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WHAT IS NEW IN CANCER CACHEXIA COMPREHENSION AND TREATMENT?

O QUE É CONHECIDO NA COMPREENSÃO E TRATAMENTO DA CAQUEXIA ONCOLÓGICA?

A.R.
ARTIGO DE REVISÃO

Mariana Dias[1*] ; Susana Irving[2] ; Paula Alves[2] ; Marta Correia[1]

[1] Escola Superior de Biotecnologia da Universidade Católica Portuguesa, Rua de Diogo Botelho, n.º 1327, 4169-005 Porto, Portugal

[2] Instituto Português de Oncologia do Porto Francisco Gentil, EPE, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal

*Endereço para correspondência:

Mariana Ferreira Dias
Escola Superior de Biotecnologia da Universidade Católica Portuguesa, Rua de Diogo Botelho, n.º 1327, 4169-005 Porto, Portugal
mariana.dias.98@gmail.com

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ABSTRACT

Cancer cachexia is a multifactorial syndrome, associated with an underlying illness, characterized by involuntary weight loss and skeleton muscle mass impairment and reduction, with or without loss of fat mass. It emerges within a systemic inflammation and metabolic disturbance setting, entailing a significant impact in treatment toxicity, quality of life, functional capacity and mortality. Although the conventional nutritional support includes symptom management, inflammation and metabolic modulation and treatment effectiveness, it is not able to fully revert cancer cachexia. The nutritional goals are to provide adequate energy and protein intake along with a combination of anti-inflammatory agents and other nutrients. In this review we focus on the effect of certain nutrients and bioactive molecules in muscle loss, inflammation and cancer cachexia (β-hydroxy-β-methyl butyrate, branched chain amino acids, polyunsaturated fatty acids, carnitine, polyphenols and vitamin D). Food sources providing the later nutrients/molecules should be endorsed, in addition to a conventional nutritional support, as it is expected to entail specific functions in cancer cachexia.

KEYWORDS

Cancer cachexia, Nutrition support, Cancer cachexia treatment

RESUMO

A caquexia oncológica é uma síndrome multifatorial, associada a uma doença subjacente, caracterizada por perda involuntária de peso e comprometimento e redução da massa muscular esquelética, com ou sem perda de massa gorda. Surge em cenário de inflamação sistémica e distúrbio metabólico, acarretando um impacto significativo na toxicidade do tratamento, qualidade de vida, capacidade funcional e mortalidade. Embora o suporte nutricional convencional inclua o controlo de sintomas, inflamação e modulação metabólica e eficácia do tratamento, ele não é capaz de reverter totalmente a caquexia oncológica. Os objetivos nutricionais são fornecer uma ingestão energética e proteica adequadas, juntamente com uma combinação de agentes anti-inflamatórios e outros nutrientes. Nesta revisão, o foco está no efeito de certos nutrientes e moléculas bioativas na perda muscular, inflamação e caquexia oncológica (β-hidroxi-β-metil butirato, aminoácidos de cadeia ramificada, ácidos gordos polinsaturados, carnitina, polifenóis e vitamina D). Fontes alimentares que forneçam os nutrientes/moléculas mencionados devem ser recomendadas, em adição a um suporte nutricional convencional, pois é esperado que exerçam funções específicas na caquexia oncológica.

PALAVRAS-CHAVE

Caquexia oncológica, Suporte nutricional, Tratamento da Caquexia oncológica

INTRODUCTION

Cachexia Definition

Cachexia is defined as a multifactorial depletion syndrome characterized by the presence of systemic inflammation leading to unvoluntary weight loss, continuous loss of skeletal muscle mass, with or without fat mass loss, which is not reversible through conventional nutrition, leading to a progressive impairment of functional capabilities" (1-4). Nowadays, the pathophysiological definition of cachexia is malnutrition plus disease-related metabolic alterations (systemic inflammation) (5).

There are different cachexia subtypes including cancer cachexia and they differ in the underlying inflammatory disease (cancer, chronic obstructive pulmonary disease, inflammatory bowel disease, congestive heart failure or chronic kidney disease) (3,6).

Cancer cachexia is characterized by systemic inflammation and metabolic disturbances caused by the presence of the tumor, resulting in greater toxicity of treatments, reduced quality of life, decreased functional capacities and greater mortality from the disease (3-5, 7-9). Due to the systemic inflammation, cachexia affects multiple organs (10).

Although cachexia and sarcopenia are often mentioned as synonyms, these are distinct terms. Sarcopenia is defined as the progressive loss of skeletal muscle mass, strength and performance, with a high risk of adverse effects (11). Unlike cachexia, sarcopenia does not require the presence of an underlying inflammatory disease. Thus, an individual

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with cachexia is sarcopenic, but an individual with sarcopenia may not be in a cachectic state (12).

Cancer Cachexia Stages

Cancer cachexia comprises the following stages, pre-cachexia, cachexia and refractory cachexia. The type of cancer and its stage, the presence of systemic inflammation, reduced food intake and resistance to cancer treatment contribute to the progression to more advanced stages of cachexia, and a patient may not go through all stages (2-3, 5). Patients in the pre-cachexia stage are at risk of malnutrition and present as clinical and metabolic signs, anorexia, weight loss less than 5% and impaired glucose tolerance (2, 11, 13-14).

Patients with any of the following criteria: weight loss greater than 5% in the last 6 months; weight loss greater than 2% and current BMI less than 20kg/m^2; appendicular skeletal muscle mass index less than 7.2kg/m^2 in males and less than 5.5 kg/m^2 in females (indicator of sarcopenia) joined with weight loss greater than 2% and who have not entered the refractory phase, are diagnosed with cachexia (15). Nutritional intervention should be implemented as early as possible, particularly in the pre-cachexia and cachexia stages, as it is more effective, allowing benefit optimization and delay or reduction of the adverse effects of cachexia (12-13).

Refractory cachexia occurs in a situation of advanced cancer disease or in the absence of a response to cancer therapy. This stage of cachexia is associated with reduced performance and an expected lifespan of less than 3 months (2,15). At this stage, the patient will have no benefit in starting treatments aimed at increasing lean mass and muscle function, procedures should be taken only to relieve the symptoms in order to improve the patient's quality of life. Nutritional recommendations are also not a matter of concern at this stage. The focus should be on satisfying hunger and thirst, although these are often absent in these patients (16-18). Artificial nutrition and hydration do not represent additional benefits at this stage of the disease. That, given its invasive nature, increases the patient's suffering and the need for several weeks until improvements are observed (17,19).

Etiopathogenesis of Cancer Cachexia

Cachexia results in metabolic dysregulation that translates into energy imbalance, increased lipid and protein catabolism, and neurohormonal dysregulation (6).

Cachexia-promoting factors such as pro-inflammatory cytokines and other mediators produced by the tumor are responsible for this disturbance. The increase in pro-inflammatory cytokines results in neuroinflammation, leading to inhibition of the orexigenic pathway (appetite stimulation) and activation of the anorexigenic pathway (appetite suppression). These changes lead to a decrease in food intake and activate muscle and lipid catabolism (5, 9, 20-23).

Altered resting energy expenditure (REE) is common in cancer. A higher energy expenditure is the most common. However, there are also cases where the metabolic rate is decreased. Patients with hyper- and hypometabolism are subject to greater toxicity from cancer treatment compared to patients with a normal metabolism (10). On the contrary, the total energy expenditure (TEE is usually lower, compared to healthy individuals, due to the decrease in physical activity. Decreased physical activity further exacerbates muscle wasting over time (24). However, the low GET corresponds to an adaptive response to circumvent the difference between an elevated REE and the severe reduction in food intake and physical activity (25).

Muscle degradation in cachexia results from the activation of proteolysis triggered by the ubiquitin-dependent proteosome and autophagy carried out by lysosomes. This occurs by the activation of factors such as nuclear factor kB (NF-kB) and the forkhead transcription factor family box O (FOXO). Pro-inflammatory cytokines, as well as myostatin, activin A, proteolysis-inducing factor (PIF) and glucocorticoids are responsible for activating these pathways (10, 21). On the other hand, anabolic processes are inhibited, translating into the inhibition of mTOR-dependent protein synthesis. This is due to reduced IGF-1 levels as well as the development of insulin resistance. When faced with intense proteolysis, amino acids go to the liver, serving as a substrate for gluconeogenesis and for the synthesis of acute-phase proteins such as C-reactive protein (CRP). Acute phase protein synthesis promotes the release of cytokines by macrophages, exacerbating inflammation (20, 23).

Lipid catabolism is of great importance since it often precedes the loss of muscle mass in the evolution of cachexia (23). This catabolism consists of an excessive increase in lipolysis with a decrease in lipogenesis and also the presence of disturbances in the entry of fatty acids into cells. For this reason, high levels of serum triacyl glycerides (TAGs) and cholesterol, fatty acids and glycerol are common in these patients. Another change in adipose tissue is the conversion of white adipose cells into brown adipose cells, a phenomenon known as "browning" of adipose tissue. This phenomenon contributes to lipid depletion and increased energy expenditure without energy production (futile cycle) (21, 26-27).

In these patients, it is also common to coexist a dysfunction of the intestinal barrier allowing the translocation of bacteria and the diffusion of pro-inflammatory molecules, activating the systemic inflammatory response and increasing muscle catabolism (10).

METHODOLOGY

This systematic review included studies from 2010 until 2022. The following databases were used: Pubmed/Medline, US National Library of Medicine's PubMed, ISI'sWeb of Knowledge, Cochrane, and Scopus databases using the key words cancer cachexia AND cancer cachexia treatment or therapy. Two reviewers (MC and MD) screened the studies to be included which were randomized clinical trials (RCTs), surveys, observational studies such as cohort and case-control studies, revisions and metanalysis. All disagreements were debated until a consensus was reached with the assistance of a third subsequent reviewer (SCI). A total of 272 papers were found, 223 studies were excluded because they did not match the proposed search criteria, leaving a total of 49 articles that were included.

Nutritional Intervention

Due to the occurrence of inflammation and catabolism, the cachexia state is often resistant to nutritional intervention. Nutritional intervention allows for the relief of symptoms, but per se, in advanced stages of cachexia, it is unable to reverse it (3, 28). Thus, a multidisciplinary approach including the measurement of symptoms with nutritional impact, reduction of inflammation and treatment of metabolic and endocrine disorders is the way forward to improve the functional capacity and quality of life of patients, increase tolerance to anticancer therapy and avoid treatment interruptions (1, 5, 15, 29-30). The nutritional approach must take into account body composition, energy expenditure, food intake, symptoms with nutritional impact, food intolerances and aversions, biochemical parameters, functional capacity, psychological status, namely, motivation and cooperation, autonomy and whether there is a need for support with meals (5, 30-32).

The energy recommendations proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) for cancer patients are 25 to 30 kcal/kg/day (1, 30). In clinical practice, it is recommended to start

with 25 to 35 kcal/kg/day, reserving the maximum limit for outpatients, young, underweight and male (15). In patients with head and neck cancer the minimum energy requirements are 30 kcal/kg/day (15, 33). The minimum protein intake recommended by ESPEN is 1 g/kg/day, the ideal intake being 1.2-1.5 g of protein/kg/day (1, 15, 30-31, 33). However, in cases of severe depletion, it may be necessary to increase the protein intake to values closer to 2 g/kg/day, especially in cases of inactivity, systemic inflammation and advanced age, since these factors induce resistance to anabolism, impaired protein synthesis and stimulate catabolism. The increase in protein intake and/or energy intake must be progressive to avoid the refeeding syndrome (1, 12,15, 33).

In 2011, Fearon et al. considered five aspects to take into account in the classification, monitoring and assessment of cachexia, namely, anorexia or low food intake, catabolic state, energy depletion, muscle mass and strength, and functional and psychosocial impact (11).

Regarding the nutritional component, inadequate food intake in cancer patients is very common. To assess low food intake, it is important to identify the existence of neuroinflammation and symptoms with nutritional impact (chemosensory changes, nausea, reduced intestinal motility, diarrhea and medication side effects) as some of these can be easily corrected in order to optimize the nutritional status. Energy and protein intakes must be frequently evaluated and quantified, as they are essential to maintain a good nutritional status (2, 5, 9, 15).

In 2018, new diagnostic criteria for Malnutrition were established by the Global Leadership Initiative on Malnutrition (GLIM) and its current diagnosis requires the combination of at least one etiological criterion (reduced absorption or intake, or inflammation due to acute or chronic disease) and a phenotypic criterion (involuntary weight loss, low BMI (body mass index) or decreased muscle mass (34). Thus, cachectic cancer patients have a high nutritional risk as they present most or all the criteria for the diagnosis of malnutrition.

ESPEN recommends identifying patients at nutritional risk at the time of disease diagnosis. To assess the existence or absence of malnutrition, it is necessary to implement nutritional screenings such as the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Screening-2002 (NRS-2002), the Mini Nutritional Assessment (MNA), the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST). The patient-generated subjective global assessment (PG-SGA) combines the identification of risk with the assessment of nutritional status for what is considered the gold standard as it was designed specifically for cancer patients. When nutritional risk is detected, the PG-SGA can be applied to help defining a nutritional intervention (5, 12, 28).

According to ESPEN, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics, patients diagnosed at nutritional risk, with malnutrition, or whose diet is expected to be compromised for more than 5 days, should have nutritional monitoring as early as possible in order to control the symptoms that impair proper nutrition (35-37).

Initially, nutritional intervention involves less invasive approaches (nutritional recommendations). If this approach is not enough, oral nutritional supplements are prescribed and only if these are not effective, artificial nutrition (via tube feeding or NPT) is used (1).

Supplementation

Supplementation has many benefits for cancer patients. It helps achieving energy and protein recommendations and consequently reduces weight loss and improves the quality of life in malnourished patients. Supplementation should be implemented if the patient continues to lose weight, even if dietary changes have been made in parallel, such as protein-calorie fortification of the diet (28).

Vitamins A, E and C, as well as selenium, are powerful antioxidants and can interfere with the effectiveness of cancer treatments. Although they are generally beneficial, supplementation should only be carried out in case of deficit and in amounts close to the daily intake recommendations for healthy individuals (12,15,38-40).

Regarding specific supplementation for cachectic cancer patients, there are some promising compounds.

Hydroxymethylbutyrate (HMB) is a bioactive metabolite resulting from the amino acid leucine, which inhibits muscle catabolism and promotes protein synthesis, and also has functions that regulate inflammation (12, 41-42). There is a recommendation of 1–1.5 g/kg of protein, enriched by leucine, to help reestablish muscle in sarcopenic patients (41). HMB cannot be obtained in sufficient quantity through the diet due to the low rate of conversion of leucine to HMB. On the other hand, it has a high half-life in the bloodstream when compared to leucine, allowing a longer duration of its anticachetic effects (43-44). HMB supplementation (usually 3g/day) is usually consumed in HMB calcium salt and is especially effective in elderly patients, as there is a decrease in endogenous HMB. The effects will be appear in over 4 weeks (4, 30, 42, 44-45).

Supplementation of branched chain amino acids (BCAA's) (leucine, isoleucine and valine) also stimulates protein anabolism, increased body weight and BMI (Body Mass Index), but has no effect on muscle strength (28, 39).

Polyunsaturated fatty acids activate antitumor mechanisms and reduce chemotherapy toxicity. They are also responsible for inhibiting exacerbated protein catabolism, reducing systemic inflammation, and increasing appetite, food intake and body weight (12, 39-41). Omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), inhibit exacerbated protein catabolism due to neoplasia and their supplementation is frequently used in patients undergoing treatments (39,46). In cancer cachexia the recommended intake of EPA is about 2 g/day and the effects will be noticed in about 4 to 12 weeks (4). Omega- 3's are associated with a reduction of sarcopenia development, improvement in quality of life and better response to chemotherapy with reduced side effects. In addition to the functions described, eicosapentaenoic acid (EPA) also stimulates insulin sensitivity (12,46-47). Combining omega-3s (2-4g/day) with strength training results in increased strength and muscle mass. This junction appears to decrease resistance to anabolism, which is a frequent condition in elderly individuals (39).

Carnitine is responsible for transporting fatty acids to the mitochondria, promoting lipid oxidation and preventing the accumulation of lipids in the liver (4, 8, 28). Carnitine deficiency is found in many cancer cachexia patients due to decreased dietary intake, an underlying cause of cancer cachexia (4). Its use (4 a 6g/day of L-carnitine) in patients undergoing chemotherapy or chemoradiotherapy, when compared to control, has shown positive effects in reducing fatigue, maintaining albumin and lymphocyte levels during chemotherapy, attenuating weight loss and improving nutritional status and quality of life (8). Carnitine supplementation should be maintained for over 4 weeks for optimal results in cancer cachexia. Nonetheless, it is best to test patients for carnitine deficiency before starting supplementation (4). However, some adverse effects were identified among these, diarrhea and nausea (28, 45).

Polyphenols (quercetin, resveratrol) have antioxidative and anti-inflammatory properties. Cancer cachexia involves inflammation so these components help reducing inflammation and there are reports of weight gain, better appetite, and quality of life associated with polyphenols (41).

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Finally, Vitamin D appears to attenuate muscle depletion and may be useful in combination with protein supplements to enhance their effectiveness (12).

Despite the beneficial effects of these compounds, further studies are needed to determine the appropriate and safe dose, as well as to better understand the influence of this supplementation on tumor progression (28).

Pharmacological Therapies

Cancer cachexia has a strong inflammatory component and for the reason, pharmacological agents which target proinflammatory cytokines (or their associated receptors) have been studied (48).

Additionally, other agents such as appetite stimulants (corticosteroids, progesterone analogues, cannabinoids, serotonin antagonists, ghrelin) and nutritional supplementation help to increase food intake, having beneficial effects on weight gain and symptomatology with nutritional impact (29,49). Also, Enobosarm is a selective androgen receptor modulator, that is associated with an increase in lean muscle mass and better physical capacity in cancer patients with cachexia (49). Metformin, an oral type 2 diabetes mellitus drug, increases food intake in cancer patients. Metformin combined with insulin treatment declined the progression of cachexia and improved the metabolism of cancer patients by increasing their total body fat (49). Also, Nonsteroidal anti-inflammatory drugs (NSAIDs) like Celecoxib have an effect on inflammation and lead to an increase in Body weight, body mass index, and quality of life of cancer patients (48).

Physical Activity

Cancer patients often have reduced physical activity. Reducing physical activity increases the rate of muscle wasting over time (24). Physical exercise, namely strength training and aerobic exercise, allows preserving and/or recovering muscle mass, strength and function, as well as reducing systemic inflammation (decreased pro-inflammatory cytokines) and increasing aerobic capacity, and should therefore, be implemented according to the capabilities of each patient (15).

CRITICAL ANALYSIS

Frequently, cancer patients have a significant propensity to develop cancer cachexia syndrome. Therefore, it is essential a timely nutritional intervention, facilitated by a multidisciplinary approach, so that nutritional needs can be met. However, both specialist referrals or collaboration requests often occur late, commonly when there is an worsening of symptoms, specifically those with nutritional impact, or at the installation of cachexia, at an already more advanced stage. Although it is recommended to incorporate nutritional support early, ie. at the time of diagnosis, this recommendation seems seldom feasible. Several limitations may contribute for this mismatch and untimely nutritional provision, such as an inadequate nutrition specialist: patient ratio, at outpatient clinics and for inpatient nutritional support. All of these challenges seem to have consequences on clinical outcomes. Recently, targeted energy and protein supplementation has been gathering support as an important aid to reach nutritional goals for these patients. Specific compounds such as HMB, L-Carnitine, branched chain amino acids (BCAA's) and omega-3 fatty acids, have all shown potential benefits in reversing cachexia. Nevertheless, further studies are needed, because despite showing several positive effects, there are still pending questions concerning safe dosage, interference with anticancer treatments, as well as their impact on disease progression.

CONCLUSIONS

Neoplastic cachexia is defined as "a multifactorial depletion syndrome characterized by involuntary weight loss with continuous loss of skeletal muscle mass with or without loss of fat mass, that is not fully reversible through conventional nutritional support leading to progressive impairment of functional capacities" (1-3). This metabolic syndrome results in metabolic dysregulation (negative energy balance), increased lipid and protein catabolism, and neurohormonal dysregulation (decreased appetite) (6). Thus, nutritional assessment at the time of diagnosis of the disease is essential to detect malnutrition at an early stage and to proceed with nutritional monitoring of malnourished individuals or those at nutritional risk. Nutritional support reduces the symptoms and attenuates the loss of muscle mass, however, due to the exacerbated inflammation and catabolism characteristic of cachexia, these patients often present resistance to nutritional intervention (12, 28). As cachexia is not fully reversible through nutritional support, a multidisciplinary approach is needed, in order to eliminate symptoms with nutritional impact, reduce inflammation and treat metabolic and endocrine disorders to provide a better response to treatment, fewer complications from health and a better prognosis (1, 7, 12, 29).

CONFLICTS OF INTEREST

None of the authors reported a conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors MD, PA, SI and MC participated in the design of the study, interpretation of results and the writing of the article as well as revision of the entire manuscript.

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