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REVIEW ARTICLE

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Nutrological and pharmacological therapy in patients with neoplasms and cachexia: a systematic review

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Abstract

Introduction: Cancer cachexia (CC) is a multifactorial syndrome that is generally characterized by continuous loss of skeletal muscle mass with or without fat loss, often accompanied by anorexia, weakness, and fatigue. Cancer cachexia is associated with low tolerance to antitumor treatments, reduced quality of life, and a negative impact on survival. Unintentional weight loss has been associated with a negative impact on multiple outcomes in cancer patients, including survival and quality of life. **Objective:** It was to present the main evidence of nutritional and pharmacological therapy for cachectic cancer patients through a systematic review. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from June to August 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 105 articles were found. 51 articles were assessed and 14 were included in this systematic review. Considering the Cochrane risk of bias tool, the overall assessment resulted in 11 studies with a high risk of bias and 22 studies that did not meet the GRADE criteria. It was concluded that the nutritional consequences of cancer treatments should be identified early with screening and assessment of nutritional status. Nutritional intervention includes screening and appropriate nutritional assessment, which should begin early in the course of the disease to reduce or delay negative effects on therapy and quality of life. Liquid nutritional supplements may be useful to help increase caloric intake. Numerous investigations have reported orexigenic activity associated with progestational agents, such as megestrol acetate and medroxyprogesterone. Megestrol acetate has received the most attention in randomized clinical trials of cancer patients. The use of corticosteroids and mirtazapine for weight gain and pain control was also highlighted. Enteral immunonutrition is an effective nutritional intervention that improves immune function in patients undergoing gastric cancer surgery.

Keywords: Nutrological therapy. Cancer. Cachexia. Pharmacological treatments.

Introduction

Cancer cachexia (CC) is a multifactorial syndrome that is generally characterized by continuous loss of skeletal muscle mass with or without fat loss, often accompanied by anorexia, weakness, and fatigue **[1,2]**. CC is the term applied to this collection of abnormalities associated with weight loss in cancer patients. Conventional nutritional support cannot fully reverse it and leads to progressive functional impairment. The pathophysiology is characterized by a negative energy and protein balance, driven by a variable combination of reduced food intake and abnormal metabolism **[3,4]**.

Cancer cachexia is associated with poor tolerance to antitumor treatments, reduced quality of life, and a negative impact on survival. Unintentional weight loss has been associated with a negative impact on multiple outcomes in cancer patients, including survival and quality of life **[5-8]**. Cancer patients frequently experience unintentional weight loss due to gastrointestinal dysfunction caused by the malignancy or treatment of the malignancy. They may experience weight loss due to inadequate nutrient intake treatment-induced abnormalities in gastrointestinal function or other symptoms of nutritional impact related to treatment **[1,2,9]**.

Metabolic abnormalities that contribute to increased energy expenditure reported in some weight-reduced cancer patients include increased hepatic glucose production, increased lipolysis with increased production of glycerol and free fatty acids, and increased protein turnover compared with healthy volunteers and cancer patients who do not experience weight reduction **[3,10,11]**.

Therefore, the present study aimed to present the main evidence of nutritional and pharmacological therapy of cancer patients and cachectic patients through a systematic review.

Methods

Study Design

The present study followed an international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/20/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 07/20/2024.

Data Sources and Search Strategy

The search strategies for this systematic review were based on the descriptors (DeCS / MeSH Terms): "Nutrological therapy. Cancer. Cachexia. Pharmacological treatments". The search was carried out from June to August 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Boolean terms "OR", "AND" and the operator "NOT" were used to target the scientific articles of interest.

Study quality and risk of bias

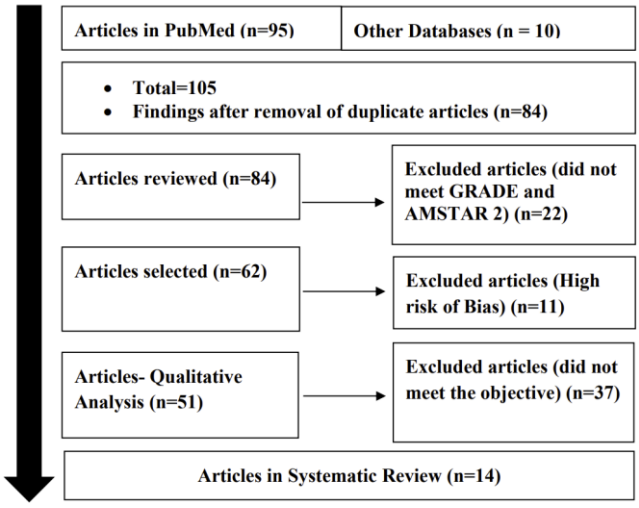
Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Literature Findings

A total of 105 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 51 articles. A total of 14 articles were assessed in full and included and developed in the present systematic review study (Figure 1). Considering the Cochrane risk of bias tool, the overall assessment resulted in 11 studies with a high risk of bias and 22 studies that did not meet GRADE.

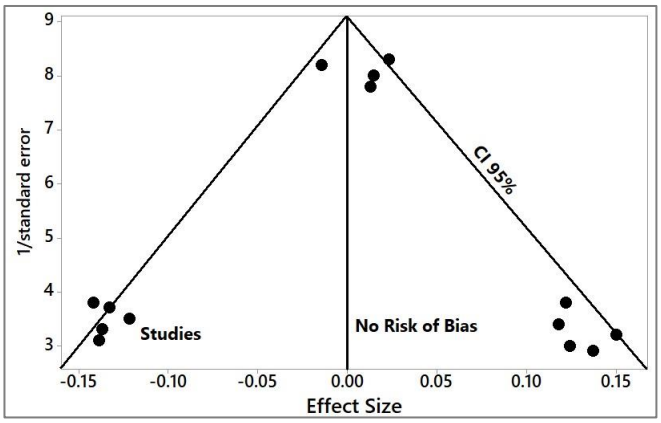
Figure 1. Article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=14 studies).



Source: Own authorship.

Main Findings

The symptoms associated with CC are thought to be caused, in part, by tumor-induced alterations in host metabolism that result in systemic inflammation and abnormal neurohormonal responses **[1,2]**. The sarcopenia observed in many patients with CC is caused, in part, by increased activation of circulating proteolysis-inducing factor (PIF) and skeletal muscle protein degradation via the ubiquitin-proteasome pathway. Other implicated abnormalities include insulin resistance and decreased circulating levels of insulin-like growth factor-1 (IGF-1) **[2]**.

Fat loss has been associated with upregulated fat mobilization factors. Changes in appetite are associated with hypothalamic changes affecting neuropeptide (neuropeptide Y) and peripheral hormone (ghrelin and leptin) metabolism. The normal metabolic effect of elevated circulating leptin concentrations is to decrease appetite, whereas elevated ghrelin concentrations stimulate appetite. Decreased hypothalamic responsiveness to peripheral signals to increase appetite is considered an underlying cause of the anorexia observed in CC **[11]**.

Diagnosis of Cancer Cachexia

Fearon et al 2011 **[10]** reported three diagnostic stages: pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia is defined as <5% involuntary weight loss in the presence of other metabolic abnormalities such as anorexia or poor glucose control. Cachexia is defined as >5% involuntary weight loss in the past 6 months or a body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2% or signs of sarcopenia and ongoing weight loss >2%.

Sarcopenia has been defined by a variety of assessment tools, including arm muscle area, appendicular skeletal muscle index determined by dual-energy X-ray absorptiometry, computed tomography, or fat-free mass determined by bioelectrical impedance. Refractory cachexia is defined by the clinical presentation of the patient, such as rapidly progressive cancer that is unresponsive to treatment and a life expectancy of <3 Months **[2,3]**.

Prevention of Nutrological Changes Due to Cancer Treatment

The nutritional consequences of cancer treatments should be identified early with screening and assessment of nutritional status **[1]**. There is no single treatment plan for CC due to the multifactorial characteristics of the syndrome. However, three areas that appear to be critical for the treatment of CC are appropriate antitumor therapy, nutritional intervention, and supportive pharmacologic intervention **[2]**. Successful response to appropriate cancer therapy should result in improvement of CC symptoms. Patients who respond poorly to cancer therapy are often those with progressive CC symptoms **[12]**.

Pharmacological agents aimed at improving appetite and combating metabolic abnormalities that cause inefficient nutrient utilization are currently the mainstay for the treatment of CC. Several agents have been investigated for their effects on weight, muscle wasting, and quality of life. However, few are commercially available for use **[7]**. Considerations for choosing the most appropriate treatment include the effect on appetite, weight, quality of life, risk of adverse effects, cost, and availability of the agent **[1]**.

The ideal pharmacological agent for the treatment of CC should have positive effects on appetite, support the maintenance or replacement of cell mass, and improve quality of life while minimizing the adverse effects of tumor treatment. Unfortunately, no currently available pharmacological agent meets all of these criteria. Therefore, the choice of pharmacological agent(s) for the treatment of CC should be based on the patient's clinical status, including gastrointestinal

status, as well as the patient's and caregiver's goals for therapy [12].

Enteral Nutrological Therapy

Nutritional intervention includes appropriate nutritional screening and assessment, which should begin early in the disease course to reduce or delay negative effects on therapy and quality of life [1]. Symptoms of nutritional impact should be adequately treated to minimize the role of gastrointestinal dysfunction in preventing adequate oral intake. For example, antiemetic or prokinetic therapy should be maximized for the treatment of nausea and vomiting or delayed gastric emptying. Treatment of pain and symptoms of depression should also be maximized. The role of single nutrients such as amino acids and other micronutrients and their effect on CC is unclear. However, liquid nutritional supplements may be useful to help increase caloric intake [13-16].

In addition, patients with head neck, and upper gastrointestinal cancer are particularly susceptible to malnutrition, which worsens both their prognosis and quality of life and may result in the need for enteral nutrition. One study examined the impact of enteral nutrition on quality of life in a matched sample. Fifty cancer patients were included in two matched subgroups: with enteral nutrition (study group) and without enteral nutrition (matched group). The analysis revealed that weight loss, group type, and age were the main factors influencing patients' quality of life. Compared with all cancer patients in general, the scores of patients in both groups were below reference values for functional scales and exceeded reference values or were similar for fatigue and vomiting/nausea. Patients who received enteral nutrition more frequently scored lower on functional scales and higher on symptomatic scales than the control group. These findings emphasize the complex relationship between cancer, nutritional status, and quality of life [17].

Enteral immunonutrition is a nutritional intervention that has been studied in postoperative patients with gastric cancer, but its efficacy is controversial. A metaanalysis study evaluated the effects of enteral immunonutrition and enteral nutrition on immune function in patients undergoing gastric cancer surgery. A total of 12 studies were included for qualitative and quantitative analyses, with 1124 patients, including 565 patients in the enteral immunonutrition group and 559 in the enteral nutrition group (controls). CD4+ levels, lymphocytes, transferrin concentrations, and systemic inflammatory response syndrome were not significantly different between the enteral immunonutrition and enteral nutrition groups. However, CD8+, immunoglobulins G and M, proalbumin concentrations, CD4+/CD8+, and infectious complications were significantly higher in the enteral immunonutrition group than in the enteral nutrition group. A sensitivity analysis showed consistent results after the exclusion of each study [18].

Pharmacological Agents in Cancer Cachexia

A wide variety of pharmacological agents have been investigated for potential orexigenic activity, as well as their effects on cytokine and hormone metabolism and other anabolic or catabolic pathways, in an attempt to reverse the symptoms of CC and improve quality of life. However, success with available agents is extremely variable, often providing minimal efficacy. Although there appears to be a positive effect on appetite for many patients, there is minimal increase in lean body mass (LBM) and total body weight for many responding patients, but many patients continue to lose weight throughout the period despite pharmacologic intervention [12].

Although weight gain may not be a reasonable goal for many patients, prevention of weight loss and LBM loss, as well as improvement in appetite and quality of life, maybe achievable for others. More recent data suggest that the use of combination therapy may be more effective than a single-agent approach [19].

Numerous investigations have reported orexigenic activity associated with progestational agents such as megestrol acetate and medroxyprogesterone. Megestrol acetate has received the most attention in randomized clinical trials of cancer patients. Improvement in QOL has been demonstrated in several prospective studies in patients with CC treated with megestrol acetate, but no survival benefit has been shown [20]. Megestrol acetate is generally well tolerated, but most adverse effects associated with its use as an appetite stimulant in cancer patients have been reported with short-term use, usually <12 weeks. The risk of adverse effects with long-term use is not well reported. Reported adverse effects include hyperglycemia and adrenal insufficiency. An association with a small increased risk of developing edema and impotence in men, as well as higher rates of venous thrombotic episodes, has also been reported [21].

Also, corticosteroids have been widely used for the treatment of a variety of symptoms in cancer patients, including appetite stimulation. Several mechanisms of action have been proposed, including modulation of the hypothalamic-pituitaryadrenergic (HPA) axis, modulation of proinflammatory cytokines, and reduction of peritumoral edema. Improved appetite and quality of life have been reported in several comparative studies of corticosteroid therapy compared with placebo, but the effect is short-lived

(<4 weeks), and long-term use is associated with negative nitrogen balance, calcium loss, glucose intolerance, and immunosuppression [22].

Mirtazapine has been investigated for its effects on pain, quality of life, nausea, anxiety, insomnia, appetite, and weight gain in patients with advanced cancer. Improvements in appetite and quality of life have been reported in non-depressed patients with CC or anorexia who received 15 to 30 mg of mirtazapine. However, the effect on weight gain was variable. More clinical data are needed before mirtazapine can be recommended for routine use as a treatment for CC [23].

Anabolic agents are used in an attempt to enhance muscle anabolism. Very few studies have reported the use of oxandrolone in cancer patients. An important consideration for the use of oxandrolone in cancer patients is that it is contraindicated in testosterone-sensitive malignancies, such as prostate or male breast cancer [24]. Finally, a systematic review of randomized controlled trials of EPA and DHA supplementation in cancer patients undergoing treatment reported a beneficial role for ω-3 fatty acids. Treatment regimens included radiotherapy, chemotherapy, or a combination of the two. Ω-3 supplements were provided as a soft gel supplement or as part of a fish oil-enriched nutritional supplement. The authors reported that EPA and DHA given as fish oil in doses ranging from 600 mg/d to 3.6 g/d promoted weight maintenance or gain during treatment, improved or minimized loss of lean mass as assessed by bioimpedance, and improved quality of life as defined by physical function scores and global health status [25].

Conclusion

It was concluded that the nutrological consequences of cancer treatments should be identified early with screening and assessment of nutritional status. Nutritional intervention includes screening and appropriate nutrological assessment, which should begin early in the course of the disease to reduce or delay negative effects on therapy and quality of life. Liquid nutritional supplements may be useful to help increase caloric intake. Numerous investigations have reported orexigenic activity associated with progestational agents such as megestrol acetate and medroxyprogesterone. Megestrol acetate has received the most attention in randomized clinical trials of cancer patients. The use of corticosteroids and mirtazapine for weight gain and pain control was also highlighted. Enteral immunonutrition is an effective nutritional intervention that improves immune function in patients undergoing gastric cancer surgery.

CRediT

Author contributions **Conceptualization**- Karlla Gabrielly Claudino Santos, Vittor Cândido Soares, Sarah Rachel Pereira de Moura Lima, Lucila Maria de Almeida Lopes; **Data curation-** Karlla Gabrielly Claudino Santos, Vittor Cândido Soares, Ricardo de Oliveira Carvalho, Simone Drbal de Oliveira, Divina Seila de Oliveira, Jeffeson Alexandre Azevedo de Araujo, Sarah Bernardon de Oliveira, Hugo Menezes Lopes; **Formal Analysis-** Karlla Gabrielly Claudino Santos; Sarah Rachel Pereira de Moura Lima, Lucila Maria de Almeida Lopes, Ricardo de Oliveira Carvalho, Simone Drbal de Oliveira, Divina Seila de Oliveira, Hugo Menezes Lopes; **Investigation-** Karlla Gabrielly Claudino Santos, Vittor Cândido Soares, Jeffeson Alexandre Azevedo de Araujo, Sarah Bernardon de Oliveira, Hugo Menezes Lopes; **Methodology-** Karlla Gabrielly Claudino Santos, Vittor Cândido Soares, Sarah Rachel Pereira de Moura Lima, Lucila Maria de Almeida Lopes; **Project administration-** Karlla Gabrielly Claudino Santos; **Supervision:** Karlla Gabrielly Claudino Santos; **Writing - original draft-** Karlla Gabrielly Claudino Santos; Vittor Cândido Soares, Sarah Rachel Pereira de Moura Lima, Lucila Maria de Almeida Lopes, Ricardo de Oliveira Carvalho, Simone Drbal de Oliveira, Divina Seila de Oliveira, Jeffeson Alexandre Azevedo de Araujo, Sarah Bernardon de Oliveira, Hugo Menezes Lopes; **Writing- review & editing-** Karlla Gabrielly Claudino Santos; Vittor Cândido Soares, Sarah Rachel Pereira de Moura Lima, Lucila Maria de Almeida Lopes, Ricardo de Oliveira Carvalho, Simone Drbal de Oliveira, Divina Seila de Oliveira, Jeffeson Alexandre Azevedo de Araujo, Sarah Bernardon de Oliveira, Hugo Menezes Lopes.

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Informed Consent

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