Review

Diagnosing cachexia

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Practice Points

- Deterioration of nutritional status is frequently observed in the clinical course of acute and chronic diseases, and contributes to worse outcome.
- Disease-associated malnutrition, also defined as cachexia, is characterized not only by weight loss, but by muscle wasting as well.
- In different clinical settings, muscle wasting has been demonstrated to robustly predict complications.
- Many definitions of cachexia exist, yielding to different assessment criteria.
- Despite the lack of a unifying definition of cachexia, involuntary weight loss and increased inflammatory response appear key factors for the diagnosis of cachexia.
- Cachexia is a syndrome with a continuum of signs and symptoms ranging from subtle metabolic disturbances to nutritional devastation.
- Changes in appetite, increased inflammatory response, metabolic disturbances and minimal, if any, weight loss allow the diagnosis of precachexia.
- Direct and affordable measurement of muscle mass is still not available, but muscle functional assessment provides relevant insights into muscle wasting during disease.

SUMMARY Cachexia is a clinically relevant factor, and its presence should be proactively investigated in hospitalized patients and outpatients. Unfortunately, a unifying definition and generally accepted diagnostic criteria do not yet exist, contributing to the skepticism of many doctors toward nutrition diagnosis in patients. However, the key features of cachexia are the presence of weight loss, increased inflammatory response and muscle wasting. It is now also accepted that the cachexia syndrome progresses from the stage of precachexia to overt cachexia

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to refractory cachexia. Direct measurement of muscle mass is still not routinely considered in daily clinical practice, owing to a number of reasons. However, the functional assessment of muscle strength may provide relevant insights into the deterioration of muscle mass during cachexia.

Progressive deterioration of nutritional status is frequently observed in patients suffering from acute and chronic diseases. Nevertheless, the clinical consequences of this specific malnutrition syndrome, also known as disease-associated malnutrition or cachexia, are often overlooked, and therefore not prevented/treated. A potential reason for the lack of awareness among healthcare professionals regarding the relevance of cachexia may lie in the difficulty of recognizing and diagnosing it, due to poor education. In this review, we aim to discuss the current controversies regarding the definition of cachexia, and provide doctors, without specific expertise in the field of nutritional care and therapy, easy tools to identify cachectic patients.

During illness, human metabolism is altered, the severity of impairment being mostly related to the degree of the inflammatory response induced by the underlying disease. Under physiological conditions, carbohydrate, protein and lipid metabolisms adapt to prolonged periods of starvation by triggering a reduction of energy expenditure in order to minimize weight loss [1]. Furthermore, anorexia and/or starvation trigger an adaptive metabolic response that compensates for reduced food intake by favoring the use of adipose tissue as energy source, simultaneously sparing protein stores (i.e., muscle mass)[1]. Consequently, healthy individuals may sustain long periods of minimal food intake without devastation of their nutritional status. A clear example is given by patients with anorexia nervosa, whose functional status is marginally impaired, even after months of quantitatively and qualitatively inadequate food intake and in the presence of significant weight loss [2]. By contrast, during disease, the attendant and unavoidable inflammatory response triggers multisystemic metabolic and behavioral adaptive responses, which are characterized, among other features, by reduced food intake, increased energy expenditure, insulin resistance, increased proteolysis and lipolysis [3]. Also, inflammatory response inhibits the activation of the protective metabolic pathways which preserve body composition during simple starvation, further contributing to progressive deterioration of nutritional status, as reflected by accelerated weight loss, muscle wasting and adipose tissue deprivation [3].

It is interesting to note that disease-associated malnutrition is a syndrome that has been described since the time of Hippocrates. Nevertheless, it has received little attention until very recently. The reasons for the lack of clinical and scientific interest are manifold, and likely include the ignorance of the relevance of body composition and inflammation in determining good or bad health, but also the large prevalence of malnutrition among the population, until the 1950s, which made any weight loss during disease trivial. Another reason could be linked to the specificity of Western culture, which has been influenced by different religions and philosophies. In Western culture in particular, until recently disease has been associated, in the mind of many patients, with sinful behavior. Interestingly, for many religions and philosophies that influenced Western culture, fasting is a strategy to be excused of sins. Therefore, it could be speculated that anorexia and weight loss associated to diseases could have not triggered any clinical reaction by doctors and patients, the latter considering malnutrition a remedy for illness/sin.

From the clinical point of view, disease-associated malnutrition is highly relevant, since it likely represents the most frequent comorbidity observed in acute and chronic patients [4]. It also exerts negative effects on patients' morbidity, mortality and quality of life (QoL) [5]. Therefore, a proactive approach to recognition and treatment of disease-associated malnutrition is clinically meaningful, since it may improve patients' clinical outcome. However, significant benefits can be achieved only when nutritional therapy is started early during the clinical journey of patients, since the pathogenesis of disease-associated malnutrition leads to unstoppable weight loss and functional impairment, and accelerates the metabolic death.

Disease-associated malnutrition & cachexia: different syndromes or different names for the same syndrome?

Malnutrition is a clinically relevant factor, in either healthy or disease states. However, as

previously mentioned, malnutrition deriving from the presence of an underlying disease impacts more severely and more rapidly on patients' clinical outcome. It is therefore appropriate to distinguish weight loss (i.e., the hallmark of malnutrition), deriving from mere chronic reduction of food intake from that deriving from the profound metabolic changes secondary to the presence of an illness, either acute or chronic. Recently, Jensen *et al.* proposed a unifying definition of malnutrition syndromes, and pointed to the presence and severity of the inflammatory response as the discriminatory factor [6]. They suggested that for nutrition diagnosis in adults and in the clinical practice setting, the following nomenclature should be used: 'starvation-related malnutrition', when there is chronic starvation without inflammation; 'chronic disease-related malnutrition', when inflammation is chronic and of mild to moderate degree; and 'acute disease or injury-related malnutrition', when inflammation is acute and of a severe degree [6]. Although this nomenclature is easy, intuitive and etiology-based, some authors believe that a clearer separation between malnutrition from starvation and malnutrition from inflammatory response should be made in order to avoid misunderstanding, particularly among lay people. Therefore, the word 'cachexia' is frequently used to define disease-related malnutrition.

It is important to note that the use of different terminology to define nutritional devastation during disease may also result from the different backgrounds of the health professionals who contributed to these definitions. In particular, experts with a specific background in nutritional care aim to define malnutrition of disease within the general framework of the many malnutrition syndromes (i.e., kwashiorkor, marasmus, protein-energy malnutrition, and so on). Alongside this effort, other professionals from different disciplines, including cardiology, surgery, oncology, among others, are focusing selectively on this syndrome. It is acknowledged that both efforts substantially enhanced the understanding of the key features of cachexia/disease-associated malnutrition and are paving the way to effective therapies. On the other hand, cachexia/disease-associated malnutrition is still not widely recognized by doctors, and competition between definitions may generate more confusion among health professionals than their recognition. In this light, Dechanphunkul *et al.* found that in 117 publications, nutritional status was described diversely, ranging from merely one to all six of the following features: weight loss, body composition, quantity/type of food intake, symptoms impacting oral intake, inflammation and altered metabolism [7]. Methods of assessment of each feature were also inconsistent [7]. It is therefore important that different groups of experts join forces to come up with unifying and globally accepted definitions of the syndrome and its key features.

Cachexia derives from two greek words, which mean 'bad condition', and is generally associated with extreme weight loss and muscle wasting. To provide a uniform understanding of the meaning of the term 'cachexia' across different clinical settings, a consensus has been reached among specialists from different disciplines [8]. The experts agreed that 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. From this definition it is evident that cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism, and is associated with increased morbidity.

Conceptually, the terms 'disease-related malnutrition' and 'cachexia' share similarities, since both are pointing to the relevance of the constellation of symptoms and metabolic disturbances induced by the inflammatory response, and they do not refer to different degrees of weight loss or wasting. Yet, there is no general consensus on whether one should replace the other, but they are used indifferently based on the personal attitude of the health-related professional. This increases confusion among nonspecialist and lay people, and serves to generate skepticism on the relevance of nutrition diagnosis in the clinical setting. In fact, in medicine the equation 'one disease = one term' is of the utmost importance.

Unfortunately, more confusion is generated by the proposal to use specific nomenclatures according to the underlying diseases. Many studies suggest that most of the pathogenic mechanisms underlying nutritional deterioration are

the same across different diseases, and indeed, the terms 'cancer cachexia', 'cardiac cachexia', 'pulmonary cachexia', and so on, are generally accepted. However, the International Society of Renal Nutrition and Metabolism suggested that in patients with chronic kidney disease and acute kidney disease, the term 'protein-energy wasting' should be preferred since in their nomenclature 'cachexia' refers to a severe form of protein-energy wasting that occurs infrequently in kidney disease [9]. Although it is acknowledged that the term 'protein-energy wasting' precisely defines the main characteristic of disease-associated malnutrition, we believe that using a different definition for each of the malnutrition syndromes developing during the clinical journey of different diseases could lead to confusion, particularly among health professionals without a specific knowledge of nutritional care.

A similar evolution of the nomenclature also occurred for cancer cachexia. Aiming to make the definition of cancer cachexia more selective and predictive of clinical outcome, a group of experts defined cancer cachexia as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [10]. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. More importantly, the staging of cancer cachexia has been proposed [10]. Indeed, cancer cachexia is a continuum ranging from subtle metabolic changes to overt nutritional wasting. Therefore, the following stages of cancer cachexia have been proposed: 'precachexia', 'cachexia' and 'refractory cachexia', the latter highlighting the clinical irreversibility of nutritional decline in its most advanced form [10].

It is acknowledged that the continuous development of new definitions of cachexia aims at providing clinicians with powerful tools in order to predict patient outcome. However, it is important to remember that very few papers have tested these operational definitions in the clinical setting. This highlights the need to launch an international and prospective collection of nutrition-related markers in large populations of patients, in order to match this information with clinical data and assess the relevance of the proposed definitions. Initial, but very limited attempts have recently been published. As an example, in a very limited sample of lung cancer patients, it has been shown that the prevalence of precachexia is approximately 20% upon cancer diagnosis, but neither correlation with QoL nor survival could be found [11]. Letilovic and Vrhovac have demonstrated that adding more criteria to the definition of cachexia 'reduces' its prevalence in patients with malignant disease or chronic heart failure [12]. They are indicative of differences in laboratory and clinical features of cachectic patients but do not influence their survival [12]. Similarly, Thoresen *et al.* demonstrated in cancer patients that the prevalence of cachexia ranges from 22 to 55% according to the different assessment criteria [13]. Vigano *et al.* applied the definitions of cancer cachexia stages to 207 patients with advanced non-small-cell lung or gastrointestinal cancers from the Human Cancer Cachexia Database [14]. Patients were therefore categorized as noncachectic, precachectic, cachectic or in refractory cachexia. Then, the relationships between cancer cachexia stages and selected outcomes were tested. The cancer cachexia stages were significantly correlated with patient-centered indicators, including overall symptom burden, QoL, tolerability to chemotherapy, body composition, hospital stay and survival [14]. However, precachectic and cachectic patients behaved similarly in all these outcomes but were significantly different from noncachectic and refractory cachectic patients. More recently, Wallengren *et al.* demonstrated that in cancer patients weight loss, fatigue and markers of systemic inflammation were most strongly and consistently associated with adverse QoL, reduced functional abilities, more symptoms and shorter survival [15]. They also confirmed that the prevalence of cachexia using different definitions varied widely, indicating a need to further explore and validate diagnostic criteria for cancer cachexia.

Diagnosing cachexia

As previously mentioned, cachexia is a clinically relevant factor. Consequently, its presence should be investigated, diagnosed early and treated quickly. However, the lack of a unifying definition and validated assessment criteria make the interest of doctors toward cachexia still suboptimal. However, this should not justify the poor nutritional care patients are receiving worldwide,

since the impact of malnutrition and nutrition risk, as easily assessed by validated screening tools (i.e., MNA® [Nestlé, Switzerland], NRS-2002, MUST, and so on), has been recognized by international agencies, including the Council of Europe, the European Parliament and the Joint Commission International. However, making a step further (i.e., diagnosing cachexia and separating it from not-better-specified malnutrition) may require careful consideration.

According to the different assessment criteria proposed during recent years **(Table 1)**, it may appear difficult to diagnose cachexia using a unique approach. Considering the current lack of large trials testing the predictive role of different criteria, physicians may decide to follow any of the proposed frameworks. However, it seems that a few signs and symptoms play a key role in every framework so far proposed. In particular, involuntary weight loss and inflammatory markers appear to represent the basic requirements for diagnosing cachexia, irrespective of the underlying disease. Considering that human metabolism has developed biochemical pathways to protect body weight even during fasting and starvation, then the clinical relevance of involuntary weight loss as a strong signal of metabolic failure becomes self-evident.

Many studies have already shown that during disease, inflammation, as measured by levels of CRP or proinflammatory cytokines (i.e., TNF, IL-1 and IL-6), and involuntary weight loss is a solid prognostic factor. Therefore, it seems appropriate that these signs should be proactively assessed in every patient in order to diagnose cachexia. In patients with stable body weight or minimal weight loss (e.g., <5% usual body weight), the presence of precachexia should be evaluated by measuring inflammatory markers, assessing changes of eating behavior (e.g., reduced appetite, early satiety, and so on) or metabolic abnormalities (e.g., recent onset insulin resistance) [16].

Considering that all definitions of cachexia refer to muscle wasting, it seems odd that assessment of muscle mass is not considered as the only criteria for diagnosing cachexia. This contradiction reflects the difficulty of measuring muscle mass in a reliable and affordable way in daily practice. Depletion of muscle mass is a solid predictor of outcome [17], but the currently available tools to measure fat-free mass (i.e., bioimpedance analysis, dual-energy x-ray absorptiometry scan, computed tomography) have limitations in terms of reliability, costs and exposure risk. Therefore, their use in daily clinical practice is not implemented. However, we acknowledge that at least during the last decade, muscle mass was not routinely assessed due to the lack of robust and convincing evidence demonstrating its impact on clinical outcome. Now this evidence is available and is shaping the assessment of clinical risk. Therefore, it is expected that in the next few years, body composition analysis will be frequently requested not only by clinical nutritionists, but also by other specialists (e.g., gastroenterologists, intensivists, oncologists, and so on). The increasing interest toward patients' muscularity may also lead to the development of new tools, which increase sensitivity and specificity of the measurements of muscle mass.

A surrogate marker of muscle mass is muscle function. In this light, functional measurement of muscle mass (e.g., handgrip strength, 6-min walking test, chair sit-to-stand test and so on) could be used in daily practice. Although limitations to their use exist, since they require adequate cognitive status of the patients, Norman *et al.* showed that both men and women exhibit a significant stepwise decrease of handgrip strength with increasing weight loss [18].

Conclusion

Cachexia is a clinically relevant factor, and optimization of healthcare provided to hospitalized patients and outpatients should include its early recognition and prompt treatment. A unifying definition of cachexia is not yet available. Nevertheless, nutrition risk screening should be implemented in all clinical settings, as recommended by international agencies. Further to screening, precachexia and cachexia should be proactively investigated by using assessment criteria issued by international scientific societies and panels of experts. Although large clinical trials have not yet assessed the robustness of the different criteria in predicting clinical outcome, it seems that increased inflammatory response, changes in appetite and metabolic abnormalities, in the absence of significant weight loss, are good markers of precachexia when simultaneously present. On the other hand, weight loss and increased inflammatory response are the key factors allowing the diagnosis of cachexia. Recent data underline the importance of

Table 1. Definitions and assessment criteria of cachexia.

Nomenclature	Definition	Assessment criteria	Ref.
Chronic disease-related malnutrition	Malnutrition with chronic mild-to-moderate inflammation	Weight loss Inflammatory markers	[6]
Acute disease or injury-related malnutrition	Malnutrition with acute and severe inflammation	Weight loss Inflammatory markers	[6]
Cachexia	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	Weight loss of at least 5% in 12 months or less in the presence of underlying illness (or BMI <20), plus three of the following criteria: Decreased muscle strength (lowest tertile); Fatigue; Anorexia; Low fat-free mass index; Abnormal biochemistry: Increased inflammatory markers CRP (>5.0 mg/l), IL-6 (>4.0 pg/ml); Anemia (<12 g/dl); Low serum albumin (<3.2 g/dl)	[8]
Protein-energy wasting	Loss of body protein and fuel reserves	Low serum levels of albumin, transthyretin or cholesterol; reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy); reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference)	[9]
Precachexia	Early stage of cachexia	Underlying chronic disease; unintentional weight loss ≤5% (if any) of usual body weight during the last 6 months; chronic or recurrent systemic inflammatory response; anorexia or anorexia-related symptoms	[16]
Cancer cachexia	Multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment	Weight loss >5% over the past 6 months (in absence of simple starvation); or: BMI <20 and any degree of weight loss >2%; or appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2) and any degree of weight loss >2%	[10]
Cancer precachexia	Initial stage of cancer cachexia	Weight loss <5% Anorexia and metabolic change	[10]
Cancer refractory cachexia	Cachexia not responsive to any treatment	Variable degree of cachexia Cancer disease both procatabolic and not responsive to anticancer treatment Low performance score <3 months expected survival	[10]

diagnosing and treating cachexia early in the clinical journey of patients. In particular, Prado *et al.* showed that refractory cachexia develops approximately 90 days before death, whereas before this threshold cancer patients still have anabolic capacities that should be exploited [19]. Direct measurement of muscle mass is still limited in daily clinical practice, but the functional assessment of muscle strength may provide relevant insights into the deterioration of muscle mass during cachexia.

Although the management of cachexia was not intended to be covered by our review, we acknowledge that this is a key issue in the comprehensive approach to cachexia. In particular, it is still not clear which professional should be consulted and should take responsibility for the treatment of cachectic patients. Considering that cachexia is a multifactorial syndrome, it then appears self evident that the effective treatment should include different expertise. In fact, dietary strategies are needed to obtain hyperaminoacidemia during cachexia, which has been shown to promote muscle accretion [20]. Anti-inflammatory therapies should also be included to mitigate anabolic resistance. Physical exercise has been shown to enhance muscle protein synthesis. Finally, psychological support may help

cachectic patients to be compliant to the recommendations received. Therefore, it appears that a multidisciplinary team including doctors, dietitians, nurses, physical therapists, psychologists and pharmacists may better address the patient-centered issues that are associated with the onset of cachexia. We acknowledge that such a 'dream team' may not be easily available in every institution worldwide owing to the costs associated with hiring different professionals. However, we feel that every health professional should recognize that addressing the singularity represented by each patient is the unavoidable first step to prevent/treat cachexia. This means that health professionals should devote more time to listen to patients. After all, when it comes to diseases, doctors are the experts, but when it comes to symptoms, then patients are the experts.

Future perspective

During the last few years, more clinical interest and scientific efforts have focused on cachexia, owing to the growing awareness that it represents a relevant comorbidity for patients suffering from acute and chronic diseases. In the future, the relationship of cachexia with clinical outcome will be strengthened, leading to recognition of muscle mass as a key factor dictating therapy of the underlying disease. A clear example is given by oncology, in which chemotherapy dosing is still based on body mass, rather than muscularity [21]. We therefore believe that tools and equipments to assess body composition will become a standard requirement in hospitals and out-patient clinics. This will lead to a more personalized medicine, increasing effectiveness and reducing costs and complications.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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