



Nutrological and pharmacological approaches to cancer cachexia: a systematic review

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Abstract

Introduction: Cancer cachexia (CC) is a multifactorial syndrome that is generally characterized by the continuous loss of skeletal muscle mass with or without fat loss, often accompanied by anorexia, weakness, and fatigue. 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. **Objective:** It was to present the main evidence of the nutrological and pharmacological treatment of cancer cachexia through a systematic review. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from October a December 2023 in 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:** A total of 127 articles were found. A total of 67 articles were evaluated and 24 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 10 studies with a high risk of bias and 10 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $X^2=74.5\%>50\%$. Based on the results, symptoms associated with cancer cachexia are thought to be caused by tumor-induced changes in host metabolism that result in systemic inflammation and abnormal neurohormonal responses. The sarcopenia

seen in many patients with cancer cachexia is caused, in part, by increased activation of circulating proteolysis-inducing factor (PIF) and skeletal muscle protein breakdown by the ubiquitin-proteasome pathways. The nutritional consequences of cancer treatments must be identified early with screening and assessment of nutritional status. Nutritional intervention includes screening and appropriate nutritional assessment, which should begin early in the disease course 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 controlled trials of cancer patients. Also noteworthy was the use of corticosteroids and mirtazapine for weight gain and pain control.

Keywords: Cancer cachexia. Treatments. Nutrition. Pharmaceuticals.

Introduction

Cancer cachexia (CC) is a multifactorial syndrome that is generally characterized by ongoing loss of skeletal muscle mass with or without fat loss, often accompanied by anorexia, weakness, and fatigue. Cancer cachexia (CC) is the term applied to this collection of abnormalities associated with weight loss in tumor patients [1,2].

It cannot be fully reversed by conventional nutritional support 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]. 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 [4-6].

Cancer patients often experience unintentional weight loss due to gastrointestinal dysfunction caused by the malignancy or treatment of the malignancy [7,8]. They may experience weight loss due to inadequate nutrient intake treatment-induced abnormalities in gastrointestinal function or other treatment-related nutritional impact symptoms [9-13].

Metabolic abnormalities that contribute to increased energy expenditure (REE) 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 [14,15].

Therefore, the present study aims to present the main evidence of the nutrological and pharmacological treatment of cancer cachexia through a systematic review.

Methods

Study Design

The systematic review rules of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 11/15/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Cancer cachexia. Treatments. Nutrition. Pharmaceuticals*". The search was carried out from October to December 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE

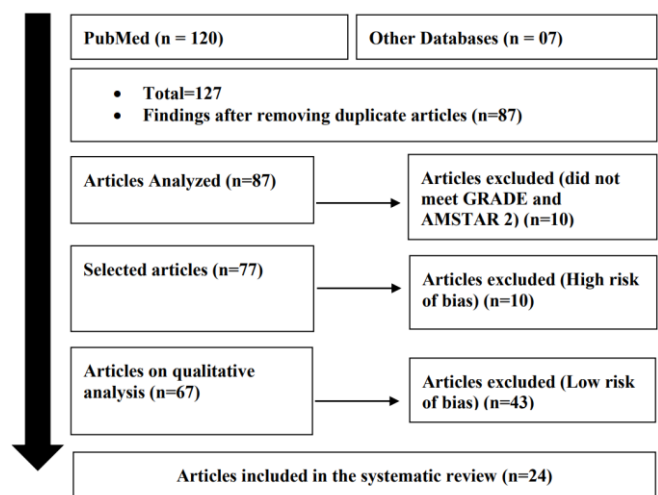
instrument and the risk of bias was analyzed according to the Cochrane instrument. The methodological quality of AMSTAR-2 and the risk of bias were analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Literary Findings

A total of 127 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was carried out, removing articles that did not include the topic of this article, resulting in 67 articles. A total of 24 articles were evaluated in full and included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 10 studies with a high risk of bias and 10 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $X^2=74.5\%>50\%$.

Figure 1. Flowchart of the article selection process.

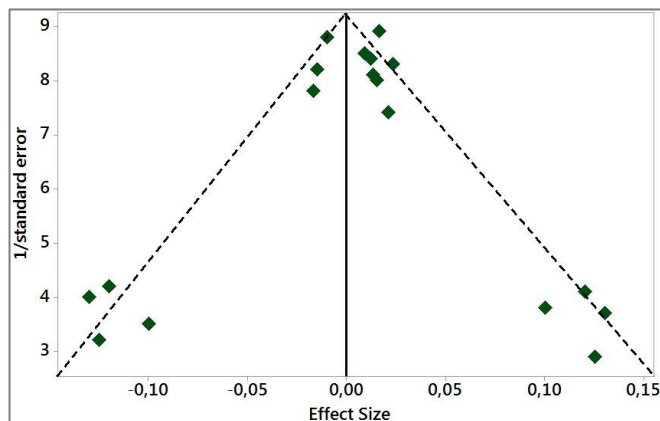


Source: Own authorship.

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 the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, suggesting no 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 presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph

(Ntotal=24 studies evaluated in full in the systematic review).



Source: Own authorship.

Major Significance and Clinical Findings

Symptoms associated with CC are believed to be caused, in part, by tumor-induced changes in host metabolism that result in systemic inflammation and abnormal neurohormonal responses [1-3]. 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 pathways. Other abnormalities implicated include insulin resistance and decreased circulating levels of insulin-like growth factor 1 (IGF-1) [4].

Fat loss has been linked to upregulated fat mobilization factors. Changes in appetite are associated with hypothalamic changes that affect neuropeptide (neuropeptide Y) and peripheral hormone (ghrelin and leptin) metabolism. The normal metabolic effect of high concentrations of circulating leptin is to decrease appetite, while high concentrations of ghrelin stimulate appetite. Decreased hypothalamic response to peripheral signals to increase appetite is considered an underlying cause of the anorexia observed in CC [15].

Fearon et al 2011 [14] reported three diagnostic stages: pre-cachexia, cachexia, and refractory cachexia. Precachexia 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 last 6 months or a body mass index (BMI) < 20 kg/m² 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 patient's clinical

presentation, such as rapidly progressive cancer that does not respond to treatment and life expectancy < 3 months [14].

Nutritional Interventions

The nutritional consequences of oncological treatments must be identified early with screening and assessment of nutritional status [4]. There is no single treatment plan for CC due to the multifactorial characteristics of the syndrome. However, three areas that appear to be fundamental to the treatment of CC are appropriate antitumor treatment, nutritional intervention, and supportive pharmacological intervention. Successful response to appropriate oncologic therapy should result in improvement in CC symptoms. Patients who respond poorly to oncologic therapy are often those with progressive symptoms of CC [16].

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 mass loss, and quality of life. However, few are commercially available for use [11].

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 [1,4]. 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, minimizing the adverse effects of tumor treatment. Unfortunately, no currently available pharmacological agent meets all criteria. Thus, 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 [16].

Nutritional intervention includes appropriate nutritional screening and assessment, which should begin early in the course of the disease to reduce or delay negative effects on therapy and quality of life. Symptoms of nutritional impact must be adequately treated to minimize the role of gastrointestinal dysfunction, preventing adequate oral intake [2,3]. 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 [17].

Pharmacological Agents

A wide variety of pharmacological agents have been investigated for potential orexigenic activity, as well as their effects on cytokine and hormonal metabolism and other anabolic or catabolic pathways, in an attempt to reverse CC symptoms and improve quality of life. However, success with the use of available agents is extremely variable, often providing minimal efficacy. Although there appears to be a positive effect on appetite for many patients, there is a minimal increase in lean body mass (LBM) and total body weight for many responding patients, but many patients continue to lose weight despite pharmacological intervention [16].

Although weight gain may not be a reasonable goal for many patients, preventing weight loss and loss of lean body mass, as well as improving appetite and quality of life, can be achieved for others. More recent data suggest that the use of combination therapy may be more effective than a single-agent approach [18]. 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 CC patients treated with megestrol acetate, but survival benefit has not been shown [19].

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, generally < 12 weeks. The risk of adverse effects with prolonged use is not well reported. Reported adverse effects include hyperglycemia and adrenal insufficiency. An association with a small increase in the risk of developing edema and impotence in men, as well as higher rates of venous thrombotic episodes, has also been reported [20].

Corticosteroids have been widely used to treat a variety of symptoms in cancer patients, including appetite stimulation. Several mechanisms of action have been proposed, including modulation of the hypothalamic-pituitary-adrenergic (HPA) axis, modulation of pro-inflammatory 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, intolerance glucose and immunosuppression [21].

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 [22].

Anabolic agents are used in an attempt to improve 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 includes the contraindication for use in testosterone-sensitive malignancies such as prostate or male breast cancer [23].

A systematic review of randomized controlled clinical 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 nutritional supplement enriched with fish oil. The authors reported that EPA and DHA provided as fish oil at doses ranging from 600 mg/d to 3.6 g/d promoted weight maintenance or gain during treatment, improved or minimized lean mass loss, as assessed by bioimpedance, and improved quality of life, as defined by physical function scores and global health status [24].

Conclusion

Symptoms associated with cancer cachexia are believed to be caused by tumor-induced changes in host metabolism that result in systemic inflammation and abnormal neurohormonal responses. The sarcopenia observed in many patients with cancer cachexia is caused, in part, by increased activation of circulating proteolysis-inducing factor (PIF) and skeletal muscle protein degradation via the ubiquitin-proteasome pathways. The nutritional consequences of oncological treatments must be identified early with screening and assessment of nutritional status. Nutritional intervention includes appropriate nutritional screening and 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.

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Ethical Approval

Not applicable.

Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

Peer review process

It was performed.

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