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OPINION PAPER

Cachexia: A new definition

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Wasting disease

Summary

On December 13th and 14th a group of scientists and clinicians met in Washington, DC, for the cachexia consensus conference. At the present time, there is no widely agreed upon operational definition of cachexia. The lack of a definition accepted by clinician and researchers has limited identification and treatment of cachectic patient as well as the development and approval of potential therapeutic agents. The definition that emerged is: "cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (*corrected for fluid retention*) or growth failure in children (*excluding endocrine disorders*). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity. While this definition has not been tested in epidemiological or intervention studies, a consensus operational definition provides an opportunity for increased research.

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Definition

Cachexia has long been recognized as a syndrome associated with many illnesses. However, the underlying mechanisms causing cachexia are not well understood and there is no

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universally agreed upon definition. It is essential to have a specific definition so clinicians can recognize the problem and institute corrective measures to treat cachexia.¹ On December 13th and 14th, 2006, scientists and clinicians met in Washington, DC, to reach a consensus on the definition of the constellation of abnormalities that have been grouped under the name cachexia. After 2 days of discussion, a definition for cachexia was arrived at by a consensus vote. Each of the sentences that follow were included only if a 75% majority of the group approved. The definition that emerged is: "cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (*corrected for fluid*

retention) or growth failure in children (*excluding endocrine disorders*). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity (Fig. 1).

Cachexia is infrequently identified or diagnosed and rarely treated. Our purpose is to define the phenomenon, discuss how it can be identified and describe current and potential therapies. Because there has been no universally accepted definition of cachexia, its identification has been problematic and causal mechanisms are poorly understood. Increased nitrogen excretion resulting from increased

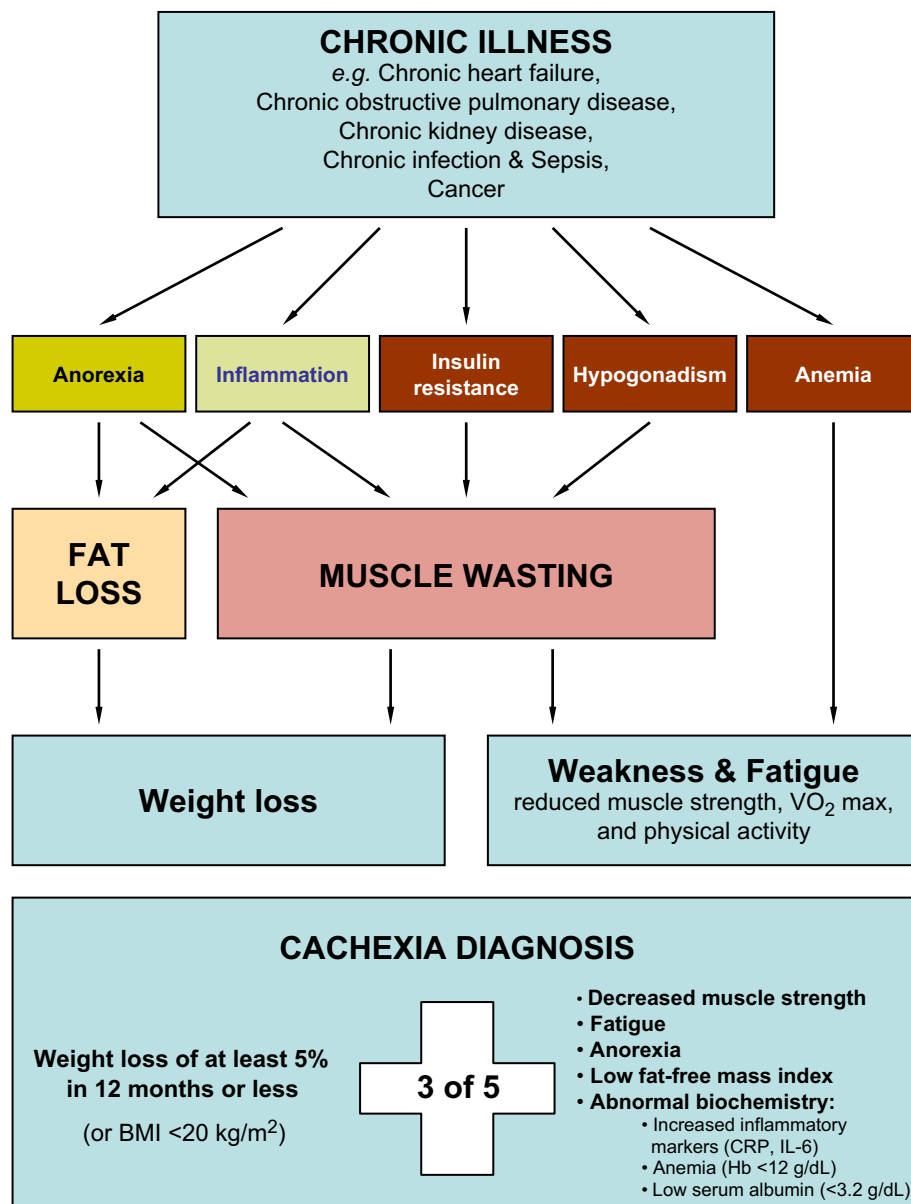


Figure 1 Conceptual representation of the definition: cachexia results from adaptation to an underlying illness such as cancer. The illness creates an environment that may be characterized by inflammation, loss of appetite (anorexia), low levels of testosterone and other anabolic hormones, and anemia. Decreased food intake and anorexia result in loss of body and muscle mass. In addition, inflammation, insulin resistance, and low levels of anabolic hormones result in muscle wasting.

muscle protein degradation has been described as a component of cachexia. Paradoxically, in these conditions measured rates of muscle protein synthesis may be elevated because there is increased availability of amino acids resulting from accelerated muscle protein degradation.² Fat tissue wasting is not as well established, it appears to be regularly present in patients with weight loss associated with malignancies,³ chronic heart failure⁴ HIV infection⁵ or chronic kidney disease.⁶ Cachexia is generally associated with loss of appetite so losses of body weight and muscle are accelerated. In such cases, the process of cachexia may be misinterpreted as caused by malnutrition.

Weight loss

Weight loss is a powerful independent variable that predicts mortality in patients with cancer.^{7,8} Anker⁹ has demonstrated that cardiac cachexia is associated with a poor prognosis, independently of functional severity, age, and exercise capacity and cardiac function. Weight loss is associated with increased mortality among elderly people discharged from a hospital¹⁰; in elderly nursing home patients a 5% or greater weight loss in a month is associated with a 10-fold increase risk of death.¹¹ In patients with HIV infection, a weight loss of as little as 3% has been related to increased morbidity and mortality,^{12,13} and the risk of death increases with increasing magnitude of weight loss of decreasing BMI.¹⁴ Therapies that slow or prevent weight loss *per se* are presumed to exert beneficial effects on mortality but this conclusion has yet to be established in intervention trials. Therapies that slow disease progression (like ACE inhibitors in heart failure or effective anti-retroviral therapy in HIV infection) can prevent weight loss and subsequent adverse responses.^{15,16} For these reasons, weight loss alone has been used as the prime clinical manifestation of cachexia because body composition is difficult to measure with precision in a clinical setting. Fouladiun et al.¹⁷ examined changes in body composition, diet, and inflammatory markers in cachectic patients with cancer. They found that anorexia and loss of body fat was a powerful predictor of mortality. On the other hand, Fearon et al.³ stated that "weight loss alone does not identify the full effect of cachexia on physical function and is not a prognostic variable". This lack of agreement may be reflective of the difficulty in measuring body composition changes accurately in many patients with cachexia. Clearly, body weight changes can be accurately assessed and the preponderance of evidence is that it is highly predictive of morbidity and mortality in cachectic patients.

Skeletal muscle

As noted, muscle wasting is important in the pathophysiology of cachexia and a major cause of fatigue¹⁸ in patients. Accelerated or exaggerated loss of skeletal muscle mass distinguishes cachexia from the weight loss due solely to reduced energy intake. Several groups of investigators have suggested that actomyosin, actin and myosin are selectively targeted for degradation in clinical conditions associated with cachexia.^{19–21} Selective targeting of skeletal muscle

is at least in part due to the systemic inflammation that frequently accompanies clinical conditions associated with cachexia. Indeed, Lecker and co-workers²² concluded that a common transcriptional program is associated with skeletal muscle atrophy in animals with uremia, fasting, cancer, and streptozotocin-induced diabetes. The common feature of cachexia, loss of muscle mass, suggests that therapies targeting muscle or inflammatory pathways may be effective in reducing the devastating effects of cachexia.

The consensus panel developed a set of diagnostic criteria to allow clinicians and researchers to make a definitive diagnosis of cachexia (Table 1). The key component was at least a 5% loss of edema-free body weight during the previous 12 months or less. The time frame may be disease specific and is likely to be shorter in cancer (3–6 months) and longer in chronic kidney or heart failure or COPD (12 months). In cases where a history of weight loss cannot be documented, a body mass index (BMI) of $<20.0 \text{ kg/m}^2$ was considered sufficient to establish a diagnosis of cachexia. More research is needed in this area as there was disagreement among participants about the critical level of BMI indicating loss of lean body mass (alternatives ranged from 18.5 to 22.0 kg/m^2). Other diagnostic criteria for cachexia besides loss of muscle mass or evidence of accelerated protein degradation in muscle are decreased muscle strength, fatigue, anorexia, low muscle (fat-free) mass, and biochemical abnormalities characteristic of inflammation, anemia or hypoalbuminemia (Table 1). We believe that staging of cachexia is possible and will prove useful. For future research, we suggest classifying the degree of cachexia as *mild*, *moderate* or *severe*, depending on whether the observed weight loss within the previous 12 months (or less) is $>5\%$, $>10\%$ or $>15\%$, respectively.

Nutritional factors

It is important to distinguish cachexia from starvation, malabsorption, hyperthyroidism, dehydration or sarcopenia (though these conditions may represent a pre-cachectic state) and from subcutaneous fat loss (lipoatrophy), which can occur as a side effect of some antiretroviral therapies in HIV. Sarcopenia is defined as the age-associated decrease in skeletal muscle mass²³ resulting from a variety of causes including decreased physical activity and/or decreased production of anabolic hormones. Sarcopenia is not associated with weight loss so if weight loss becomes significant, cachexia may be diagnosed. Anorexia-induced weight loss is due to decreased energy intake and should be treated with a nutritional intervention. For example, loss of appetite (with no underlying disease) in elderly people is not uncommon and, if left untreated, results in involuntary weight loss and increased mortality.²⁴ The term, malnutrition is frequently used in the context of cachexia research but it should be avoided because it suggests that the disease is mainly associated with nutritional problems (or nutritional failure) and implies that the problem can be resolved by adequate nutrition and/or by overcoming problems of absorption or utilization of nutrients.²⁰ Although malnutrition is often present in cachexia, the

Table 1 Diagnostic criteria for wasting disease (cachexia) in adults

Weight loss of at least 5%* in 12 months or less in the presence of underlying illness**, PLUS THREE of the following criteria:

- Decreased muscle strength (lowest tertile^{38,39})
- Fatigue***
- Anorexia^{27****}
- Low fat-free mass index^{40,41,#}
- Abnormal biochemistry
 - a) increased inflammatory markers CRP (>5.0 mg/l), IL-6 >4.0 pg/ml⁴²
 - b) Anemia (<12 g/dl)
 - c) Low serum albumin (<3.2 g/dl)

The literature on cachexia is growing but still somewhat limited. This is particularly true of specific diagnostic criteria. The criteria, below, represents the clinical experiences of the clinicians on the consensus panel and the limited data on patients with cachexia. The following needs to be excluded: starvation, malabsorption, primary depression, hyperthyroidism and age-related loss of muscle mass.

*Edema-free.

**In cases where weight loss cannot be documents a BMI <20.0 kg/m² is sufficient.

***Fatigue is defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.¹⁸

****Limited food intake (i.e. total caloric intake less than 20 kcal/kg body weight/d; <70% of usual food intake) or poor appetite.

#Lean tissue depletion (i.e. mid upper arm muscle circumference <10th percentile for age and gender; appendicle skeletal muscle index by DEXA (kg/m²) by DXA <5.45 in females and <7.25 in males.

clinical characteristic of cachexia is that it cannot be successfully treated with nutrition alone.

One difficulty in identifying cachexia is that it is often associated with loss of appetite. Anorexia occurs in other conditions that are not associated with cachexia, such as use of certain medications, depression,²⁵ age-associated decrease in appetite regulation, or gastro-intestinal problems (e.g. constipation, or delayed gastric emptying.²⁶ For this reason, cachexia should only be diagnosed in the presence of weight loss if at least three of the five conditions identified in Table 1.

Anorexia is a predictor of subsequent weight loss and mortality and can be estimated using the Simplified Nutrition Assessment Questionnaire.²⁷ Muscle strength may be measured by handgrip strength as this is a commonly made measure and a strong predictor of morbidity and mortality.²⁸ Fatigue is frequently associated with cachexia^{29,30} as is low muscle (fat-free) mass,¹⁷ and biochemical abnormalities of anemia³¹ hypoalbuminemia or inflammation.³ Because loss of skeletal muscle mass defines cachexia, and because DEXA instruments are commonly found in hospitals, every effort should be made to quantify body composition, and in particular, appendicular skeletal muscle mass.

Treatment options and conclusions

The treatment options for cachexia are limited. Unfortunately, refeeding a patient with cachexia does not correct the underlying problem. Even with total parenteral nutrition, weight stabilization does not prevent the continuing loss of skeletal muscle mass or correct the underlying abnormality in the metabolic state. Potential strategies for treating cachexia target skeletal muscle wasting in the presence of adequate nutrition.³² Some potential pharmacological agents include androgens, selective androgen receptor modulators, anti-myostatin drugs, growth hormone and insulin-like growth factor, and potential orexigenic agents such as melanocortin antagonists and the growth hormone secretagogue, ghrelin, however data demonstrating effectiveness of these agents is

lacking. At the present time, anti-inflammatory trials in cachectic patient (heart failure and cancer) have not been promising.^{33,34} However, if inflammation is an important cause of the cachexia a continued examination of anti-inflammatory or anti-cytokine agents should occur. Orexi-genic drugs with additional positive effects on inflammation or nitrogen retention may also be effective, particularly when used in combination with other therapeutic approaches. At the present time, evidence-based treatments for cachexia are in short supply.

A standard definition of cachexia will help address a number of outstanding questions. In patients with cachexia:

- Does the prevention or reversal of weight loss alone result in improvement in morbidity and mortality?
- Will targeting skeletal muscle and preventing its loss improve outcomes in cachectic patients?
- What is the importance of nutrition and exercise plus muscle anabolic therapies in patients being treated for cachexia?
- What is the role of fat loss in cachexia?
- Are cytokines or inflammation central to the pathophysiology of cachexia?
- Does treatment of the underlying illness completely resolve cachexia?
- In patients with cancer, does treatment of cachexia increase the opportunities for cancer treatment? By improving outcomes does treatment of cachexia increase the number of chemotherapy options, for example?
- Is the future of cachexia therapy in combination therapy?
- What are appropriate endpoints for regulatory approval of cachexia therapies?
- Can and should the consensus definition of cachexia be further refined?

The causes of cachexia are complex and, at the present time, not completely understood. Consequently, there are no specific criteria for its identification or treatment options. As the treatment of diseases such as cancer, heart failure, COPD, HIV infection, and kidney disease becomes

increasingly effective, the diagnosis and treatment of cachexia associated with these diseases will become important goals to improve morbidity, mortality, and particularly, the quality of life. This has been shown in patients with AIDS where effective treatments have reduced the incidence of cachexia but not fully prevented it.^{35–37} Weight loss remains a powerful predictor of mortality in this condition despite modern treatments.

The consensus panel believes that the field of cachexia research has made significant progress over the last 10–15 years. Our goal is to unify the diagnostic approach to cachexia to promote future research initiatives in all types of cachexia on all levels of intervention. We welcome any suggestion to further improve the definition of cachexia/wasting disease and hope for a broad discussion of our first consensus document.³⁵

Conflict of interest statement

None declared.

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