Cachexia

Subjects: Pathology
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Cachexia is a multifactorial syndrome characterized by body weight loss, declining muscle mass and function, wasting, and inflammation of adipose tissues accompanied by metabolic disarrangement, anorexia, systemic inflammation, and insulin resistance. Cachexia is associated with several acute and chronic disease states such as cancer, chronic obstructive pulmonary disease (COPD), heart and kidney failure, and acquired and autoimmune diseases and also pharmacological treatments such as chemotherapy.

cachexia syndrome diagnosis

1. Clinical relevance

The clinical relevance of cachexia is shown by its impact on both the prognosis and the efficacy of treatment against the underlying disease as well as survival time and quality of life. Yet, the importance of this syndrome is often overlooked by healthcare professionals. The lack of commonly agreed-upon diagnostic criteria for cachexia, and the poor attention given to the nutritional status of the patients, have made it difficult to establish efficient clinical management of this syndrome, which remains largely obscured by the underlying diseases.

A key aspect of the growing interest in the clinical management of cachexia has been the need for its accurate definition. Although a consensus definition for cachexia has been reached, guidelines for its diagnosis and clinical management are still poorly diffused. Considering that up to 80% of cancer patients develop cachexia, and at least 20% of cancer-related deaths per year [1][2] are directly attributed to this syndrome, there has been a strong need to reach a consensus on the definition of cachexia in order to improve the clinical management of cancer patients.

2. The Evolving Concept of Cachexia

Cachexia is a multifactorial syndrome occurring during both acute and persistent catabolic events such as malnutrition and chronic degenerative diseases. The concept of “chronic degeneration” can create confusion when associated with a complex syndrome like cachexia. By definition, chronic degeneration determines the progressive loss of function or deterioration of a tissue or organ in the absence of a single causing event (e.g., an acute trauma) and is responsible for premature disability, mortality, and morbidity. This picture highlights the clinical relevance of cachexia. Nevertheless, the progression of degeneration may be faster or slower in absolute terms. In healthy aging, for example (without the presence of any disease), these processes are significantly slower and occur significantly later than those observed in degenerative diseases. By contrast, cachexia arising from acute events (i.e., nondegenerative events in the long term), such as trauma, burn, acute infection, or toxicity, can be

reversed by therapy interventions aimed at the primary cause of cachexia, even though the signs of cachexia often last for a long time following the recovery of the patient.

Indeed, cachexia is associated with a plethora of chronic diseases, which, for their nature, can be all considered degenerative diseases, including cancer, organ failure (COPD), heart or kidney failure, infectious (AIDS), autoimmune (rheumatoid arthritis), metabolic (diabetes) diseases, etc. All these conditions share several underlying mechanisms and ultimately have a similar output, i.e., severe muscle wasting. However, the multifactorial origin of cachexia and its multisystem involvement made the study of this syndrome in the context of underlying chronic diseases complicated and, consequently, difficult to develop a definition of cachexia. Therefore, the current definition of cachexia is the result of a prolonged effort and continuous evolution; the major advances toward a definition of cachexia, which would be both accurate at the molecular level and clinically exploitable are summarized in Table 1.

Overall, the efforts to reach an accurate and clinically-sound definition of cachexia are important for several reasons: (1) to heighten the awareness of conditions potentially inducing cachexia; (2) to improve the staging of cachexia, thus helping in the identification of novel diagnostic/prognostic markers; and to (3) speed up the diagnosis of cachexia. Each “new” definition of cachexia presented in Table 1 amended the previous definition, ameliorating and, somehow, replacing it. These guidelines definitely helped to deal with the diagnosis and management of cachexia. An important issue that still awaits clarification is the relationship between cachexia and malnutrition [3]. Indeed, while not all malnourished patients are cachectic, all cachectic patients are invariably malnourished [4].

Table 1. The evolving concept of cachexia. Listed here are the criteria for the diagnosis of malnutrition, precachexia, and cachexia, including its severity with (from left to right): the corresponding reference, the definition of the cachectic status, and highlights of the main diagnostic criteria used. Cachexia was initially distinguished from anorexia or malnutrition, and, over the years, the progressive nature of muscle wasting (and its relevance to survival) has been highlighted. Ultimately, a staging was proposed for the severity of cachexia depending on the initial status of the patients.

	Source	Definition	Criteria
Cachexia	Evans W. J. et al., 2008	Complex metabolic syndrome associated with underlying illness and characterized by the loss of muscle with or without the loss of fat mass	Weight loss > 5% in the past 12 months and underlying chronic disease; or BMI < 20 and 3 out of the next 5 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)
Chronic disease-related vs. acute	Jensen G. L. et al.,	Malnutrition with chronic mild to moderate and severe	Weight loss; inflammatory markers

	Source	Definition	Criteria
disease/injury-related malnutrition	2010	inflammation, respectively	
Precachexia	Muscaritoli M. et al., 2010	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
Cancer precachexia	Fearon K. et al., 2011	Early stage of cancer cachexia	Weight loss < 5%; anorexia and metabolic change
Cancer cachexia	Fearon K. et al., 2011	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 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%
Severity of cancer cachexia	Martin L. et al., 2015	Bivariate analysis to estimate the severity of weight loss (WL) as a function of initial BMI: five degrees of severity are associated with differential median survival	Severity from grade 0 (BMI > 25 Kg/m^2, WL < 2.5%) to grade 4 (BMI < 20 Kg/m^2, WL > 6% or BMI < 22 Kg/m^2, WL > 11% or BMI < 28 Kg/m^2, WL > 15% etc.)

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