

Highlights on Cachexia, from the 4th Cachexia Conference Tampa (FL), 6-9 Dec 2007

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Abstract

Cachexia is a syndrome associated with many chronic diseases and is an independent risk factor for mortality. Yet it is only in these last years that cachexia has received increasing attention, as the recently instituted international congress on this topic indicates. Here we review some of the most noteworthy contributions presented at the 4th Cachexia Conference in December 2007. Of particular relevance is the fact that an official definition of cachexia was at last formulated. The definition of cachexia, as well as of its diagnostic criteria, will help both the clinical management of and basic research on this complex, multi-factorial syndrome.

Key Words: Muscle wasting; cytokines; cancer; skeletal muscle pathology

Basic Applied Myology 18 (5): 109-114, 2008

For long a neglected syndrome, cachexia has now gained international attention. Cachexia largely affects patients with chronic diseases, its prevalence ranging from 24% in patients with COPD [37] to 87% in patients with gastric cancer [26].

Cachexia is now acknowledged to be a common and serious complication in many chronic diseases (Table 1), and to be associated with a poor prognosis. This syndrome has been reported to be responsible for at least 20% of cancer deaths [20]. Cachexia also accounts for 15% of the deaths due to sepsis-induced organ dysfunction [14]. We recently reviewed recent discoveries that have cast light upon the molecular mechanisms underlying cachexia [11].

A cachexia conference is held every two years to bring together the growing number of basic researchers and clinicians involved in the study of cachexia. This mini-review highlights some of the contents of the last cachexia conference and discusses what the authors of this review consider to be the main topics.

The definition of cachexia: what is cachexia and what is it not.

A major effort has recently been dedicated to reach a consensus definition of cachexia. The lack of an official, widely accepted definition of cachexia may have, until now, led to its prevalence being underestimated, to misdiagnoses and to conflicting data being reported. Cachexia, also named “Wasting Disease Syndrome” (WDS), has been defined as follows: “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 and growth failure in children. 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” [32].

Table 1. Types of cachexia-associated illness. Several acute or chronic conditions are associated with cachexia. Abbreviations: AIDS, Acquired Immune Deficiency Syndrome; CF, CHF, Chronic heart failure; CKF, Chronic Kidney Failure; COPD, Chronic obstructive Pulmonary Disease; IBD, Inflammatory Bowel Disease; Inf., Infection; RA, Rheumatoid Arthritis.

CANCER	INFECTION	ORGAN FAILURE	AUTOIMMUNE DISEASE	METABOLIC FAILURE	OTHERS
Cancer	AIDS Chronic Inf. Sepsis	CHF COPD Cirrhosis CKF/Nephropathy	RA IBD CF	Thyrototoxicosis Cushing's disease Type I Diabetes	Head injury Burn Transplant

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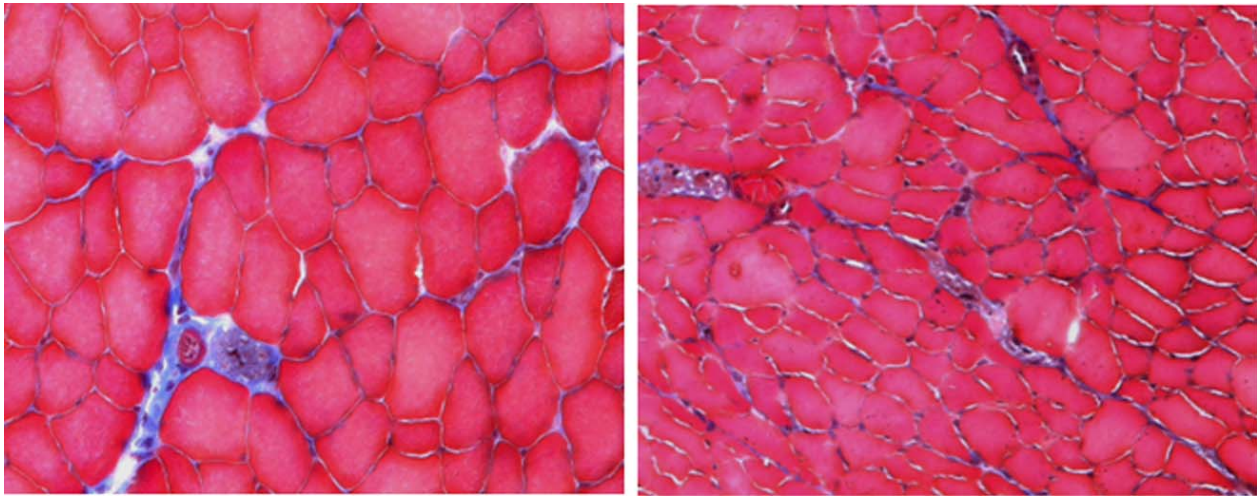


Fig. 1 Masson trichrome staining of cross-sectional cryosections of the Tibialis anterior muscle from control (left panel) and C26 tumor-bearing (right panel) mice. The tumor load induces severe muscle fiber atrophy.

Moreover, the pre-cachexia stage has been defined as muscle loss in the absence of weight loss [32]. Some diagnostic criteria follow the definition of cachexia. To be recognized as cachectic, a patient should experience weight loss of at least 5% in no more than 12 months in the presence of a primary disease and at least three of the following: decreased muscle strength; fatigue; anorexia; low fat-free mass index; abnormal biochemistry (e.g. inflammatory and/or protein degradation markers). Worthy of note is the mandatory presence of an underlying illness to define a wasting status as cachexia. A range of acute and chronic illnesses associated with cachexia are listed in Table 1. These conditions are not necessarily diseases. Indeed, even traumatic events, such as burn injuries, may have a long lasting effect on muscle metabolism. As reported by Wolfe, muscle hyper-metabolism is significantly altered for up to 12 months following burns in humans [39].

Muscle fiber atrophy is a hallmark of cachexia (Figure 1). A great effort is currently being dedicated to define whether and, if so, to what extent cachexia differs from other conditions characterized by muscle atrophy. As pointed out by Evans, cachectic patients are often inactive. This represents a confounding factor that should be taken into account. However, bed rest can be distinguished from cachexia by at least four parameters that are altered in different ways in these two conditions: 1) protein synthesis is downregulated in bed rest and upregulated in cachexia; 2) protein degradation is unaltered in bed rest and upregulated in cachexia; 3) fat mass is increased in bed rest and decreased in cachexia; 4) total energy expenditure is decreased in bed rest and increased in cachexia [17]. When Argiles compared sarcopenia and cachexia, he observed that these two syndromes share similarities such as increased protein degradation, increased levels

of circulating cytokines and apoptosis. However, sarcopenia can be distinguished from cachexia by the fact that i) protein synthesis is decreased in sarcopenia and increased in cachexia, and ii) uncoupling protein (UCP) levels are increased in sarcopenia and decreased in cachexia. UCPs may play an important role in protecting muscle from damage and wasting since they counteract ROS formation. An interesting poster by Bennani-Baiti et al. summarized the biochemical abnormalities underlying muscle wasting in starvation compared with a variety of cachectic conditions, showing that starvation is different from cachexia (as highlighted by decreased resting energy expenditure, minor alterations in glucose levels, etc.). Different cachectic states share similarities, such as being resistant to nutritional support (with the important exception of AIDS-cachexia), hypermetabolism, and protein and lipid breakdown [5].

The heterogeneity and complexity of cachexia from a clinical point of view are mirrored by the wide range of the experimental animal models currently available. Several options are available to study cancer cachexia: a detailed comparison of tumor-bearing rodents reveals that the MCG101 (mouse) is a good model of anorexia, the MAC16 (mouse) is excellent to study metabolic affects, while the Yoshida AH-130 (rat) and the Lewis lung carcinoma (mouse) show massive wasting [6]. We and others have successfully exploited the C26-carcinoma-bearing mouse model (Figure 1) to study the molecular mechanisms underlying cachexia [7, 34,1]. Common disadvantages of these animal models include the fact that none reproduces clinical settings (e.g. polymedicated patients) and many lack human inflammatory responses [6].

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Circulating factors: cytokines and biomarkers

There is overwhelming evidence in humans that increased levels of circulating cytokines are associated with cachexia. The factors most frequently reported to be altered in cachectic patients include IL-1, IL-6, IL-8, IL-10, TNF, IFN- γ , VEGF-A and VEGF-C [22, 23, 16]. These data are in agreement with data from animal models of cachexia [4,10]. Other findings that point to the involvement of cytokines in the pathogenesis of cachexia are: cytokines have a risk predictive value; they trigger muscle wasting; anti-cytokine antibody treatment blocks muscle wasting in both experimental models and patients [33, 12]. It is worth noting that anorexia, bed rest and other muscle wasting conditions do not involve cytokines, which indicates that cytokines are sufficient, though not required to induce muscle wasting. In addition, factors other than cytokines, such as PIF or angiotensin II, also induce muscle wasting.

A major effort is currently being made to find reliable and early markers of cachexia. The search for specific circulating markers of cachexia has so far been unsuccessful – cytokines are characteristic of, though not exclusive to, cachexia. A comparison of cachectic and non-cachectic patients affected by CHF has yielded a complex picture of altered levels of serum markers which, it has been proposed, highlights the cachectic state; this includes increased levels of catabolic factors (epinephrine, norepinephrine, TNF, cortisol), increased or unchanged levels of anabolic factors (GH, IGF-I), and increased markers of protein metabolism (uric acid) [36]. Interestingly, a tissue specific marker of muscle wasting was presented by Mitch. In various conditions of muscle wasting, such as chronic kidney failure in immobilized patients, caspase-3 has been found to degrade actomyosin complexes, thereby producing a characteristic 14 kDa fragment of actin that acts as a marker of muscle wasting in the insoluble fraction of muscle extracts [30, 40].

Cachexia as a multisystemic syndrome: the relevance of tissue-tissue interactions

“Although cachexia is characterized above all by fat and lean body mass wastage, fat and skeletal muscle tissues are unlikely to be the only tissues directly involved in this multifactorial, complex syndrome. The neuroendocrinology of the cachectic response to chronic illness is well known, and has recently been reviewed by Weekers [38]. As far as skeletal muscle wasting is concerned, there appears to be a marked interaction with at least two other tissues, i.e. fat and the intestinal mucosa. Fat tissue is the primary energy store and an important endocrine organ, which in turn affects muscle homeostasis. High fat content (not simply BMI) correlates with a lower risk of mortality and decreased weight loss from lean tissue [15]. While decreased food intake due to anorexia is widely

recognized as being responsible for the negative balance of muscle homeostasis in cachexia, the role of poor absorption of nutrients by the intestine was highlighted for the first time in this conference. The proposed model is a vicious circle in which organ failure induces chronic inflammation, which in turn damages the intestinal barrier. The intestinal mucosa becomes infected by a wide range of bacteria. LPS may further exacerbate the damage to the mucosa, which in turn leads to reduced efficiency in nutrient absorption [27].

We think that these reports highlight a novel, general point of view according to which the issue of tissue homeostasis and function is considered to be a result of cross-tissue interactions and cross-talk between different tissues at the organismal level.

Intracellular pathways regulating cachexia

Cardiomyoplasty Some years ago, the important discovery that an array of genes is actively induced in cachexia indicated that muscle wasting is not due to a general down-regulation of muscle proteins, but rather to a highly selective protein targeting process [1]. Since then, various transcription factors have been identified as targets or triggers involved in the cellular responses that ultimately lead to muscle wasting.

The FoxO subfamily of Fox transcription factors plays a variety of roles in a broad assortment of physiological processes, including cellular differentiation, tumor suppression, metabolism, cell cycle arrest, cell death and protection from stress (reviewed by Arden, [3]). The best poster award was given to the work presented by the group led by Marco Sandri, who showed that FoxO transcription factors are required for the induction of autophagy in skeletal muscle. They identified the substrates of autophagy in mitochondria and presented a model in which the lysosome-mediated reduction in mitochondrial content leads to muscle loss. FoxO3 independently controls two major proteolytic systems involved in cachexia: the ubiquitin-proteasome and the autophagy-lysosome systems [28].

An additional transcription factor that plays a major role in muscle wasting is NF- κ B [8]. The central role of NF- κ B in triggering muscle atrophy has been confirmed in various experimental models, as extensively reported at the meeting. It is noteworthy that NF- κ B inhibition has been shown to counteract cancer cachexia [23], which may be important for future pharmacological treatments [31].

A NF- κ B-independent, FoxO1-dependent mechanism is responsible for cachexia triggered by myostatin [29]. Signaling downstream of myostatin involves CIF, a Zn-finger transcription factor that regulates atrogen-1 expression through FoxO1 [21]. Worthy of mention was a poster with data showing that genetic or pharmacological inhibition of myostatin fails to inhibit muscle wasting in cancer cachexia [25]. This

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finding suggests that myostatin is not involved in mediating cancer-cachexia, though it does mediate muscle wasting in other systems [19].

The characterization of signal transduction downstream of cytokines continues. In particular, signaling pathways downstream of IL-6 receptor activation are reported to require STAT3 in animal models of cancer cachexia. In addition, STAT3 activation mediates muscle wasting.

Therapy for cachexia

Current treatments in human clinical trials aimed at cachexia include the use of growth factors, anabolic agents, appetite stimulants and nutrients, anti-inflammatory therapies and exercise (<http://www.clinicaltrials.gov>).

Stimulating innovative approaches and novel ideas were presented at the conference. Ghrelin has multiple regulatory functions that ultimately lead to food intake and energy balance regulation. Ghrelin antagonists and agonists are now available for clinical experimentation. Ghrelin agonists can be exploited against cachexia: the ghrelin analogue BIM increases food intake and body weight in patients with CHF, cancer and kidney failure [13]. TNF and erythropoietin were presented as the Lucifer and Gabriel of cytokines by Antony Cerami [9]. While erythropoietin-mediated pathways may conceivably be stimulated to counteract the negative effects of TNF on tissue homeostasis, erythropoietin analogs need to be developed to avoid hematopoietic effects and the risk of thrombosis.

One exciting study that holds promise for future applications is the work by Fuster et al., whose aim was to test whether hibernating bear plasma has an antiproteolytic effect on incubated rat skeletal muscle [18]. The rationale for this hypothesis is that, in rodents and humans, inactivity or starvation leads to atrophy of skeletal muscle. By contrast, in overwintering bears, inactivity does not provoke any loss in the number or reduction in the size of skeletal muscle cells. This points to the existence of mechanisms that protect hibernating mammals from muscle wasting. Indeed, incubation of rat skeletal muscle in the presence of hibernating bear plasma reduced by 40% the net proteolytic rate, thereby indicating the existence of a powerful proteolytic inhibitor in the circulation of hibernating bears.

Conclusion

Great advances have been made in recent years in our understanding of the pathophysiology of cachexia. While the results of some phase II clinical trials designed to combat cachexia associated with specific chronic diseases are promising, there is a definite need for further basic and clinical research. There are a number of fruitful directions that such research may take. Skeletal muscle, which is one of the tissues affected most in cachexia, is of considerable relevance

to patients' survival and quality of life. The identification of muscle-specific mechanisms underlying protein and organelle degradation has raised the possibility of a tissue-specific pharmacological intervention, though this has yet to be translated into clinical practice. While skeletal muscle and fat tissue are known to be major targets in cachexia, it is not clear whether and, if so, to what extent other tissues are severely affected by cachexia. In addition, the tissue-tissue interactions involved in the onset of skeletal muscle wasting have not been fully understood either, nor is an adequate nutritional strategy yet available to treat cachexia. Studies on muscle metabolism have found a reduced fat oxidative capacity that resembles that observed in diabetes and obesity, and suggest that patients may benefit from a nutritional intervention, especially if combined with pharmacological treatment [35]. Similarly, how physical activity affects cachectic skeletal muscle homeostasis and function is still far from clear (reviewed in a meta-analysis by Perniconi et al., in this issue). These are some of the major issues that warrant consideration in future research projects and meetings. The next Cachexia conference is to be held in Barcelona in December 2009 (<http://www.cachexia.org/>).

The full text of the abstracts of the 4th Cachexia Conference is available at <http://www.lms-events.com/18/>

Abbreviation

AIDS, Acquired Immune Deficiency Syndrome; BMI, Body Mass Index; CHF, Chronic Heart Failure; CKF, Chronic Kidney Failure; COPD, Chronic Obstructive Pulmonary Disease; GH, Growth Hormone; IBD, Inflammatory Bowel Disease; IGF, Insulin-like Growth Factor; IL, Interleukin; PIF, Proteolysis Inducing Factor; RA, Rheumatoid Arthritis; STAT, Signal Transducers and Activators of Transcription; TNF, Tumor Necrosis Factor; VEGF, Vascular Endothelial Growth Factor

Acknowledgements

The financial support of "Progetti di Ateneo" of Sapienza University of Rome (C26A07ZNSE) and AFM (Pr. # 12688) is gratefully acknowledged. Figure 1 is a courtesy of Dr. Emanuele Berardi.

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