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EDITORIAL

Cachexia as a major underestimated and unmet medical need: facts and numbers

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Abstract Cachexia is a serious, however underestimated and underrecognised medical consequence of malignant cancer, chronic heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cystic fibrosis, rheumatoid arthritis, Alzheimer's disease, infectious diseases, and many other chronic illnesses. The prevalence of cachexia is high, ranging from 5% to 15% in CHF or COPD to 60% to 80% in advanced cancer. By population prevalence, the most frequent cachexia subtypes are in order: COPD cachexia, cardiac cachexia (in CHF), cancer cachexia, and CKD cachexia. In industrialized countries (North America, Europe, Japan), the overall prevalence of cachexia (due to any disease) is growing and currently about 1%, i.e., about nine million patients. The relative prevalence of cachexia is somewhat less in Asia, but is a growing problem there as well. In absolute terms, cachexia is, in Asia (due to the larger population), as least as big a problem as in the Western world. Cachexia is also a big medical problem in South America and Africa, but data are scarce. A consensus statement recently proposed to diagnose cachexia in chronic diseases when there is weight loss exceeding 5% within the previous 3–12 months combined with symptoms characteristic for cachexia (e.g., fatigue), loss of skeletal muscle and biochemical abnormalities (e.g., anemia or inflammation). Treatment approaches using anabolics, anti-catabolic therapies, appetite stimulants, and nutritional interventions are under development. A more thorough understanding of the pathophysiology of cachexia development and progression is needed that likely will lead to combination therapies being developed. These efforts are greatly needed as presence of cachexia is always associated with high-mortality and poor-symptom status and dismal quality of life. It is thought that in cancer, more than 30% of patients die due to cachexia and more than 50% of patients with cancer die with cachexia being present. In other chronic illnesses, one can estimate that up to 30% of patients die with some degree of cachexia being present. Mortality rates of patients with cachexia range from 10% to 15% per year (COPD), to 20% to 30% per year (CHF, CKD) to 80% in cancer.

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1 Cachexia over the centuries

Cachexia has been known for centuries. Hippocrates wrote that “the flesh is consumed and becomes water,... the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest, and thighs melt away... The illness is fatal.” [1] The term cachexia has Greek roots, a combination of the words kakós (bad) and hexis (condition or appearance) [2]. It is not exactly clear who suggested to use the term cachexia to describe involuntary weight loss in the context of chronic illness, but the first written documentation of cardiac cachexia, for example, dates back to 1860 when Charles Mauriac, a French physician, described a “commonly observed secondary phenomenon in patients affected with diseases of the heart... a peculiar state of

Table 1 Prevalence of cachexia and definitions used in studies of diseases frequently associated with body wasting

Disease	Classification	Reference	Definitions used	Number of patients	Prevalence of cachexia (%)
Cancer	Advanced head and neck cancer	Lees [17]	Incidence of any weight loss (mean weight loss 6.5 kg~10% of body weight)	n=100	57
	Non-small cell lung cancer	DeWys et al. [18]	Weight loss >5% of body weight at diagnosis	n=3,047	36
	Pancreatic cancer, perioperative	Bachmann et al. [19]	Cachexia: weight loss >10% of the pre-illness stable body weight	n=227	40.5
	Pancreatic cancer	DeWys et al. [18]	Weight loss >5% of body weight at diagnosis	n=3,047	54
	Colorectal cancer	DeWys et al. [18]	Weight loss >5% of body weight at diagnosis	n=3,047	28
Chronic heart failure	Ambulatory stable disease	Anker et al. [20]	Cachexia: weight loss >7.5% over at least 6 months	n=171	16
	Outpatients participating in the SOLVD trials	Anker et al. [20]	Cachexia: weight loss >5% over at least 6 months	n=1,929	42
Chronic kidney disease	Advanced CKD with or without haemodialysis	Mak & Cheung [21]	Malnutrition-inflammation-cachexia syndrome		30–60
Chronic obstructive pulmonary disease (COPD)	Outpatients with moderate to severe COPD	Koehler et al. [22]	Cachexia: weight loss >7.5%	n=103	33
		Vermeeren et al. [23]	Nutritional depletion: BMI≤21 kg/m^2 and/or fat-free mass index≤15 kg/m^2 (women) or≤16 kg/m^2 (men)	n=389	27
		Wilson et al. [24]	Malnutrition: less than 90% of ideal body weight	n=779	35
	Patients admitted for pulmonary rehabilitation	Schols et al. [25]	Malnutrition: less than 90% of ideal body weight	n=255	35
Rheumatoid arthritis		Elkan et al. [26]	Rheumatoid cachexia: fat-free mass index below the 25th percentile and fat mass index above the 50th percentile	n=80	m: 26 f: 18
		Roubenoff et al. [27]	Measurement of body cell mass	n=24	67

cachexia which is... conventionally designated cardiac cachexia" [2]. He was not the only one to acknowledge the importance of body wasting. Herta Müller, winner of the 2009 Nobel Prize for literature, wrote that "once the flesh has disappeared from the body, carrying the bones becomes a burden; it draws you down into the earth [3]".

1.1 Why a new journal?

Given the fact that cachexia has been known for such a long time, why do we think that the time is ripe to publish a new journal, the *Journal of Cachexia, Sarcopenia and Muscle*? Cachexia is a serious, however underestimated and underrecognised medical problem that is observed as a consequence of malignant cancer, chronic heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cystic fibrosis, rheumatoid arthritis, Alzheimer's disease, infectious diseases, and many other chronic illnesses. Death normally ensues when weight loss exceeds 30% [4], and it has been estimated that about 50% of patients with cancer have some degree of cachexia at the time of their death [5]. In starvation, weight loss exceeding 40% of body weight is not compatible with life [6]. Neither do we understand the pathophysiology of cachexia in its entirety, nor do we have approved treatments against involuntary weight loss other than appetite stimulants (http://www.drugs.com/pro/megestrol.html) and recombinant human growth hormone (somatropin; http://www.drugs.com/pro/serostim.html) in AIDS-associated body wasting. We believe that cachexia requires more attention, not only by physicians and other health care professionals, but also by the general public. Indeed, body weight is a dynamic parameter and has a certain rhythm over the lifespan [7], and public opinion is currently more concerned with weight gain than with weight loss. Public awareness in chronic diseases needs to be redirected, and people need to understand that weight gain may be beneficial in certain clinical situations.

1.2 What is cachexia?

An important consideration in understanding and managing cachexia is that many misconceptions exist with regards to weight loss. Laviano and colleagues recently suggested somewhat depressingly that cachexia represents a state in which "all you can eat is yourself" [8]. On the other hand, descriptive terms such as "cachexia", "anorexia", "sarcopenia", "malnutrition" and even "hypercatabolism" are frequently regarded as synonyms by researchers and clinicians [9]. Whilst malnutrition is reversible when adequate amounts of food are provided, cachexia is not treatable by this approach. Indeed, cachectic patients usually present with progressive weight loss along with body composition alterations and disturbed homeostasis of many body systems, particularly of fat tissue and muscle [4, 9, 10]. In fact, loss of fat tissue appears to be similar important in the pathophysiology of cachexia like loss of muscle even though fat, unlike muscle, cannot generate its own thermic energy. Rheumatoid arthritis may be an exeption to the rule of weight loss being the defining feature of cachexia. In rheumatoid arthritis loss of fat-free mass is often accompanied by increased fat mass and therefore stable body weight [11]. A final common pathway of body wasting has not been established as yet, but evidence suggests that activation of neuroendocrine and inflammatory systems, increased lipolysis, lack of appetite and malabsorption all play a role [4, 9, 10]. Overall, an anabolic–catabolic dysbalance exists although the mechanisms of weight loss appear to differ between clinical syndromes: Whilst in cachectic patients with cancer or COPD a reduction in muscle protein synthesis plays a prominent role, in heart failure-associated cardiac cachexia, there is incrased muscle protein breakdown and reduced synthesis [10, 12].

Cachexia has been described in many different chronic illnesses. The prevalence of cachexia is high, ranging from 5% to 15% in advanced CHF or COPD to 60% to 80% in advanced cancer (Table 1). When one calculates the population prevalence of cachexia, it can be estimated that the most frequent cachexia subtypes are in order: COPD cachexia, cardiac (CHF) cachexia, cancer cachexia and CKD cachexia. In industrialized countries (North America, Europe, Japan), the overall prevalence of cachexia (due to any disease) is growing and currently about 1%, i.e., about nine million patients. The relative prevalence of cachexia is somewhat less in Asia, but is a growing problem also in Asian countries and in absolute terms (due to the larger population) as least as big a problem as in the Western world. Data on cachexia in South America and Africa are scarce, but the cachexia problem is big in these continents too. For many of the illnesses in which cachexia may ultimately develop, clinicians do not "automatically" sense an association with involuntary weight loss. Additionally, researchers have used various definitions to describe cachexia (Table 1), which not only yielded difficulties in comparing study results but also uncertainty as to whether or not the diagnosis of cachexia should be made in clinical practice. These unsatisfying circumstances have made the need for a standardized definition of cachexia paramount in recent years [13, 14].

1.3 Defining a frequent clinical problem

Many definitions used in studies of cachexia in different illnesses have focused on weight loss alone, and few acknowledged the importance of body composition or

Table 2 Diagnostic criteria for cachexia

1. Presence of a chronic disease PLUS
2. Loss of body weight≥5% within the previous 12 months or less PLUS
3. Presence of at least three of the following:
Reduced muscle strength
Fatigue
Anorexia
Low fat-free mass index
Abnormal biochemistry
Inflammation
Anemia
Low albumin

Adapted from [16]

temporal components of weight change. In cardiac cachexia, for example, it is necessary to consider the presence of edema, and only non-edematous weight loss can be considered appropriate [15]. Changes in body composition are not easily detectable, and may require even advanced technologies such as dual energy X-ray absorptiometry. This has to be considered when proposing a definition of cachexia that should be easily applicable in clinical settings.

In addition to the above, the definition of cachexia should not only pick up manifest cachexia but also identify patients at risk of developing this syndrome. A consensus meeting was recently held to define cachexia, finally reaching a clinical definition that can be applied in almost any clinical entity. It was eventually published in 2008 [16]. Weight loss is at the forefront of that definition, and it was agreed to diagnose cachexia in chronic diseases when there is weight loss exceeding 5% within the previous 3–12 months combined with symptoms characteristic for cachexia (e.g., fatigue), loss of skeletal muscle, and biochemical abnormalities (e.g., anemia or inflammation) [16]. The criteria together with the full definition of cachexia are given in Table 2. When applying this tool in clinical practice, however, it has to be kept in mind that the new definition has not been evaluated for its clinical usefulness or its value as a prognostic marker. Such studies are under way.

Currently, no specific treatment is available for cachectic patients. Treatment approaches using anabolics, anti-catabolic therapies, appetite stimulants, and nutritional interventions are under development [9]. Indeed, many different approaches have been investigated in clinical studies; however, many of them were hampered by small sample size. A more thorough understanding of the pathophysiology of cachexia development and progression is needed that likely will lead even to combination therapies being developed. These efforts are greatly needed as the presence of cachexia is always associated with a high-mortality and poor-symptom status and dismal quality of life.

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