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Cardiac cachexia: A systematic overview

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ABSTRACT

Cardiac cachexia as a terminal stage of chronic heart failure carries a poor prognosis. The definition of this clinical syndrome has been a matter of debate in recent years. This review describes the ongoing discussion about this issue and the complex pathophysiology of cardiac cachexia and chronic heart failure with particular focus on immunological, metabolic, and hormonal aspects at the intracellular and extracellular level. These include regulators such as neuropeptide Y, leptin, melanocortins, ghrelin, growth hormone, and insulin. The regulation of feeding is discussed as are nutritional aspects in the treatment of the disease. The mechanisms of wasting in different body compartments are described. Moreover, we discuss several therapeutic approaches. These include appetite stimulants like megestrol acetate, medroxyprogesterone acetate, and cannabinoids. Other drug classes of interest comprise angiotensin-converting enzyme inhibitors, beta-blockers, anabolic steroids, beta-adrenergic agonists, anti-inflammatory substances, statins, thalidomide, proteasome inhibitors, and pentoxifylline.

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1. Introduction

The treatment of chronic heart failure (CHF) has made significant advances over the last two decades. This applies likewise for the establishment of the diagnosis of this syndrome using different single and multi-biomarker approaches (Cowie et al., 1997; Kempf et al., 2007; von Haehling et al., 2007b). Even more so, our understanding of the disease has developed from the rather simplistic model of mere pump failure to that of a complex disease that affects multiple body systems. Despite this, the clinical perspective remains poor, because about half of the patients with CHF die within 4 years of diagnosis (Remme & Swedberg, 2001). This truly devastating prognosis is comparable to that of some types of cancer (Stewart et al., 2001). Overall, the incidence of CHF is steadily increasing in most European countries and in the United States. Current estimates amount to an incidence of 0.1–0.5% per year, and the numbers are doubling with each decade to reach 3% in those over the age of 75. The prevalence of CHF has been estimated at around 0.3–2.4%, which implies that

5 million people in the United States are affected (American Heart Association, 2005). Heart failure accounts for 970,000 hospitalizations and 12–15 million outpatient office visits in this country per year. This causes health-care associated costs of 28 billion US-dollar.

The situation worsens considerably once cardiac cachexia has been diagnosed. Although the definition of this clinical entity has been subject to debate over years (see below), all researchers have unanimously agreed on the poor prognosis of the cachectic patient. In unselected patients with CHF, mortality rates were as high as 50% in the cachectic subset compared to 17% in the non-cachectic subset at 18 months of follow-up (Anker et al., 1997a,b,c). Cachexia is not a unique feature of CHF, but is also seen in terminal stages of other chronic illnesses, including cancer, sepsis, rheumatoid arthritis, and acquired immunodeficiency syndrome (AIDS).

Cachexia is not only associated with poor outcomes, but also with an unfavourable response to drug treatment and poor quality of life. It has been observed in patients with cancer that survival is impaired already at a weight loss of 5% (Dewys et al., 1980). Weight loss exceeding 30% is incompatible with life (Fearon et al., 1992). It is among the most common misconceptions that one of the underlying causes of cachexia is anorexia, i.e. loss of appetite. Although anorexia is certainly a common feature of the diseases leading to the development of cachexia, this feature alone cannot explain the metabolic changes observed during this perturbation. Importantly, nutritional supplementation cannot reverse the process of losing weight in patients with genuine cachexia, which is possible in patients who suffer from starvation or anorexia. Still, nutritional aspects have to be considered when treating patients with cachexia.

Weight loss in the cachectic patient predominantly affects muscle protein, however, bone and fat tissue are likewise affected later in the course of the disease. The factors that trigger the progression from clinically and body weight stable, ambulatory CHF to cardiac cachexia remain poorly understood. The timelines differ widely between patients. The aim of this review is to provide a broad overview of the current knowledge of cardiac cachexia. This includes the ongoing discussion about how to define cachexia, intracellular and extra-cellular signalling, and potential therapeutic approaches.

2. Definition of cardiac cachexia

Body weight is a dynamic parameter, and it has a certain rhythm over the lifespan (Wallace & Schwartz, 2002). Currently, public opinion is more concerned with weight gain than weight loss, and therefore most of the programs in adults are aiming at the reduction of body size (Dansinger et al., 2007). However, weight loss due to body wasting may reflect serious disease and has to be considered with particular attention. Cachexia (Greek: kakós – bad; hexis – condition) constitutes its terminal phase and develops in advanced stages of various chronic illnesses, e.g. CHF, chronic obstructive pulmonary disease, or cancer. The syndrome of body wasting has been recognized for centuries. A picturesque clinical description of cachexia was provided by Hippocrates already in the ancient Greece: "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." (Doehner & Anker, 2002). This description is still used for didactic purposes whilst its applicability in everyday clinical practice is being challenged. Nowadays, and also in line with evidence based medicine, clear cut definitions are of major importance for identification and management of certain diseases or medical conditions. However, in the field of body wasting and cachexia, the important question of a universal definition is still debated (Springer et al., 2006b; Lainscak et al., 2008; Evans et al., 2008).

Cardiac cachexia as a clinical entity is acknowledged as a complex syndrome, which is associated with poor outcomes (Anker et al., 2004; Morley et al., 2006). No single reason for cachexia exists. Patients usually experience progressive weight loss with body composition alterations and disturbed homeostasis of several body systems. There is evidence for activation of neuroendocrine and inflammatory systems, increased lipolysis, muscle wasting, lack of appetite, and malabsorption whilst the importance of individual pathways and the exact interplay remain unknown (see below) (von Haehling et al., 2007a; Strassburg et al., 2005). Additional confusion is caused by several terms used when describing body wasting. Indeed, descriptive terms such as "cachexia", "anorexia", "sarcopenia", "malnutrition" and even "hypercatabolism", are being (mis)used by researchers and clinicians and are frequently regarded as synonyms. Again, important differences exist and one should be careful how and when to use individual terms. The process of sarcopenia, which is regarded as age associated "normal" muscle wasting (Evans, 1995), may not result in significant weight changes, because loss of muscle and increases in fat mass are frequently balanced. In contrast to cachexia, malnutrition and anorexia are reversible with adequate food intake. Loss of appetite or anorexia causes loss of fat mass rather than muscle tissue. Malnutrition is also associated with body wasting, predominantly of fat tissue. Both anorexia and malnutrition can be cured by adequate nutrition alone, which, however, is insufficient to treat cachexia (Springer et al., 2006b). Lastly, the term hypercatabolism cannot be evaluated during clinical examination and neglects the other side of the coin, the anabolic processes (Springer et al., 2006a).

Several definitions have been used in different studies. Most of them focused on weight loss alone, and only a few acknowledged the importance of body composition or temporal components of weight change. Regarded from a historical point of view, the first reports focused on body fat content and defined a cut-off at a body fat content <15% for men and <22% for women or as the percentage of ideal weight <90% (Carr et al., 1989). In 1994, the loss of body weight was acknowledged and cachexia was considered in patients with loss of ≥10% of lean tissue (Freeman & Roubenoff, 1994). This definition is hampered mainly by the requirement for dual energy X-ray absorptiometry (DEXA), which even today is not usually part of a clinical work-up. In cardiac cachexia, one has to consider the presence of oedema, and only non-oedematous weight loss can be considered appropriate.

In view of the significant prevalence and devastating prognosis once cachexia is present, the authors are proponents for a clinical definition of cachexia rather than relying on complicated tests or devices. The definition should embrace all the elements of evidence-based medicine, should be validated for the prognostic significance but should be feasible for use in clinical practice (Lainscak et al., 2008). Of the reported definitions, the one derived from the SOLVD (Studies of Left Ventricular Dysfunction) database is the most appropriate (Anker et al., 2003a,b,c). In this observational study, a cut-off of non-oedematous weight loss of >6% of total body weight over a period of 6 or more months turned out to be strongest predictor of mortality among cut-offs from 5% to 15%. The strength of this analysis is adoption of two critical issues in cachexia, namely weight loss and its dynamics, frequently neglected in earlier reports. At this stage it is important to add that the severity of cardiac cachexia may not always correlate with classical criteria of disease severity as New York Heart Association (NYHA) functional class, left ventricular ejection fraction, or exercise duration (Anker et al., 1997a). Cardiac cachexia even may not be associated with morphological cardiac changes as seen by magnetic resonance imaging or echocardiography (Florea et al., 2002, 2004).

The current state-of-the art approach to define cardiac cachexia will probably be adopted sometime in the future. It might be necessary to add some laboratory, clinical and functional parameters to be able to identify cachexia and body wasting in an early phase. Ideally, patients at risk for the development of cachexia should be identified as early as possible, however, no effective treatment of manifest cachexia is available yet (Springer et al., 2006a). A recent report of a 3-factor profile in cancer patients (weight loss ≥10%, food intake ≤1500 kcal/day, and C-reactive protein level ≥10 mg/dl) has