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Review Article

# Anorexia–cachexia syndrome in pancreatic cancer: Recent advances and new pharmacological approach

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ABSTRACT

About 80% of all pancreatic ductal adenocarcinoma patients suffer from a wasting syndrome referred to as the "cancer anorexia–cachexia syndrome" (CACS) characterized by abnormally low weight, weakness and loss of skeletal muscle mass with or without loss of body fat, which directly impacts overall survival, quality of life, and physical activity. The aim of this review was to examine recent findings about CACS' pathophysiology and to describe the current pharmacological approaches. In recent years many efforts were made to improve our knowledge of CACS; currently we know that cachexia arises from a complex and multifactorial interaction between various mechanisms including inflammation, anorexia/malnutrition, alterations of protein and lipid metabolism; consequently its management requires multidisciplinary and multipharmacological approach that should address the different causes underlying this clinical event. On these premises, several drugs have been proposed starting from the first pharmacological treatment based on progestational agents or corticosteroids; most of them are in the preclinical phase, but some have already reached the clinical experimentation stage. In conclusion, to date, there is no standard effective treatment and further studies are needed to unravel the basic mechanisms underlying CACS and to develop newer therapeutic strategies with the hope to improve the quality of life of pancreatic cancer patients.



**Contents**



## 1. Introduction

Pancreatic ductal adenocarcinoma (PDA) is currently one of the most aggressive gastrointestinal carcinomas accounting for a 5-year survival rate of less than 5% and a death-to-incidence ratio of 0.99 [1].

Despite important treatment progress, the survival rate of patients with PDA has not significantly improved over the last few decades [2]. Close to 90% of PDA have advanced disease at presentation; as a consequence, palliative care is the only treatment option for most of these patients. On the other hand, even when the neoplasm is suitable for resection, surgery offers a five-year survival rate of about 25% [3]. Almost all patients with PDA develop metastases and die from the debilitating metabolic effects of their unrestrained growth. The median survival of patients with locally advanced and metastatic disease is 6–9 months and 3–6 months, respectively [4,5]. One reason contributing to this high

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mortality is cancer cachexia, defined as an unintended weight loss of more than 10% in 6 months, which is present in more than 80% of PDA [6,7], with progressive body fat and muscle tissue wasting with associated worsening of their clinical status, lower quality of life and a high mortality rate.

Over the last few years, important new developments regarding the pathogenesis of pancreatic cancer cachexia have been achieved in order to identify palliative measures in this patient population that could also be cost effective [8]. Knowledge of the mechanisms of cancer anorexia–cachexia syndrome is of great importance to lead to effective therapeutic interventions for several aspects of the syndrome. Nevertheless, cachexia remains a poorly understood process whose mechanisms have received only limited attention from cancer researchers [9]. More clinical research is needed to clarify this important subject [10].

## 2. Review

### 2.1. Definition and pathogenesis of anorexia–cachexia in pancreatic cancer

Many patients with advanced cancer undergo a wasting syndrome characterized by anorexia, loss of weight, asthenia, and a poor prognosis, referred to as the "cancer anorexia–cachexia syndrome" (CACS) [11].

In cancer patients, anorexia and cachexia can co-exist; while anorexia is defined as the loss of the desire to eat, which frequently leads to reduced food intake, cachexia is characterized by profound loss (up to 80%) of both adipose tissue and skeletal muscle mass that eventually leads to hypoalbuminemia and asthenia, which, together with anemia, a frequent comorbidity in cancer patients, limit physical activity and consequently inhibit protein synthesis [12]. Loss of both skeletal muscle and fat distinguishes it from starvation (where lean body mass is preserved at first).

CACS impacts not only upon prognosis but also on patients' quality of life [13]; actually cachexia is so destructive that this process taps into other sources of energy, namely skeletal muscle and adipose tissue when energy expenditure exceeds food intake. As a consequence, nutritional status is compromised in direct response to tumor-induced alterations in the metabolism [14]. Moreover cachexia adversely affects the immune response of the host against infections and withstand treatment by chemotherapy and radiotherapy. Weight loss is an important prognostic factor in cancer; the higher the extent of weight loss, the shorter the survival time [15]. Reduction in food intake (<1500 kcal/day), together with a weight loss of 10% or greater and a systemic inflammatory response are considered prognostic parameters. Weight loss and the wasting process cannot be reversed by nutritional supplements in cancer patients. Patients with CACS die when there is 25–30% of total body weight loss, but weight loss alone cannot be a prognostic factor, because it cannot identify the complete effect of cachexia. Proteolysis-inducing factors which cause wasting, and increased energy expenditure have been identified, and they are also considered as important factors that contribute to the wasting process [16,17].

Unfortunately, there is no clear consensus definition of this common problem in cancer patients leading to an insufficient knowledge of the etiology of the condition. Earlier definitions of cachexia stated "a wasting syndrome involving loss of muscle and fat directly caused by tumor factors, or indirectly caused by an aberrant host response to tumor presence" [18]. However, more recent definitions have downplayed the importance of fat loss and describe cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" [19], thus highlighting the unique consequences of muscle wasting—the hallmark of cachexia. A recent consensus definition has been proposed to include further factors to diagnose the cachexia syndrome such as involuntary weight loss, decreased muscle mass, anorexia, and biochemical alterations (C-Reactive Protein (CRP), albumin, hemoglobin [16,19]).

CACS arises from a complex interaction between cancer growth and host response resulting in progressive weight loss that is the consequence of a negative protein and energy balance often associated with signs of inflammation [20]. The mechanism by which PDA provokes the loss of the host's muscle mass is presently thought to be complex and multifactorial. It involves multiple pathways: procachectic and proinflammatory signals from tumor cells, systemic inflammation in the host, and widespread metabolic changes (increased resting energy expenditure and alterations in metabolism of protein, fat, and carbohydrate). Whether it is primarily driven by the tumor or as a result of the host response to the tumor has yet to be fully elucidated [21]. The pathogenesis of CACS in PDA is summarized in Fig. 1 [10]; in synthesis, PDA can lead to a reduction in nutritional intake, because of pancreatic cancer-associated stenosis of the duodenum or maldigestion with exocrine pancreatic insufficiency, malaise, taste alterations and/or loss of appetite. In addition, early satiety due to a lack of gastric accommodation, gastroparesis or delayed pyloric emptying is always present and it is accompanied by early postprandial bloating and severe nausea [10]. This condition may be worsened by the side effects of treatment such as radiotherapy or chemotherapy which decrease food intake. It is also a common experience for physicians to observe deep changes in smell and taste in PDA, with frequent aversion to specific foods capable of recalling unpleasant feelings, thus contributing to increasing anorexia [10].

Although anorexia is a common symptom in cachexia, it should not be used as a synonym. Cachexia is associated with characteristic metabolic alterations that are not present in anorexia [22]. While loss of appetite and resultant decrease in energy intake undoubtedly contribute to weight loss associated with cancer cachexia, whether anorexia occurs by an independent process or is a result of the inflammatory process of cachexia is not

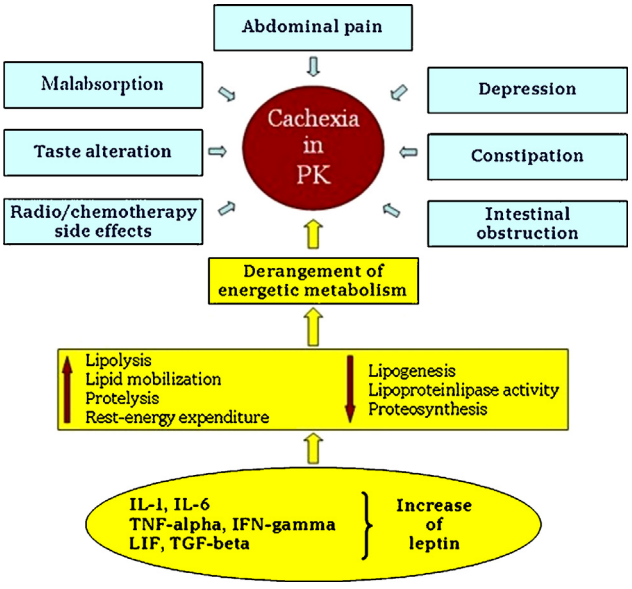


**Fig. 1.** Pathogenesis of cachexia in pancreatic cancer (PK: pancreatic cancer; IL-1: interleukin-1; IL-6: interleukin-6; TNF-alpha: tumor necrosis factor-alpha; IFN-gamma: interferon-gamma; LIF: leukemia inhibitor factor; TGF-beta: transforming growth factor-beta).
Modified from: Uomo et al. [10].

fully understood. Anorexia itself may have a number of components—nausea, altered taste sensation, swallowing difficulties, or depression. The failure of aggressive supplementary nutritional regimes to reverse weight loss in many patients points to primacy of the cachexia disease process [12]. In other terms, weight and muscle loss is not accounted for by the diminished nutritional intake alone but it is thought that lack of appetite is secondary to factors produced by the tumor itself or by the immune response to the cancer disease. This process is the consequence of a negative protein and energy balance often associated with signs of inflammation and includes cytokine production, release of lipid-mobilizing and proteolysis-inducing agents and alterations in intermediary metabolism [23]. Cytokines may inhibit the neuropeptide Y pathway or mimic negative feedback action of leptin on the hypothalamus, leading to anorexia [24,25]. In addition, leptin levels regulate rest energy expenditure (high levels are capable of determining a considerable increase of energy expenditure). Therefore, the equilibrium of body weight and energy regulation appears to be seriously compromised, in PDA through increased leptin levels, and oriented toward a continuous suppression of appetite and increase of energy expenditure [26].

Associated metabolic changes interest the main nutrients and are all oriented to a hypermetabolic status. Abnormalities in lipid metabolism include enhanced lipid mobilization (through the production of a specific lipid mobilizing factor by the tumor), decreased synthesis, and decreased activity of lipoprotein-lipase [27]. Protein metabolism is also affected by activation of proteolysis and inhibition of protein synthesis; this results in a continuous loss of skeletal muscle mass and also appears to be related to the presence of a specific cancer proteolysis-inducing factor in the serum [28]. Protein degradation leads to the release of amino acids which are utilized in large amounts by the liver for gluconeogenesis. This extensive consumption of amino acids causes wasting of lean body mass; in fact, glucose production for brain needs cannot be replaced in PDA by the production of ketone bodies because of the severe depletion of body fat. The glucose catabolism by involving anaerobic metabolism more than oxidative metabolism may account for an additional daily energy loss [29].

### 2.2. Treatment options

The primary end-points of optimal treatment of cancer cachexia are improvements in lean body mass, resting energy expenditure, fatigue, anorexia, quality of life, performance status, and a reduction in pro-inflammatory cytokines [21].

Although remarkable progress in preclinical and clinical research has been achieved in recent years, the currently available treatment options are still limited for this condition.

Considering the complex clinical picture and the multifactorial pathogenesis of anorexia and cachexia syndrome, it is believed that its clinical management requires a multidisciplinary and multi-drug treatment.

On these premises, several therapeutic approaches were proposed. Most of them are in the preclinical phase, while others are available in clinical practice [30].

Despite trials of conventional and/or aggressive nutritional support using different feeding techniques, the cachectic state cannot be overcome by nutritional support alone [19]. Patients with CACS have failed to gain consistent significant benefits in terms of weight gain, quality of life or survival. All the same, traditional approaches using enteral or parenteral nutrition in patients with PDA undergoing pancreatic surgery have demonstrated no benefit either for symptoms control or for survival [11,31].

The two major options for pharmacological therapy have been either progestational agents or corticosteroids, as reported in Table 1. Among the orexigenic agents, megestrol acetate (Megace)

**Table 1**
Pharmacological options for management of CACS (cancer anorexia–cachexia syndrome).

| | Agent | Clinical effect | Hypothetical mechanism of action |
|---|---|---|---|
| Anabolic agents | Corticosteroids | Improves anorexia and weakness; no improvement in weight or calorie intake; well tolerated; effects short lasting | Not established. May inhibit prostaglandin metabolism and central euphoric effect |
| | Nandrolone decanoate | Decrease in weight loss | Not established. Promote protein nitrogen accumulation |
| | Oxandrolone | No published randomized clinical trials in cancer cohort | Not established |
| | Insulin | Increases whole body fat and carbohydrate intake | Not established |
| | Adenosine triphosphate (ATP) | Stabilizes weight loss and increases energy intake | Not established |
| Appetite stimulants | Progesterones: megestrol acetate (MA) | Improves appetite, calorie intake and weight (not lean body mass) | MA: may increase the central appetite stimulant neuropeptide |
| | Medroxyprogesterone (MP) | | MP: reduces serotonin and cytokine production by Peripheral Blood Mononuclear Cells (PBMCs) |
| | Cannabinoids: dronabinol | No benefit when added to MA; inferior to MA when used alone. No increase in appetite or quality of life | May act on endorphin receptors, reduce prostaglandin synthesis or inhibit IL-1 secretion |
| Cytokine inhibitors | Cyproheptadine | No improvement in weight gain | Serotonin antagonist with antihistaminic properties |
| | Thalidomide | Attenuates weight loss, increases lean body mass | Immunomodulatory: downregulates TNF-α (by destabilizing mRNA), NFκB, pro-inflammatory cytokines, COX2 |
| | Pentoxifylline | No improvement in appetite or weight in cachectic patients | Phosphodiesterase inhibitor: inhibits TNF gene transcription |
| | Eicosapentaenoic acid (EPA) | Insufficient evidence to establish whether EPA is better than placebo | In vitro attenuates increased cAMP activity and lipolysis by lipid-mobilizing factor (LMF) |
| | Melatonin | Improves cachexia (term not defined) and one year survival increased in advanced NCSC lung cancer | Immunomodulatory, downregulates TNF production |
| Anti-inflammatories | Non-steroid anti-inflammatory drugs | Reduced inflammatory markers, reduced resting energy expenditure, preservation of total body fat | Not established. May downregulate systemic inflammatory response to tumor |

is the most studied and widely prescribed progestational agent to treat CACS. Several randomized control trials have demonstrated that this drug, at doses ranging from 160 to 1600 mg/day significantly improves appetite with respect to placebo [32]; moreover a recent meta-analysis reported that megestrol improves weight gain and appetite [33]. However, many adverse events such as thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hyperglycemia, hypertension, adrenal suppression, and adrenal insufficiency if the drug is abruptly discontinued have been reported. As a consequence, megestrol should not be prescribed in cases of thromboembolic/thrombotic disease, heart disease, or for patients at risk for serious fluid retention [34].

Corticosteroids, such as dexamethasone, have been studied and used to treat anorexia and cachexia. The corticosteroid decreases the inflammatory state, and has efficacy with preventing chemotherapy related nausea/vomiting. Randomized clinical trials showed that corticosteroid medications may stimulate appetites in patients with advanced cancer [35]. Nevertheless, these studies were not able to show any substantial non-fluid weight gain in treated patients [35]. Corticosteroids, although widely used, have significant side effects including protein breakdown, insulin resistance, water retention, and adrenal suppression and should only be used for short periods and in selected cases [36,37]. However, if treatment is indicated and the patient has a history of deep venous thrombosis, corticosteroid use can be considered as an alternative to megestrol [38].

Several other drugs have been evaluated as agents to ameliorate CACS. These include antiserotonergic agents, branched-chain amino acids, eicosapentanoic acid, thalidomide, melanocortin antagonists and antimyostatin agents-all of which act on the feeding-regulatory circuitry to increase appetite and inhibit illness-derived catabolic elements [23].

Cyproheptadine is an anti-serotoninergic drug with antihistaminic properties that has been shown to have a slight appetite-stimulant effect in a number of human conditions [39]. A randomized, controlled trial found mild appetite stimulation in patients with advanced cancer, although it did not prevent progressive weight loss [40]. Studies on the effects of cyproheptadine in progressive weight loss in patients with cancer or other causes of cachexia suggest that cyproheptadine has a beneficial effect on appetite stimulation but only slight effects on weight gain [40–42].

Eicosapentaenoic acid (EPA), a long-chain polyunsaturated fatty acid of the omega-3 (n-3) family, has been studied in relation to cancer cachexia for over 15 years. It is of interest in the context of cancer cachexia as it has potential to impact on both the underlying metabolic abnormalities of tumor-induced weight loss, as well as modulation of immune function [21]. Despite initial studies showing anabolic effects, principally gains of lean body mass, improvements in grip strength, quality of life, and reductions in IL-6 and proteolysis-inducing factor could be achieved in a variety of cancers [11], including pancreatic cancer [43,44], analysis of RCTs only, using the Cochrane approach, did not show any differences between EPA supplementation and placebo [45]. Three phase III trials have shown that EPA does relatively little for cancer anorexia and cachexia when tested in the setting of either EPA versus placebo or EPA versus megestrol [45].

Since proinflammatory cytokines, especially tumor necrosis factor-alpha, play a prominent role in the pathogenesis of CACS in pancreatic cancer, systemic inflammation remains an important area for novel therapeutic targets in combating this syndrome. Thalidomide, which is an inhibitor of tumor necrosis factor-alpha synthesis, may represent a rational therapeutic approach [10]. In 2005, Gordon et al. [46] published the results of an interesting study aimed at assessing the safety and efficacy of thalidomide in attenuating weight loss in patients with CACS secondary to advanced pancreatic cancer. The study population consisted of 50 patients (who had lost at least 10% of their body weight) randomized to receive thalidomide 200 mg/day or a placebo for 24 weeks in a single center, double blind, randomized controlled trial. The primary outcome of the study was a change in weight and nutritional status. The conclusions of the study strongly suggest that thalidomide was effective for attenuating loss of weight and lean body mass in patients with CACS due to advanced pancreatic cancer; furthermore, the drug was well-tolerated with additional advantages related to oral administration and to the low cost of the treatment [10].

Recently, Sanchetee assessed in a single-center double-blind study whether thalidomide or thalidomide with olanzapine and megestrol acetate were safe and effective treatments of the late symptom of CACS in gastrointestinal cancer [47]. Fifty patients with GI cancers who had lost 10% of the body weight were included in the study. Sixteen patients were randomized to thalidomide 100 mg daily; and 17 patients to thalidomide 100 mg, olanzipine 5 mg, and megestrol acetate 80 mg daily. They were evaluated at four weeks. Twelve patients were randomized to a thalidomide only group, and eight to a control group; they were evaluated at eight weeks. At four weeks, patients in the thalidomide-olanzipine megestrol group had gained 0.37 kg in weight and 1.0 $cm^3$ in arm muscle mass, compared with a loss of 2.21 kg of weight (absolute difference – 2.59 kg; $P = 0.005$) and 4.6 $cm^3$ in arm muscle mass (absolute difference – 5.6 $cm^3$; $P = 0.002$) in the thalidomide only group. At eight weeks, patients in the thalidomide–olanzipine megestrol group had lost 0.06 kg in weight and 0.5 $cm^3$ in arm muscle mass, while patients in the thalidomide only group lost 3.62 kg in weight (absolute difference – 3.57; $P = 0.034$) and 8.4 $cm^3$ (absolute difference – 7.9 $cm^3$; $P = 0.014$). Improvement in physical functioning positively correlated with weight gain ($P = 0.001$). The authors concluded that the thalidomide–olanzapine megestrol acetate combination attenuated weight loss and loss of lean body mass in patients with GI cancers who experienced CACS [47].

Due to the lack of clinical efficacy of agents which seemed promising in the laboratory setting, ongoing research has continued to explore new therapeutic targets and to develop new agents. Much of this has focused on manipulation of the melanocortin system of appetite regulation [48]. Activation of the Melanocortin-4-receptor (MC4R) in murine models decreases food-seeking behavior, increases basal metabolic rate, and decreases lean body mass [49]; as a consequence treatment with a MC4R antagonist attenuated these responses [50]. Similarly, exciting data have arisen from a preliminary study of ghrelin, an endogenous ligand for the growth hormone secretagogue receptors [51,52]. It is synthesized principally in the stomach and is released in response to fasting [52]. Evidence that ghrelin exerts anti-inflammatory actions has been accumulating [53]. Ghrelin induces the anti-inflammatory cytokine IL-10 [54,55], suppressing the production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α both in vitro [56,57], and in vivo [54,58,59]. Additionally, ghrelin inhibits the activation of NF-κB, which controls the production of multiple proinflammatory cytokines during inflammatory insults [55,57,58]. Quite recently, a phase II randomized, placebo-controlled, double-blind study, using an oral ghrelin mimetic named RG1291, demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients [60]. In addition, Garcia and others recently conducted a randomized, double-blind, placebo-controlled pilot study with anamorelin, another oral ghrelin mimetic, in 16 patients with cachexia and observed improvements in weight and trends to suggest greater food intake [61]. These findings promoted further study, and larger trials are ongoing.

Current studies are investigating an approach of drug combinations to reverse cancer cachexia [9,62,63]. A recent study with 332 patients comparing medroxyprogesterone, megestrol acetate, oral supplementation with eicosapentaenoic acid, L-carnitine, and thalidomide found that the combination therapy was superior to any of the other treatment arms with single drug treatment [63]. Combination therapy led to increased lean body mass, decreased resting energy expenditure, and improved appetite [63]. Until an effective intervention for reversing CACS is developed, early intervention with nutritional support and prevention of treatment-related morbidities (e.g., nausea, vomiting, diarrhea, dysphagia, pain, or depression) is advised [63,64].

## 3. Conclusions

Considering the complex clinical picture and the multifactorial pathogenesis of CACS, one single therapy may not be completely successful and its management should address the different causes underlying this clinical event. Many drugs including appetite stimulants, thalidomide, cytokine inhibitors, steroids, nonsteroidal anti-inflammatory drugs, branched-chain amino acids, eicosapentaenoic acid, and antiserotoninergic drugs have been proposed and validated in clinical trials, while others are still under investigation. On the other hands, nutritional, psychological, and behavioral therapies are important components also and should be incorporated into a multidisciplinary approach to this complex medical problem. Despite several years of coordinated efforts in basic and clinical research, the practice guidelines for the prevention and treatment of CACS are lacking. Further clinical trials are needed to improve and refine current strategies to counteract cancer cachexia using multimodal interventions, including nutritional supplementation, anabolic agents, and anti-inflammatory drugs along with an appropriate physical exercise program.

## Conflict of interests

The authors declare no conflicts of interest.

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