EFFECTS OF THE USE OF IMMUNE-MODULATING FORMULAS IN SURGICAL PATIENTS WITH GASTROINTESTINAL TRACT CANCER

EFEITOS DO USO DE FÓRMULAS IMUNOMODULADORAS EM PACIENTES CIRÚRGICOS PORTADORES DE CÂNCER DO TRATO GASTROINTESTINAL

Simone Gonzaga do Carmo[1], Renata Costa Fortes[2]

Cite as:
Carmo SG, Fortes RC. Effects of the use of immune-modulating formulas in surgical patients with gastrointestinal tract cancer. Revista Científica Sena Aires. 2019; 8(1): 96-111.

RESUMO

O objetivo deste estudo foi investigar os efeitos do uso de fórmulas imunomoduladoras sobre os desfechos clínicos e as taxas de complicações perioperatórias e hospitalares em pacientes cirúrgicos com câncer do trato gastrointestinal. Trata-se de uma revisão integrativa em que foram utilizados os descritores "enteral nutrition", "surgery", "gastrointestinal neoplasms", "arginine", "omega 3 fatty acids" e "glutamine" combinados aos operadores booleanos "and" e "or" em bases de dados indexadas. Foram encontrados 460 artigos, sendo utilizados 19 (4,1%) após a aplicação de critérios de seleção. Os estudos analisados ressaltam a importância do uso das fórmulas imunomoduladoras para pacientes cirúrgicos e oncológicos, em períodos específicos, devido aos seus efeitos benéficos sobre o estado nutricional e sistema imunitário dos pacientes.

Descritores: Nutrição enteral; Imunonutrição; Fatores imunológicos; Neoplasias gastrointestinais; Procedimentos cirúrgicos eletivos.

ABSTRACT

This study examines the effects of immune-modulating formulas in surgical patients with gastrointestinal tract cancer. It is an integrative review in which the following descriptors were used: "enteral nutrition", "surgery", "gastrointestinal neoplasms", "arginine", "omega 3 fatty acids" and "glutamine", with Boolean operators "and" and "or" in specialized indexed databases. 460 contributions were found and 19 articles (4.1%) were selected according with additional criteria. The articles emphasize the relevance of immune-modulating formulas in surgical and oncological patients for specific periods of time, due to their beneficial effects for patients' nutritional status and immune system.

Descriptors: Enteral nutrition; Immunonutrition; Immunological factors; Gastrointestinal neoplasms; Elective surgical procedures.

REVISA

[1] Nutritionist. Clinical Nutrition Resident. Hospital Regional da Asa Norte. Federal District, Brazil

[2] Nutritionist. PhD in Human Nutrition. Fundação de Ensino e Pesquisa em Ciências da Saúde, Escola Superior em Ciências da Saúde. Federal District, Brazil. rcfortes@gmail.com

Recebido: 21/06/2018
Aprovado: 6/08/2018

INTRODUCTION

The nutritional status of hospitalized patients has direct effects on their clinical evolution. Cases of malnutrition and/or nutritional risk generally lead to negative consequences, since patients' responses to trauma lead to additional clinical effects.[1-2]

Malnutrition is a decisive factor among surgical patients, since it influences many aspects, such as the appearance of complications, delays in the healing of wounds, increased hospitalization time and a higher mortality risk.[3]

In patients submitted to gastrointestinal tract surgeries, particularly oncological surgeries, morbidity rates and postsurgery complications are usually more significant.[4] They also have a higher predisposition to develop hospital malnutrition, since cancer is a catabolic disease leading to harmful nutritional outcomes and negative prognoses.[4-5]

Patient responses to trauma, infections and metabolic stress are linked to altered immune functions, which frequently appear in surgical oncological patients. However, there are signs that such functions can be modulated by specific nutrients known as immune or immune-modulating nutrients.[4]

Immunonutrition is defined as nutrients' capacity to influence the activities of immune system cells, either via specific or associated nutrient supplementation, which can lead to physiological and biochemical effects in the face of immunosuppressive conditions.[5]

Many studies have supported immunonutrition as an effective strategy to reduce the severity and the risks of postsurgery complications in patients submitted to major elective surgeries, with reductions in hospitalization time and costs.[4,6-7]

This study reviews the specialized literature on the use of nutritional formulas composed by immunonutrients in patients submitted to elective oncological surgeries in the gastrointestinal tract and their effects on surgery outcomes, as well as on the reduction of perioperative and in-hospital complications.

METHOD

This is an integrative literature review on the administration of immunonutrition to oncological patients submitted to gastrointestinal tract surgeries, including scientific articles published in indexed databases and full text directories in the period of 2010-2016.

The following databases were consulted: Medline (Academic Search Premier), PubMed (National Library of Medicine and National Institute of Health, USA), DOAJ (Directory of Open Access Journals), Lilacs (Latin-American and Caribbean Health Science Literature), IBECS (Spanish Bibliographical Health Science Index), Cochrane, international databases and SciELO. Its search words included some descriptors available at the Health Sciences Descriptors (DeCS) database, via combined terms and Boolean operators "AND" and "OR", for instance: "enteral nutrition" AND "surgery" AND "gastrointestinal neoplasms" AND "arginine" OR "fatty acids, omega-3" OR "glutamine".

Search filters included language – with an option for articles in English, Spanish and Portuguese -, researches with adults or elders of both genders, and a focus on nutritional therapy. Article selection was based on titles and abstracts, including original articles and meta-analyses that correlate the above-mentioned descriptors, as well as the subject matter. This search did not include articles with sample groups of individuals under 18 years old and studies with laboratory animals.

RESULTS AND DISCUSSION

According to the above-mentioned criteria, this search identified 462 articles in the searched databases. 387 articles were discarded after using the period, language and sample group filters, leading to a group of 75 articles to be studied and analyzed. The final selection resulted from a reading of abstracts and articles, after which 19 articles were selected for literature review (Figure 1).

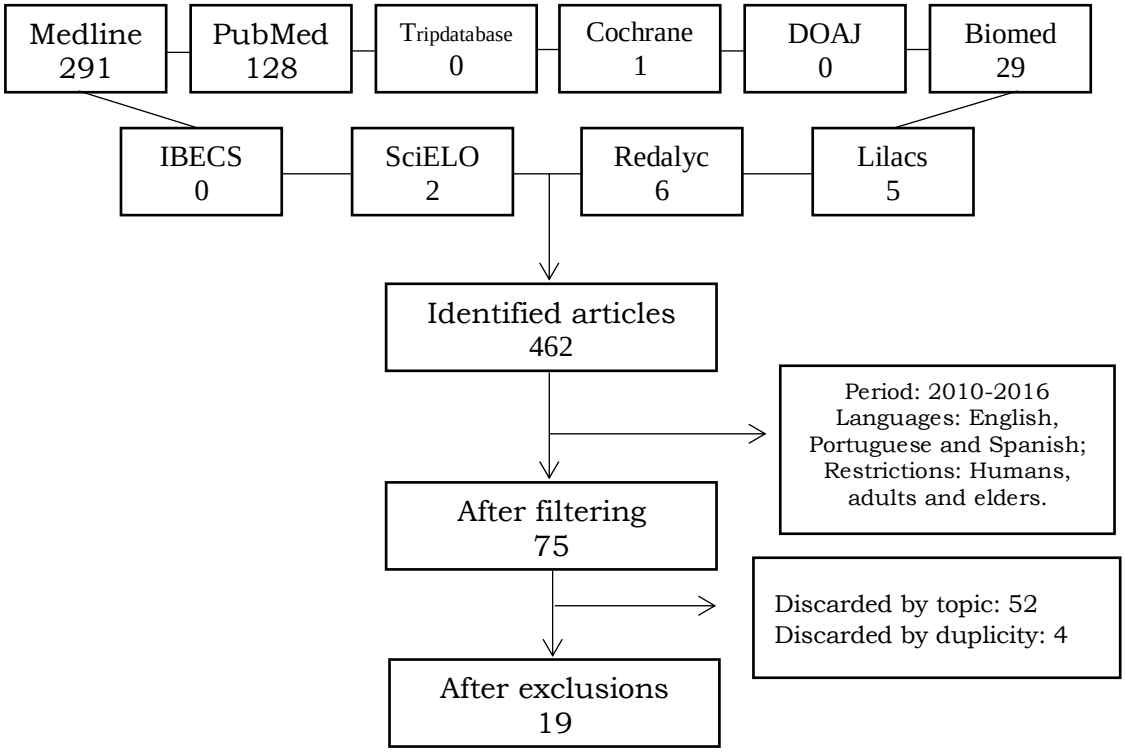

Figure 1: Flowchart describing article search for this integrative review

After the selection stage, articles were analyzed according to topics related to surgery type, condition and nutritional risk, and nutritional supplementation, as well as dosage and administration time of nutritional formulas in connection with patients' clinical outcomes. Such outcomes included inflammatory cytokine changes hospitalization period, postsurgery complications, infections, gastrointestinal symptoms, the need for intensive care or parenteral nutrition, and number of deaths as an outcome of supplementation with immunomodulation formulas.

Assessment of nutritional status of oncological surgery patients

Malnutrition is a frequent component in the nutritional diagnoses of oncological patients. It is also known as cachexia and in characterized by excessive loss of weight, anorexia, immune system depletion and asthenia. Malnutrition prevalence among such patients can reach levels ranging from 20% to 80%, with a link between malnutrition grade and tumor location.[4,8] The main factors contributing to malnutrition appearance include intense catabolism, metabolic changes, stress, diet and inadequate nutrient intake.[9]

Malignant tumors can appear in different regions of the gastrointestinal tract and severely affect patients' health and life quality. Each patient's prognosis depends on tumor staging, but survival estimates are of approximately five years in 20% of the cases. Gastric neoplasia levels have reduced in recent years, but it still considered the fifth most frequent type of cancer and one of the most far-reaching public health problems of the present, accounting for approximately 738 thousand annual deaths worldwide.[9]

Many therapies are now available for treating cancer, including chemotherapy and radiotherapy. But in relation to gastrointestinal neoplasias, surgical procedures continue to be the primary treatment form. Despite the advances both in the field and in terms of surgery techniques, the current procedures may lead to complications in connection with factors that can change immunological functions and produce inflammatory responses, especially in the cases of malnutrition, in which complications can affect up to 40% of the patients.[1] In some esophagus cancer cases, for instance, postsurgery morbidity reaches high rates ranging from 43% to 60%.[10] Postsurgery morbidity rates often range from 35% to 50% of the cases. But despite the usual risks, surgery procedures continue to be the key to success in the treatment of such diseases.[2]

The reduction of risk rates and postsurgery complications is connected with perioperative care, especially among patients submitted to major surgeries,[2] since such surgeries act as a relevant stimulus to inflammatory responses. In case of increased inflammatory response, metabolism acceleration becomes necessary, causing the rapid consumption of energy stores, altering immunological functions and leading to organic deterioration and eventual postsurgery complications.[1] Patients' nutritional intake is a relevant condition that can interfere in their outcomes, influencing the healing process and their clinical evolution, hospitalization time and, consequently, hospital costs. [8]

In recent years, enteral nutrition has been often used as nutritional support for oncological patients submitted to surgery procedures, with the aim of improving their response. Adequate caloric and protein intake via nutritional support has led patients to experience benefits in terms of reducing the impact of postsurgery catabolism.[4,8] In addition to intake adjustment to individual needs, specific substances administered in supraphysiological dosage can modulate immune and metabolic responses, interfering in postsurgery outcomes in cases of inflammatory, immune and oxidative stress. These nutrients involved in response modulation processes are called immunomodulators.[11]

Immune-modulating nutrients

Many nutritional support formulas have appeared since the 1990s. The current formulas include options enriched with immune-modulating nutrients associating L-arginine, glutamine, omega 3 fatty acids and nucleotides.[11] These substances can act against diseases and help patients with high metabolic stress levels resulting from surgeries, modulating their immunological and metabolic responses.[9] The recourse to enhanced dietary therapy based on associated immunonutrients has been linked to benefits such as reduced postsurgery complications, infections and hospitalization time,[2,11] plus positive postsurgery effects in the face of immunosuppressive conditions, and in visceral microperfusion cases.[5]

L-arginine is a semi-essential amino acid. In stress situations, it is considered a conditionally essential option due to its important immune-modulating effects. It can have positive effects on relevant biological, physiological and immunological activities,

acting on the proliferation and maturing of T cells, which exert an essential role in the body's defense system. L-arginine is also involved in blood pressure regulation, tissue perfusion, cell metabolism and in the synthesis of nitric oxide, which are key factors in healing processes.[9,12] The synthesis of hormones such as insulin, glucagon, and growth hormone are also related to the presence of arginine.[12]

Omega 3 polyunsaturated fatty acids, in turn, are considered essential for health and a source of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish oil. They have important anti-inflammatory effects, reducing platelet aggregation and potential inflammation,[9] and they act as regulators of eicosanoids, which are less inflammatory than omega 6 fatty acids.[10] Omega 3 fatty acids are also important in signal transduction and cell membrane synthesis, since they are active in the phospholipids responsible for membrane fluidity. They are precursors of biological processes[9] that can suppress tumor growth by promoting apoptosis and reduce the effects of systemic inflammatory response, since they increase the proliferation of anti-inflammatory cytokines such as interleukins IL-10 and IL-13. Finally, they are involved in the differentiation of antigen receptors, in antibody production and presentation of antigens.[13]

Nucleotide molecules are precursors of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which are important for protein synthesis and lymphocyte homeostasis maintenance. They are also responsible for reducing human susceptibility to infections and for intestinal reconstitution, especially in parenteral nutrition cases. The needs of the human body increase in stress situations, and deficiencies can cause T cell function loss and reduced interleukins.[9,11]

Glutamine is one of the best known amino acids. It is conditionally essential in several physiological processes[9] and is an important element of cell differentiation and growth.[14] It also plays a role in the synthesis of nucleotides, proteins and cytokines, in antigen presentation,[9] in the proliferation of immune system cells and as a source of energy for intestine cells. Glutamine is also responsible for preventing the degradation of muscle cells, since its oxidation serves as a source of nitrogen and is used in the synthesis of amino acids and proteins.[14]

In spite of the human body's substantial reserves of glutamine, stress situations such as traumas, surgeries, burn injuries and sepsis can lead to its sharp depletion, since consumption in these cases surpasses the synthesis ability. In some cases, such situations can lead to a need for supplementation to prevent inflammatory processes. Glutamine can also raise the levels of T CD3+ cells, since it stimulates lymphocytes-mediated response. The benefits of its use include the enhanced recovery of intestine cells by providing them with energy, and prevention against mucosal atrophy and bacterial adhesion and translocation.[11,14]

Immunomodulation in surgical patients

Nutritional therapy for patients submitted to major surgeries must be aimed not only to the recovery of their nutritional status, but also to strengthening their immune system. Its adequate administration and management in order to prepare patients for surgeries is an important pre-surgery management aspect, since its effects can affect their surgical outcomes.[11]

Infections are among the possible complications of tumor resection surgeries. They include wound infections and abdominal abscesses pneumonia, in addition to infections of the urinary tract and air passages, and sepsis. Additional complications

may occur, for instance, fistulae, acute kidney injuries and cardiovascular events.[6] It is estimated that infectious complications occur in 30% of the cases, while anastomosis dehiscence occurs with 15% of the patients. Such complications are frequent causes of increased hospitalization time.[15]

In surgery outcomes, the control of the immunological system must be assessed not only in relation to the existence of complications and hospitalization time, but also to inflammatory and anti-inflammatory markers expressed by patients. Among many pro-inflammatory markers currently used to assess inflammatory processes, one finds IL-2 or IL-6, C-reactive protein (CRP), tumor necrosis factor (TNF-α) and procalcitonin (PCT) as sensitive post-trauma / sepsis markers. These markers tend to increase in the case of infections and inflammations, for instance PCT, which is found in thyroid cells. PCT concentration in healthy individuals is 0.01g/nL, but it is higher in patients with bacterial or viral infections, autoimmune diseases or infections related to inflammatory responses, with a degree of awareness about the possible severity of complications and inflammation.[16] On the other hand, T CD4+ and CD8+ cells, and interleukins IL-1, IL-10 and IL-13 are among the available anti-inflammatory factors.[13] T lymphocytes, in particular CD4+ and CD8+ are involved in autoimmune response. CD4+/CD8+ rates below 1 are considered mortality-predictive in gastric cancer patients, and eventual rate increases are linked to immune system improvements in patients.[16]

In recent years, studies have associated improvements of nutrition and immune system by resorting to enteral formulas with the purpose of providing patients with the necessary and adequate nutrients. New therapeutic strategies have also been sought in order to modify the metabolic response caused by stress.[1] The *European Society for Clinical Nutrition and Metabolism* (ESPEN) recommends the administration of enteral nutrition via immune-modulating formulas both in the pre- and postsurgery stages, with a suggested use for five to seven days independently of the nutritional risks for an individual. Such use can be extended to 14 days in cases of malnutrition, with a view to reducing complication risks.[1,8]

The use of immune-modulating supplements in oncologic GIT surgery patients

Many studies attest to the effects of formulas containing immunomodulators on the human immune system. The immunoglobulins (Ig) that act in the body's defenses increase significantly in patients submitted to gastric tumor resection surgery, showing a beneficial response in their immune and humoral system in comparison to patients who received conventional nutrition formulas. The highest increases were observed in the levels of IgA, IgG, IgM, $CD4^+$, $CD3^+$ and nK cells, with a reduction in the levels of cytokines such as IL-6 and TNF-α. The observed increase in the above-cited mediators allows modulating the immune system's response, especially in the gastrointestinal tract.[5,9]

Formulas containing immunomodulators can be used in distinct hospitalization periods with various efficacy rates, but a general reduction-trend is always observed in relation to complication rates and hospitalization time. Complications were observed to decrease from 53% to 36%, from 54% to 33,5%, and from 50% to 36.5% in presurgical, perisurgical and postsurgical periods, respectively.[17] Meta-analyses that assessed the use of immunomodulating supplements in oncological surgery patients found a significant reduction of their hospitalization time.[5,11,14] Five studies assessed by meta-analysis encompassing 748 surgery patients who received supplements in the pre- and postsurgical periods found that patients experienced a reduction in both periods. Comparing the use of distinct formulas in presurgical and postsurgical periods, three

studies encompassing 403 patients randomized in two groups did not found any relevant difference.[5] A highlight among the complications that experienced a significant decrease is that of aponeurosis dehiscence. In this regard, no significant change was observed in mortality rates.[11] However, meta-analysis studies identified a decrease in morbidity rates.[5,11]

Many studies analyze formulas that associate the following immune-modulating nutrients: L-arginine, EPA, DHA and nucleotides.[1-2,8,18] In a study by Gomez Sanchez et al., 2011, a total of 50 patients with neoplasias in the upper gastrointestinal tract were randomized according to their nutritional status in three groups: eutrophic, non-supplemented malnourished and supplemented malnourished. Patients received the formulas according to their group for a period of 10 days before their surgeries in a volume of 237mL/day. After this intervention, significant decreases were observed in the number of episodes of diarrhea, vomit, abdominal distension, and wound and air passage infection among the recipients of immune-modulating supplements. Diarrhea episodes were observed in 25%, 5% and 0% of the non-supplemented malnourished, supplemented malnourished and eutrophic patients, respectively. Vomit episodes occurred in 53%, 0% and 20% of the patients in the same groups. Abdominal distention was detected in 68%, 5.6% and 18.8% of the patients, respectively. Wound infections were observed in 25% of the non-supplemented malnourished patients and 6.3% of the eutrophic patients, and was absent among supplemented malnourished patients. Hospitalization time was reduced for supplemented malnourished patients, vis-à-vis non-supplemented malnourished and eutrophic patients.[8] Gomez Sanches also administered this therapy to 82 patients with colorectal neoplasia and observed similar results, with relevant decreases in diarrhea, vomit, and wound and air passage infection rates, and hospitalization time among non-supplemented malnourished patients. A difference, in this latter case, regards abdominal distention, for which a reduction was observed, albeit insignificant. Abdominal distention rates, in this case, were 36% for non-supplemented malnourished patients, 28.6% of the supplemented malnourished patients, and 23% in the group of eutrophic patients.[4]

The immunomodulating formula was assessed in 54 gastric cancer patients, while 50 patients received a conventional formula for a postsurgical period of seven days. A significant decrease occurred in the rates of infectious complications, systemic inflammatory response syndrome (SIRS), anastomosis dehiscence and hospitalization time, in addition to an increase in the development of delayed infections in the control group in comparison to the supplemented group. The levels of serum albumin, total protein and CD4+ cells in the first and third postsurgical days were significantly higher in the group treated with immunomodulators, showing that the formula was effective in terms of modulating patients' immune system.[18] In another research, Giber-Pabst et al., 2013, assessed individuals with gastrointestinal cancer categorized as eutrophic patients, who received the formula in the three final days before surgery, while the conventional formula was given to a control group. Nausea and vomit episodes were observed in the supplemented group, whereas diarrhea episodes were observed in the

control group. No significant differences were observed in relation to surgery duration, intra-operative blood loss, transfusion needs and mortality rates.[1] The administration time may explain the reason why no significant results were obtained, considering that many studies establish a minimum period of five days.[1,8]

The *Nutritional Risk Screening 2002* (NRS 2002) reports that persons in situation of nutritional risk tend to develop higher complication rates. 152 patients categorized as at risk were distributed into two groups. The first group of patients (n = 73) received the immunomodulating supplement, whereas the second (n = 72) received a nutritional supplement with an isonitrogenous and isocaloric formula via oral route in a volume of 600mL/day for a five-day period. No benefits were noticed in relation to patients' infectious and non-infectious complications. But despite the fact that benefits were neither seen in the immune-modulating therapy in relation to general and infectious complications, nor in relation to hospitalization time, there was still a trend of reduced severe complications and reduced ICU permanence for users of the immunomodulating supplement: the ICU time and average overall hospitalization period were of 1.3 x 1.8 days and 16 x 19 days, respectively, for the immunomodulated and control groups. If one does not consider non-colorectal surgery cases, only 27 supplemented patients developed postsurgical complications, compared to 35 non-supplemented patients. Yet, the interpretation of results must be careful, since 46% of all patients consumed only limited amounts of the nutritional supplement, for tolerance reasons.[2] This study's results are somehow contradictory when one bears in mind that several meta-analysis assessments point to the supplement's benefits,[5,11] but such contrast can be explained by considering that high intolerance rates may have led to an interpretation bias.

Meta-analysis assessments of the isolated effects of glutamine have pointed out to its beneficial effects. Several reviewed studies indicate an increase in serum levels of pre-albumin and albumin, transferrin and immunologic factors IgG, IgM, IgA, $CD3^+$ and CD4/CD8, plus reduced infectious complication rates and hospitalization time. Albumin levels were assessed by six studies in 356 patients, whereas transferrin levels were assessed in 274 patients, and pre-albumin plus immunoglobulins in 324 patients. Immunoglobulins were assessed in different groups, showing that factor concentrations can significantly increase with the use of immunomodulators. $CD3^+$, $CD4^+$ and $CD8^+$ levels, and CD3/CD4 and T cell rates were assessed in 322 patients by five studies, which found that even when $CD4^+$ and $CD8^+$ rates did not change significantly, there was still an increase in $CD3^+$ and CD3/CD4 levels, thus suggesting that glutamine is capable of promoting a proliferation of T cells. Total protein rates assessed in 122 patients did not present any change with the use of glutamine. On their turn, infectious complications in 872 gastric patients experienced a significant decrease.[14]

Differently from glutamine, the studies that researched other immunonutrients in an isolated way did not find significant benefits. The administration of 4.5g/day of L-arginine in patients with gastric neoplasia was followed by an increase in CD4+ rates on the seventh

postsurgical day. Higher CD8+ rates were also noticed, though without a significance.[12] EPA and DHA immunonutrients administered at the dosages of 3.44g and 1.40g per day, respectively, to patients with esophageal cancer for seven days in their pre- and postsurgical periods did not evince significant differences of morbidity, mortality, hospitalization time and T-cell or monocyte appearance, though the number of complication episodes in the group that received immunomodulators was lower than in the control group.[10] Distinct dosages with 2g of EPA and 1g of DHA during the same period administered to colorectal neoplasia patients were not followed by a significant decrease in the number of infectious and non-infectious complication episodes, ICU permanence time, readmission and hospitalization period,[15] thus showing their higher efficacy in the outcomes of studies about formulas with associated immunonutrients.

There are many different ways of resorting to immune-modulating nutritional therapy in cases of major surgeries, for instance, in parenteral nutrition. A study on 88 patients who received parenteral nutrition therapy one day before and seven days after gastric and colorectal tumor resection surgeries observed that the administration of a formula enriched with omega 3 fatty acids did not lead to significant differences in CRP, TNFα, IL-6 and PCT levels, except in the cases of free and triglyceride fatty acids, which experienced a decrease in the supplemented patients.[19] On the other hand, Wei Z., *et al.*, 2014, observed a reduction in inflammatory markers assessing patients who received 0.2g/kg/day of omega 3 fatty acids for six days via total parenteral nutrition (TPN). No significant changes were noticed in total protein, albumin, pre-albumin, transferrin and total cholesterol levels, but a significant increase was found in terms of white cells and reduced IL-1b, IL-6 and TNFα levels after the surgery. As to outcomes such as wound, urinary and air passage infections, despite being more frequent in the control group, such difference was not seen as significant.[13] According to studies that assessed 305 malnourished patients submitted to total and subtotal gastric resection, including 152 patients who received an immune-modulating formula with arginine, glutamine, EPA and DHA, and 153 patients who received the conventional oligomeric formula in addition to TPN for 14 days before their presurgical period. In the group of supplemented patients, a significant decrease was observed in the rates of infectious complications and mortality.[3] Another research assessed groups of patients submitted to gastrointestinal neoplasia resection. 43 patients received conventional enteral diet, while 41 patients received immune-modulating enteral diet; 41 patients received standard parenteral nutrition and 42 patients received immune-modulating parenteral nutrition. Postsurgical nutrition was maintained for seven days for all groups. The immune-modulating formula included glutamine (0.1g/kg/day) and omega 3 (0.1g/kg). From the 84 patients who received the conventional formula, 23 experienced infectious complications; and from the 83 who received the immune-modulating formula, 20 had infectious complications. But no significant difference was observed in the appearance of complications among patients fed via parenteral or enteral nutrition.[20] Patients with esophageal neoplasia who

received TPN with omega 3 experienced an increase in their CD4+/CD8+ ratio and a decrease in PCT levels on the sixth postsurgical day, showing therefore the importance of reducing inflammation and benefiting immune functions.[16]

In spite of the observed divergences among some studies, it is a consensus that presurgical treatment of gastrointestinal neoplasias should last from five to seven days with a daily dosage of 500-1000mL of the immune-modulating formula. However, some data show that only a combination of supplementation in presurgical and postsurgical periods can reduce postsurgical morbidity rates.[2]

Impacts of the use of immune-modulators for hospitalization costs

In addition to the importance of immune-modulators for the above-mentioned surgery patients, some estimates have pointed to their relative impact on hospitalization costs.[6,17] Considering the decrease in infectious complication levels, the estimated economy approached US$3,300. And considering hospitalization time, costs decreased by approximately US$6,000 per patient.[6] Also regarding impacts on hospital costs, some previous studies found an average cost of €5,778 and €4,132, respectively, for the treatment of complications in patients who did not receive immune-modulating supplements vis-à-vis patients who received them, including presurgical expenses with immune-modulating formulas for patients of the second group. And the costs of those who used them in the perioperative period were €1,814 and €1,195, respectively. With the decrease in complication expenses due to the use of immune-modulating nutrition, the costs with hospitalization as a consequence of complications fell from an estimated average of €10,901 to nearly € 1,195 and €1,814 per patient, considering that the costs of patients who did not and did develop complications were €1,276 and € 2,292, respectively. Immune-modulating formulas led to distinct results in different periods, with €1,895, €1,158 and €829 for the presurgical, perisurgical and postsurgical periods, respectively. [17-20] Independently of the period of utilization, the economy of costs show that benefits reach beyond individual patients into the public health realm. Table 1 describes the main characteristics of the reviewed studies.

Table 1: Characteristics of the studies covered by this research' systematic review

Reference	Type of Study	Sample Group	Contents formula	Route / Dosage / Period	Results
Gomez Sanchez M. B., et al, 2011	Randomized clinical trial	High GIT neoplasia n= 50 Normally nourished (16) Supplemented malnourished (18) Non-supplemented malnourished (16)	L-arginine, RNA and Omega 3 fatty acids, hypercaloric and hyperprotei c diet	OA: 237mL/day for 10 days, presurgical	Decreased number of episodes of diarrhea, vomit, wound and air passage infection, and abdominal distention
Gomez Sanchez M. B., et al, 2010	Randomized clinical trial	Colorectal neoplasia n= 82 Normally nourished (34) Supplemented malnourished (26) Non-supplemented malnourished (22)	L-arginine, RNA and Omega 3 fatty acids, hypercaloric and hyperprotei c diet	OA: 237mL/day for 10 days, presurgical	Reduced hospitalization time and fewer episodes of wound infection, vomit and diarrhea. Increased patient satisfaction at surgical procedures. Non-significant decrease in intra-abdominal abscesses, air passage infections, anastomosis and wall dehiscence, and abdominal distention
Song, G.M, et al, 2015 (Meta-analysis)	Meta-analysis	Gastric neoplasia n = 785 (9 citations)	L-arginine, glutamine, omega 3 fatty acids, RNA and nucleotides	OA/NGT: 500-1000mL/day for 5-8 days, presurgical and postsurgical*	Increased levels of IgA, IgG, IgM, CD4+, CD3 and nK cells. Reduced IL-6 and TNF-α levels
Osland, E. et al, 2013 (Meta-analysis)	Systematic review	GIT neoplasia n = 2005 (20 citations)	L-arginine, nucleotides, omega 3 fatty acids and RNA	OA/NGT: 750-2400mL/day for 5-7days, presurgical and postsurgical*	Reduced hospitalization time, less anastomosis dehiscence and non-infectious and infectious complication episodes

Giger – Pabst, M.D., et al 2012	Double-blind randomized clinical trial	GIT neoplasia patient – Eutrophic n= 108 Control (53) Immune-modulating (55)	L-arginine, RNA and Omega 3 fatty acids, hypercaloric and hyperprotei c diet	OA: 750ml/day for 3 days, presurgical	No significant benefits were noticed
Hubner M, et al, 2012	Double-blind randomized clinical trial	GIT surgeries – Patients in situation of nutritional risk n = 145 Control (72) Immune-modulating (73)	L-arginine, RNA and Omega 3 fatty acids, hypercaloric and hyperprotei c diet	OA: 600mL/day for 5 days, presurgical	Reduced hospitalization time and ICU needs. Complication rates unaltered
Klek, S. et al, 2011	Placebo-controlled randomized clinical trial	GIT neoplasia –Malnourished n= 167 Conventional enteral (43) Immune-modulating enteral (41) Conventional Np (41) Immune-modulating Np (42)	Glutamine and omega 3 fatty acids	OA/TPN: Glutamine 0.1g/kg/day and omega 3 fatty acids 0.1g/kg/day for 14 days (presurgical) and 7 days (postsurgical)	Reduced infectious complication rates. Unaltered rates of complications among patients fed via TPN or EN
Zhang, Y., et al, 2012 (Meta-analysis)	Systematic review	GIT neoplasia n = 1246 (19 studies) Control (625) Immune-modulating (621)	L-arginine, omega 3 fatty acids, glutamine and RNA	OA: 750mL/day or according to individual needs (25 kcal/kg/day) for 4 days, presurgical	Reduced postsurgical infectious complications and hospitalization time
Mauskopf, J. A, et al, 2012 (Meta-analysis)	Systematic review	GIT neoplasia n = 889	L-arginine, RNA and Omega 3 fatty acids, hypercaloric and hyperprotei c diet	-	Reduced hospitalization time and costs

Kang K., et al, 2015. (Meta-analysis)	Meta-analysis	GIT neoplasia n = 1034 (13 citations)	Glutamine	OA/EN/PN: from 0.2g/kg to 30g for 5-10 days*	Increased serum levels of albumin, transferrin and pre-albumin, IgG, IgM, IgA, CD3+, CD4/CD8. Reduced infectious complications and hospitalization time
Klek, S., et al, 2011	Placebo-controlled randomized clinical trial	GIT neoplasia - Malnourished n= 305 Immune-modulating (152) Control (153)	L-arginine, glutamine, EPA and DHA	TPN: 14 days in combination with NGT containing immune-modulating nutrition: 20mL/hr	Reduced infectious complications and mortality rates
Ma, C. J., et al, 2015	Double-blind randomized clinical trial	Gastric and colorectal neoplasia n = 88 Control (41) Immune-modulating (41)	Omega 3 fatty acids	TPN: 80-140mg/kg for 1 day (presurgical) and 7 days (postsurgical)	No significant differences in CRP, TNFα, IL-6 and PCT levels
Sorensen, L., et al, 2014	Randomized clinical trial	Colorectal neoplasia n = 148 Control (64) Immune-modulating (65)	Omega 3 fatty acids	OA: 2g EPA and 1g DHA/day for 7 days, presurgical	No significant differences in the appearance of infectious and non-infectious complications
Wei, Z., et al, 2014	Placebo-controlled randomized clinical trial	Gastric neoplasia n = 56 Control (26) Immune-modulating (20)	Omega 3 fatty acids	TPN: 0,2g/kg/day for 6 days, postsurgical	Increased number of white cells, reduced IL-1b, IL-6 and TNFα levels. No significant differences in total protein, albumin, pre-albumin, transferrin and cholesterol levels
Sorensen, L., et al, 2013	Randomized clinical trial	Colorectal neoplasia n= 148 Control (74) Immune-modulating (74)	EPA and DHA	OA: 200mL containing 2g of EPA and 1g DHA for 7 days, presurgical and postsurgical	Reduced levels of intra-abdominal abscesses, but no significant decrease in infectious and non-infectious complications, ICU permanence, readmissions and hospitalization time

Chevrou-Severac, C. H., et al, 2013 (Meta-analysis)	Systematic review	Gastrointestinal neoplasia n = 460 (21 citations)	L-arginine, nucleotides and omega 3 fatty acids	-	Reduced risk in relation to complications, hospitalization costs and treatment of complications
Marano, L. et al, 2013	Randomized clinical trial	Gastric neoplasia n = 109 Control (55) Immune-modulating (54)	L-arginine, RNA and omega 3 fatty acids	EN: 120mL/day for 7 days, postsurgical	Reduced infectious complications, anastomosis dehiscence and hospitalization time. No significant difference in mortality rates
Zhao, H., et al, 2013	Clinical trial	Gastric neoplasia n = 73 Control (36) Immune-modulating (37)	L-arginine	EN: 500mL/day containing 9g/L of L-arginine, for 7 days, postsurgical	Increased $CD4^+$, Nk, IgM and IgG levels, non-significant increase in $CD8^+$ levels
Long, H., et al, 2013	Clinical trial	Esophageal neoplasia n = 60 Control (30) Immune-modulating (30)	Omega 3 fatty acids	NP: $0.17 g^{-1} kg^{-1}$/day for 6 days, postsurgical	Increased $CD4^+/CD8^+$ ratio and reduced PCT inflammation markers
Sultan, J., et al, 2012	Randomized clinical trial	Esophageal and gastric neoplasia n = 221 Control (66) Conventional (63) Immune-modulating (66)	Omega 3 fatty acids, EPA and DHA	OA: 675mL/day containing EPA 0.51g/100mL and DHA 0.22g/100ml for 7 days, presurgical and postsurgical	No significant differences in morbidity, mortality, hospitalization time, T cell or monocyte expression

Notes: CRP = C-reactive protein; EN = Enteral nutrition; GIT = Gastrointestinal tract; Ig = Immunoglobulin; IL = Interleukins; NGT = Nasogastric tube; OA = Oral administration; PCT = Procalcitonin; PN = Parenteral nutrition; TNF = Tumor necrosis factor; TPN = Total parenteral nutrition. * Dosage and administration period vary according to each study.

FINAL REMARKS

A diversity of effects were observed as results of immune-modulating formulas in oncological patients submitted to gastrointestinal tract surgery, in addition to distinct effects from the use of immunonutrients: increased protective factors and reduced infectious complications and hospitalization time. A highlight is the use of associated formulas and specific durations, for instance, in presurgical and perisurgical periods, since introduced therapies need some time in order to act and strengthen the human immune system.

Nutritional conditions are closely linked to the clinical outcomes experienced by surgical patients, and it is indispensable to count on adequate nutritional preparedness. Nutritional therapy based on immunonutrients is proving to be necessary as a means to improve patients' immune system, reduce postsurgical complications and improve life quality and prognoses.

The search for scientific knowledge has been increasingly guided by methodologies such as randomized and controlled clinical trials, which enable directing the provision of effective care in the field of health, since they allow obtaining knowledge on the actual effects of formulas with a relevant level of reliability. As secondary information sources, the systematic reviews and meta-analytic studies assessed above also allowed to observe such effects.

REFERENCES

1. Giger-Pabst U, Lange J, Maurer C, Bucher C, Schreiber V, Schlumpf R, et al. Short-term preoperative supplementation of an immunoenriched diet does not improve clinical outcome in well-nourished patients undergoing abdominal cancer surgery. Nutrition. 2013;29(5):724-9.
2. Hubner M, Cerantola Y, Grass F, Bertrand PC, Schafer M, Demartines N. Preoperative immunonutrition in patients at nutritional risk: results of a double-blinded randomized clinical trial. Eur J Clin Nutr. 2012;66(7):850-5.
3. Klek S, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, et al. The immunomodulating enteral nutrition in malnourished surgical patients - a prospective, randomized, double-blind clinical trial. Clin Nutr. 2011;30(3):282-8.
4. Gomez Sanchez MB, Garcia-Talavera Espin NV, Sanchez Alvarez C, Zomeno Ros AI, Hernandez MN, Gomez Ramos MJ, et al. Perioperative nutritional support in patients with colorectal neoplasms. Nutricion hospitalaria. 2010;25(5):797-805.
5. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol. 2012;21(2):e87-95.
6. Mauskopf JA, Candrilli SD, Chevrou-Severac H, Ochoa JB. Immunonutrition for patients undergoing elective surgery for gastrointestinal cancer: impact on hospital costs. World J Surg Oncol. 2012;10:136.
7. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol. 2013;75(3):645-62.
8. Gomez Sanchez MB, Garcia Talavera Espin NV, Monedero Saiz T, Sanchez Alvarez C, Zomeno Ros AI, Nicolas Hernandez M, et al.

Evaluation of perioperative nutritional therapy in patients with gastrointestinal tract neoplasms. Nutr Hosp. 2011;26(5):1073-80.
9. Song GM, Tian X, Liang H, Yi LJ, Zhou JG, Zeng Z, et al. Role of Enteral Immunonutrition in Patients Undergoing Surgery for Gastric Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine. 2015;94(31):e1311.
10. Sultan J, Griffin SM, Di Franco F, Kirby JA, Shenton BK, Seal CJ, et al. Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. Br J Surg. 2012;99(3):346-55.
11. 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 Journal of parenteral and enteral nutrition. 2014;38(1):53-69.
12. Zhao H, Zhao H, Wang Y, Jing H, Ding Q, Xue J. Randomized clinical trial of arginine-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing gastric cancer surgery. J Cancer Res Clin Oncol. 2013;139(9):1465-70.
13. Wei Z, Wang W, Chen J, Yang D, Yan R, Cai Q. A prospective, randomized, controlled study of omega-3 fish oil fat emulsion-based parenteral nutrition for patients following surgical resection of gastric tumors. Nutr J. 2014;13:25.
14. Kang K, Shu XL, Zhang YS, Liu XL, Zhao J. Effect of glutamine enriched nutrition support on surgical patients with gastrointestinal tumor: a meta-analysis of randomized controlled trials. Chin Med J (Engl). 2015;128(2):245-51.
15. Sorensen LS, Thorlacius-Ussing O, Schmidt EB, Rasmussen HH, Lundbye-Christensen S, Calder PC, et al. Randomized clinical trial of perioperative omega-3 fatty acid supplements in elective colorectal cancer surgery. Br J Surg. 2014;101(2):33-42.
16. Long H, Yang H, Lin Y, Situ D, Liu W. Fish oil-supplemented parenteral nutrition in patients following esophageal cancer surgery: effect on inflammation and immune function. Nutr Cancer. 2013;65(1):71-5.
17. Chevrou-Severac H, Pinget C, Cerantola Y, Demartines N, Wasserfallen JB, Schafer M. Cost-effectiveness analysis of immune-modulating nutritional support for gastrointestinal cancer patients. Clin Nutr. 2014;33(4):649-54.
18. Marano L, Porfidia R, Pezzella M, Grassia M, Petrillo M, Esposito G, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol. 2013;20(12):3912-8.
19. Ma CJ, Wu JM, Tsai HL, Huang CW, Lu CY, Sun LC, et al. Prospective double-blind randomized study on the efficacy and safety of an n-3 fatty acid enriched intravenous fat emulsion in postsurgical gastric and colorectal cancer patients. Nutr J. 2015;14:9.
20. Klek S, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, et al. Perioperative nutrition in malnourished surgical cancer patients - a prospective, randomized, controlled clinical trial. Clin Nutr.2011;30(6):708-13.