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Review Article

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Immunomodulatory diets in patients with gastrointestinal tract cancer: Integrative review

Dietas imunomoduladoras em pacientes com câncer do trato gastrointestinal: Revisão integrativa

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Abstract
Introduction: The cancer patient undergoes a series of metabolic and nutritional changes due to the disease and the treatments used. Studies reveal that supplementation with enteral formulas and immunomodulatory diets with specific nutrients can improve nutritional status, the immune system and act in the modulation of the inflammatory response. **Objective:** Analyzing through the literature the effect of immunomodulatory diets in surgical patients with cancer of the gastrointestinal tract. **Materials and methods:** This is an integrative literature review study, using articles indexed in the VHL, PubMed and SciELO databases through the descriptors: "enteral nutrition", "surgery", "gastrointestinal neoplasia", "arginine", "Omega-3 fatty acids" and "glutamine", combined with the Boolean operator "AND", available in Portuguese, English and Spanish, published in the last 10 years. **Results:** A total of 236 articles were found and 11 made up the sample after applying the inclusion criteria. Studies show that supplementation with immunomodulatory diets in surgical patients with cancer of the gastrointestinal tract is effective, since they help in improving the inflammatory and immunological response, and in the nutritional status, preventing weight loss, reducing postoperative complications, enabling a better recovery and reducing the length of hospital stay. **Conclusions:** Nutritional therapy with immunomodulatory diets contributes positively to the treatment, recovery and reduction of complications in cancer patients. It is suggested that further studies be carried out to promote more scientific evidence necessary to establish supplementation protocols for surgical cases of patients with neoplasms of the gastrointestinal tract.
Keywords: immunomodulation; enteral nutrition; gastrointestinal neoplasms.

Resumo
Introdução: O paciente oncológico sofre uma série de alterações metabólicas e nutricionais em decorrência da doença e dos tratamentos utilizados. Estudos revelam que a suplementação com fórmulas enterais e dietas imunomoduladoras com nutrientes específicos podem melhorar o estado nutricional, o sistema imunológico e agir na modulação da resposta inflamatória. **Objetivo:** Analisar através da literatura o efeito de dietas imunomoduladoras em pacientes cirúrgicos com câncer do trato gastrointestinal. **Materiais e métodos:** Trata-se de um estudo de revisão integrativa da literatura, utilizando artigos indexados nas bases de dados BVS, PubMed e SciELO através dos descritores: "nutrição enteral", "cirurgia", "neoplasia gastrointestinal", "arginina", "ácidos graxos ômega-3" e "glutamina", combinados ao operador booleano "AND", disponíveis nos idiomas português, inglês e espanhol, publicados nos últimos 10 anos. **Resultados:** Foram encontrados no total 236 artigos e 11 compuseram a

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amostra após aplicação dos critérios de inclusão. Estudos demonstram que a suplementação com dietas imunomoduladoras em pacientes cirúrgicos de câncer do trato gastrointestinal é eficaz, visto que auxiliam na melhora da resposta inflamatória, imunológica, e no estado nutricional, prevenindo a perda de peso, diminuindo as complicações pós-operatórias, possibilitando uma melhor recuperação e redução do tempo de permanência hospitalar. **Conclusões:** A terapia nutricional com dietas imunomoduladoras contribui positivamente no tratamento, recuperação e redução de complicações em pacientes oncológicos. Sugere-se a realização de novos estudos para promoção de mais evidências científicas necessárias para estabelecimento de protocolos de suplementação para casos cirúrgicos de pacientes com neoplasias do trato gastrointestinal..
Palavras-chave: imunomodulação; nutrição enteral; neoplasias gastrointestinais.

Introdução

Cancer is one of the main public health problems worldwide, ranked fourth as a leading cause of premature mortality in most countries. The mortality incidence and rate have been increasingly high around the globe, pointing to an increase about 620,000 new cases each year until 2022[1].

Regarding mortality due to malignant tumors, gastrointestinal tract cancer appears as the fourth most common cause, as stomach cancer is the second. Meanwhile, the survival rate for colon cancer is good if early[2] diagnosed.

The disease and treatment applied on cancer patients plays metabolic and nutritional changes as results, which may lead to a protein-calorie malnutrition. These changes negatively influence the treatment due to a nutritional deficit, leading to a reduced response to treatment and affecting the quality of life of patients. Several factors as age, type and stage of cancer along as the treatment[3] represents the rising and severity of malnutrition.

Malnutrition rate in cancer patients ranges from 40% up to 80% with gastrointestinal cancer, in which oral food intake is insufficient and bowel function is generally impaired. There must be nutritional supplements on diet in order to supply the energy needs on hospitalized patients, once their nutritional status directly reflects onto the clinical evolution[4].

Improvements on nutritional status and immune system through enteral nutrition formula had been useful on studies performed in recent years. In order to modify the metabolic response due to stress[5], several other types of treatment are still being sought, although, the administration of enteral formulas provide the correct amount of nutrients.

Immunomodulatory diets with specific nutrients, such as: arginine, glutamine, fatty acids, etc., may incur directly or indirectly on the immune system by modulating the inflammatory response and helping to treat patients suffering from cachexia and cancer[4,6].

European Society of Parenteral and Enteral Nutrition (ESPEN) suggests that enteral nutrition along with immune-modulating formulas is useful on both pre- and post-surgery on patients. Such recommendation includes the individual's nutritional risk, within a period of five to seven days, lasting for fourteen days in cases of malnutrition to reduce the risk of complications. The recommendation for immune-modulating formulas in submitted patients to elective surgeries has a level A of high scientific evidence, proving to be beneficial for surgeries on gastrointestinal tract[5,7].

Immunonutrition is the major factor in the pre-surgery, being able to improve the post-surgery. Lately, formulas containing immunonutrients have brought a new meaning to the recovery process of hospitalized patients after major intestinal surgery. These nutrients modulates the immune response by promoting protein

synthesis, which leads to a favorable patient prognostic[8].

In the light of the foregoing, this study aims to analyze the effect of immune-modulating diets on surgical patients suffering from gastrointestinal tract cancer based on the scientific literature.

Materiais e Métodos

Amostra e tipo de estudo

This study is an integrative literature review, matching to a broad method. It also includes studies from different methodology approaches, enabling the synthesis and analysis of research findings[9].

Delineamento da pesquisa

This review was performed from May to July 2020. Articles chosen by title, abstracts and year of publication followed process of question formulation. Collected data from original essays presenting analysis and observed results as well as research findings to guide the problem: "Which scientific evidences are presented regarding effects of immune-modulating diets on surgical patients suffering from gastrointestinal tract cancer?"

PICO strategy is presented on the problem guiding line, being an acronym for *Patient*, *Intervention*, *Comparison* and *Outcome.* According to Santos, Pimenta and Nobre[10], PICO is referred to População, Fenômeno, Contexto and Desfecho. Cancer patients as "População"; immune-modulating diets in "Fenômeno", "Context" for pre- and post-surgery; immune/inflammatory response and nutritional status improvement as "Desfecho".

Critérios de Inclusão e Exclusão

Inclusion criteria is based on clinical experiments and studies with patients, published from 2010 to 2020. Related scientific articles in Portuguese, English and Spanish, addressing themes as enteral nutrition, surgery, gastrointestinal cancer, arginine, omega-3 fatty acids and glutamine were included. Nevertheless, non-thematic studies, such as performed on animals, meta-analysis and reviews are excluded.

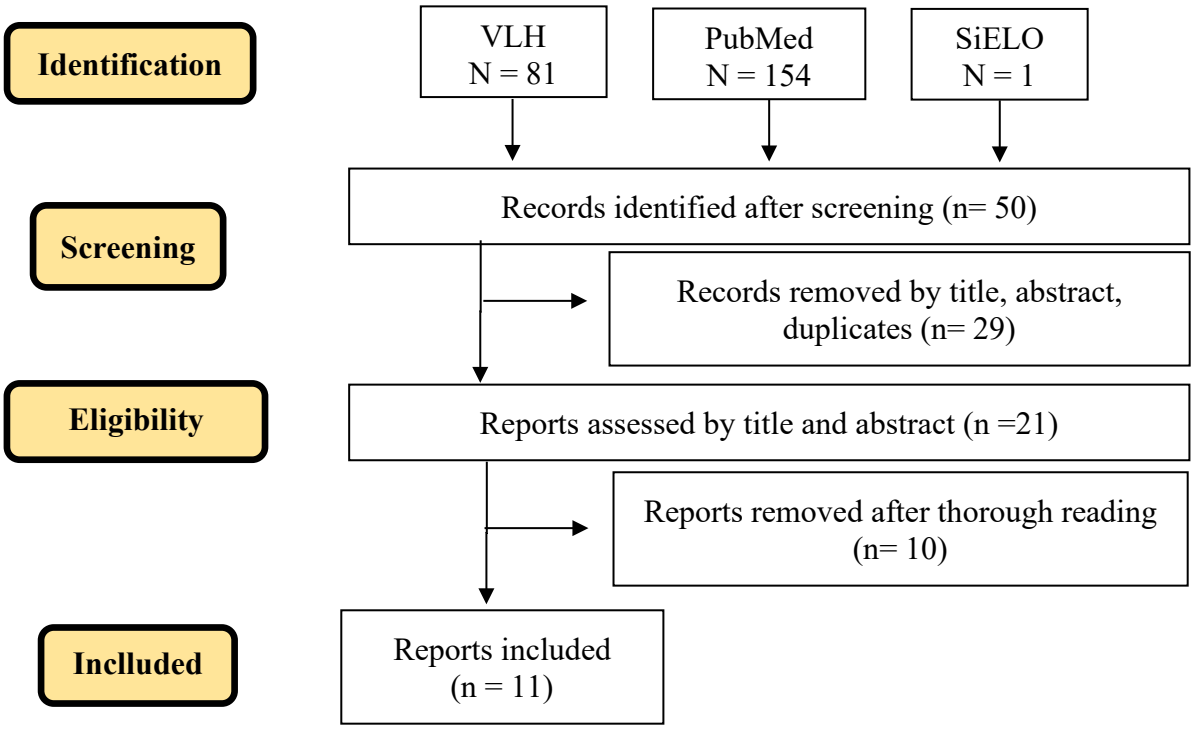
Procedimentos

Applied filters narrowed research period focusing on *Virtual Health Library* (VHL), *PubMed* and *Scientifc Electronic Library Online* (SciELO), through keywords as enteral nutrition, surgery, gastrointestinal cancer, arginine, omega-3 fatty acids and glutamine. According to DeCS and MeSH, combined keywords to Boolean operator (AND) resulted in: 1) "nutrição enteral and cirurgia and câncer gastrointestinal and glutamina"; 2) "nutrição enteral and cirurgia and câncer gastrointestinal and arginina"; 3) "nutrição enteral and cirurgia and câncer gastrointestinal and ácidos graxos omega-3", as well as translated into English and Spanish for better results.

Resultados

A total number of 236 studies had been found. Applied filters selected 50 from 236 studies, 29 of them being excluded due to divergences on title and abstract. At the end, only 11 studies were analyzed to collect samples. According to collected database, *Figure 1* (Prism Flowchart) reveals the selected studies.

Figure 1 – Flowchart of article selection process in the review (*Prisma Flow*).



Source: *Guimarães, Silva e Sales* (2020), adapted from Moher, Liberati, Tetzlaff e Altman[11].

All 11 selected scientific articles are classified as Experimental Studies. A particular instrument performed collected data extraction. The studies were inserted in table 1 according to authors, date of publication, objective, sample, diets, supplementation followed by results and conclusion.

Immune-modulating supplementation on studies including glutamine, arginine and omega 3 were analyzed in patients suffering from gastrointestinal cancer. Studies samples ranged from 20 to 326 surgical patients over the age of 18 years.

Table 1. Summary of main characteristics of the articles included for review. Teresina, Brazil, 2020.

Author/ Year published	Type of study	Objective	Sample	Diet content	Supplementation	Main results/ findings
Ma C, *et al.,* (2018)[4]	Prospective study, randomized, double blind	To determine whether an immune-modulating nutrient-enriched EN diet can improve nutritional status and reduce postoperative infection and surgery-induced immune suppression in patients with gastric cancer or GIST undergoing major surgery.	34 patients with gastric adenocarcinoma or gastric GIST undergoing elective curative surgery Study group: (n=17) Control group: (n=17)	Glutamine, arginine and fish oil	Study group: ordinary diet plus 400 mL/day for 3-5 days before surgery. On postoperative day 4, patients received a semi-liquid diet plus 400 mL/day of the supplementary diet. On days 5-14 or until discharge 1200 mL/day of the selected diet and a further oral soft diet. Control group: standard diet from 3 days before surgery until postoperative day 14 or discharge.	No significant differences were observed between the two groups in selected laboratory and inflammatory parameters, or in their net change, before and after treatment. Immune-modulating nutrient-enriched EN had no prominent immunomodulation effect compared with that of standard EN.
Liu H, *et al*., (2012)[12]	Randomized controlled study	To determine whether enteral nutrition (EN) was effective on the nutritional state, immunological function, surgical results and on days of hospital stay after total gastrectomy surgery on patients with advanced gastric cancer (AGC).	78 patients undergone total gastrectomy previously with ACG. Spread in 3 groups: Group #1: EN immuno-enhanced (EN + glutamine) (n=28); Group #2: standard EN (n=24); Group #3: control group (n=26).	Glutamine and arginine	Group #1: standard EN enriched with Gln (12,5 g/L) and arginine (9,0 g/L); Group #2: standard EN, 500 ml/bottle (20,0g - PT, 9,5g - LIP, 61,5g - CHO, 7,5g - fiber, 3g - minerals, 0,15g - vitamins), which provides 500 kcal from overall diet. Group #3: received nutritional support - CHO (5% and 10% glucose), during liquid food and semi-liquid intake.	Groups #1 and #2 had a faster onset of latus and shorter hospital stays than #3. On postoperative day 12, serum levels of pt, albumin, proalbumin and transferrin in groups #1 and #2 were significantly higher than in group #3. $CD4^+$ T cells, NK, IgM and IgG levels in group 1 increased and were significantly higher than before the operation, and groups 2 and 3. The EN immuno-enriched may improve the nutritional status and immune function of patients with AGC after total gastrectomy.
Abe T, *et al.,* (2018)[13]	Observational study	To examine the influence of post-operative GFO administration on a short-term peri-operative surgery. As well as the outcomes and post-operative complications after radical transthoracic	326 patients with esophageal cancer, Study group (n=189): received perioperative treatment with GFO	Glutamine, fiber and oligosaccharide	IMPACT (750 mL/day) on all patients during 5 days before surgery. Study group: received 3 bottles/day of GFO on via oral or transluminal feeding for 5 days on	SIRS' duration was significantly shorter on the GFO group when compared to the control group. Furthermore the PCR value was significantly smaller on the GFO group than in the control on the

		esophagectomy treatment in patients with thoracic esophageal cancer.	(glutamine, fiber and oligosaccharide). Control group (n=137): none.		pre- and post-operative (4 hrs - 250 mL/day) periods. It was gradually incremented to 1500 mL/day on day 4. The supplementation continued up to day 14.	second postoperative day. Perioperative use of enteral supplementation with glutamine, fiber, and oligosaccharide probably contributes to the reduction of early surgical stress after esophagectomy.
Kleck S*, et al.,* (2016)[14]	Randomized clinical trial	To determine if the usage of postoperative enteral nutrition enriched with glutamine, arginine and omega-3 fatty acids affects survival of patients diagnosed with stomach cancer.	99 patients who underwent gastric cancer surgery. Study group: (n=45) Control group: (n=54)	Glutamine, arginine and omega-3 fatty acids.	Study group (EEN): Reconvan 20 mL/h on day 1st postoperative, 50 mL/h on day 2, 75 mL/h on day 3 and 100 mL/h from days 4 to 7 Control group: Peptisorb	No significant difference was revealed between groups. Analysis suggests the EEN group may present lower risks on the first year after surgery. A significant reduction in the risk of death was seen during the first 6 months following surgery in the EEN group in stage IV patients. However, its use caused no influence on the risk of death when patients were analyzed together. The study does not support the beneficial effect of enriched enteral nutrition in long-term survival.
Marano L*, et al.,* (2013)[15]	Randomized controlled clinical trial	To evaluate the impact of early postoperative enteral immunonutrion in a homogeneous group of patients with gastric cancer undergone total gastrectomy.	109 patients diagnosed with gastric cancer. Study group: (n=54) Control group: (n=55)	Arginine, omega-3 fatty acids and ribonucleic acid (RNA)	Study group (n=54): immuno-enriched enteral diet IMPACT Control group (n=55): standard enteral diet. Nutrition via jejunostomy was applied on both groups 6 hrs after surgery until the seventh posteroperative day.	In comparison the study group suffered significantly less with SIRS than the control group. Although the postoperative CD4 and T-cells count decreased in both groups, such reduction was emphasized on the supplemented group rather than the control group. Early postoperative enteral with immunonutrients significantly improves clinical and immunological outcomes in patients undergone gastrectomy for gastric cancer.

Nagano T, *et al.,* (2013)[16]	Randomized controlled clinical trial	To compare the effects of antioxidant-enriched enteral nutrition (AeEN) and immune-enhancing enteral nutrition (IeEN), in patients undergone esophagectomy for cancer, with respect to nutrition, immune-inflammatory response, antioxidant capacity, and clinical conditions.	20 patients undergone esophagectomy as cancer treatmeant. AeEN group (n= 10) IeEN group (n= 10)	Arginine, polyunsaturated omega-3 fatty acids and nucleotides	AeEN group (n=10): 800 ml of Anom via oral feeding during 5 days before surgery. 7 days post-surgery: administered 400 to 1.600 mL with gastrostomy. IeEN group (n=10): 750–1000 mL IMPACT via oral feeding for 5 days before surgery. 7 days post surgery: administered 500-1.500 mL with gastrostomy.	The enteral nutritions (Anom and IMPACT) unraveled similar effets on nutrition, immuno-inflammatory reaction, oxidative stress, and on clinical results, after esophagectomy due cancer when used during the perioperative period.
Van Barneveld, *et al*., (2016)[17]	Preliminary prospective randomized study	To evaluate the benefits of enteral and parenteral nutrition with supplementation of glutamine, arginine and citrulline in patients with advanced rectal cancer, or otherwise requiring severe surgery.	123 patients with locally advanced or recurrent rectal carcinoma requiring major rectal surgery. Study group: (n=61); Control group: (n=62)	Glutamine, arginine and citrulline	Enteral nutrition group: received a nasojejunal-auto-migratory tube, during pre-operative stage. Parenteral nutrition group: received a jugular catheter, with 200 mL of Depeptiven/day to ensure larger amino acids supply. Supplemental EEN and EPN nutrition was provided for 5 days postoperatively. The nutrition started 8 hrs after surgery at 500 mL/24hrs. In the following day it was increased to 1L/24hrs and in the 2nd day to 2L/24hrs.	Lower concentrations of glutamine and arginine were found in the eteral nutrition group when compared to the parental group. Although the latter attained better clinical outcome regarding amino acids measures. Thus, amino acids supplementation did not achieve significant results. In particular, there was no relation between the observed beneficial effects of early parenteral and enteral nutrition.
Sultan, *et al*., (2012)[18]	Prospective randomized study	To enlighten whether enteral nutrition enriched with particular PUFA improves the postoperative progress of patients diagnosed with esophagectomy. The means of action is the comparison of a immune-modulating diet consisting of EPA, GLA and antioxidants versus one with isocaloric and isonitrogenic elements.	92 requested patients, 5 excluded and 87 remained. Study group: (n= 42); Control group: (n= 45)	Omega-3 fatty acids (O-3FAs)	Group #1 (IED) received Oxepa (O-3FAs rich) alongside EPA (51 g/100ml) and 22g/100ml of DHA during 7 days pre- and post-surgery. Enteral group (NEE) received Ensure Plus (enteric food) — 5 kcal/ml, 6-25g/100 mL of protein. For 7 days pre- and post-surgery Control group: was given no preoperative nutritional support.	Immunonutrition before and after surgery was unable to convey an advantageous overall clinical outcome, when compared to standard isocaloric and isonitrogenic enteral feeding.
Matsuda, *et al*., (2017)[19]	Clinical study, prospective, randomized	To study the effects of parenteral administration of omega-3 and of fatty acids at plasma lactate levels	26 patients scheduled for gastric cancer surgery. Study group:	Immunomodulatory diet enriched EPA, GLA and	All patients were given enteral nutrition within 48hrs after surgery at 10 mL/h; with a 10 mL/h	The study allows for conclusion of potential efficacy of the employment of enteral immunomodulatory diets enriched

		on gastric cancer patients undergone gastrectomy.	(n= 12) Control group: (n= 14)	antioxidants versus standard isocaloric-isonitrogenou diet.	increase every 2 days until 30 mL/h. Enteral feeding was then reduced to 400 mL/day and was discontinued after a two weeks period.	with EPA, GLA and antioxidants in patients who had a thoracic esophagectomy.
Makay, *et al*., (2011)[20]	Clinical study, prospective, randomized	To examine the outcomes of parenteral omega-3 and fatty acids administration on plasma lactate levels present in gastric cancer patients subsequent to gastrectomy.	26 patients scheduled for gastric cancer surgery. Study group: (n= 12) Control gruop: (n= 14)	Omega-3 fatty acids	Group 1 received enteral nutrition (NP) with w-6 FAs. Group 2 was fed with w-6 and w-3 FAs. All remained on NP for 5 days during post-surgery period, following this protocol: 3g of glucose per kg of body weight + 1,2 g/kg amino acids. 0,8 g/kg w-6 FAs were supplied to both groups via internal central venous catheter.	No distinct advantage was noticed regarding post-surgery immunonutrients with w-3 FAs in patients subjected to upper gastrointestinal surgery due to gastric cancer.
Long, *et al*., (2013)[21]	Clinical study, randomized	To investigate whether polyunsaturated omega-3 fatty acids supplementation (PUFAs) on enteral nutrition (NP) is able to reduce inflammation and increase immune function in patients who underwent esophageal cancer surgery.	60 patients (aged 36 to 76) subjected to esophageal cancer surgery. Control group: (n= 30) Study group: (n= 30)	Omega-3 fatty acids (PUFAs)	Control group (n=30) received total parenteral nutrition, only with soybean oil. Study group (n=30) received omega-3 PUFAs with fish and soybean oil. Dosage of omega-3 PUFAs was 0,17 g/kg during the first 7 days after surgery.	One concludes omega-3 (PUFAs) supplementation diminishes procalcitonin (PCT) production - inflammatory response marker. Furthermore it improved CD4+ / CD8+ production in patients undergone esophageal cancer surgery.

Legend: GIST- gastrointestinal stromal tumor; EN- enteral nutrition; AGC- advanced gastric cancer; GFO- glutamine, fiber and oligosaccharide; AeEN- enteral nutrition enriched with antioxidants; IeEN- immune-enhancing enteral nutrition; VO- oral feeding; Gln- glutamine; PT- proteins; LIP- lipids; CHO- carbohydrate; EEN- enriched enteral nutrition; IgG- immunoglobulin G; IgM- immunoglobulin M; PCR- C-reativa protein; RNA- ribonucleic acid; PUFAs or FAs – polyunsaturated fatty acid; PCT – procalcitonin; w-3 – omega-3; w-6 – omega-6; EEN or NE – enteral nutrition; EPN or PN – parenteral nutrition; IED – immune-enhancing diet; SIRS – Systemic Inflammatory Response Syndrome, GLA - gamma-linolenic.
Source: Research data, 2020.

Immune-modulating therapy has been exensively studied due to the capacity to provide several benefits to cancer patients. Positive results regarding therapy had been shown, such as 1) improvement in Systemic Inflammatory Response Syndrome (SIRS) by reducing inflammation; 2) promoting nutritional status while reducing malnutrition; 3) related post-surgery problems; 4) reduction time in hospital stay. A different methodology and doses as well as divergent experiment time have shown insignificant results on immune-modulating therapy while compared with regular enteral nutrition.

Observing the correct supplementation dose is crucial on the overall results, despite the lack of protocol-specified for doses. Different concentration among the available immunonutrients - glutamine, arginine and omega-3 fatty acids - on standard supplementation interfere on the results.

Experiment time on immune-modulating therapy is also important to the results: 1) ranging from 3 to 5 days on pre-surgery; 2) 7 up to 14 days on post-surgery, complying with ESPEN suggestion regarding malnutrition with an A[5] level of recommendation.

Discussão

Cachexia in oncology patients

Cachexia is an excessive weight loss leading to immune system depletion followed by anorexia and asthenia. A decreased response to treatment can affect the quality of life of patients, increasing the risk of infections after surgery elevating morbidity and mortality rate. Factors as occurrence, stage of cancer and treatment defines response of patients. Metabolic changes, intense metabolism function, stress, high-fat diet, in addition to poor nutrition[5,2,22], are the most common factors for cancer development.

Patient-Generated Subjective Global Assessment (PG-SGA) is the applied method to identify nutritional impact regarding cachexia risk in cancer patients. PG-SGA must be scored within 48 hours after hospital admission to define cachexia risk as well as to choose an appropriated nutritional therapy. On both pre- and post-surgery period[23,2], high-risk and cachectic patients must be thoroughly reevaluated.

Cachexia and involuntary weight loss is about 15 up to 80% on cancer patients. Metabolism changes can increase cachexia risk in gastrointestinal cancer patients, affecting prognosis and quality of life of patients[24].

Gastrointestinal cancer inpatients may frequently suffer infections during hospital admission[15] and post-surgery period due to metabolism changes. Thus, nutritional therapy must be preferably implemented in low-risk cases of cachexia but also to improve patient nutrition.

Therefore, side effects of cancer treatment along with gastrointestinal defects or anorexia in patients require the correct nutritional support. An immediately[25] nutritional therapy must be provided to cachectic patients, mainly those being still treated.

Nutritional therapy implementation usually involves food-fortification and oral supplements. Even though gastrointestinal function is properly, enteral feeding by tube is fundamental in patients with dysphagia to ensure the intake of nutrients[6].

Implementation of immune-modulating nutrients on diets, such as glutamine, arginine, omega-3 fatty acids and nucleotides have showed beneficial effects on the immune system compared with regular enteral diets. Immune-modulating diets can also provide benefits during cancer treatment[7,6] on cachectic and non-cachectic patients.

A study performed with 78 patients in advanced gastrointestinal cancer had shown better results on patients fed with enteral nutrition based on immune-

modulating nutrients. Intestine and immune system[12] had recovered faster due to albumin, pre-albumin and transferrin on enteral diets.

Immune-modulating nutrients on diets to fight cancer

Immune-modulating therapy is a wide approach to strengthen immune system and decrease complications on patients. The improvement of immune system and intestinal mucosal barrier function as well as the reduction on inflammatory response[26] of the patient is the purpose of immune-modulating therapy. Supplementation with immune-modulating therapy is provided by standard immunonutrients.

Implementation of nutrients such as glutamine, arginine, omega-3 fatty acids, nucleic acids and antioxidants is useful to reduce complications on patients. Burns, traumas and major surgery effects can be reduced as well as an increase in immunology and inflammation response improving clinical results[4].

Immune-modulating implementation improves clinical conditions of patients, such as supporting on post-surgery, reducing abdominal pain and keeping up with intestinal mucosal barrier function. Glutamine is an important amino acid to recover intestinal function but also to strengthen immunity. Therefore, this study plays a fundamental role to reduce possible side effects of chemotherapy and hospital stay in the immune system of patients[12].

On the other hand, enteral nutrition is a mean to avoid cachexia caused by cancer. Liaocheng People's Hospital established a study with 46 patients suffering from radiation enteritis. The experimental group was supplemented with glutamine, fish oil and Peptisorb, promoting some tolerance to enteral nutrition, a lower rate of flatulence and diarrhea compared to the control group during the hospital stay. As results of the test, the recovery of epithelial cells as well as better intestinal immune response and a decreased intestinal oxidative damage[27] was promoted by glutamine and other immunonutrients supplementation.

Glutamine is primarily synthesized in skeletal muscle from the catabolism of branched chain amino acids, being a fundamental immunonutrient. Some of glutamine functions include nucleotides, cytokines and proteins synthesis. Besides of being an energy source for intestinal cells, glutamine synthesis prevents cells expansion and intestinal mucosal atrophy, as well as bacterial adhesion and translocation. Glutamine is the most important fuel for lymphocytes and macrophages, being a precursor of glutathione and responsible for taking action on the antioxidant defense system. Despite of being the most abundant amino acid in the human body, glutamine supplementation helps on stress, surgical, traumas and burns conditions in order to prevent inflammatory response[4,5,26].

Arginine is a non-essential amino acid that plays a role in nitric oxide synthesis, related to gene expression and cell-mediated immunity stimulation. Secretion of hormones such as glucagon and insulin have an immune-modulating effect due to arginine synthesis. Arginine also helps on proliferation and maturation of T lymphocytes by reducing production of proinflammatory mediators on IL-1, IL-6 and TNF-α. Another point is the capacity of improving cell immunity on CD4 and CD8 lymphocytes, promoting tissue growth after an infection or trauma[4,26].

Omega-3 fatty acids are essential sources of Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA). In this context, DHA and EPA are able to promote flexibility in cell membranes in a vital process. Omega-3 fatty acids have some anti-inflammatory effects able to interrupt tumor growth by apoptosis. Supplementation with omega-3 fatty acids can also boost pro-inflammatory potential while reducing effects of systemic inflammatory response besides synthesize prostaglandins (PG) and thromboxane A2 (TXA2) [5,26].

Immune-modulating therapy implementation had showed a significant accuracy during pre-, peri and post-surgery period regarding complications for patients undergoing gastrointestinal cancer surgery. Accordingly, the study suggests the promotion of arginine, omega-3 fatty acids and nucleotides to shorten hospitalization and recovery of patients. Immune-modulating therapy has been widely implemented in these patients to prevent complications during the post-surgery and infections leading to a hospital cost reduction[28].

Major surgeries require crucial amino acids to ensure the body's homeostasis and also to prevent the patients to be affected by oxidative stress or catabolism during critical trauma stage. Gluntamin-Arginine play an important role by stimulating Nitric Oxide, consequently promoting vasodilation, neoangiogenesis and boosting the immune system, healing faster and helping in intestinal anastomosis cases[17].

Support from antioxidants is also important to prevent colon cancer as an inhibitor of gastric epithelial hyperproliferation. Therefore, ascorbic acid and beta-carotene implies on reducing Tumor Necrosis Factor in the intestine, induced by *H. pylori*, being responsible for gastric cancer and atrophic gastritis[29].

Immune-modulating therapy in inflammatory and immune response

As depletion of the body energy supply in patients suffering from gastrointestinal cancer is recurrent, unintentional weight loss is unavoidable. Nutritional therapy is required to prevent further weight loss, lessen injurious effects of long-term perioperative and reduce post-surgery infections during the patient recovery. In this regard, enteral nutritional support with immunomodulators has been widely implemented by health professionals[30].

Inadequate ingestion over a 14 days period on post-surgery results in increased risk of patient mortality. In fact, low protein and calorie intake leads to longer hospital stays, being a factor to prevail cachexia. The adequate dose of Glutamine, Omega-3 and Arginine minimize nutritional and metabolic impact. According to the observational study on some hospitalized patients, significant changes are presented between the control and the supplemented group. Since complications in evidence were minimum, the recovery occurred at a fast and effective pace leading to a diminished surgical trauma[31].

A study has presented improved immunity and reduced Systemic Inflammatory Response Syndrome (SIRS) in supplemented patients, compared to those who received standard enteral nutrition. A number of 109 patients with gastric cancer had been fed by immune-modulating supplementation diet of Arginine, omega-3 fatty acids and RNA. Another study with 78 surgical patients followed by total gastrectomy showed a positive outcome while improving immune system and promoting shorter hospital stay[12,15] base on Glutamine and Arginine supplementation.

Nutrition is not limited to providing patients with adequate amounts of protein, lipid and carbohydrate intake. On the contrary, the focus is the strength of immune system and restoration of metabolic response to infectious agents but also serve to physiological needs of the body. Thus, regular food ingestion combined to enteral nutrition improves weight recovery and immunity in hospitalized patients. Therefore, attesting enteral feeding allows more efficacy when compared with parenteral and jejunal nutrition. Modulating Formulas containing nucleotides, antioxidants, omega-3 and amino acids considered gold standard, which has shown positive outcomes in treated patients[32].

Conclusão

Enteral supplementation with omega-3 fatty acids, Glutamine, Arginine, and other nutrients (antioxidants EPA and GLA, fiber and ribonucleic acid) pre- and post-surgery contributes favorably to recover cancer patients. Reduction on catabolism, diminished inflammatory response and cachexia are leading factors to evidence analyzed results. Improvements on nutritional status and immune system, as well as decline the hospital stay of patients have also been observed.

In order to establish supplementation protocols for surgical patients regarding gastrointestinal cancer, supplementation effects by immune-modulating diets in a large number of participants should be analyzed on further studies.

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