Effects of branched-chain amino acid supplementation on nutritional status in cancer patients: protocol for a systematic review and meta-analysis of randomized clinical trials

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Highlights

- Branched-chain amino acids could provide valuable nutrition for cancer patients.
- Protocol for systematic review aims to evaluate if the supplementation is effective.
- Only randomized clinical trials will be included in this protocol.

Abstract

Introduction: Cancer is a growing public health problem in the world. Poor nutrition is one of the factors that significantly influences the worsening of the disease's prognosis, prolonged treatment and reduced quality of life. Branched-chain amino acids (BCAAs) may influence various tumor phenotypes and play a role as a marker of neoplastic pathology. This study aimed to conduct a systematic review of randomized clinical trials (RCTs) to assess whether BCAA supplementation pre-, peri and post-oncological treatment brings benefits to the clinical outcomes and nutritional status of patients diagnosed with cancer.
Methods: Our review will encompass all RCTs, without publication date limitations, that are published in English, Portuguese, or Spanish and examine the impact of BCAAs on nutritional status in cancer patients. Studies will be sourced from databases such as PubMed, Web of Science, Embase, and SciELO. To be eligible, studies must include adults, involve oral supplementation of BCAAs, not limited to any dosage or duration, feature a control group, and assess outcomes such as clinical outcomes and nutritional status, such as quality of life, inflammation biomarkers, mortality, and lean mass. The Risk of Bias 2.0 will be employed to evaluate the risk of bias, and the PEDro scale will be applied to assess the quality of evidence. Statistical analyses will be conducted using JASP for Windows.
Discussion: This systematic review and meta-analysis included RCTs that evaluated the effects of BCAA supplementation in cancer patients and may contribute to the advancement of knowledge in Nutrition in oncology.

Keywords: Branched-chain amino acids, Nutritional status, Cancer, Mortality, Inflammation, Meta-Analysis

Introduction

Cancer is a growing public health problem in Brazil, currently the second leading cause of death in the world and the country. Its classification includes more than 100 diseases characterized by the disorderly growth of cells in the human body [1] that can infiltrate neighbouring tissues or reach distant organs [2]. It has a multifactorial etiology and its origin is associated with exposure to carcinogenic factors, which can be physical, chemical or biological in nature, or genetic predisposition [1]. Data from the National Cancer Institute (INCA) of the Ministry of Health show that modifiable risk factors have already been identified, namely: inadequate eating habits, sedentary lifestyle, infectious agents, tobacco and alcohol use, environmental pollution, contaminated food, use of drugs containing hormones, obesity, immunosuppression, reproductive factors and socioeconomic status [3].

In 2021, in Brazil, 120,784 male deaths and 110,910 female deaths were recorded due to malignant neoplasms, according to data obtained by the INCA [4]. In 2023, 583,947 cases were diagnosed in Brazil according to DataSUS [5]. It is estimated that from 2023 to 2025, 704,000 new cases of cancer will arise in Brazil each year, with the highest incidence being in the South and Southeast, totaling 70% of the incidence. [6]. These data show a growing incidence of the disease in the country, proving the need for new treatment options. The importance of updated therapies to reduce mortality, improve quality of life and strengthen the health system as a whole is evident, to more effectively address the increase in cancer cases in Brazil.

Accurate and early diagnosis of cancer is essential for adequate and efficient treatment. Each type of cancer requires specific treatment, which may include: surgery, radiotherapy, chemotherapy [7] or palliative care, i.e. health care provided to people with progressive, serious disease that threatens their continued life [8].

Cancer patients are susceptible to symptoms arising from the disease itself and from side effects that predispose the treatments. These symptoms include physiological changes that make it difficult for the patient to eat and can result in anorexia, cachexia and other nutritional changes. Given the above, poor nutrition is one of the factors that significantly influences the worsening of the disease's prognosis, prolonged treatment and reduced quality of life [9]. The nutritional problems of patients with malignant tumors are more severe, and therefore, malnutrition has negative effects on these patients [10]. In this scenario, inflammation and malnutrition are linked, as inflammation decreases while nutritional status improves. For this reason, it is crucial to plan nutritional interventions strategically, reverse nutritional depletion and minimize complications arising from treatment [11]. There are several recommendations regarding the diet of cancer patients, such as: staying eutrophic, consuming whole grains, vegetables, and fruits, and avoiding ultra-processed foods, processed meats, alcohol and dietary supplements. However, there are still many gaps in this field of quality scientific research that need to be filled to improve care for cancer patients [12].

Branched-chain amino acids (BCAAs) are essential amino acids [13] and are divided into: L-leucine, L-isoleucine and L-valine. BCAAs can be acquired through ingesting protein-rich foods, as they are derived from proteins. BCAAs play an important role in the production of hormones, elimination of nitrogenous waste, wound healing and stimulating the synthesis and breakdown of proteins in skeletal muscles and other tissues [14]. Leucine is a nutritional stimulus for the serine/threonine protein kinase target of rapamycin complex (mTOR) [15], which is an anabolic signal related to muscle protein synthesis, consequently having a link with strength and muscle hypertrophy [16]. Altered BCAA metabolism may be an indicator of systemic changes in the metabolism of patients with certain types of this disease and affect the main characteristics of cancer. In other words, the metabolism of these amino acids may influence various tumor phenotypes and play a role as a marker of neoplastic pathology [17]. Some clinical studies have observed that BCAA supplementation during radiotherapy or drug treatment may have a positive response concerning biochemical and amino acid parameters in patients with liver cancer [13]. Furthermore, it is suggested that BCAA supplementation in patients with cachexia brings benefits to nitrogen balance and muscle protein metabolism [18]

There is a systematic review in the literature that addresses the efficacy of BCAA use in cancer patients undergoing surgery (perioperative), excluding patients undergoing concomitant chemotherapy, radiation or radiofrequency ablation. Even so, there are still many gaps and myths surrounding oncology. In this context, our study aims to observe the global status of all types of cancer. Therefore, this study is aimed at nutritionists and researchers who are interested in supplements that bring benefits to cancer patients. Therefore, this study aimed to conduct a systematic review of randomized clinical trials (RCTs) to assess whether BCAA supplementation pre-, peri and post-oncological treatment brings benefits to the clinical outcomes and nutritional status of patients diagnosed with cancer.

Scientific Methods

In order to guarantee the quality of the selected studies and minimize possible risks of bias, this protocol will be written following the list of 27 items and criteria established by the PRISMA method (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) [19]. The Systematic Review was registered on the PROSPERO platform under number CRD42024536920 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=536920).

According to the PICO strategy, the selected studies followed the following criteria according to Table 1, as can be seen below.

Table 1: PICO strategy for the systematic review.

Acronymn	Criterion
(P) Population	Healthy human beings, adults and elderly, with cancer, without restriction and age or type of neoplasia.
(I) Intervention	Oral supplementation of branched-chain amino acids, not limited to any dosage or duration.
(C) Comparator	Supplementation in capsules containing placebo.
(O) Outcomes	Clinical outcomes and nutritional status, such as quality of life, inflammation biomarkers, mortality, and lean mass.

Databases

Studies considered eligible were searched on the PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://clarivate.com/products/scientific-and-academic-research/research-discovery-and-workflow-solutions/webofscience-platform/), SciElo (https://scielo.org/en/), Embase (https://www.embase.com/) and Google Scholar (https://scholar.google.com/) platforms. Clinical trials registry databases were used to consult studies that are in progress or that have not yet been published, namely: Clinical Trial.gov (https://clinicaltrials.gov/), Brazilian Clinical Trials Registry (REBEC) (https://ensaiosclinicos.gov.br/) and International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform).

The study eligibility criteria were RCTs written in English, Portuguese and Spanish. Literature reviews, case-control studies, cohort studies, case reports, letters to the editor, co-treatment studies and animal studies were excluded from this systematic review. Medical Subject Headings (MeSH) (https://www.ncbi.nlm.nih.gov/mesh/) with terms and keywords were used in isolation or combination, applied to the title and abstract, to select articles, together with the Boolean operators "AND" and "OR". Additionally, a search was performed with specific terms for randomized clinical trials.

This systematic review was conducted by two reviewers who independently selected plausible studies, first considering the title and abstract and then the full paper. In addition, the studies were exported to ".ris" or ".txt" format files and later imported into the Rayyan platform (https://www.rayyan.ai/), which served as a support tool for reviewers to remove duplicates and manage references.

Only full texts were included. The relevant data or general information extracted from each study were: the first author's surname, study title, year of publication, journal name, and study methods used to measure results. For eligible studies with results presented in graphs, we contacted the authors by email to obtain this data, or we used the GetDate Graph Digitizer 2.26 software to extract the data.

Risks of bias analysis were assessed by two researchers independently using the Cochrane Risk of Bias (RoB) 2.0 tool, as described in the handbook [20–22]. We considered the following categories for assessment: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other relevant biases. If there were any disagreements regarding study selection, they would be initially resolved by consensus, and when this was not possible, the disagreements would be resolved arbitrarily by a third reviewer. The PEDro scale, which assesses the quality of RCTs in systematic reviews, was included in this review because of its sensitivity and comprehensiveness in assessing the methodological quality of studies.

Statistical Analysis

The analyses will be performed to estimate the effect of branched-chain amino acids supplemented alone or in combination on the clinical outcomes and nutritional status of cancer patients compared to placebo. For outcomes presented with the same unit of measurement, the summarized effect estimate was described as mean differences (MD) accompanied by their 95% confidence interval (95% CI).

In cases where the authors present the data in different units, the summarized effect estimate was presented as standardized mean difference (SMD), as it takes into account the size of the effect of the intervention in each study concerning the variability observed in that study, together with its 95% CI. Considering that the SMD provides a generic interpretation (absolute unit, SMD), the possibility of transforming the SMD into the most familiar unit of the instrument or a proportion (%) was verified, making the data in language more appropriate to the outcome analyzed.

To summarize the data, the MD or SMD of each study was pooled using a random effect model, appropriate for the data, since the studies presented inconsistency due to differences in population characteristics (clinical heterogeneity) or methodological characteristics (methodological heterogeneity), presenting different effect sizes between the studies. Since the 95% CI described for the random effect refers to the uncertainty in the location of the mean of effects in the different studies, to better interpret it, we included the values of the 95% prediction interval (95% PI), whose objective was to present the uncertainty interval of the effect for future RCTs [21].

To investigate the consistency of the effect of branched-chain amino acid supplementation across studies, the analysis of the degree of heterogeneity (relative variability in effect estimates attributed by heterogeneity) was tested with the Higgins inconsistency test (I^2) for each pairwise comparison [20,23]. To explore heterogeneity ($P<0.05$), subgroup analyses (observational) or meta-regression (statistical; if there are more than 10 studies) were used for effect modifiers with normal distribution in the quartile-quartile plot (qq-plot) and confirmed by the Shapiro-Wilk test ($P>0.05$) [19].

Associated with this, to identify discrepant data from the meta-analysis, the imprecision of the effect estimate described by the heterogeneity was also visually observed using the absence of overlap of the 95% CI in the forest plots to identify possible outliers [23]. Because selective publication and/or suppression of publication of specific results causes bias and consequently reduces the validity of the results [24], when applicable (more than 10 studies; more than 1 study with statistically significant data; studies with different sample sizes), the Egger test, accompanied by the funnel plot, was presented to detect possible publication bias [25]. If publication bias was identified (Egger's test, $P<0.1$), the trim and fill method was used to identify and correct the asymmetry of the funnel plot and the corrected data were added to the description of the original data (without the cutting and imputation of data performed by the trim and fill method) [26,27].

Discussion

This systematic review and meta-analysis included RCTs that evaluated the effects of BCAA supplementation in cancer patients. This study brings new findings and divergences on the subject. To date, it is possible to report that in the literature there is a predominance of studies carried out in people with hepatocellular carcinoma. What can also be said is that most of the studies carried out had as a result of BCAA supplementation mainly the increase in serum albumin levels in cancer patients.

One study included in this systematic review showed that nutritional education, together with the use of BCAA granules, increased serum albumin levels in 32 of 77 cancer patients [28]. Furthermore, results from other included studies corroborate this statement [29,30]. Furthermore, a research recommendation from the ESPEN Expert Group states that in critically ill adults BCAAs increase muscle protein synthesis [31]. Cancer patients can be considered seriously ill, and therefore, the hypothesis raised in this systematic review possibly goes against these beneficial results. Thus, BCAA supplementation appears to be a relevant strategy for nutritional support in cancer treatment, according to the previously discussed study, as well as the recommendation of experts, based on the evidence.

Conclusions

According to the observations used to prepare this protocol, it is suspected that BCAA supplementation may bring potential benefits, mainly in the nutritional status and length of hospital stay in cancer patients. Current evidence indicates that nutritional biomarkers, such as serum albumin, demonstrate an increase in their levels with BCAA supplementation compared to control groups. Most of the studies analyzed reveal that BCAA appears to be a positive alternative for nutritional status and biomarkers of protein metabolism, predominantly in hepatocellular carcinoma.

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