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Review article

Cardiac cachexia – Up-to-date 2015

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ABSTRACT

Cachexia is defined as unintended loss of 5% of the original body weight of a patient with edema within 3–12 months in combination with typical symptoms of a chronic disease. Prevalence of cardiac cachexia (CC) in chronic heart failure (CHF) is 5–15%, with an annual mortality rate of 20–30%. The condition involves loss of lean body mass (skeletal muscle), body fat, and, to a lesser extent, also bone tissue. In pathophysiological terms, cachexia is associated with complex alterations in neurohormonal and immunological status, catabolism prevailing over anabolism, and activation of pro-inflammatory cytokines, with the key role played by TNF-α. The pro-inflammatory response is believed to be induced by reduced blood supply to the intestine and intestinal wall edema in the presence of congestion facilitating entry of bacteria and endotoxins into the circulation. Other processes include reduced perfusion of the skeletal muscle, its atrophy, and abnormal myocyte metabolism characterized by depletion of energy-rich substances (loss of ATP, creatine, and glycogen), excess of water and lactate, as well as impaired oxidative metabolism. Research at the level of the "atrophising" muscle cell has focused on the ubiquitin–proteasome system, growth differentiation factor-15, myostatin, and other muscle cell regulatory proteins. Novel biomarkers of CC, anabolism/catabolism, and skeletal muscle status include ghrelin, adiponectin, C-terminal agrin fragment, growth differentiation factor-15, N-terminal propeptide of type III procollagen, myostatin, and D3-creatine estimated using the dilution method. Promising results in the treatment of cachexia have been reported with ghrelin receptor agonists (anamorelin), selective androgen receptor modulators (enobosarm), and some beta-blockers (espindolol); research into myostatin antagonists is under way. Aerobic exercise has been shown to have a beneficial effect. Though recommended, no hard data are currently available to document the value of nutritional support.

Contents

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Introduction

The first to describe cachexia (severe body wasting) was Hippocrates around 400 BC [1]. In a 2008 consensus document, the condition was defined as unintended loss of at least 5% of one's original body weight (free of edema) within 3–12 months characterized by loss of muscle mass with/without fat mass loss. Cachexia is associated with chronic disease and typical symptoms (Fig. 1) [2]. In cardiology, the initial diagnostic criterion is mean body weight prior to the development of chronic heart failure (CHF) [3].

Typically concurring with serious chronic conditions (malignancies, chronic heart failure, chronic obstructive lung disease, chronic renal failure, extensive burns, neurological disorders, and other conditions), cachexia is the result of predominantly catabolic processes. Unlike cachexia, the term sarcopenia refers to loss of muscle mass due to natural reduction of anabolic processes [4]. Global prevalence of cachexia, irrespective of its etiology, is estimated to be about 1%, that is, 9 million people worldwide [5]. The average costs of treating a cachectic patient in the United States have been estimated to be USD 10,000 [6]. The prevalence of cardiac cachexia (CC) is reported to be 5–15% [7–9]. The prognosis of cachectic patients with CHF is very grim, with mortality rates 2–3 times higher compared with non-cachectic CHF patients regardless of their functional class, age, exercise tolerance, and left ventricular ejection fraction (LVEF) [10–12].

Annual mortality rate of cachexia is 20–30% [9]. Although associated with serious sequels for the patient, CC tends to be underdiagnosed and often unrecognized until late stages.

1. Presence of a chronic disease
   +
2. Weight loss ≥ 5% over the preceding 3–12 months
   +
3. Presence of at least 3 of the following symptoms:
   - decreased muscle strength;
   - fatigue;
   - anorexia;
   - loss of lean body mass (skeletal muscle);
   - changes in laboratory values;
   - signs of inflammation;
   - anemia;
   - low albumin levels.

Fig. 1 – Diagnostic criteria for cachexia [2].

The main feature of CC is loss of lean fat mass and body fat [13]. Some authors have shown that body fat loss predicts a grimmer prognosis, with loss of lean body mass resulting in lower quality of life [14–16]. Loss of lean body mass, no matter how eventually harmful, is originally a protective mechanism as reduction of oxygen consumption in soft tissue and circulating fluid volume decreases the demands placed on the failing myocardium [17]. Cardiac cachexia is divided into two types: (1) classical, occurring in patients with severe heart failure and (2) nosocomial in the postoperative state [18].

Nutritional aspects

Weight loss (wasting syndrome) eventually leading to cachexia may develop as a combination of inadequate protein intake, poor enteral nutrient absorption, catabolic processes resulting in excess nitrogen loss, inadequate anabolism, and physical inactivity [19]. While inadequate protein/energy intake per se will only rarely lead to cachexia, combined micronutrient and macronutrient deficiency contributes to disease progression [20,21].

Generally, in healthy individuals, the total energy expenditure (EE) is the sum of resting energy expenditure (REE) and energy expenditure induced by physical activity (PAEE). The body temperature factor in connection with CHF does not play a crucial role and therefore can be omitted in the following considerations.

$$EE = REE + PAEE$$

Compared with healthy subjects, in patients with CHF, the resting energy expenditure is initially increased due to hypermetabolism (REE increase about 10%), being likely the first step toward weight loss [22,23]. Physical activity begins to decrease. Later, once cachexia has developed, resting energy expenditure drops below the value of healthy individuals. Simultaneously, the physical activity is greatly limited. Thus the total daily energy expenditure is reduced by 25% compared to healthy subjects and 20% compared to CHF patients without cachexia (Fig. 2 and Table 1) [24].

Analysis of the 7-day meal plan of non-obese CHF patients (BMI < 25) documented inadequate energy intake. Energy availability (=energy intake minus REE) was lower by 41% compared with that of healthy controls [25]. Another study by the same group further specified these results again confirming total energy expenditure of CHF patients compared with controls (Table 2) [26].

Mention should also be made of the role of micronutrient deficiency in the development of CC. Nine-month micronutrient