Abstract

Introduction: Immunonutrients are nutrients which are able to modulate the inflammatory response and have been used in diets for cancer patients, especially those who will undergo major surgery, with the aim of contributing to the reduction of postsurgical complications such as infection, morbidity, mortality and hospital stay. The purpose of this study was to analyze the effects of supplementation with immunonutrients in gastric cancer patients undergoing surgery.

Methods: We searched the Lilacs (Latin American and Caribbean Health Sciences), PubMed (US National Library of Medicine National Institutes of Health) and Scopus databases of original articles published in Portuguese, English or Spanish, without restriction on the period publishing. The MeSH descriptors used in the search strategy were: immunonutrition, immunonutrition, gastric cancer, gastric neoplasm, stomach cancer, stomach neoplasm.

Results: The search strategy retrieved 40 records from the selection criteria, with 10 included in the review. Six studies underwent immunomodulatory treatment before surgery, of which three ones underwent the treatment for seven days; two studies, for five days; and one, from five to seven days. Three studies provided the immunonutrients after surgery; in this case, the duration of treatment was for seven days. Two studies offered supplementation immunonutrients before and after surgery.

Conclusion: The utilization of immunonutrients in patients with gastric cancer before and after surgical procedures can contribute to improving the defense mechanisms of the body and control the inflammatory response.

Keywords: Immunonutrition; Arginine; Glutamine; Omega 3; Ribonucleic acid; Gastric cancer

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Introduction

Gastric cancer is one of the most common malignant tumors of the upper gastrointestinal tract, which adversely affects the health and quality of life of patients. Malnutrition and dysfunction of the immune system are consequences usually observed in these patients [1-3].

As one of its functions, the immune system contributes to the maintenance of the organism integrity. In cancer patients, the immune system plays an important role, such as to contribute to the fight against cancer development as well as to adequate recovery after radiation and chemotherapy and surgical treatments [4-7].

Thus, the diet for cancer patients, in addition to seek to prevent and/or reverse the deterioration of the nutritional status, improve nitrogen balance and assist in the management of symptoms such as nausea and vomiting, need to be directed to contribute to the improvement of immune response [1,8,9].

The diets added with immunonutrients are called immunomodulatory and have been used for cancer patients, especially those who will undergo major surgery, by the fact that they present the ability to modulate the immune response, contributing to the reduction of post-surgical complications such as infection, morbidity, mortality and hospital stay [1,10-12].

The immunonutrients most used in diets are arginine, glutamine, omega 3 and nucleotides (RNA) [13-16]. The functions of those nutrients include anti-inflammatory effects and wound healing of the arginine; the prevention of muscular atrophy, of the effects of cellular apoptosis, of bacterial translocation and improves intestinal immune function related supplementation with glutamine; the action of omega 3 in the cyclooxygenase inhibition, reduction in systemic inflammation and proinflammatory response and the role of nucleotides in increased total lymphocyte count in the proper functioning of the immune system, in the integrity of the mucosa and in the process cell turnover [13-17].

This study aims to analyze the impact of using of immunonutrients on the length of hospital stay, postoperative complications and immune function in patients with gastric cancer undergoing surgical procedures.

Method

The search strategy includes research in the LILACS, PubMed and Scopus databases. It was used the search strategy: (immunonutrition OR “immuno nutrition”) and (“gastric cancer” OR "gastric neoplasm" OR "stomach cancer" OR "stomach neoplasm"). For the selection of articles, the following inclusion criteria were defined: articles published in Portuguese, English and/or Spanish, without restriction on the publication period. Exclusion criteria were studies review, studies that have included cancer patients in places other than the stomach and animal studies.

Headings

Physiological and nutritional implications of gastric cancer

Gastric cancer is the fourth most common malign tumor and the second cause of cancer death in the world18. As a metabolic disease usually provides severe damage to the health of the patient as depletion of nutritional reserves, malnutrition and immune system dysfunction [1-3]. In this context, immunonutrients have been used in diets for patients with gastric cancer, especially for those who will undergo major surgery, with the aim to prevent and/or reverse the deterioration of the nutritional status, improve nitrogen balance and contribute improved immune response [1,8,9].

Immunomodulators and his acting
Among the important amino acids, arginine becomes essential in situations of hypercatabolism. Its effect on the immune system is related to the proliferation of T lymphocytes and the production of nitric oxide, which, in small quantities, exhibits anti-inflammatory effect. Arginine also participates in the proline production, important nutrient in collagen synthesis and wound healing process [17,19-22].

Glutamine exerts beneficial effect on immune function by stimulating the production of B and T lymphocytes and immunoglobulin A and, in the enterocytes, contributes to intestinal integrity, prevents muscle atrophy and minimizes the effects of apoptosis, reduces bacterial translocation and improves intestinal immune function. In addition, glutamine is an important energy substrate for cells of the immune system such as macrophages and lymphocytes [17,22-24].

The immunomodulatory effect of omega-3 fatty acids consists of its anti-inflammatory activity and has important effects in patients with trauma, such as substitution of arachidonic acid for membrane phospholipids and cyclooxygenase inhibiting, reducing systemic inflammation through of lower 4-series leukotirene synthesis and prostaglandins E2. In addition, omega 3 fatty acids, by stimulating of prostaglandin E3 and type 3 thromboxanes synthesis contributes to reduction of platelet function and of the proinflammatory response [17,22,25,26].

The nucleotides, precursors of DNA and RNA nucleic acids, contribute to the appropriate function of the immune system by increasing the total lymphocyte count. In situations of metabolic stress, the required amounts of nucleotides are larger, to restore and maintain the appropriate functioning of the immune system, mucosal integrity and cell turnover process [17,22].

**Immunonutrition in gastric cancer patients undergoing surgery**

Fourty articles were identified, among wich 10 were selected because met all inclusion criteria. Four studies performing the immunomodulatory treatment before surgery [27-30]. From these studies, two performed the treatment for seven days [27,29]; one study, in five days 30; and in another, it lasted between five to seven days [28].

Four studies covered immunonutrients after surgery [31-34] with treatment for seven days. Two studies offered supplementation with immunonutrients before and after surgery [35,36].

**Studies that made use of the immunomodulatory supplement before surgery**

In the study by Okamoto et al. (2009) 27, with 60 Japanese patients aged 41-90 years with gastric cancer, the patients who received supplementation of 7.50ml of immunomodulating diet with 7.50kcal, 9.6g of arginine, 3.1g of omega 3 and 0.96g RNA seven consecutive days prior to surgery showed fewer infectious complications after surgery than the group that received diet without immunomodulators (6% vs 28%, p <0.05) and had shorter duration of systemic inflammatory response syndrome that the control group (0.77 ± 0.9 days vs 1.34 ± 1.45 days).

Kamocki et al. (2013) 28, in a study conducted in Poland with 44 gastric cancer patients, aged 31-84 years, found that glutamine and omega 3 administration for seven days before surgery contributed to the improvement of the phagocytic activity, represented by elevated fraction of phagocytic thrombocytes of 1.08 to 1.26 after immunomodulating therapy (p <0.01) and increased of the phagocytic index of thrombocytes of 0.99 to 1.1 after administration of immunonutrients (p <0.01). The improvement of the phagocytic activity is a relevant factor in the treatment of cancer patients, since the decrease in phagocytic activity can promote both...
inflammation and the development of cancer37.

In Brazil, a prospective intervention study with 37 gastric cancer patients with an average age of 60 years, showed that patients who received formula with 7.5g of arginine, 0.7g of EPA, 1.1g of DHA and 1.2g of nucleotides (RNA) for seven days before surgery showed an increase in the C-reactive protein levels (0.1 to 1.5 mg/dl) and IL-6 (2.0 to 14.2 pg/ml) as well as increased in the ratio of Thelper/Tsuppressor (CD4: CD8) (2.3 ± 1.0) in the postoperative period 29. The increase in C-reactive protein and interleukin 6 levels are factors that may contribute to increased risk of complications and morbidity in patients with cancer, including in postoperative period, while the increase in CD4: CD8 ratio represents improvement in the immune response [38-40].

A randomized controlled trial with 244 Japanese patients aged 26-79 years with gastric cancer, received, in addition to the normal diet, 1000 ml/day of formula with 12.8g arginine, 2g of EPA, 1.4g of DHA and of 1.3mg of RNA, five consecutive days before cirurgia 30. The incidence of local wound infection was observed in 27 patients in the group receiving immunonutrition and 23 control group patients (without immunonutrients) (RR: 1.9, 95% CI: 0.66-1.78). Infectious complications occurred in 30 patients in Immunonutrition group and 27 in the control group (RR: 1.11, 95% CI: 0.59 to 2.08). The overall rate of postoperative morbidity in the groups with immunonutrition and control was 30.8 and 26.1%, respectively (RR: 1.18, 0.78-1.78). In this study, supplementation with immunonutrients in the preoperative period did not contribute to the recovery of immune function.

**Studies that made use of immunomodulatory supplement after surgery**

Marano et al. (2013) 31, in a study conducted in Italy with 109 patients aged 49-83 years with gastric cancer, observed that the group receiving the immunomodulatory diet with arginine, omega 3 fatty acids and ribonucleic acid (RNA) for seven days after surgery, showed less post-operative infectious complications (7.4% vs 20%, p <0.05), lower anastomotic leak rate (3.7% vs. 7.3%, p <0.05) and reduction of hospital stay period (12.7 ± 2.3 days vs 15.9 ± 3.4 days, p = 0.029) than the control group.

In Spain, a study with 60 patients with a mean age of 68 who had gastric cancer, showed that supplementation with arginine, omega 3 and RNA, seven consecutive days after surgery, resulted in fewer episodes of complications as the surgical wound healing, when compared to the control group, which received no immunonutrients (0 vs. 8, p = 0.005)32.

Researchers identified in 40 Chinese patients aged 31-75 years with gastric cancer that patients who received formula enriched with arginine, glutamine and omega-3 for seven days after surgery showed elevated levels of immunoglobulin A (IgA) (3, 04 vs 2:54, p <0.05), IgG (13.22 vs. 12.18; p <0.05) and IgM (1:45 vs 1.71, p <0.05), interleukin-2 (368.6 vs. 317.7, p <0.01 ), CD4:CD8 ratio (2.92 vs 1.77, p <0.05), and low levels of interleukin-6 (411.1 versus 519.3, p <0.01) and TNF-α (320.6 versus 439.7, p <0.01) than patients who received standard diet33.

Klek et al. (2005) 34, assessing105 patients aged 38-77 years with gastric cancer, divided in three groups: group A with standard diet, group B with glutamine and group C with omega-3, all with diet for seven days in postoperative, recorded lower rates of postoperative complications in group B (23%) and C (26.6%) than in group A (36.6%). The length of hospital stay was also lower in groups B and C compared to group A.

**Studies that made use of immunomodulatory supplement before and after surgery**

In Poland, was conducted an intervention study with 51 patients with gastric cancer in the age range from 18
to 82 years divided into four grupos. Group 1 received glutamine and omega 3 fatty acids for 5 to 10 days, in the preoperative phase; for postoperative phase provided, in addition to elemental diet, glutamine and omega 3 fatty acids for five days. Group 2 received formula with arginine for 5 to 10 days preoperatively and supplementation with arginine for five days postoperatively. Group 3 received glutamine and omega 3 fatty acids preoperatively for five to 10 days; there was no supplementation in the postoperative period. Group 4 did not receive supplementation before or after surgery. The percentage of phagocytizing platelets and phagocytic index before and after surgery increased in group 2 (1.111-1.25 P <0.05, and 1011-1083, P <0.05, respectively). In the other groups no statistically significant difference were observed, showing that immunonutrition in the perioperative period may help to improve the phagocytic activity in gastric cancer patients undergoing surgery. As the reduction of phagocytic activity can promote both inflammation and the development of cancer, the improvement of the phagocytic activity may contribute to the treatment of cancer patients.

In a prospective randomized clinical trial with 30 Italian patients aged 18 to 75 years with gastric cancer, divided in two groups: one group received the immunonutrients before and after surgery and the other only after cirurgia. Patients who received immunonutrients both before and after surgery showed early postoperative impairment of phagocytosis, Delayed Hypersensitivity Response (DHR), the total number of lymphocytes, and CD4:CD8 ratio, high levels of interleukin-2 receptors (IL-2R) and prealbumin (PA), and low levels of interleukin-6 (IL-6) that group received only after surgery, all these results with p <0.05. In general, patients who received immunonutrients before and after surgery showed better inflammatory response and increasing the synthesis of constitutive proteins which exhibit short half-life.

Evidence Summary

This review enables to realize that there are evidences of the positive aspects of the use of immunomodulatory diets in patients with gastric cancer.

Based on these studies, it was observed that the immunonutrients can be preoperatively introduced into the diet of cancer patients for major surgery for seven to ten day prior to the surgical procedure, and removed on the day of surgery. Postoperatively, supplementation may occur about six hours after surgery for seven days.

Among the benefits of using immunonutrients in the diet of cancer patients preoperatively for major surgery stood out the improved response inflamatória, the phagocytic activity and CD4:CD ratio. In relation to incidence of infectious complications in the postoperative period, the results were different, since in a decreased and another increase following supplementation with immunonutrients in comparison with the group normal diet.

The studies also showed adverse effects after supplementation with immunonutrients in the preoperative period as higher overall rate of postoperative morbidity and elevated C-reactive protein and IL-6.

The supplementation with immunonutrients in the postoperative period shown to reduce the incidence of postoperative infectious complications, anastomotic leak, mean hospital stay, complications about the surgical wound healing, high levels of IgA, IgG, IgM, IL-23, CD4:CD8 ratio and low levels of IL-6 and TNF-α.

The studies that provided the immunonutrients before
and after surgery reported an increase in phagocytic activity, prevention of early postoperative impairment of phagocytosis, improved delayed hypersensitivity response (DHR), increased CD4:CD8 ratio, elevated levels of interleukin-2 receptors (IL-2R) and Prealbumin (PA), and decreased levels of interleukin-6 (IL-6).

**Conclusion**

The supplementation with immunonutrients in preoperative period in patients with gastric cancer undergoing major surgery may contribute to the improvement of the inflammatory response, phagocytic activity and increased of the CD4:CD8 ratio. In the postoperative period, the immunonutrients can help to reduce the incidence of mortality, morbidity, reduced postoperative infectious complications, anastomotic leak and complications as the surgical wound healing. In the perioperative period, immunonutrients can contribute to increased phagocytic activity, prevent early postoperative impairment of phagocytosis, improve the delayed hypersensitivity response (DHR), increase CD4:CD8 ratio, raise levels of interleukin-2 receptors (IL-2R) and Prealbumin (BP) and reducing levels of interleukin-6 (IL-6).

Further research would see desirable to determine doses of these immunomodulators nutrients according the various aspects of clinical application as tumor stage, previous nutritional status of the patient and therapeutic neoadjuvant.

**References**


