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REVIEW ARTICLE

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The benefits of glutamine in the treatment of patients with cancer

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Abstract

The subject of this study is the benefits of immunonutrition or immunomodulation, based on the concept that malnutrition impairs immune function. It is a therapeutic approach in an artificial form of food with the function of rebuilding cells for the immune response, which involves specific amino acids such as arginine, glutamine, and fiber. In this sense, it is intended to deal specifically with glutamine, which is a "conditionally essential" amino acid, as its concentration in plasma can decrease by up to 50% during stress, causing a deficiency condition. In the treatment of cancer patients, glutamine constitutes an immunomodulatory nutrient, being a fundamental substrate for the cells of the immune system, stimulating the multiplication of lymphocytes, the differentiation of B cells, the production of interleukin 1, and the phagocytosis of macrophages. The high use of glutamine by lymphocytes and macrophages suggests that the provision of this amino acid is of paramount importance for the functioning of these cells and also for the proper functioning of the immune response. Important in viral infections and in combating tumor cells, Natural Killer (NK) cells are dependent on adequate glutamine stores for their proliferation. It also exerts a local immunostimulating effect, increasing intestinal T cells, and is a precursor of an important intracellular antioxidant, glutathione. This is bibliographical research, of a qualitative nature, carried out through specialized scientific articles on the chosen topic.

Keywords: Immunomodulation. Glutamine. Amino Acid. Cancer. Treatment.

Introduction

According to the National Cancer Institute-INCA (2010) [1], the term cancer is used generically to represent a set of more than 100 diseases, including malignant tumors from different locations. An important cause of disease and death in Brazil, since 2003, malignant neoplasms are the second leading cause of death in the population, representing almost 17% of deaths from known causes, reported in 2007 in the Mortality Information System (SIM). Other authors said that each year, according to data from the World Health Organization (WHO), cancer affects at least nine million people, is considered the second cause of death, surpassed only by cardiovascular ones [2].

Some studies have shown that the most frequent tumors are those of the respiratory and gastrointestinal tract, with the most affected organs being the small intestine, fecal appendix, and rectum [3]. According to Hallay (2002) [4], there is evidence available on the role of immunonutrition in the treatment of cancer patients. It is a form of artificial nutrition that aims to renew cells for an immune response involving specific amino acids such as glutamine.

In this sense, glutamine is the most abundant free amino acid in plasma and muscle tissue, comprising 20% of the free amino acids in the blood and more than 50% of the skeletal muscle amino acid pool. It is also found in relatively high concentrations in other body tissues [5].

In this sense, the present study aimed to report the benefits of glutamine in the treatment of cancer patients.

Methods

This is a literature review, based on literature published in recent years, in the Scielo, PubMed, Medline, Cochrane Collaboration, Scopus (Elsevier), and LILACS databases, with the following descriptors: cancer, immunomodulation, amino acids, glutamine. It can be concluded that the use of glutamine in cancer treatment can be a viable option.

Results and Discussion

Glutamine as as food supplement

According to Boligon and Huth (2010) [6], the amino acid glutamine can be used as a food supplement in patients who have feeding difficulties due to advanced degrees of mucositis and need parenteral or enteral nutritional support, with good results. As for the ability to prevent or reduce the severity of mucositis when it is already installed, it has not yet been well established in the literature.

Glutamine is the most abundant amino acid, surpassing any other, and has several roles in the body [7]. Nutritionally it is classified as a non-essential amino acid as it can be synthesized by the body from other amino acids. There are authors who place it as a "conditionally essential" amino acid, as its concentration in plasma can decrease by up to 50% during stress, causing a deficiency condition [8,9].

According to Mero et al., (2009) [5], glutamine comprises 20% of the free amino acids in the blood and more than 50% of the skeletal muscle amino acid pool. It is also found in relatively high concentrations in other body tissues. Glutamine supplementation can reduce degradation and increase protein synthesis in skeletal muscle tissue. Still, the main tissue responsible for the synthesis, storage, and release of glutamine is the muscle tissue, which presents the activity of the enzymes glutamine synthetase and aminotransferase of branched-chain amino acids [10]. Glutamine is actively transported into cells via a sodium-dependent system, resulting in energy expenditure. The transport of this substance through the muscle cell membrane is fast and its speed is superior to all other amino acids [2].

According to D'Souza and Tuck (2004) [11], individuals weighing approximately 70 kg have about 70-80 g of glutamine, distributed throughout the body. In blood, the concentration (glutaminemia) is around 500-700µmol/L. Tissue concentration and glutaminemia can be influenced by the activity of the enzyme glutamine synthetase or glutaminase. Some types of cells, such as those in the immune system, kidneys, and intestine, have high glutaminase activity and are therefore considered to be tissues that consume the substance. On the other hand, skeletal muscles, lungs, liver, brain, and, possibly, adipose tissue present high activity of the glutamine-synthetase enzyme, thus being considered synthesizing tissues. In addition to the protective effect of glutamine on the immune system, Berk et al. (2008, p. 1186) observed that patients diagnosed with advanced cancer supplemented with glutamine had a strong tendency to increase body mass at the expense of others, who had a weight loss of 2% to 10% of total body weight [12].

Kim (2011) [13] comments that, however, glutamine is depleted in muscle reserves during severe metabolic stress, such as sepsis and major surgery. Glutamine is the essential component in the optimal functioning of neutrophils and macrophages, and also in lymphocyte proliferation. This amino acid provides fuel for rapidly dividing cells (particularly lymphocytes and enterocytes). Glutamine is also a precursor to the endogenous antioxidant glutathione. Glutamine is synthesized in the skeletal system and secreted into the bloodstream to then reach the tissues. Kidney, liver, intestinal and immune system cells are the most important glutamine consumers.

The proliferation and development of cells, especially of the immune system, the acid-base balance, the transport of ammonia between tissues, the donation of carbon skeletons for gluconeogenesis, among others, are some of the functions in which the substance is involved and still it is linked to the maintenance of the basic functions of organs such as the kidneys, liver, heart, intestines, neurons, lymphocytes, macrophages, neutrophils, pancreatic beta cells, among others [14,15].

Besides, glutamine plays an important role in cell-mediated immunity and in the integrity of the intestinal mucosa. Glutamine supplementation during illness improves the intestinal barrier, lymphocyte function and preserves lean body mass [16]. Glutamine protects the body against septic shock by preventing glutathione depletion and thus reducing cell death that occurs during shock. In surgical and cancer patients, glutamine supplementation decreases the production of some pro-inflammatory cytokines [17].

Studies Related to the use of glutamine in the treatment of diseases

Glutamine appears to have a trophic effect on the intestinal mucosa and is a primary nitrogenous substrate. The use of glutamine can improve the function of the intestinal barrier and increase the absorptive capacity, and it can be used orally, enteral, or parenterally. Studies on the efficacy of parenteral glutamine with the administration of 0.5g/kg/day for 6 days in 40 patients before gastrectomy. According to the results, there was a decrease in the infection rate, an increase in the levels of CD4 and CD8, responsible for translating the signals and initiating the activation of lymphocytes, a decrease in-hospital stay, and a decrease in C-Reactive Protein (CRP), capable of evaluating the extent and activity of inflammation, of IL2, which induces the maturation of B lymphocytes and T cell maturation, and TNF, involved in systemic inflammation [18].

According to Lobo et al., (2006) [19], a study with glutamine supplementation through the enteral route in 25 patients starting with 50mL/h, reaching the patients' caloric needs in 72 hours, for at least one week. As a result, an increase in the maturity of total lymphocytes was obtained, leading to a significant improvement in the immune response of patients undergoing surgical procedures. Although the diet with glutamine and without glutamine was well tolerated, it did not find statistical significance in relation to the improvement in nutritional status. Evidence from studies with patients suffering from metastatic colorectal carcinoma also demonstrates that glutamine acts in the protection and growth of the gastrointestinal mucosa, thus reducing changes in intestinal absorption and permeability [20].

An experiment carried out offered immunomodulating agents, including glutamine, for patients with colorectal cancer. It was found in these patients, after the surgical procedure, improvement in the function of immune cells. Patients in the supplemented group had higher serum values of glutamine, NK, IgG and IgM, asparagine, and CD4 than patients in the control group. These compounds are essential for the immune response and recognition of a wide variety of foreign substances to the organism. This benefit can be explained by the fact that glutamine is the preferential source of fuel for enterocytes, lymphocytes, and macrophages, improving the immune response and the function of the intestinal barrier, with a consequent reduction in bacterial translocation [21]. Cancer that affects the head and neck region includes malignant tumors of the face, nasal cavities, paranasal sinuses, mouth, pharynx, larynx, thyroid, salivary glands, the soft tissue of the neck, parathyroid, and scalp tumors. Treatment for these types of tumors consists of surgery and/or radiotherapy for early lesions and combination therapy with chemotherapy for advanced lesions. All treatment modalities including surgery, radiotherapy, and chemotherapy will directly or indirectly affect the nutritional status of the patient.

Patients with head and neck cancer are at increased risk of malnutrition. Inadequate eating habits associated with excessive alcohol and tobacco consumption, often observed among these patients, contribute to the increased nutritional risk. In addition, the location of the tumor causes dysphagia, odynophagia, trismus, and taste alterations, resulting in a decrease in food intake. The evident nutritional loss in these patients reduces treatment tolerance, therefore, their nutritional status needs to be constantly monitored [20].

Also, the impact of the use of glutamine in patients with head and neck cancer undergoing chemotherapy and radiotherapy treatment was evaluated by a study where it was concluded that supplementation with this amino acid helps in the prevention of mucositis, especially grades III and IV, which levels prevent normal and adequate food and nutrition, and the maintenance of the nutritional status of these patients. This result can be explained by the multiplicity of glutamine functions and its importance in disease states that delay the inflammatory response of debulking or infections and would activate T lymphocytes. Systemic Inflammatory Response Syndrome (SIRS) is one of the many conditions related to inflammation systemic, organ dysfunction, and organ failure. Its four criteria are body temperature > 38°C or 20 movements/minute or pCO_2 90bpm; leukocytosis: more than 12,000 cells per mm^3, or more than 10% immature cells in the periphery. SIRS is a subset of cytokine storms in which there is abnormal regulation of several cytokines [22].

Fever and leukocytosis are characteristic of the acute phase of the reaction, whereas tachycardia is usually the initial sign of hemodynamic compromise. Tachypnea may be related to metabolic stress due to infection and inflammation, but it may also be a sign of the threat of inadequate perfusion, resulting in the onset of metabolism anaerobic cell [23].

In a prospective randomized clinical trial, patients whose glutamine was added to total parenteral nutrition, who had at least two SIRS criteria, admitted to the Intensive Care Unit, were analyzed. It was concluded that the dipeptide glutamine added to total parenteral therapy significantly decreases white blood cell and NK cell counts, which should be associated with suppression of inflammation and improvement of clinical recovery. Larger, controlled clinical trials are needed to determine the potential efficacy of glutamine nutritional supplementation as an adjunct therapy in critical illnesses [16].

The importance of glutamine for cancer patients

According to Silva (2006) [24], glutamine, as it constitutes an immunomodulatory nutrient, is a fundamental substrate for the cells of the immune system, stimulating the multiplication of lymphocytes, the differentiation of B cells, the production of interleukin 1, and the phagocytosis of macrophages. The high use of glutamine by lymphocytes and macrophages suggests that the provision of this amino acid is of paramount importance for the functioning of these cells and also for the proper functioning of the immune response. Important in viral infections and in combating tumor cells, Natural Killer (NK) cells are dependent on adequate glutamine stores for their proliferation. It also exerts a local immunostimulating effect, increasing intestinal T cells, and is a precursor of an important intracellular antioxidant, glutathione.

The gastrointestinal tract is the main means of the utilization of glutamine, having its uptake fundamentally in the epithelial cells of the small intestine villi. The increasing incidence of esophageal and stomach cancer has awakened its study and understanding [25]. Patients with cancer of the upper gastrointestinal tract can be supplemented. Just a few days of preoperative immunonutrition feeding are already beneficial as they reduce postoperative infections [19].

According to Fillmann et al., (2007) [26], supplementation with glutamine enhances the cellular immune response and as such improves the prognosis of patients undergoing gastrointestinal surgery. There is a decrease in the incidence of infection, low levels of microbial colonization, improvements in the nitrogen balance, and a reduction of about a week in a hospital stay. Digestive tract cells are the most rapidly replicating and the gastrointestinal tract is potentially the most important source of bacterial translocation. Thus, glutamine acts to protect the intestinal barrier, due to the increase in glutathione, which acts against reactive oxygen species, acting as an antioxidant and thus decreasing the formation of free radicals and the replication of tumor cells.

Adverse effects

Studies on the benefits of glutamine supplementation in the treatment of cancer patients concluded that glutamine acts as a respiratory substrate for tumor cells. The tumor cell can use any substrate as a source of energy, including amino acids, glucose, lipids, and ketone bodies. Of these, glucose and glutamine are abundant nutrients needed for cell division that feed on multiple pathways necessary to support cell growth [27].

According to Mazurek et al., (1997) [28], highly malignant neoplasms can increase with little vascularizetion due to the high glutaminolysis and glycolytic rates that make up for this lack of vascularization, allowing the tumor to survive in areas with low oxygenation. When oxygen is scarce, there is improved conversion of glutamine to glutathione, an important agent that controls the accumulation of reactive chemical oxygen-containing molecules that damage normal cells.

When the researchers used a glutaminase inhibitor, the growth of cancerous B cells was stopped. Santos (2007) [29] comments that glutamine is an important precursor of glucose in post-absorptive states, contributing to the addition of a new carbon for the formation of glucose, being the link between carbohydrate and protein metabolism. Studies have evaluated the effects of glutamine administration on oxidative stress in women with breast cancer undergoing chemotherapy, being administered 15g/kg/day of glutamine orally. They concluded that, in this type of cancer, glutamine did not offer protection against local or systemic oxidative stress, which can be explained by the fact that tumor cells present in the breast do not replicate rapidly [30].

Conclusion

Innovations in immunonutrition therapy in critically ill patients such as cancer patients, whether or not aggravated by chemotherapy and/or surgery, are of fundamental importance in the pursuit of quality of life for these patients. Thus, the use of immunomodulators such as glutamine, arginine, and fibers in some pathological conditions has been shown to be important for the treatment of such patients. length of hospital stay and increasing muscle mass. The route of supplementation with glutamine will depend on the patient's physiological conditions to adequately receive the diet, the type of cancer committed, as well as the amount to be administered. It is noticed that the enteral route is the most used, mainly because it increases the maturity of total lymphocytes and brings improvements to patients. Glutamine in situations of stress in the body, such as cancer, becomes an essential and essential amino acid in the treatment of cancer patients because it is an excellent and important immunomodulator. However, studies prove that, in the absence of glucose, studies mention that glutamine is an energy source for tumor cells. Thus, it is necessary to carry out new randomized clinical trials proving the safety and efficacy of this therapy. Thus, the study carried out here, far from exhausting the subject,

sought to collaborate with the chosen topic, in order to verify and better assess the influence of parenteral therapy with glutamine in clinical oncology patients, considering its risks, benefits, and safety.

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