Amino acids and cancer: potential for therapies?

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Purpose of review
Cancer patients may have a variety of disorders associated with systemic inflammation caused by disease progression. Consequently, we have protein hypercatabolism. In view of this, protein and amino acid adequacy should be considered in relation to nutritional behavior. Therefore, this review aims to evaluate the influence of protein and amino acids in the nutritional therapy of cancer.

Recent findings
Diets with adequate protein levels appear to be beneficial in the treatment of cancer; guidelines suggest consumption of greater than 1.0–1.5 g/kg body weight/day. In patients diagnosed with malnutrition, sarcopenia, or cachexia, it is recommended to use the maximum amount of protein (1.5 g/kg of weight/day) to adapt the diet. In addition, based on the evidence found, there is no consensus on the dose and effects in cancer patients of amino acids such as branched-chain amino acids, glutamine, arginine, and creatine.

Summary
When evaluating the components of the diet of cancer patients, the protein recommendation should be greater than 1.0–1.5 g/kg of weight/day, with a distribution between animal and vegetable proteins. We found little evidence demonstrating clinical benefits regarding individual or combined amino acid supplementation. Still, it is unclear how the use, dose, and specificity for different types of cancer should be prescribed or at what stage of treatment amino acids should be prescribed.

Keywords
amino acids, cancer, nutrition therapy, protein

INTRODUCTION

Cancer is a disorder in the proliferation and accumulation of malignant cells, which are functionally and morphologically different from healthy cells [1]. Consequently, neoplasia induces a systemic inflammatory response that leads to neuroendocrine changes, increased proteolysis, and a negative nitrogen balance. In addition, there is a loss of appetite and decreased food intake. Therefore, developing pathologies secondary to cancer is possible, such as malnutrition, sarcopenia, and cachexia, which are often diagnostic [2].

Given this scenario, nutritional therapy is part of the multidisciplinary approach to cancer patient care. Therefore, nutritional screening and early diagnosis of disorders secondary to cancer are beneficial and help to build individualized and efficient consultations for these patients. The adequacy of macronutrients, especially protein, makes the patient's clinical routine toward their treatment more effective [3,4▪▪]. Nutritional guidelines endorse protein intake around greater than 1.0– 1.5 g/kg body weight/day [4▪▪]. However, many uncertainties limit the implementation of nutritional guidelines and conduct for the use of proteins and amino acids, such as the fragility of robust methodologies and randomized clinical trials to understand the dose and effect, in addition to the different types of cancer.

Therefore, this review aims to describe and highlight studies focusing on current evidence in view of protein and amino acid recommendations, in addition to outlining the action of these nutrients in the metabolism of cancer patients.

IMPACT OF CANCER-DERIVED INFLAMMATION ON MUSCLE WASTING

Cancer patients often lose their appetite and experience weight loss; both neoplastic and immune

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KEY POINTS

- Patients with cancer may present disorders secondary to the underlying disease, such as malnutrition, sarcopenia, and cachexia, as a result of the exacerbation of systemic inflammation (high C-reactive protein, neutrophil–lymphocyte ratio, and/or pro-inflammatory cytokines).
- The protein recommendation for cancer patients is greater than 1.0–1.5 g/kg of body weight/day; in patients diagnosed with malnutrition, the use of the upper limit is indicated, consisting of 65% of protein of animal origin.
- In relation to amino acids, there is some positive and negative evidence to recommend supplementation. Although leucine is an avenue for new studies, there is no clinical evidence if this amino acid attenuates muscle wasting in sarcopenia or cachectic patients. However, randomized clinical trials should be conducted to comprehend the effects of supplementation.
- Creatine supplementation to clinically treat cancer patients requires caution as evidence has demonstrated controversial findings on cancer metastasis.
- Arginine has an immunomodulatory function, so studies suggest that this nutrient can be supplemented at all stages of cancer treatment as a protein source.
- Glutamine supplementation can be considered well tolerated for cancer patients, particularly in ameliorating mucositis.

system cells are determinants for the development of symptoms of cancer [5]. Enhanced inflammatory responses intervened by pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), increase the expression of muscle atrophy-specific protein ligases (E3), including atrogin-1/MAFbx and muscle ring finger-1 (MURF-1) impairing the molecular pathways of muscle protein synthesis [6,7].

Furthermore, with this exacerbated inflammatory condition, ubiquitin–proteasome activation may occur from the target protein pathway of rapamycin in mammals (mTORC1), causing protein degradation of myocytes [7,8]. Together, there is a decrease in protein synthesis and the installation of a hypermetabolic state, thus favoring a catabolic state in the cancer patient, further intensifying muscle depletion [3,8].

Another parallel and dependent mechanism to this condition is that physiologically, the hypothalamus is responsible for controlling food intake and energy expenditure. In summary, with the activation of the inflammatory condition triggered by cytokines, the body develops adeptly by suppressing appetite by inverting the secretion of neuropeptides (activating anorexigenic and inhibiting orexigenic) [5].

The result of hypercatabolism caused by intense inflammatory activity associated with decreased food intake can lead patients to insufficient protein–energy reserves, leading to malnutrition, sarcopenia, and cachexia [5]. In addition to these conditions, we still have several factors that present greater risks for developing the associated disorders mentioned above, such as advanced types of cancer, including head and neck, lung, gastrointestinal tract, liver, and pancreas; side effects of oncological treatments (chemotherapy, surgery, and radiotherapy) causing cytotoxic damage to tumor cells; and the presence of early satiety, changes in smell or taste, dysphagia, and odynophagia [3,5,8].

Therefore, it is common to find in these patients a marked loss of muscle or muscle atrophy, a decrease in food intake, especially proteins and essential amino acids for muscle synthesis, a reduced functional capacity, and a reduced quality of life [2]; thus leading to an increased risk of morbidity and mortality for these cancer patients. This highlights the importance of protein synthesis and maintenance of muscle mass with a focus on energy intake, quality, and quantity of proteins and essential amino acids [5].

THERAPEUTIC CONDUCT FOR PROTEINS IN CANCER

Poor food intake and consequent nutritional loss often occur in cancer patients, thus leading to negative clinical results. Therefore, nutritional therapy, especially when performed early, is part of the support for these patients, whose objective is to maintain quality of life and greater tolerance to cancer treatment [4▪▪,5,9,10,11▪▪].

Current and international consensus on nutrition with an oncological focus has established the important role of nutritional therapy in cancer patients [4▪▪]. These documents describe objectives and targets for macronutrient intake. The protein recommendation described in these guidelines for these patients is greater than 1.0–1.5 g/kg of weight/day, and for patients already diagnosed with malnutrition, sarcopenia, and cachexia secondary to cancer, the recommendation is the maximum limit (1.5 g/ kg of weight/day) [4▪▪].

In a recent narrative review, Laviano [11▪▪] concluded that the ideal protein recommendation is the same as previously mentioned for patients with digestive cancer. In addition, patients at risk or diagnosed with malnutrition should be prescribed

diets with an upper protein limit to recover and maintain muscle function. Finally, the author also suggests combining nutritional therapy with physical activity for better results [12].

However, some factors limit the expansion of these recommendations in oncological nutritional practice, such as differences in types of cancer and their particularities [8]. In addition to fragility, guidelines seem to centralize the nutritional approach during periods of exacerbation of the inflammatory process. In periods when this does not occur, the high protein recommendation seems uncertain [4▪▪,9,10,11▪▪,12].

Furthermore, it is unclear whether a diet rich in proteins or specific amino acids is beneficial for preserving and recovering muscle mass or for increasing the immune response in cancer patients. Still, it is not clear what the protein recommendation is in relation to the different phases of oncological treatment and what would be the ideal period of this recommendation to favor clinically positive results [3,5,9,10,11▪▪].

Studies such as Clauss *et al.* [12] observed that a low protein intake (being <1.0 g/kg of body weight/day) was found in one-third of the study sample (20 patients diagnosed with pancreatic cancer), the majority being patients at risk of malnutrition. In contrast, a recent systematic review assessed whether high protein intake should be considered for cancer patients undergoing treatment [8]. The authors found eight studies, of which one was a randomized controlled trial. The review comprised a total sample of 554 patients with head and neck, lung, and esophageal cancer. The included studies were heterogeneous among themselves and revealed methodological uncertainties. Still, the results seem to suggest that only protein intake greater than 1.4 g/kg is associated with muscle maintenance [8].

In addition, the quality of the protein is also discussed, that is, what should be the proportion of animal and plant-based protein in the distribution of the daily diet of cancer patients. Animal proteins provide greater anabolic stimuli compared with plant-based protein foods and are, therefore, better for muscle health. However, when we think of cancer patients, early satiety is one of the symptoms present during treatment. However, regardless of the satiating effects, more plant-based proteins are required than animal-derived products to obtain adequate amino acid intake [13▪▪].

Studies on the type of protein that should be consumed, that is, animal vs. plant in relation to the type of cancer and treatment time, are scarce. It is also worth noting that even in healthy humans, the ideal plant/animal ratio to support muscle mass has not been established. However, Ford *et al.* [13▪▪] inferred that a minimum of 65% animal protein intake can be considered an ideal starting point for supporting muscle anabolism in people undergoing active cancer treatment. Additionally, future studies should determine the optimal ratio of animal protein vs. plant protein to support muscle mass in cancer patients.

THERAPEUTIC BEHAVIOR FOR CANCER: AMINO ACID SUPPLEMENTATION

In general, some questions remain unanswered regarding metabolism function and the extent to which amino acid intake may benefit patients with cancer-induced cachexia. Among the nutritional strategies of cancer patients, increased protein intake can be effective in providing amino acids, especially those with a supposed anticatabolic action [3,4▪▪,14–18].

Thus, in the following topics and Table 1, special attention is directed to the function of some key amino acids and derivatives: branched-chain amino acids (BCAs; isoleucine, valine, and leucine), glutamine, arginine, and creatine. Additionally, a discussion addresses how these amino acids, and their derivatives may be involved in maintaining muscle mass.

BRANCHED-CHAIN AMINO ACIDS

BCAs (leucine, isoleucine, and valine) are essential amino acids involved in immune responses and may play roles in malnutrition and sarcopenia in cancer patients. However, they are not produced by the body, their source being protein intake. BCAAs are essential substrates for maintaining protein synthesis and play an important anabolic role, in addition to participating in protein renewal metabolism and being metabolized in skeletal muscle [19–21].

The use of these amino acids has been extensively studied in cancer patients, especially in those with loss of muscle mass and/or function [22,23▪▪]. The way that BCAAs act is via mTOR, leading to greater availability of the final substrate for the metabolization of these amino acids in the muscle [6]. In their systematic review, Cogo *et al.* [17] concluded that BCAA supplementation during the oncological surgical period is well tolerated and indicated that BCAAs reduce postoperative complications, such as infections, in addition to the presence of ascites. They guarantee this result through clinical trials with robust methodological designs that use supplements enriched with BCAAs.

Among BCAAs, leucine stands out as a promising amino acid as it metabolically regulates muscle protein synthesis, the most common being mTORC1, via

Table 1. Amino acid intervention studies in cancer patients

References	Study design and population	Experimental protocol	Results
Herrera-Martínez *et al.* [24▪]	Randomized clinical trial Patients with cancer (undergoing systemic treatment)	Nutritional treatment with oral high protein supplements based on whey protein (control group) Versus hypercaloric and high protein oral supplement (OS) enriched with leucine (intervention group) Over a period of 12 weeks	Nutritional support with hypercaloric, hyperproteic (with whey protein) OS, and vitamin D supplementation were associated with the maintenance of body composition and improvements in functionality and in quality of life in patients with cancer undergoing systemic treatment. No significant benefits were observed when a leucine-enriched formula was used.
Boisselier *et al.* [37]	Phase III double-blind multicenter study (NCT01149642) Patients with head and neck squamous cell cancer (HNSCC) treated with concomitant cisplatin and radiotherapy (CRT)	Oral supplementation (three sachets/day) of a formula enriched with l-arginine and omega-3 (n-3) fatty and ribonucleic acids (experimental arm) or an isonitrogenic isocaloric control (control arm) For 5 days before each one of three cycles of cisplatin	Although this immunomodulatory formula was unable to reduce severe mucositis during CRT, the results suggest that the long-term survival of HNSCC patients who adhered to treatment was improved.
Kuroki *et al.* [18]	A phase II study Patients with head and neck squamous cell carcinoma (HNSCC) in chemoradiotherapy	HNSCC patients undergoing PBCRT were randomly assigned to the mixture of the HMB/Arg/Gln (beta-hydroxy-beta-methylbutyrate, arginine, and glutamine) intervention cohort (group I) and nonintervention (group NI) 2) The incidences of ≧ grade 3 mucositis (primary endpoint), ≧ grade 2 mucositis, and opioid usage and the degree of body weight loss (secondary endpoints) were compared between group I and group NI	HMB/Arg/Gln administration demonstrated inhibitory effects on the progression of grade 3 mucositis and cancer cachexia in HNSCC patients treated with chemoradiotherapy.
Storck *et al.* [25]	Single-center, randomized trial examined a multimodal therapy Over 12 weeks in patients with advanced cancer	The intervention group received a leucine-rich supplement in combination with a nutrition and physical exercise program Patients in the control group received standard care	The present study showed substantial improvement in handgrip strength through the implementation of a multimodal therapy including nutritional counseling, physical exercise, and a leucine-rich supplement in advanced cancer patients. The positive effect on energy and protein intake, as well as good adherence to the program, demonstrated the feasibility of the program, and the clinical course data highlighted the safety of the program. However, the study was not able to answer the question of whether the individual-added leucine-rich supplement had a positive impact on the multimodal program.

activation of phosphorylation of protein S6 kinase 1 (S6K1) of the eukaryotic initiation binding factor protein (4EBP1), thus increasing the protein balance in the muscle [2].

Even so, leucine supplementation in cancer patients still lacks consensus on its use and dose/effect [23▪▪,24▪]. In their review, Beaudry and Law [23▪▪] aimed to evaluate preclinical studies with leucine supplementation. They concluded that current studies indicated that a diet rich in leucine can attenuate muscle loss in cancer; however, these studies have methodological differences, thus making it difficult to apply their results. Hence, there is a need for more preclinical work and clinical trials exploring the potential ability of leucine to modulate protein turnover and immune responses, in

addition to the dose/effect of leucine supplementation in cancer patients [23▪▪].

Storck *et al.* [25] conducted a randomized study over 12 weeks in patients with advanced cancer. The intervention group received a leucine-rich supplement in combination with a nutrition and exercise program, and the control group received standard care. In their results, they observed a substantial improvement in handgrip strength through the implementation of multidisciplinary therapy, including nutritional counseling, physical exercise, and a supplement rich in leucine in patients with advanced cancer. The positive effect on energy and protein intake, as well as good adherence to the program, demonstrated the feasibility of the program, and data from the clinical course highlighted the safety of the program. However, the study was not able to answer the question of whether the individual leucine-rich supplement had a positive impact on the multidisciplinary program [25].

GLUTAMINE

Glutamine (Gln) is the amino acid most consumed by the body. It is involved in a series of metabolic reactions, including energy production, and is acquired through the diet and synthesized in the body. Gln is present in all tissues and organs, and its anabolic properties are different according to the cell type. For example, Gln in the gastrointestinal tract and immune system acts as a protective barrier against infections [26–28]. In muscles, during phases of exacerbated catabolism, it is used as a source of nitrogen or an energy pathway [27,28]. In conditions of lack of this amino acid, the muscle becomes an endogenous source of Gln, which is important for muscular status [29].

Although both Gln and glucose can be used as energy for tumor progression through the Krebs cycle, generating ATP, the contribution of this amino acid is much smaller than glucose as the use of Gln for this purpose is extremely variable, depending on the type of tumor. However, in general, the benefits of Gln outweigh its harmful effects [28]. Mayers and Vander Heiden [30] concluded that Gln has a physiological importance in maintaining health during cancer treatment. For example, Gln deficiency during cancer treatment can lead to sarcopenia and lymphopenia, leading to negative manifestations [30].

The adequate amount of Gln in a normal protein diet is around 10–20 g/day, but it can be higher in a high protein diet (20–40 g/day) in cases of hypercatabolic state [31]. This amino acid is commonly used in mucositis, esophagitis, and enteritis cases. When such situations are exacerbated in cancer patients undergoing treatment, Gln supplementation is recommended at a safe dose of ~4 g, either orally or enterally [28].

A systematic review and meta-analysis performed with head and neck squamous cell cancer found that Gln supplementation confers benefits in avoiding and improving radiation-mediated mucositis [32▪].

Given the above, Gln supplementation can be considered well tolerated for cancer patients, particularly in ameliorating mucositis. However, more randomized clinical trial studies should be carried out to standardize the dose and effect on muscle health and standardize the use of this amino acid for all types of cancer.

ARGININE

Tumor progression is linked to immunological interactions within the tumor environment [33]. Arginine is metabolized mainly by arginase-1 (Arg1) and nitric oxide synthase (NOS) in myeloid cells. The review by Yang *et al.* [34] noted that studies have observed that reducing arginine in the human body attenuates the function and proliferation of T cells, which can be reversed by arginine supplementation. Furthermore, under arginine restriction, T cells downregulate CD3ζ expression, preventing TCR (T-cell receptor) expression, leading to reduced proliferation and cytokine secretion. Arginine transporter, cationic amino acid transporter-1 (CAT1), supports naive and memory $CD4^+$ T cells and $CD8^+$ T cells to maintain T-cell proliferation and activation [34].

Therefore, it is possible to state that arginine-containing diets can, in addition to helping the patient's nutritional status, also increase the immune response against the tumor [33]. From this immunomodulatory function of arginine, studies suggest that this nutrient can be supplemented in all stages of cancer treatment as a protein source, especially in surgical cases [2,35].

Arginine is present in three sources: foods that contribute to 25–30% of our diet, such as eggs, fish, legumes, and nuts; endogenous synthesis from the conversion of citrulline into arginine through a sequence of reactions in the kidneys, providing between 15–20 g; and protein renewal from amino acid recycling [3,4▪▪,36].

In a study by Boisselier *et al.* [37], patients with head and neck cancer receiving adjuvant chemotherapy and radiotherapy were randomized to supplementation with an oral nutritional supplement enriched with arginine, omega-3 fatty acids, and ribonucleic acids for 5 days before chemotherapy and for three cycles of treatment. In their results,

no significant effects were observed on the incidence of severe mucositis nor overall survival at 3 years. However, in 75% of compliant patients, overall survival was significantly improved in the arginine-enriched group compared with the control groups. The authors hypothesized that this outcome offered sufficient caloric intake to patients during treatment, along with the addition of immunonutrients, which appears to improve the nutritional status of these patients while also improving their immune response. However, the authors conclude that the positive results cannot be associated only with arginine as the supplement offered contained other modulating nutrients, which may have possibly participated in these results [37].

Therefore, in view of the above, more studies should be carried out with a focus on types of cancer that best adhere to the use of arginine, in addition to the consensus of the daily dose to be supplemented with this amino acid.

CREATINE

Creatine is an organic acid containing nitrogen in its molecule. This nutrient is found in abundance in the human body, with about 120–140 g in a healthy adult. About 2–4 g of creatine are obtained daily from diets enriched with creatine sources such as fish, poultry, and red meat. Creatine is synthesized by the liver and kidneys, where it is phosphorylated by creatine kinase into phosphocreatine, becoming an important metabolite for energy buffering in the body. The relationship of creatine and its analog (cyclocreatine) with cancer is observed by the suppression that creatine causes in tumor growth, with the manipulation of energy buffering of neoplastic cells or cytotoxic T cells (CD8) [38,39] (Fig. 1).

Cell multiplication in cancer happens quickly and requires much energy. In this context, decreasing energy may be a strategy to limit the proliferation of neoplastic cells. One strategy could be using a creatine analog, where energy formation through metabolizing this analog is difficult because of the different kinetic and thermodynamic properties, thus hindering energy production for tumor multiplication [2,39,40].

However, studies suggest that in most types of cancer (liver, breast, vulva, and pancreas), high creatine levels are associated with accelerated tumor progression [38–40]. However, the correlation between creatine levels and cancer progression is unclear, so creatine may function differently in different stages and environments of cancer progression. In addition, there is no consensus on the daily dose of creatine, so more studies should be carried out to standardize the dose and effect of creatine use in cancer patients [41,42].

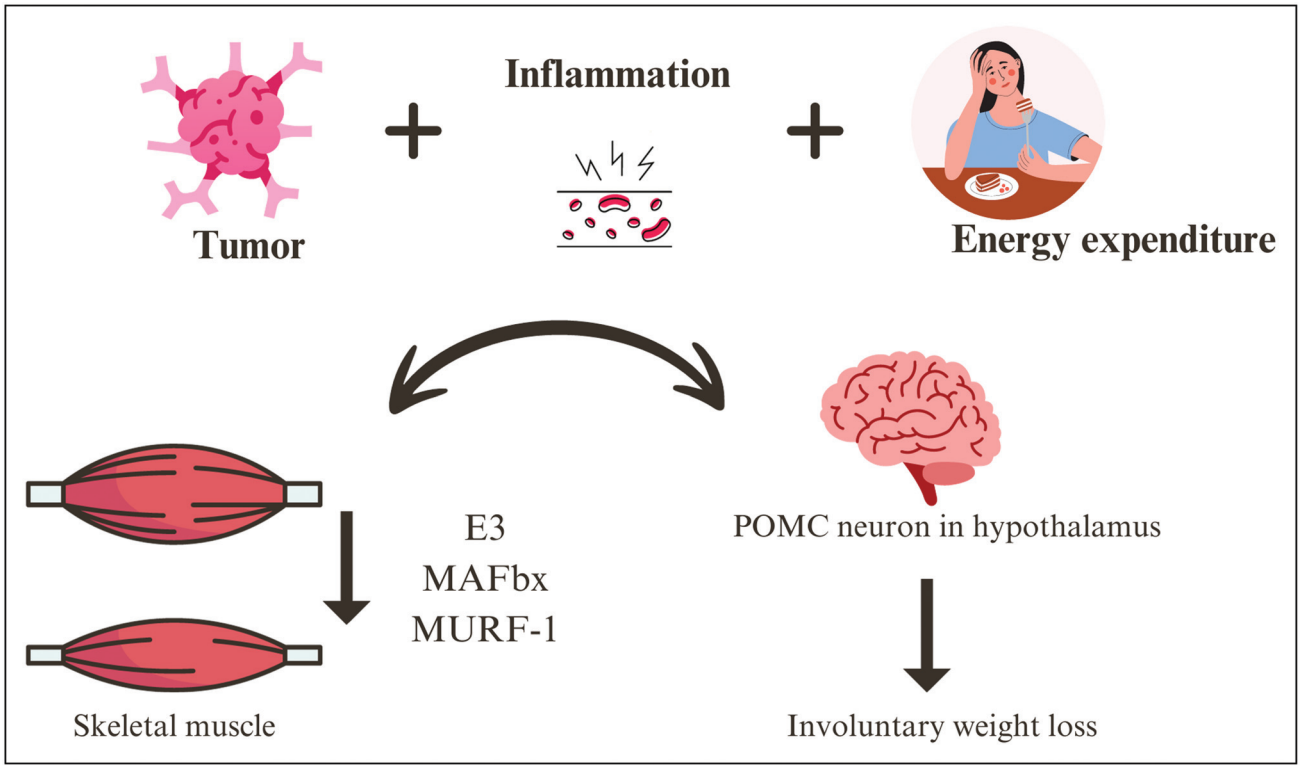

FIGURE 1. Interactions between tumor growth, energy expenditure, metabolism, weight, and muscle mass changes. E3, muscle atrophy-specific protein ligases; MAFbx, Atrogin-1; MURF-1, Muscle Ring Finger 1; POMC, Proopiomelanocortin.

CONCLUSION

In this narrative review, the main points about the use of protein and amino acids were discussed against the cancer-induced scenario during its various stages. When evaluating the components of the diet for oncology patients, the protein recommendation should be more than 1.0–1.5 g/kg of body weight/day, with a distribution between animal and vegetable proteins. Regarding isolated or combined amino acid supplementation, it seems that the use, dose, and specificity for the different types of cancer, or which phase (anabolic or catabolic) the supplement should be prescribed, is not clear. Therefore, we still need clinical trials with methodological robustness to reach a consensus on the dose and effect of using amino acids for cancer patients in clinical routines.

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Conflicts of interest

There are no conflicts of interest.

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