

## Review

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# Clinical Management of Cancer-Related Cachexia: Review of the Literature

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## ABSTRACT

Cachexia is among the most debilitating and life-threatening aspects of cancer, especially in the palliative care setting. It represents a metabolic syndrome affecting essential functional circuits involved in the regulation of homeostasis, with symptoms including anorexia, and fat and muscle tissue wasting. Most patients experiencing cachexia do not receive proper management and suffer a profoundly distressing experience, affecting not only the patients, but also the entire family. Thus, oncologists and palliative care clinicians must understand its complex pathophysiology and treatment. This article will review special considerations about the anorexia-cachexia syndrome and which interventions are most effective in relieving this condition.

**KEYWORDS:** Cachexia; Interleukins; Metabolic syndrome; Hypercatabolic state; Anorexia-cachexia.

## INTRODUCTION

Signs and symptoms of cachexia have been reported since the time of Hippocrates. He described it as a syndrome of wasting and progressive inanition among ill or dying patients.<sup>1</sup> The word cachexia is derived from the Greek *kakos* “bad” and *hexis* “condition”. Cachexia represents the clinical consequence of a chronic, systemic inflammatory response, and its manifestations differ considerably from those of starvation.

Cachexia is a multifactorial devastating syndrome, and is essentially irreversible; it affects about 50-80% of cancer patients, usually in advanced stages of the disease.<sup>2</sup> It results in substantial weight loss, which is, by definition, more than 5% of the usual weight during the prior 6 months.<sup>3</sup> It is clinically distinguished by anorexia, emaciation, weakness, and fatigue. It results in damaged immunologic function, tissue consumption, and status performance decline, and cannot be nutritionally reversed.<sup>4</sup>

Cancer-related cachexia involves fat and muscle mass loss, and reflects catabolic metabolism that is induced by an abnormal host response to the tumor. Its clinical implications are profound, and the weight loss is associated with decreased adherence to treatment, prolonged hospital stays, and reduced survival.<sup>5</sup> Moreover, unintentional severe weight loss jeopardizes the cancer patient’s quality of life and sense of dignity.

The preservation of dignity should be a goal in palliative cancer treatment, because its loss is prominently associated with certain types of suffering commonly seen among the terminally ill.<sup>6</sup>

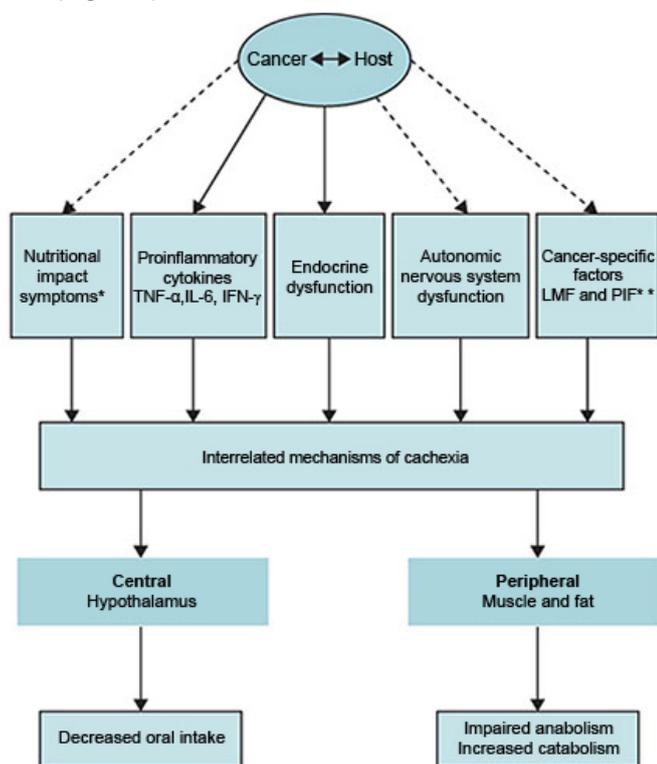
## RELEVANT PATHOPHYSIOLOGY

Cancer-related cachexia etiology is not yet fully understood, but is certainly multifac-

torial, with a rather complex pathogenesis. Several cytokines, tumor factors, and hormones have been implicated, particularly Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Interleukins (IL), proteoglycan, insulin, adrenalin, corticotropin, human growth hormone and insulin-like growth factor.<sup>7,8</sup> Most studies have detected elevations in peripheral blood mononuclear cell cytokine concentrations, especially TNF- $\alpha$  and IL-6, in weight-losing patients with cancer.<sup>9</sup>

Cachexia may be etiologically classified as primary or secondary. Primary cachexia is due to metabolic decompensation caused by the basic illness. Generally, its origin involves an increase in inflammatory activity and insulin resistance, anorexia, hypogonadism, and anemia.<sup>10</sup> Secondary cachexia involves the aggravating factors of primary cachexia, such as poor nutrition (due to a decrease in oral intake or intestinal absorption capacity, or protein loss), muscle mass loss due to other causes (prolonged inactivity, sarcopenia), or hypercatabolic states.<sup>11</sup> Cancer-related cachexia often evolves into a negative energy and protein balance, enhanced by a combination of reduced food intake and metabolic changes. Hence, hypermetabolism and reduced energy consumption due to anorexia may constitute a vicious cycle in the development of cachexia.<sup>12</sup>

Understanding the immune response associated with cachexia may improve future pharmacological modification of cytokines. In addition, the multifactorial contributions to the mechanisms of cachexia indicate that a multimodal approach might be necessary to treat cachexia and its associated symptoms (Figure 1).<sup>13</sup>



\*Poor appetite nausea, early satiety, and dysgeusia  
 \*\*Lipid-mobilizing factor(LBF), Proteolysis-inducing factor(PIC)  
 \*\*\*Lipid-mobilizing factor(LBF), Proteolysis-inducing factor(PIC)  
**Figure 1:** Cancer related cachexia mechanisms.<sup>14</sup>

All palliative care patients should be screened for nutritional status and weight loss. The clinical assessment of patients with anorexia or cachexia includes an accurate history that is focused on nutritional issues, including risk factors that compromise the ability to obtain or take in nutrition, and a physical examination focusing on loss of subcutaneous fat, muscle wasting (temporal region, deltoids, and quadriceps, with loss of bulk and tone assessed by palpation), and edema (sacral or ankle) or ascites.<sup>15</sup> An international consensus recommended five areas to be assessed in cachexia: depletion of stores, muscle mass and strength, anorexia/reduced food intake, catabolic drivers, and functional/psychosocial effects.

A comprehensive assessment for anorexia and cachexia should also take into account other symptoms that may affect appetite and caloric intake. These include symptoms that may be related to the underlying illness, symptoms and syndromes that may contribute to reduced caloric intake, and symptoms that might be the consequence of cachexia. In particular, pain, xerostomia, nausea, constipation, and depression are frequent in patients with chronic illness and may result in decreased caloric intake if not adequately treated.<sup>16</sup>

Some other strategies are also being introduced in the evaluation of the patient, such as Bioelectrical Impedance Analysis (BIA)<sup>17</sup> and computed tomography, even when images are acquired during routine care.<sup>18</sup> These strategies can be highly useful in long-term follow-up, when body changes often accelerate and the evaluation becomes more complex.

**TREATMENT RECOMMENDATIONS**

Cachexia used to be considered an inevitable consequence of cancer progression, without effective therapeutic interventions. Although there have been advances with several clinical essays showing enhanced clinical results, it should be emphasized that there is still no standard treatment for cachexia.<sup>19</sup> Once the syndrome mechanisms are multifactorial, a broad multidisciplinary approach that employs pharmacological and non-pharmacological interventions is the most efficient strategy in order to reverse or stabilize the weight and muscle mass loss.<sup>20</sup>

Ideally, the treatment should be individualized, taking into consideration the clinical status of the patient, the main mechanisms of weight loss, and a patient’s expectations for treatment. Although many patients and their relatives realize that the lack of appetite is a significant problem, cachexia patients may have different priorities, and their therapeutic options may vary considerably. For most, the maintenance of lean mass and functionality should be important, while others would rather have preservation of appetite in order to enjoy meals with family and friends as the main goal.

It is important to detect and treat the reversible causes, such as dry mouth, stomatitis, severe constipation, pain, and de-

pression, among others. Thus, increasing the nutritional component alone is insufficient.

### Pharmacological Interventions

The pharmacological treatment of the anorexia-cachexia syndrome includes the use of orexigenic agents (appetite stimulants), anticatabolic agents (antimetabolic and anticytokine), and anabolic agents (primarily hormonal).<sup>21,22</sup>

The use of appetite stimulants is supported by solid scientific evidence. The use of progestins (megestrol acetate, starting at 160 mg/day and increasing according to the clinical response up to 480-800 mg/day, or medroxyprogesterone, starting at 1 g/day and increasing up to 5 g/day) is recommended, as they rapidly improve appetite, decrease fatigue, and lead to a general sense of well-being. These benefits were confirmed by systematic analysis<sup>23</sup> and a Cochrane meta-analysis;<sup>24</sup> unfortunately, however, the weight gain due to progestational agents seems to be predominantly from fat or fluid, instead of lean body mass. The side effects of progestin use are hypertension, hyperglycemia, water retention, hypogonadism, and thrombosis. These are clinically significant, and must be monitored carefully.

Corticosteroids have long been first-line therapy for appetite stimulation in anorexia-cachexia syndrome, and may still be helpful,<sup>25</sup> but positive effects are mainly restricted to a few weeks, due to the risks associated with prolonged use. In spite of this, their use is increasing in cancer patients subsequent to the publication of a phase III clinical trial showing benefit for fatigue relief in this population.<sup>26</sup>

Dronabinol is a cannabis derivative that stimulates the endocannabinoid system, but despite the expectation that was created with this drug class, its use has not proved effective in cancer patients' appetite improvement.<sup>27</sup>

The administration of thalidomide in low doses (100 mg/day) significantly improved appetite, nausea, and sense of wellbeing after 10 days of use in advanced cancer patients and cachexia. A retrospective study based on 200 mg/day for six months proved that the drug was tolerated and was effective as a weight and lean mass stabilizer. However, symptomatic improvement was not reproduced.<sup>28</sup>

Essential amino acid supplementation – particularly Branched-chain amino acids (BCAA) – mitigated cancer anorexia and stimulated protein synthesis, thus maintaining lean muscle mass.<sup>29</sup>

Eicosapentaenoic acid (EPA, fish oil) showed promising preliminary results, which were not completely confirmed in retrospective studies in advanced cancer patients.<sup>30</sup> However,

positive effects on quality of life and appetite were demonstrated in the same patients.

### Nutritional Approaches

Intensive and individualized nutritional counseling has proven to be effective for the maintenance of body weight and physical functioning in cancer patients.<sup>31</sup> In taking a detailed clinical history, nutritional aspects, such as preferences and eating habits, must be taken advantage of. Dietary changes following disease onset should be identified, and, when possible, a daily food log should be kept. The aim of these methods is to stimulate caloric intake and to determine if there is any energy deficit.

Nutritional support is indicated for patients with cachexia caused by obstruction of the digestive tract, or by impediments to eating, such as large head and neck tumors or severe mucositis. The use of enteral or parenteral nutrition in patients with cachexia due to different causes is controversial and generally contraindicated, and is not associated with a meaningful clinical response in cancer and cachexia patients.

### Family Support Interventions

It is clear that the multidimensional impact of anorexia-cachexia syndrome spans biopsychosocial domains and affects not only the patients, but also their families and caregivers. Nonetheless, the development and evaluation of psychosocial, educational, and informational interventions for patients with cachexia and their families and caregivers remain in their infancy.<sup>32</sup>

Families often rationalize that if food intake is increased, weight will be regained and survival increased; the failure to increase intake is equated with hastening of death. This stems partially from a lack of communication with families about the nature and causes of wasting in cachexia, as atrophy is caused by factors independent of nutritional or calorific intake, and also from the need to take an active role in treatment, with food preparation being highly symbolic of the need to nurture. This often leads to conflict between the patients and their families, as the patients' refusal of food is interpreted as a rejection of care and support, increasing anxieties over food, and ultimately contributing to a decreased quality of life.

It is important to recognize that cachexia is a condition that has profound psychological as well as physiological implications for patients and their families. Better communication from researchers and healthcare professionals with patients and their caregivers is of great importance to not only reduce the burden of disease but also provide better understanding and support during disease progression.

**Social Support Interventions**

Psychosocial evaluation in cachexia risk is essential. Many family problems usually fully emerge with cachexia, often based on the almost automatic association between the cachectic physical appearance and the proximity of death. Therefore, an in-depth evaluation of the patient’s psychological status, as well as of relatives and caregivers, might be useful in the management of a case.

Depressed mood may also lead to decreased oral intake and must be treated with counseling and antidepressants, if indicated. Some psychotropic’s might have an indirect effect on cachexia, both for the treatment of depression that can lead to anorexia, because of a direct orexigenic effect (tricyclic antidepressants), or because of the effect on other symptoms, such as nausea (mirtazapine and olanzapine).<sup>33</sup>

**Psychotherapeutic Interventions**

To eat a meal is a social activity *per se*. Therefore, for patients able to feed themselves, in the event of poor appetite or early satiety, counseling is important to maintain this activity

as long as possible. General measures, such as avoiding odors during food preparation, the use of condiments according to patient preferences, reduction of portion sizes, and having more frequent meals may improve the nutritional component, but do not seem to have an effect on symptoms or survival.<sup>34</sup>

**POTENTIAL FUTURE TREATMENTS**

Melatonin is a pleiotropic hormone that may modulate multiple mechanisms promoting cachexia in cancer, including inflammation, autonomic failure, and malabsorption. In cachectic patients with advanced cancer, oral melatonin 20 mg at night did not improve appetite, weight gain, or quality of life compared with the placebo.<sup>35</sup> Further research is required to determine whether melatonin has a role in the supportive care of patients earlier in their disease course (Figure 2).

Promising results have been seen with ghrelin, a Growth Hormone (GH) – releasing peptide that induces a positive energy balance both by decreasing fat utilization and by simulating feeding through GH-independent mechanisms, and with anamorelin, which is an oral ghrelin mimetic. Some studies in cachectic patients suggest that repeated intravenous administration of

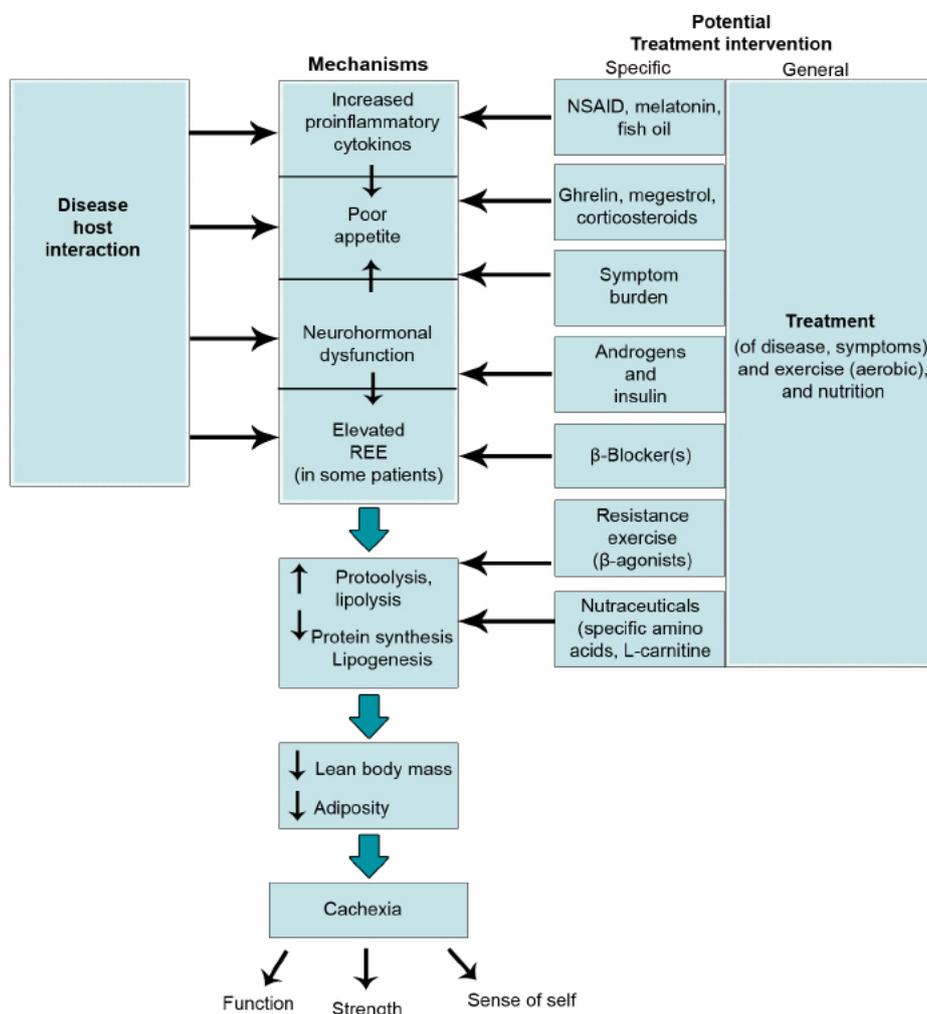


Figure 2: Multimodal treatment.<sup>14</sup>

ghrelin lessens muscle wasting and improves body composition, functional capacity, and an increase in satisfaction. However, ghrelin or anamorelin are not commercially available.<sup>36</sup>

## CONCLUSION

Cachexia is a hypercatabolic state defined as accelerated loss of skeletal muscle in the context of a chronic inflammatory response that frequently occurs in the setting of cancer, notably in those patients in palliative care. Early treatment also facilitates the use of oral nutritional supplementation, which is preferable to parenteral nutrition in the majority of cases. Once a patient has severe wasting, it may be neither practical nor ethical to intervene with anything more than supportive care.<sup>37</sup>

The best therapeutic choice for cachexia is the effective treatment of the underlying disease. Recent progress in the understanding of molecular mechanisms in cachexia may lead to new therapeutic approaches.

**CONFLICTS OF INTEREST:** None.

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