

# Clinical evaluation and optimal management of cancer cachexia

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## Abstract

Cancer anorexia–cachexia syndrome (CACS) is a complex metabolic syndrome, different from malnutrition and sarcopenia, which is very common in cancer patients. Treatment for CACS is based on nutritional support and CACS pathophysiology-modulating drugs. The most commonly used are megestrol acetate (MA) and corticosteroids. The efficacy of MA has been confirmed by multiple clinical trials and meta-analyses. Glucocorticoids are also effective but should only be used for short periods and in selected cases. Future strategies should include intensified research into potentially effective drugs ( $\omega$ -3 fatty acids, thalidomide, cannabinoids, ghrelin, bortezomib, and COX-2 inhibitors), combined treatment and new drugs (anti-IL-6 monoclonal antibodies, melanocortin,  $\beta$ -2 antagonists, and androgen receptor-modulating analogues). We propose a review based on the literature on the pathophysiology of CACS, the diagnostic criteria and treatment, and future strategies.

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**Keywords:** Cancer; Cachexia; Anorexia; Megestrol acetate; Malnutrition

## 1. Introduction

Involuntary weight loss is very common among cancer patients, especially in advanced stages of the disease. This weight loss is associated with poor tolerability of cancer treatment and reduced quality of life and survival expectations. The fundamental cause is anorexia–cachexia syndrome (ACS), a condition in which a persistently elevated basal metabolic rate is not compensated for by adequate calorie/protein intake, causing a decline in performance status and mental suffering [1–5].

To ensure the best possible quality of life, aetiological, supportive and palliative cancer care should all be provided throughout the course of the disease [6]. In this context, correct, early diagnosis of ACS and a multimodal therapeutic approach that considers all the different pathophysiological factors is of the greatest importance.

This paper is an unsystematic narrative review based on literature search using electronic databases. The objective is to present a comprehensive synthesis of the most important aspects of the diagnosis, assessment and treatment of cancer anorexia–cachexia syndrome (CACS), according to opinion of authors.

## 2. Definition of CACS and diagnostic criteria

Weight loss and malnutrition are not always synonymous with cachexia. CACS is defined as a complex metabolic syndrome associated with an underlying disease that is characterised by loss of weight and muscle mass, with or without the loss of fatty mass, often associated with anorexia, inflammatory processes, insulin resistance and increased tissue protein turnover rates [7]. The consensus criteria for the definition of CACS adopted by the majority of scientific associations are summarised in Table 1 [1,3,4,7–10].

For a diagnosis of cachexia, there must be a 5% weight loss in 12 months or a body mass index of  $<20 \text{ kg/m}^2$ , in the presence of a known chronic disease, and at least three of the following factors: loss of muscle mass; asthenia; loss of body fat; altered analytical parameters (albumin  $<3.2 \text{ g/dl}$

Table 1

Consensus criteria for the definition of CACS [1,3,4,7–10].

Complex, multifactorial metabolic syndrome that causes a negative protein and energy balance (increase in catabolic processes)
Metabolic changes can often be associated with reduced food intake
It is a condition always associated with an underlying disease (cancer or other chronic diseases such as chronic obstructive pulmonary disease, heart failure, renal impairment, etc.)
It causes loss of muscle mass
It causes weight loss
It may or may not involve loss of fatty mass
It is often associated with anorexia
It is not reversible with increased calorie-protein intake
It is different from malnutrition, sarcopenia, depression, malabsorption and hyperthyroidism
It is associated with increased morbidity and mortality
It is often associated with the detection of acute-phase inflammatory reactants (C-reactive protein, interleukin 6)
It is associated with insulin resistance

or increased inflammatory parameters such as interleukin-6  $>4.0 \text{ pg/ml}$  or C-reactive protein  $>5.0 \text{ mg/l}$ ).

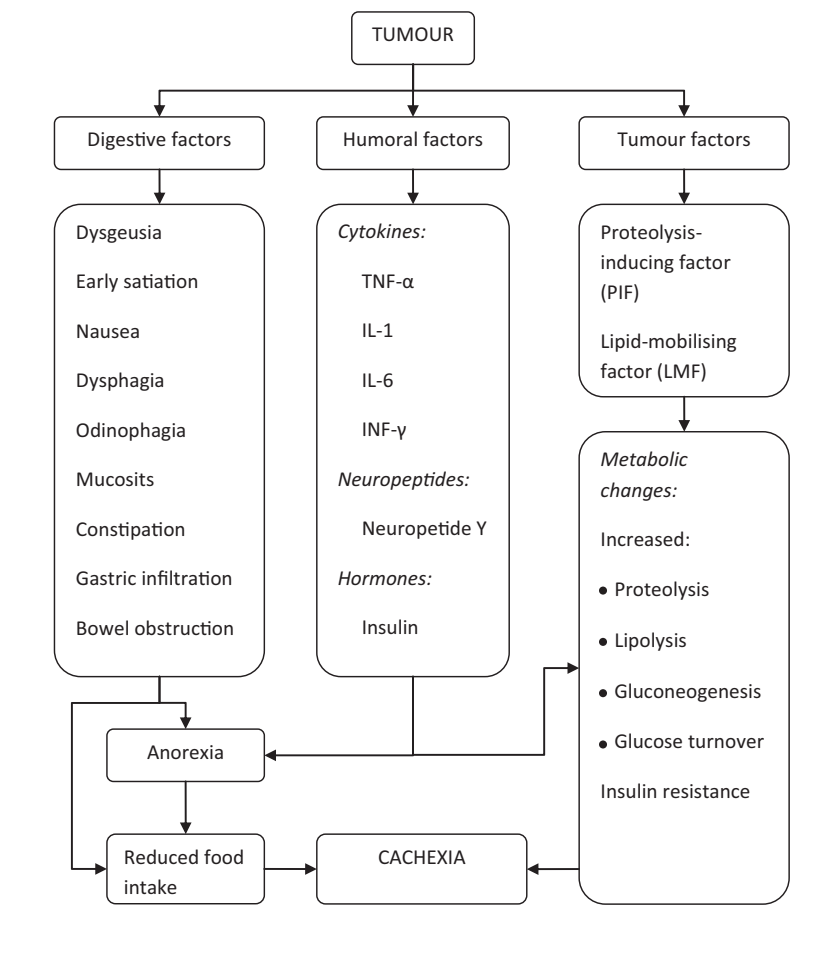
## 3. Epidemiology of CACS

The overall prevalence of CACS ranges from 40% at cancer diagnosis to 70–80% in advanced phases of the disease [11,13]. The prevalence of CACS by primary tumour is: 83–85% in pancreatic and gastric cancer; 54–60% in lung, prostate and colon cancer; 32–48% in breast cancer, sarcomas, lymphomas and leukaemias [14]. In stomach, pancreatic, prostate, colon and breast cancer, survival of patients with CACS is significantly shorter than in other patients [15]. The combination of radiotherapy and chemotherapy in oesophageal, pulmonary apex and head and neck tumours is associated with a high risk of CACS due to the swallowing disorders and mucositis commonly caused by such treatments [11]. CACS can be the direct cause of death in more than 20% of all oncology patients [2,12,15–17].

## 4. Pathophysiology of CACS [2,18–20]

CACS is a condition involving a persistently increased basal metabolic rate that is not compensated by increasing

Graph 1: Physiopathology of cancer cachexia



Graph 1. Physiopathology of cancer cachexia.

calorie/protein intake. The pathophysiology includes a series of complex metabolic mechanisms directly linked to the tumour–host interaction, associated or not with structural or functional digestive factors that allow it to become established or consolidated (Graph 1).

The digestive factors that can significantly contribute to the onset of CACS include dysgeusia, nausea, dysphagia, odynophagia, mucositis, constipation, malabsorption and intestinal obstruction. The mechanisms dependent on the host–tumour interaction, which are responsible for the metabolic and endocrine changes in CACS, include tumour (generated or modified by the tumour itself) and humoral factors (generated as the host's biological response to the presence of the tumour). The metabolic and endocrine consequences of CACS can be summarised as glucose intolerance, elevated hepatic gluconeogenesis, increased glucose turnover, reduced muscular intake of glucose, hyperlipidaemia, increased lipolysis, increased protein turnover, increased proteolysis, insulin resistance, increase in counter-regulatory hormones (catecholamines, cortisol,

glucagon) and release of rapid-response inflammatory factors.

#### 4.1. Tumour factors

The best known CACS-mediating tumour factors to date are proteolysis-inducing factor (PIF) and lipid mobilisation factor (LMF).

Proteasome is a macromolecular complex located in the cell cytosol which has a proteolytic function mediated by the peptide ubiquitin. PIF is a sulfated glycoprotein produced by some cancers that activates the proteasome–ubiquitin system responsible for increasing proteolysis. LMF is a protein similar to physiological zinc- $\alpha$ 2-glycoprotein, the function of which is to activate the lipolysis process.

#### 4.2. Humoral factors

The humoral mediators of CACS include cytokines (tumour necrosis factor  $\alpha$  [TNF- $\alpha$ ], interleukin 1 [IL-1], interleukin 6 [IL-6], interferon gamma [IFN- $\gamma$ ]),

neuropeptides (neuropeptide Y, serotonin, melanocortin) and hormones (insulin, glucagon, leptin).

TNF- $\alpha$  is one of the first known endogenous CACS mediators. It is a cytokine produced by different immune system cells and some tumours. The long-term administration of TNF- $\alpha$  in experimental animals causes weight loss, anorexia and loss of muscle and fatty mass. TNF- $\alpha$  activates protein degradation in the proteasome-ubiquitin system, mediated by its effect on transcription factors (MyoD, NF- $\kappa$ B), and reduces muscle uptake of glucose and amino acids.

The cytokines involved in CACS reduce lipogenesis and circulating lipid uptake and activate lipolysis and triglyceride mobilisation by inhibiting lipoproteinlipase. In CACS there is also an increase in melanocortin and serotonin, mediated by IL-1, and a reduction in neuropeptide Y, all anorexia determinants. The reduction in insulin production is mediated by secretion of IL-1 and IL-6. This phenomenon, associated with the increase in glucagon, cortisol and catecholamines often found in cancer patients, favours a distinctly catabolic metabolic balance. Leptin is a protein with a homeostatic effect released by fatty tissue. In situations of weight loss, leptin release is reduced and this stimulates the appetite in the central nervous system. In CACS patients, it is suspected that TNF- $\alpha$  and IL-1 interfere with the orexigenic response to leptin reduction.

Different cytokines (TNF- $\alpha$ , IL-1, IL-6, IFN- $\gamma$ ) intervene as humoral mediators of anorexia on a hypothalamic level through their interaction with the aforementioned neuropeptides and hormones, and also by inducing changes in the activity of hypothalamic neuronal ion channels.

## 5. Diagnosis and assessment of CACS

Nutritional risk can be assessed and monitored by means of anthropometric values, biological determinations, body composition, nutritional indices (combining anthropometric and biological values) and validated evaluation instruments.

### 5.1. Anthropometric values

The most commonly used anthropometric values are weight loss and body mass index (BMI). Weight loss of more than 10% in the last 6 months, or 5% in less than one month, indicate a risk of CACS. A BMI of less than 20 kg/m<sup>2</sup> is a criterion for malnutrition.

### 5.2. Biological values

Albumin, prealbumin, transferrin and C-reactive protein are circulating plasma proteins that can provide valuable information about nutritional status. Albumin of less than 3.2 g/dl indicates protein depletion and risk of malnutrition. Prealbumin is much more sensitive than albumin for monitoring nutritional changes due to its short half-life; 2 days compared to 18 for albumin. A prealbumin value of <10 mg/dl indicates malnutrition. Transferrin, an iron-carrying plasma

protein, is reduced in CACS, and a value of <100 mg/dl indicates severe malnutrition. Increased creatinine excretion, creatinine/height ratio and 3-methyl-histidine excretion are all indicators of loss of muscle mass.

In routine clinical practice, a reduction in albumin and increase in C-reactive protein (protein depletion and inflammatory response markers) together with symptoms and anthropometric values comprise the basic diagnosis of CACS.

### 5.3. Body composition (BC)

Recent studies support the value of determining BC (water, fatty mass [FM] and fat-free mass [FFM]) in the diagnosis of CACS and sarcopenia. Different methods (magnetic resonance imaging [MRI], computerised tomography [CT], bioelectrical impedance analysis [BIA]) have been used to evaluate BC.

BIA is a method commonly used because of its low cost and simplicity, but provides less information than MRI and CT. BIA does not distinguish the skeletal muscles of other fat free tissues such as the liver or metastases, which may be responsible for the increased energy expenditure. The CT and MRI allow a more accurate separation of skeletal muscle and adipose tissue, and thus a better evaluation of resting energy expenditure [3]. The mean FFM index (FFM/height<sup>2</sup>) in adults is 18.9 kg/m<sup>2</sup> in men and 15.4 kg/m<sup>2</sup> in women. In CACS there is a clear reduction in the FFM index, associated or not with loss of FM. A frank reduction in FFM is associated with a reduction in survival in advanced cancer [3,21–24]. The differential diagnosis between sarcopenia and CACS is based on the fact that FFM falls in sarcopenia but FM often increases (sarcopenic obesity, common in the elderly) [3].

Recent research highlights the importance of BC as a predictor of chemotherapy toxicity and survival [3,24–26]. Prado showed that 25% of breast cancer patients presented sarcopenia. The toxicity produced by capecitabine was significantly greater among sarcopenic patients (50% versus 20%) [3,26]. Diagnosis of sarcopenia, and differential diagnosis with CACS, is therefore important in cancer patients (Table 2) [3].

Table 2  
Differences between CACS and sarcopenia [3].

	Sarcopenia	CACS
Geriatric syndrome	+++	–
Multifactorial syndrome	+	++/+++
Metabolic syndrome	+/-	++/+++
Inflammatory markers	+/-	+++
Loss of muscle mass	++	++
Functional decline	+++	+/+++
Weight loss	+/-	+++
Anorexia	+/-	+++
Associated with underlying disease	+/-	+++

Pathophysiological importance or presence as symptom: –, no; +, low; ++, high; +++, very high.

Table 3  
Malnutrition screening tool.

		Points
Have you lost weight recently without trying?	No	0
	Not sure	2
	If yes, how much?	
	1–5 kg	1
	6–10 kg	2
	11–15 kg	3
Have you been eating poorly because of decreased appetite?	More than 15 kg	4
	Don't know	2
	No	0
	Yes	1

Total score: there is a risk of malnutrition if the score is more than 2.

#### 5.4. Nutritional indices and validated evaluation instruments

Nutritional indices and validated evaluation instruments often combine symptomatic, anthropometric and biological data.

The Malnutrition Screening Tool (MST) [27,28] and Patient-Generated Subjective Global Assessment of nutritional status (PG-SGA) [29–32] are useful validated instruments in the diagnosis of nutritional risk and CACS. The MST is a simple and short screening questionnaire (Table 3). The MST has similar sensitivity and is slightly less specific (86%) than PG-SGA. An MST score of  $\geq 2$  detects risk of malnutrition and, if necessary, the evaluation can be completed with a broader nutritional assessment such as the PG-SGA scale (Table 4).

Different clinical scales have also been developed to identify the general aspects of quality of life related to CACS. The “Functional Assessment of Anorexia and Cachexia Therapy” (A/CST-12) is a modification of the “Functional Assessment of Anorexia–Cachexia Therapy-General” (FAACT), widely

Table 4  
Global subjective assessment in cancer.

	Risk		
	A: Low	B: Medium	C: High
Weight <sup>a</sup>	<5%	5–10%	>10%
Food intake	Normal	Moderate decline	Severe decline
Swallowing problems	No	Moderate	Severe
Decline in activity	No	Moderate	Severe
Age	<65 years	>65 years	>65 years
Pressure ulcers	No	No	Yes
Fever/corticosteroids	No	Moderate	High
Cancer treatment	Low risk	Moderate risk	High risk
Loss of body fat	No	Moderate	Severe
Muscle loss	No	Moderate	Severe
Oedema/ascites	No	Moderate	Severe
Albumin <sup>a</sup>	>3.5	3–3.5	<3
Prealbumin <sup>a</sup>	>18	15–18	<15

The patient is included in the nutritional risk category (low, medium or high) which has the most values of a total of 12.

<sup>a</sup> Weight loss, albumin and prealbumin values have a special value, so if any is in category C the patient is classified as high nutritional risk irrespective of the other parameters.

Table 5  
Progressive CACS status: European Palliative Care Research Collaborative Group [36].

	Pre-cachexia	Cachexia	Refractory cachexia
Weight loss	<5%	>5%	>5%
Metabolic changes	+	+	Refractory

validated and used in clinical trials due to its high sensitivity to appetite changes [33,34]. The SCRINIO Working Group and the European Palliative Care Research Collaborative, based on expert consensus and qualitative methods (Delphi study), proposed a progressive classification system for CACS: pre-cachexia, cachexia and refractory cachexia (Table 5) [35,36].

## 6. Psychosocial impact of CACS

Most studies confirm that CACS has a direct impact on self-image, self-esteem, social relationships, relationship with one's partner and sexuality. At the end of life, asthenia, anorexia, pain, functional decline and loss of self-image are the most threatening symptoms that most concern patients [37–40]. Psychosocial support is essential in the integrative treatment of CACS.

## 7. Treatment of CACS

The treatment of CACS is based on three factors: oncological therapy; nutritional support; and specific pharmacological treatment.

### 7.1. Nutritional support

Nutritional support includes dietary advice, nutritional supplements and enteral diet. The usual recommendations are fractioned intake, food chosen according to the patient's preferences and ability to swallow, avoiding strong smells and carefully presented meals. Nutritional supplements increase calorie and protein intake according to the patient's requirements (some products are enriched with  $\omega$ -3 fatty acids). A complete enteral diet can be administered by nasogastric tube or gastrostomy in patients who are unable to swallow or present severe dysphagia. Both nutritional supplements and an enteral diet are effective if the source of malnutrition is limited nutrient intake. Multiple studies have shown that nutritional support is important in CACS, but alone, does not improve weight loss or the patient's quality of life parameters [41].

### 7.2. Pharmacological treatment of CACS

Different drugs have been studied in the treatment of CACS in the last few years (Table 6). Their pharmacological activity is based on modulation of cytokines, hormones or the different catabolic or anabolic metabolic pathways

Table 6  
Drugs with proven and potential activity in CACS.

Drugs with confirmed efficacy	
Megestrol acetate (MA)	Efficacy confirmed by multiple controlled trials and meta-analyses. High degree of recommendation
Corticosteroids	Efficacy confirmed in multiple clinical trials. Recommended in selected cases for short periods and taking into account the long-term side effects
Effective drugs that require confirmation in more controlled clinical trials	
Cannabinoids (dronabinol) <sup>a</sup>	Efficacy confirmed by controlled clinical trials. There are some contradictory research results. Further clinical research required
ω-3 fatty acids, acid <sup>a</sup>	
Bortezomib	
Non-steroidal anti-inflammatory drugs <sup>a</sup>	
Drugs the efficacy of which has not been confirmed in controlled clinical trials	
Prokinetic agents	Clinical trials have not confirmed their efficacy. Their use cannot be recommended, except for prokinetic agents (metoclopramide, cisapride) for the treatment of nausea or gastric stasis when a contributory factor to the CACS
Pentoxifylline	
Cyproheptadine	
Hydrazine sulfate	
Investigational drugs with good prospects for efficacy to be confirmed	
Ghrelin	Some drugs in preclinical research phase. Isolated clinical trials with thalidomide, ghrelin and anabolic steroids with promising but insufficient results. Cannot currently be recommended in routine practice.
Melanocortin antagonists	
β2 agonists (formoterol)	
Anti-IL-6 monoclonal antibodies	
Selective androgen receptor modulators (SARMs)	Further clinical research required
Thalidomide	
Oxandrolone	

Combination of drugs that are active in CACS: some clinical trials suggest that the combination of different drugs active in CACS is superior to monotherapy. It is a future strategy and cannot currently be recommended in routine practice. Further clinical research required.

<sup>a</sup> In monotherapy no more effective than MA.

involved in the pathophysiology of CACS. The ideal drug in CACS should increase the appetite, produce weight gain (by increasing FFM and with no fluid retention), improve quality of life, not interfere with cancer treatment and have an adequate tolerance profile.

To evaluate active pharmacological treatments in CACS, we carried out a literature review based on the following criteria: cancer; CACS; controlled clinical trials; survival; symptomatic control; validated performance status (ECOG, Karnofsky index, etc.) or quality of life scales.

### 7.3. Progestogens

Megestrol acetate (MA) is a semi-synthetic progesterone derivative synthesised in 1963 and used in the treatment of disseminated breast and endometrial cancer. Some patients treated with MA experienced weight gain and increased appetite as side effects. In 1990, Loprinzi published the results of a phase II trial comparing the administration of MA (800 mg/day) with placebo in 133 patients with CACS. The

efficacy of MA was confirmed on appetite, food intake, nausea ( $p < 0.05$ ) and weight gain (16% versus 2%;  $p = 0.003$ ). No statistically significant differences were found in toxicity [42,43]. In 1990, Bruera published a placebo controlled double-blind, crossover clinical trial on 40 patients with advanced cancer. The patients were randomised to receive MA (480 mg/day) or placebo for 7 days, after which the treatment groups were crossed over until day 15. MA was superior to placebo in terms of increased appetite and weight ( $p < 0.05$ ), and calorie intake ( $p < 0.001$ ). It was chosen as the best treatment by 66% of the patients ( $p < 0.05$ ) and 92% of the investigators ( $p < 0.001$ ) [44]. In 1993, the Food and Drug Administration (FDA) approved MA for the indication of CACS therapy [45]. Since then, multiple clinical trials have shown the efficacy of MA in both CACS and cachexia associated with other chronic conditions (acquired human immune deficiency syndrome [AIDS], geriatric cachexia and so on) [46–48]. To date, no drug has been shown to be superior to MA in efficacy and tolerability (corticosteroids, dronabinol, prokinetic agents, ω-3 fatty acids, etc.) [49–53]. MA is a well-tolerated drug with a low incidence of adverse effects (occasionally rash, rarely menstrual disorders, adrenal insufficiency, hyperglycaemia and thrombosis). Some authors suggest that weight gain could be largely due to fluid retention and oedema. However, the studies that recorded BC with BIA in patients with AIDS-related cachexia confirm a significant increase not only in water but also in FFM [46]. Thromboembolic phenomena are the most feared adverse events of MA, but their incidence is below 5%. MA causes no clotting changes other than those found in patients with advanced cancer not treated with the drug [50,54,55].

Three meta-analyses have been published about the efficacy of MA in CACS which included more than 25 controlled clinical trials (26–30) and over 3500 patients [55–57]. The control group was always either placebo or another drug potentially active in CACS (cisapride, dronabinol, eicosapentaenoic acid, corticosteroids, nandrolone). The mean dose of MA used was 480 mg/day for a median of 12 weeks of treatment. The meta-analyses confirmed that MA enhances appetite (relative risk [RR] = 2.33, 95% CI 1.52–3.59) [55–57], weight (RR = 2.16, 95% CI 1.45–3.21) [55–57] and quality of life (RR = 1.81, 95% CI 1.13–2.89) [56]. There were no significant differences in side effects relative to placebo or other drugs, except in the development of oedema (RR = 1.67–1.74) [55,56]. It was confirmed that the efficacy of MA is dose-dependent [56]. MA enhanced appetite in over 30% of the patients and boosted weight gain in 35%. The number of patients who needed to be treated (NNT) was 8 for weight gain and 3 for an improvement in anorexia. No differences in survival were found in the patients treated with MA [57].

The effect of MA in anorexia and weight gain could be related to the inhibition of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and neuropeptide Y stimulation in the hypothalamus [2,8]. In view of the data from the clinical

trials and meta-analyses, we can conclude that MA is effective in improving anorexia and weight gain with a high level of evidence (IA) and recommendation (A) [55–58]. Indeed, MA is the only drug authorised by the FDA specifically for this indication.

#### 7.4. Corticosteroids

The mechanism of action of glucocorticoids in CACS is related to the inhibition of IL-1, TNF- $\alpha$  and leptin, and an increase in neuropeptide Y levels. Different systematic literature reviews conclude that glucocorticoids (dexamethasone [3–6 mg/day], prednisone [15 mg/day], methyl prednisolone [12 mg/day]) induce an increase in appetite and weight gain. The effect, however, is short lived (less than 4 weeks) and causes more long-term side effects (insulin resistance, fluid retention, steroidal myopathy, skin fragility, adrenal insufficiency, sleep and cognitive disorders) than placebo and MA [41,50]. There is a high level of evidence (IB) and a favourable recommendation (B), provided it is used in selected cases (need for rapid onset of action), for a short period and considering the long-term adverse events.

#### 7.5. Cannabinoids

Dronabinol has been studied at doses from 2.5 to 20 mg/day. Placebo-controlled clinical trials have confirmed a reduction in nausea, increased appetite and a tendency to weight stabilisation in patients treated with dronabinol. The appetite-stimulant effect appears to be mediated by interaction with endorphin receptors, interference with IL-1 synthesis, activation of cannabinoid receptors involved in the neuronal circuit of leptin and prostaglandin synthesis inhibition. The main adverse events are euphoria, hallucinations, vertigo, psychosis and cardiovascular disorders. It is contraindicated in patients who are allergic to sesame oil, drug addicts or patients with psychiatric disorders. It should be used with caution in patients treated with other psychotropic agents. Most clinical trials were conducted in AIDS-related cachexia.

In 1994, Nelson published a phase II clinical trial that used dronabinol (5 mg/day) in a small number of patients ( $N=19$ ) with CACS. A reduction in anorexia was found in 68%, although only 53% were able to complete the trial (28 days) and 16% had to suspend the treatment because of toxicity [59].

In 2002, Jatoi published the first controlled clinical trial that compared MA with dronabinol in CACS. A total of 469 patients were treated with MA 800 mg/day or dronabinol 2.5 mg/12 h, or both. In the MA or MA-dronabinol treatment groups, there was a greater gain in both appetite and weight compared with the group taking dronabinol alone, 75% versus 49% ( $p > 0.001$ ) and 10% versus 3% ( $p < 0.05$ ) respectively. No differences in side effects were found between the three study groups, except for a greater incidence of impotence in the patients treated with MA (18% versus 4%,

$p < 0.001$ ) [51]. It is considered that dronabinol can be effective in CACS, but with a low degree of recommendation because its tolerability profile is worse than that of MA [60,61].

#### 7.6. Antiserotonergic agents

Cyproheptadine is an antihistamine and an antiserotonergic agent. Despite some promising pilot studies, controlled clinical trials have not yet confirmed its efficacy in CACS [8,67,68]. Pizotifen is an antiserotonergic drug used in the treatment of anorexia from other causes that has not been studied in cancer patients.

#### 7.7. Cytokine inhibitors

Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) inhibit PIF, TNF- $\alpha$  and IL-6 [15]. Their efficacy in CACS has not been fully confirmed in controlled clinical studies [62–66]. In 2004, Jatoi published a controlled trial that compared EPA, MA and the combination of the two drugs [52]. No significant differences in appetite gain were found between the three trial groups (69–63%). Weight gain of  $>10\%$  was significantly more common in the patients treated with MA (18% versus 6%,  $p < 0.05$ ). Toxicity was low and comparable in all the groups.

Two systematic literature reviews conclude that EPA and DHA in monotherapy show no significant differences in appetite, FFM, survival and quality of life compared with placebo [65,66]. Most authors conclude that  $\omega$ -3 fatty acids can be described as potentially active in CACS, with further research required.

Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, reduce tumour release of acute-phase reactants and cytokines. Two controlled clinical trials in CACS show that they are effective for gaining weight and muscle mass, especially when combined with progestogens (MA) [69,70]. The initial results are positive, but greater evidence based on larger clinical trials is necessary.

Pentoxifylline is a drug derived from methylxanthine used in vascular disease, with anti-inflammatory and TNF- $\alpha$  inhibition properties. Its efficacy in CACS has not been demonstrated [71].

Thalidomide has multiple immune-modulating, anti-inflammatory and TNF- $\alpha$  and IL-6 inhibition properties. Two controlled clinical trials show that it increases appetite, weight and feeling of wellbeing in CACS [72–74]. Most authors believe that the initial results are promising but that they need to be confirmed by further clinical trials.

Melatonin is an endogenous hormone secreted by the pineal gland that is used in the treatment of sleep disorders. It is suggested that its effect could be due to cytokine and TNF- $\alpha$  inhibition. Two controlled clinical trials provide indirect information about the benefit of melatonin in CACS, although neither of them was designed with that objective. The first

included 1400 patients and its objective was to study the global efficacy of melatonin in patients with advanced cancer, and the second included 200 patients to assess tolerance to chemotherapy when given in combination with melatonin. In both studies, asthenia and anorexia were significantly lower in the patients treated with melatonin versus placebo. A recent controlled clinical trial comparing melatonin versus placebo in CACS, which included 48 patients, did not find differences between two treatment groups [75]. The role played by this hormone in CACS should be explored in more clinical trial specifically designed [76].

### 7.8. Anabolic steroids

The anabolic steroids studied in CACS are oxymetholone, oxandrolone, nandrolone and fluoxymesterone. Their anabolic effect increases muscle mass with no changes in appetite or amount of food intake. Most studies were conducted in patients with cachexia of a non-oncological origin, largely in AIDS, chronic obstructive pulmonary disease or renal impairment. A controlled clinical trial confirmed that the efficacy of fluoxymesterone in CACS was comparable to that of MA [50]. Its use is not recommended, however, due to its high hepatotoxicity.

Growth hormone (GH) has an anabolic effect mediated by stimulation of the production of growth factor derived from type 1 insulin (IGF-1), a protein synthesis mediator. Resistance to GH has been confirmed in patients with chronic conditions and CACS, with high serum concentrations of the hormone and low concentrations of IGF-1. GH was approved by the FDA for the treatment of cachexia in AIDS and patients on parenteral nutrition through the small intestine. Patients treated with GH for different reasons, at a dose of 0.1 mg/kg weight/day, were found to have a mean weight gain of 2 kg, an increase in body fluid and a reduction in urine nitrogen excretion, while the hydration ratio (total body water/lean weight) remained constant [77]. Its efficacy in patients with other chronic diseases is subject to debate, and no studies have yet been published that confirm its utility in cancer patients.

Ghrelin is the natural ligand of the growth hormone receptor that produces the release of GH and neuropeptide Y. Two controlled clinical trials conducted with this peptide, or the agonist of its receptor, anamorelin (RC-1291), have confirmed its efficacy in increasing appetite and weight in CACS patients [78,79]. It is described as a potentially effective drug, but this requires confirmation by further clinical research.

Hydrazine sulfate is a phosphoenolpyruvate carboxylase, gluconeogenesis and Cori cycle inhibitor. Clinical trials have not confirmed its efficacy in CACS [80,81].

Beta-2-agonists such as clenbuterol, salbutamol or salmeterol are used to treat bronchial asthma and have a known capacity to increase muscle mass. They are currently the subject of preclinical experimentation in CACS [82].

### 7.9. Prokinetic agents

Metoclopramide or cisapride are antidopaminergic drugs with antiemetic and prokinetic effects that may relieve nausea and eating intolerance. However, controlled clinical trials have shown no efficacy in the control of anorexia and weight loss [53].

### 7.10. Bortezomib

Bortezomib is an ubiquitin–proteasome system and NF- $\kappa$ B transcription factor inhibitor used in the treatment of multiple myeloma. Despite promising initial data, a clinical trial in CACS in pancreatic cancer showed no significant effect on weight gain. It is a potentially active drug, but requires further clinical research to confirm its efficacy [41,83].

### 7.11. Combined treatment

One future research line is multimodal pharmacological treatment of CACS (combination of drugs acting on different pathophysiological pathways). A controlled clinical trial has compared 5 treatments, MA, EPA, L-carnitine, thalidomide and the combination of all of them, over a 4-month period. The results showed that the combination of the 4 drugs was superior to the drugs used alone in improving appetite and asthenia, in reducing energy expenditure at rest, in increasing FFM and reducing IL-6 [84,85].

### 7.12. Drugs in preclinical research

Ongoing studies are showing clear signs of effectiveness with the following drugs: melanocortin antagonists;  $\beta$ -2 antagonists (clenbuterol, formoterol); anti-IL-6 monoclonal antibodies; selective androgen receptor modulators (SARMs) [8,19,41,58].

## 8. Conclusion

CACS is a complex metabolic syndrome characterised by loss of weight and muscle mass, with or without loss of fatty mass, which is not compensated by adequate calorie–protein intake and is associated with anorexia, inflammatory processes, insulin resistance and an increase in tissue protein turnover. Limited food intake due to tumour growth or the side effects of therapy contributes to CACS but is not its cause. It is not the same process as malnutrition and sarcopenia, highly prevalent in patients with advanced cancer that can also cause increased frailty when receiving chemotherapy and reduce survival expectations.

The early diagnosis and a thorough assessment of CACS are very important parts of support measures in patients with advanced cancer.



Symptomatic treatment of CACS is based on nutritional support and drugs capable of modulating the cascade of metabolic disorders involved. Nutritional advice is particularly important when food intake is limited but it is not sufficient alone as treatment of CACS.

The drug most commonly used in CACS is MA (dose range 160–480 mg/day) due to its high efficacy and safety profile, confirmed in multiple clinical trials and meta-analyses. MA does not alter patient survival but significantly improves appetite and food tolerance. Some authors believe that weight gain in patients treated with MA is largely due to the development of oedema, but studies that assessed BC confirm that MA also significantly increased FFM.

Corticosteroids are very useful in CACS, provided they are used in selected cases (need for rapid effect) for short periods and taking the long-term side effects into account.

Most authors believe that  $\omega$ -3 fatty acids, thalidomide, cannabinoids, ghrelin, bortezomib, NSAIDs and COX-2 inhibitors are potentially active in CACS but it is required further clinical research to confirm their efficacy.

Different studies suggest that multimodal treatment combining different drugs that are active in cachexia may be more effective than the use of any of these drugs alone.

Future strategies for CACS are: further research on drugs that are potentially effective in CACS ( $\omega$ -3 fatty acids, thalidomide, cannabinoids, ghrelin, bortezomib, NSAIDs and COX-2 inhibitors); design of more studies with multimodal treatment regimens; and research into new drugs (anti-IL-6 monoclonal antibodies, melanocortin,  $\beta$ -2 antagonists and SARMs).

### 8.1. Limitations

The limitation of non-systematic narrative review of the literature, on a topic as broad as this, is that the selection of published information is based on criteria of clinical relevance, according mainly to the opinion of their authors.

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The authors declare to have no any involvement that can be construed as a conflict of interest.

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