evaluated in different trials [36,37,42] since considered as a prerequisite for a subsequent immunomodulatory effect.

Irrespective of the route of administration, preoperative supplementation of omega-3 fatty acids has been shown to result in an increased EPA levels in serum and cell membranes.

However, trials evaluating the immunomodulatory effects of such supplementation on postoperative inflammation have shown contrasting results [35–40,42,43,45].

Most of the studies evaluated the inflammatory response to

Table 1
Randomized clinical trials on n-3PUFAs as single pharmaconutrient.

Study	Type of surgery	# of patients	Route of administration	% malnourished patients	Pre-op administration	Post-op administration	Primary endpoint
Weiss, 2002	Upper GI	24	IV	0%	2 days	5 days	Inflammation
Ryan, 2009	Esophagectomy	53	enteral	18%	5 days	21 days	Body composition
Sultan, 2012	Esophagectomy	195	oral/enteral	8%	7 days	7 days	Infectious morbidity
de Miranda Torrinhas RS, 2012	Upper and lower GI	63	iv	19%	3	//	Postoperative outcome
Sorensen, 2014	Lower GI	148	oral	NA	7 days	7 days	Postoperative outcome
Sorensen, 2014	Lower GI	148	oral	NA	7 days	//	Inflammation
Ashida, 2017	Pancreatoduodenectomy	20	oral	25%	7 days	//	Inflammation
Healy, 2017	Esophagectomy	191	enteral	39%	5 days	50 days	Body composition
Aoyma, 2019	Total gastrectomy	123	oral	NA	7 days	21 days	Postoperative weight loss
Bakker, 2020	Lower GI	44	IV	0%	1 day	//	Inflammation
Hossain, 2020	Lower GI	61	oral	NA	5 days	21 days	Inflammation
Linecker, 2020	Liver surgery	261	IV	NA	1 day	//	Postoperative outcome

IV: intravenous; NA: not assessed.

surgical stress in terms of cytokine serum levels at different time points or their ex-vivo production. Postoperative pro-inflammatory IL-6 and IL-10 cytokine serum levels were found to be significantly reduced after preoperative intravenous administration of n-3 fatty acids in patients undergoing upper gastrointestinal or colorectal surgery [2,5]. Similarly, the monocyte HLA-DR expression, a marker of immune competence, was found to be less reduced after surgery in the same patients, if compared to control groups.

The same results were not confirmed by other studies, evaluating perioperative enteral administration of n-3 PUFAs in different surgical settings, such as gastroesophageal cancer surgery and pancreatoduodenectomy [39,40]. However, the discrepancy in these results is of difficult interpretation, since the postoperative inflammatory stress response is directly related to the magnitude of surgical trauma.

3.2. Impact on body composition

The effects of perioperative administration of n-3 PUFAs on body composition in surgical patients was evaluated in terms of postoperative lean body mass preservation [36,40,41,43].

In a trial including 53 patients undergoing esophagectomy, perioperative supplementation of n-3 PUFAs resulted, at postoperative day 21, in a maintenance of body composition when compared to control patients, in which a significant loss of lean body mass was observed with respect to preoperative condition [36]. A subsequent, larger, multicenter trial [40] conducted in an analogue setting, failed to observe similar results, showing no difference in the decrease of lean body mass at 1, 3 and 6 months following the surgical procedure.

Perioperative supplementation of n-3 PUFAs compared to standard diet did not result in any advantage in terms of postoperative lean body mass preservation also in patients who underwent total gastrectomy [41]. Similar results were observed in another randomized trial [43], including colorectal surgical patients.

3.3. Surgical outcome

The relationship between perioperative n-3 PUFAs supplementation and postoperative surgical outcome have also been reported in all the evaluated randomized trials, as a primary or secondary endpoint (Table 1). Although some studies analyzed a limited number of patients, and therefore may be underpowered to correctly detect any existing difference, a positive impact of n-3 PUFAs administration on postoperative overall, major or infectious morbidity has not been shown by any trial. On the contrary, an increase in infectious complication rate in the supplemented group was reported by one trial, including 44 colorectal cancer procedures [42]. Similarly, none of the available clinical trials reported a reduction of mortality in favor of n-3 PUFAs supplementation. Thus, no sufficient evidence in terms of clinical benefits is available from clinical studies investigating the individual impact of perioperative n-3 PUFAs in surgical patients.

4. Enteral formulas with multiple pharmaconutrients

Despite several multiple component enteral feeds are available on the market, very few of them have been tested in randomized clinical trial to prove efficacy. The most extensive investigated formulation is a combination of arginine, omega-3 fatty acids, ribonucleic acid with or without glutamine.

The development of such enteral formulas started in the 80s with extensive *in vitro* experiments first, and gradually in animal models of infection, sepsis and bacterial translocation [47–49]. The clinical use, with the first phase II studies [50–55], become available in the mid-90s. Since then, dozens of trials have been published and the results pooled in meta-analyses and systematic reviews [56–101]. The most recent meta-analysis by Shen et al. [102], included 35 randomized clinical trials (RCT), published between January 2000 and January 2022, with a total of 3,692 patients undergoing surgery for gastrointestinal cancer. The global analysis showed that compared with the control group, enteral immunonutrition (EIN) group had a significantly decreased incidence of overall complications ($RR = 0.79$, $p < 0.001$). Infectious complications in patients who received EIN were considerably lower than in the control group ($RR = 0.66$, $p < 0.001$). Compared to the control group, the incidence of surgical site infection, abdominal abscess, anastomotic leakage, bacteremia, duration of systemic inflammatory response syndrome, and duration of antibiotic therapy was significantly lower. The authors thoughtfully evaluated the effect of pharmaconutrition in several subgroups of patients undergoing gastric, esophageal, colorectal, or pancreatic cancer surgery. Possibly for a sample size effect, the beneficial properties of EIN on morbidity was mostly evident in colorectal surgery. The analysis of the different intervention periods (pre-, post-, and peri-operative supplementation of EIN) showed that all three modalities of administration had similar advantages on overall and infectious morbidity. The ability of EIN to significantly

reduce complications was evident when compared to standard isocaloric and isonitrogenous diets as well as when no nutritional supplements were used. The results also confirmed that the administration of EIN is efficacious in improving several outcomes in both malnourished and well-nourished patients. The improved outcomes seen in patients receiving pharmaconutrition translated in a reduction of the hospitalization period after surgery of approximately 2 days (95% CI: 2.98/-1.10; $p < 0.001$).

4.1. Future directions

Most of the RCTs included in the above mentioned meta-analyses were performed when the enhanced recovery after surgery (ERAS) protocols were not or only partially in use. Since ERAS pathways *per se* have been repeatedly shown to significantly reduce postoperative morbidity after colorectal surgery [103,104] and across many type of surgical interventions [105–107], it might be that the benefits of EIN are no more evident when a full ERAS is implemented. Moya et al. [108], addressed this issue and designed a RCT to test the "on top" effect of immunonutrition in patients undergoing colorectal resection under an established ERAS protocol. The study aimed to examine whether the joint implementation of immunonutrition with an ERAS program might improve morbidity, mortality, and duration of hospitalization compared with classic nutritional supplements. The authors randomized 244 patients and the results globally showed that the patients who received immunonutrition presented with fewer complications (23% vs. 35.20%; $p = 0.035$) and in particular a significant decrease in infectious complications (10.7% vs. 23.8%; $p = 0.0007$). Among the infectious complications, surgical site infections were significantly different between groups (17.2% in control vs. 5.7% in immunonutrition, $p = 0.0005$).

In the next future the role of pharmaconutrition should be tested in other two emerging fields of oncologic surgery: neoadjuvant treatments (NAT) and prehabilitation. NAT implementation in patients with cancer can cause several adverse effects such as reduced food intake, malabsorption, and nitrogen wasting. These may cause the development of malnutrition and sarcopenia [109]. Such changes in body composition can negatively impact on NAT itself, in terms of treatment completion, outcomes and access to subsequent surgery [110]. Pharmaconutrition, along with providing calories and proteins, may improve the control of inflammatory response and maintain an effective immune response in cancer patients while receiving NAT [111,112].

ERAS protocols have largely focused on optimization of the recovery pathways in the hospital setting or in the immediate pre-surgical period. Little focus has been made on optimal management of patients, particularly in a NAT setting. The pre-surgical as well as the NAT period could actually represent a window of opportunity to boost and optimize patient health, improve compliance to anticancer treatments and the nutritional status, providing a compensatory "buffer" for the postoperative reduction of physiological reserve [113]. The term "prehabilitation" defines a program that includes a series of pre-admission interventions to be initiated 3–6 weeks before surgery, aiming at improving body composition and physical performance, reducing the surgery-related morbidity and facilitating patient's recovery [114]. Cancer prehabilitation has been also defined as "a process of care that occurs between the diagnosis and the beginning of acute treatment, providing targeted interventions that improve a patient health to reduce the incidence and the severity of current and future impairments" [115]. The prehabilitation program is multimodal, including nutritional supplementation, physical exercise, and anxiety reduction strategies that should be considered in case of proven functional and nutritional deficits.

CRediT authorship contribution statement

Luca Gianotti: participate in the study design and writing, approved the final version of the manuscript. **Luca Nespoli:** participate in the study design and writing, approved the final version of the manuscript. **Marta Sandini:** participate in the study design and writing, approved the final version of the manuscript.

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