Skeletal muscle loss: cachexia, sarcopenia, and inactivity[1–3]

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ABSTRACT

Loss of skeletal muscle mass occurs during aging (sarcopenia), disease (cachexia), or inactivity (atrophy). This article contrasts and compares the metabolic causes of loss of muscle resulting from these conditions. An understanding of the underlying causes of muscle loss is critical for the development of strategies and therapies to preserve muscle mass and function. Loss of skeletal muscle protein results from an imbalance between the rate of muscle protein synthesis and degradation. Cachexia, sarcopenia, and atrophy due to inactivity are characterized by a loss of muscle mass. Each of these conditions results in a metabolic adaptation of increased protein degradation (cachexia), decreased rate of muscle protein synthesis (inactivity), or an alteration in both (sarcopenia). The clinical consequences of bedrest may mimic those of cachexia, including rapid loss of muscle, insulin resistance, and weakness. Prophylaxis against bedrest-induced atrophy includes nutrition support with an emphasis on high-quality protein. Nutritional supplementation alone may not prevent muscle loss secondary to cachexia, but, in combination with the use of an anabolic agent, it may slow or prevent muscle loss. *Am J Clin Nutr* doi: 10.3945/ajcn.2010.28608A.

INTRODUCTION

Cachexia is a metabolic condition that is always associated with an underlying illness and inflammation. It is characterized by loss of skeletal muscle and body weight. Nutritional interventions have shown limited success in preserving fat but not muscle mass. Sarcopenia is the age-associated loss of skeletal muscle and function. Sarcopenia is a life-long process with a complex and multifactorial etiology. The effects of inactivity, and in particular bedrest, may mimic those of cachexia. However, there are important metabolic distinctions with significant nutritional implications.

Cachexia has long been recognized as a condition associated with a number of chronic diseases and acute medical conditions. Cachexia has been defined by Evans et al (1) as "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" (p 795). Although cachexia is associated with both fat and muscle loss, the benefits of preserving skeletal muscle or body fat stores is still unresolved. The most obvious manifestation of cachexia is loss of body mass, and in many chronic conditions this loss of body mass may be rapid. Weight loss is associated with a significant increase in mortality risk (2) in patients with heart failure. Fat tissue wasting (lipolysis) is less well defined but appears to be regularly present in patients with weight loss

associated with malignant cancers (3), chronic heart failure (4), or chronic kidney disease (5). Chronic obstructive pulmonary disease (COPD) is associated with inflammation and muscle wasting (6).

Clinical studies have shown that the preservation of body fatness and skeletal muscle in cachectic patients can decrease mortality risk (2, 7, 8). However, important questions remain in the treatment of cachexia. If the metabolic consequence of cachexia is loss of skeletal muscle, will strategies to conserve muscle in cachectic conditions improve mortality and morbidity? Weight loss and extreme loss of body fat are the most obvious clinical manifestation of cachexia. Do strategies designed to maintain body weight, irrespective of composition of the weight, have a positive influence on outcomes? In addition, as cachexia is associated with an underlying disease, patients are often hospitalized or become extremely inactive as a result of the manifestations of the disease. Is it, therefore, possible to separate the effects of immobilization and inactivity from the metabolic effects of cachexia?

SKELETAL MUSCLE AND CACHEXIA

As noted, muscle wasting is important in the pathophysiology of cachexia and a major cause of fatigue (9) in patients. Accelerated or exaggerated loss of skeletal muscle mass distinguishes cachexia from weight loss that is due solely to reduced energy intake. Several groups of investigators have suggested that actomyosin, actin, and myosin are selectively targeted for degradation in clinical conditions associated with cachexia (10–12). Acharyya et al (10) wrote that "cachectic factors are remarkably selective in targeting myosin heavy chain." In mice with colon-26 tumors, they found that 2 markers of inflammation that are typically elevated with cachexia, tumor necrosis factor-α and interferon-γ, reduce the expression of myosin. They also reported that loss of myosin protein was associated with the ubiquitin-dependent proteosome pathway. These data suggest that myosin is a specific target and that both protein-degradative and synthetic pathways are influenced. Selective targeting of skeletal muscle is at least in part due to the systemic inflammation that frequently accompanies clinical conditions as-

sociated with cachexia. Indeed, Lecker et al (13) concluded that a common transcriptional program is associated with skeletal muscle atrophy in animals that are fasting, or have uremia, cancer, or streptozotocin-induced diabetes. Among the strongly induced genes were many involved in protein degradation, including polyubiquitins, Ub fusion proteins, the Ub ligases atrogin-1/MAFbx (muscle atrophy f box) and MuRF-1 (muscle-specific RING finger-1), multiple but not all subunits of the 20S proteasome and its 19S regulator, and cathepsin L. The common feature of cachexia, loss of muscle mass, suggests that therapies targeting muscle or inflammatory pathways that have a direct effect on skeletal muscle may be effective in reducing the devastating effects of cachexia. It also appears that the rate of muscle protein degradation is up-regulated. Indeed, nuclear transcription factor κB (NF-κB) activation may be an important regulator of skeletal muscle proteasome expression and protein degradation. Inhibitors of NF-κB completely attenuated protein degradation in murine myotubes and the NF-κB inhibitor resveratrol significantly attenuated weight loss and muscle protein degradation in mice bearing the MAC16 tumor (14).

Cachexia is also associated with a reduction in circulating anabolic hormones. Testosterone concentrations are greatly reduced in patients with cachexia, resulting in a down-regulation in the rate of muscle protein synthesis. Although circulating growth hormone and insulin-like growth factor-I (IGF-I) appear to be unchanged (compared with normal concentrations) in patients with heart failure, Hambrecht et al (15) described a resistance of skeletal muscle to the influence of growth hormone, including a 52% reduction in expression of IGF-I and IGF-I receptor.

Loss of body weight, fat, and skeletal muscle has been associated with increased mortality in patients with cachexia. COPD is associated with cachexia. In these patients, loss of appetite (16), decreased body weight, and low testosterone concentration (17), muscle mass, and functional status have been reported. Along with these changes, a large increase in NF-κB activation in skeletal muscle has been documented (18) and an increased rate of whole-body muscle protein breakdown (19) has been observed in underweight (cachectic) patients with COPD. Schols et al (8) examined >400 patients with COPD, and found that skeletal muscle mass was an independent risk for increased mortality and that body fatness presented no associated risk.

Although delivery of nutrition in patients with cachexia may provide energy and amino acids for protein synthesis, in certain cachectic conditions, providing energy and protein maintains weight but not muscle mass. In burn patients, providing continuous enteral feeding to >1.2 × resting metabolic rate increased fat mass with no effect on muscle mass (20). In patients with severe sepsis, delivery of total parenteral nutrition preserved fat mass, with no effects on skeletal muscle mass (21). In these patients, weight loss occurred when delivery of energy was less than total energy expenditure that increased as a result of a substantial increase in basal metabolic rate. Thus, fat mass can be preserved or increased in cachectic patients with appropriate delivery of energy. However, delivery of protein in these patients does not appear to preserve muscle mass.

SARCOPENIA

Reduction in lean body mass, and an accompanying increase in fat mass, are among the most striking and consistent changes associated with the advance of age. Skeletal muscle (22) and bone mass are the principal components of lean body mass to decline with age. Sarcopenia was originally described by Evans and Campbell (23) and was further defined by Evans (24) as age-related loss of muscle mass. Subsequently, a number of authors have defined sarcopenia more specifically as a subgroup of older persons with muscle-mass depletion, usually defined as being 2 SD below the mean muscle mass of younger persons (typically expressed as age 35 y) (25). This loss of muscle results in a decrease in strength, metabolic rate, and aerobic capacity and thus, in functional capacity. Newman et al (26) has shown that muscle function (strength), rather than mass, is associated with mortality risk.

Loss of skeletal muscle with advancing age begins relatively early, and continues until the end of life (22). From 20 to 80 y of age, there is an ≈30% reduction in muscle mass and a decline in cross-sectional area of ≈20% (27). This is due to a decline in both muscle fiber size and number (28). There is no consensus on whether there is a selective loss of specific muscle fiber types. Early cross-sectional studies demonstrated a shift in muscle fiber composition with a higher type I/type II fiber ratio with advancing age (29). Larsson (30) suggested a preferential loss of type II fibers with advancing age, potentially starting in early adulthood. Type II fibers show selective atrophy (with a preservation of type I fiber area) with age (31).

The etiology of sarcopenia is multifactorial and complex. Factors that have been implicated for sarcopenia include decreased physical activity level (32), declining androgen concentrations (33), specific nutritional deficiencies (dietary protein and vitamin D) (34), chronic inflammation (35, 36), insulin resistance (37), and a number of other factors. Importantly, cachexia may also contribute to sarcopenia. The effects of inactivity/sarcopenia compared with those of cachexia are shown in **Table 1**.

DECREASED PHYSICAL ACTIVITY

Decreased physical activity that occurs with aging may contribute to age-related sarcopenia. The relation between skeletal muscle mass and level of physical activity is complex. Reduction in physical activity alters body composition in a number of ways. Muscle mass is decreased while fat mass is increased (38). Hughes et al (39) examined body composition and physical activity in 54 men and 75 women over a 10-y period (age: 60.7 ± 7.8 y at baseline) and showed that higher levels of physical

TABLE 1
Comparison of the metabolic consequences of inactivity/sarcopenia to cachexia

Metabolic condition	Inactivity/ sarcopenia	Cachexia
Muscle protein synthesis	Increased	Increased
Muscle protein degradation	No change	Increased
Muscle mass, strength, and function	Decreased	Decreased
Fat mass	Increased	Decreased
Basal metabolic rate and total energy expenditure	Decreased	Increased
Inflammation	No change	Increased
Insulin resistance	Increased	Increased

activity attenuated the progression of sarcopenia. However, changes in fat-free mass may be attenuated by increased fat mass (40). That is, increasing body fatness, even in elderly people, is associated with increased muscle mass. Loss of bone mass (osteopenia) and sarcopenia are closely linked and are strongly affected by level of physical activity in pre- and post-menopausal women (41) and in older men (42). The rate of muscle loss is accelerated even more when an older person undergoes a period of enforced bedrest due to illness.

From the early studies of Cuthbertson (43) and Deitrick et al (44) to the more recent studies (45, 46), one of the most consistent and reproducible effects of prolonged bedrest is an increase in nitrogen excretion. Although early studies failed to distinguish between an increase in the rate of degradation of protein and a decrease in the rate of protein synthesis, it was well recognized that the source of the increased nitrogen excretion is skeletal muscle. The early studies of bedrest immobilization by Cuthbertson (43) and Deitrick et al (44) showed an increased muscle wasting signified by an increased nitrogen excretion. Studies using orally or intravenously administered isotopically labeled amino acids in space-flown and bed-rested individuals showed alterations in protein synthesis and degradation, with a net decrease in protein balance (47–49). Taken together, these data suggest that changes in protein metabolism during periods of bedrest or immobilization may in part be a result of decreased muscular activity.

Whole-body protein breakdown is not affected by bedrest (47, 50). Shangraw et al (47) examined the effects of 7 d of strict bedrest on indexes of protein metabolism in 6 men (age: 21–28 y). They found that bedrest increased nitrogen excretion and resulted in an average cumulative loss of 6.3 g nitrogen, and magnetic resonance imaging of the back and lower extremities revealed a 1–4% decrease in muscle volume. They observed no increase in whole-body protein breakdown. These data along with no increase in 3-methylhistidine excretion led the authors to conclude that the increased nitrogen and muscle loss resulted from an inhibition of protein synthesis. Stuart et al (49) showed that increasing dietary protein intake attenuates the rate of nitrogen loss in bed-rested subjects. In young subjects, 14 d of bedrest resulted in loss of whole-body nitrogen, with a greater loss during the second week of bedrest. Leg and whole-body lean mass also decreased after bedrest. Fractional protein synthesis decreased by 46%. The authors concluded (45, 46) that the loss of body protein with inactivity was predominantly due to a decrease in muscle protein synthesis. Small amounts of activity may be sufficient to attenuate loss of muscle, such as in loading muscle (increasing force production), when subjects are supine (50). These authors also showed that bedrest had no effect on the rate of muscle protein degradation, and muscle loading increased the rate of protein synthesis. Bedrest significantly lowered daily total energy expenditure (TEE) (51). Gretebeck et al (51) showed that 10 d of bedrest caused a 21% reduction in TEE with a TEE/basal metabolic rate of 1.2. Cachexia associated with sepsis, on the other hand, resulted in a substantial increase in resting energy expenditure and TEE (20).

Elderly people are the most likely to be placed in bed because of illness, trauma, loss of balance, or increasingly because of a greatly diminished functional capacity. Very often, the most frail and medically compromised individual is placed in bed for extremely long periods of time. National statistics show that increasing age is associated with a longer average length of stay in a hospital and patients older than 65 y account for >35% of all hospital discharges (52). A recent study showed that older people respond to an extended period of bedrest with a far greater loss of skeletal muscle mass than do young people (32). In this study, healthy older people (mean age: 67 y) responded to 10 d of bedrest with a loss of ≈1 kg of muscle from the lower extremities. In this study, the fractional synthetic rate (FSR) of skeletal muscle protein, measured over a 24 h period was reduced by 30% after the bed-rest period. This is contrasted to <500 g of muscle lost after 28 d of bedrest in young people (53). This decreased muscle mass due to bedrest in older subjects was associated with large reductions in strength, aerobic capacity, and amount of physical activity. In addition, percentage of time that subjects spent inactive increased (7.6 ± 1.8%, $P = 0.004$) (54). This increased loss of skeletal muscle, strength, and functional capacity in an elderly man or woman as a result of bedrest is very likely to make a frail but ambulatory and independent individual become nonambulatory, with an accompanying loss of functional independence. This group of investigators also showed that a supplement of essential amino acids (15 g provided 3 times daily) greatly attenuated the loss of muscle mass, decrease in FSR, and the large increase in nitrogen excretion (55).

The effects of prolonged inactivity due to illness or hospitalization will result in accelerated loss of skeletal muscle and functional capacity. In a number of ways, these changes mimic those of cachexia. A major feature of cachexia is a rapid loss of skeletal muscle. In addition to inflammation and an increased muscle protein fractional breakdown rate, cachexia is associated with insulin resistance, fatigue, muscle weakness, anemia, and an increase in metabolic rate and total energy expenditure (1). If bedrest results in a large down-regulation in muscle FSR, cachexia increases the fractional breakdown rate with a compensatory increase in muscle FSR. This is due to the stimulatory effect of increasing the intramyocellular free amino acid pool on protein synthesis.

CONCLUSIONS

The precise wording of the consensus definitions of cachexia and sarcopenia are as follows:

Cachexia: "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 (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). 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" (56).

Sarcopenia: "Sarcopenia is the age-associated loss of skeletal muscle mass and function. The causes of sarcopenia are multifactorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. Whereas cachexia may be a component of sarcopenia, the 2 conditions are not the same. The

diagnosis of sarcopenia should be considered in all older patients who present with observed declines in physical function, strength, or overall health. Sarcopenia should specifically be considered in patients who are bedridden, cannot independently rise from a chair, or who have a measured gait speed $<1.0 \text{ m} \cdot \text{s}^{-1}$. Patients who meet this initial criteria should further undergo body composition assessment using dual-energy X-ray absorptiometry with sarcopenia being defined as an appendicular lean/fat mass 2 SD less than that of young adult. A diagnosis of sarcopenia is consistent with a gait speed of <1 m/s and an appendicular lean/fat ratio <2 SD of the average of a young adult" (unpublished data, Sarcopenia Consensus Conference, Rome, Italy, November 2009).

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