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REVIEW

Loss of skeletal muscle mass in aging: Examining the relationship of starvation, sarcopenia and cachexia ☆

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Summary
A loss of body weight or skeletal muscle mass is common in older persons and is a harbinger of poor outcome. Involuntary weight loss can be categorized into three primary etiologies of starvation, sarcopenia, and cachexia. Starvation results in a loss of body fat and non-fat mass due to inadequate intake of protein and energy. Sarcopenia is associated with a reduction in muscle mass and strength occurring with normal aging, associated with a reduction in motor unit number and atrophy of muscle fibers, especially the type IIa fibers. The loss of muscle mass with aging is clinically important because it leads to diminished strength and exercise capacity. Cachexia is widely recognized as severe wasting accompanying disease states such as cancer or immunodeficiency disease, but does not have a universally accepted definition. The key clinical question is whether these changes in body composition are distinct entities or represent an interdependent continuum. The importance of defining the distinction lies in developing a targeted therapeutic approach to skeletal muscle loss and muscle strength in older persons. Failure to distinguish among these causes of skeletal muscle loss often results in frustration over the clinical response to therapeutic interventions.

Contents

☆This paper is based on the presentation given at the III Cachexia Conference (Rome, 8–10 December 2005). During the conference, experts in wasting disease, both basis scientists and clinical researchers, discussed relevant topics in the anorexia-cachexia field, including pathogenic mechanisms, diagnostic tools, current therapeutic strategies and future options. More details can be found at http://www.cachexia.org.

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"... for wasting which represents old age [sarcopenia] and wasting that is secondary to fever [cachexia] and wasting which is called doalgashi [starvation]"

...Maimonides (p. 1135–1204)

Introduction

Involuntary weight loss is common in older persons and is a harbinger of poor outcome. A body mass index (BMI, weight in kilograms divided by height in meters squared) of less than 22 has been associated with a higher 1-year mortality rate and with poorer functional status among older community-dwelling persons.[1] This higher mortality risk begins at a BMI of less than 22 in both men and women older than 65 years. At a BMI of less than 20.5 in men older than 75 years, a 20% higher mortality risk is observed. Similarly, at a BMI of less that 18.5 in women older than 75 years, there is a 40% higher mortality risk.[2] In hospitalized patients, the risk of mortality is directly associated with BMI,[3] even after controlling for recent weight loss, serum albumin, severity of illness score, and patient demographics.[4]

Although there is a strong association between BMI and mortality, the key factor in the mortality risk appears to be recent weight loss. A loss of 10% or more of body weight between age 50 and old age is associated with a 60% increase in mortality compared to persons with stable weight.[5] In institutionalized nursing home residents, a 10% loss of body weight over a 6-month interval strongly predicted mortality in the ensuing 6 months.[6] In residents who lost a least 5% of their body weight, a five- to-ten fold increased risk for death has been reported.[7,8]

A low body weight alone is not associated with an increase in mortality in epidemiological studies, when persons who lost 10% or more of their body weight were excluded.[9] Most of the large epidemiological studies have found little relationship between BMI and mortality after excluding subjects with weight loss. In persons over age 50 years who reported an unintended loss of 10 pounds or more in the year before evaluation, the age-adjusted death rate was much higher compared to persons who lost weight through diet or exercise or who maintained or gained weight.[10] Nearly all of the observational studies have found that any weight loss is associated with increased rather than decreased risk for death.[11–14]

The higher mortality rate associated with weight loss may extend even to voluntary weight loss. Paradoxically, a higher 2-year mortality was found in community living subjects who lost weight by dieting (36%) compared to those who had skeletal muscle loss (28%).[15] This data suggests that even voluntary weight loss by dieting may place older persons at risk.

The importance of weight loss lies not only in increased mortality but also in the fact that it is associated with a decline in functional status.[16] Weight loss of more than 5% in community-dwelling women 60–74 years old is associated with a two-fold increase in risk of disability over time, compared to women who did not lose weight, after adjustment for age, smoking, education, study duration, and health conditions.[17]

A large component of involuntary weight loss in older persons is a loss in fat-free mass. The fact that muscle mass decreases with age has been known for some time. Earlier work demonstrated that the excretion of urinary creatinine, a measure of muscle creatine content and total muscle mass, decreases by nearly 50% between the ages of 20 and 90 years.[18] The age-related loss of muscle mass appears to be fairly consistent, at a rate of approximately 1–2% per year past the age of 50 years.[19] This decline in muscle mass occurs in both sedentary and active aging adults. In contrast, in healthy young adults, no net change occurs in skeletal muscle mass under equilibrium conditions, due to balance in skeletal muscle protein synthesis and degradation.

This age-related reduction in muscle mass and strength is also accompanied by a reduction in motor unit number[20,21] and by atrophy of muscle fibers, especially the type IIa fibers.[22] An associated decline in protein synthesis, particularly in the synthesis of myosin heavy chains, has been observed.[23]

The loss of muscle mass with aging is clinically important because it leads to diminished strength and exercise capacity.[24] Both dynamic, static, and isokinetic muscle strength decreases with age.[25] Maximal oxygen consumption declines with age at a rate of 3–8% per decade beginning at age 30.[26] However, after correction for muscle mass, there is no important decline in VO_2Max with aging, indicating that a change in muscle mass is the significant factor.[27] The result of age-related muscle mass loss produces a decline in function. Up to 65% of older men and women report that they cannot lift ten pounds using their arms.[28]

Causes of skeletal muscle loss

The regulation of body composition is dynamic over time. Minute-to-minute composition is regulated by a person's metabolic state. Day-to-day regulation depends of insulin and glucagon. Month-to-month, hormones such as estrogens and androgens, growth hormone, prolactin, thyroid hormones, catecholamines, and corticosteroids regulate body composition. Immune mediators, such as interleukin-1

Table 1 Causes of weight loss in older persons.

Voluntary	Food restriction increased exercise
Involuntary	Starvation cachexia/anorexia sarcopenia

(IL-1), tumor necrosis factor, and interleukin-2 (IL-2), also can affect body composition through modulation of appetite and food intake and direct effects on skeletal muscle.[29]

Loss of body weight or skeletal muscle mass in older persons can result from voluntary or involuntary causes (see Table 1). Three primary categories of skeletal muscle loss include starvation, sarcopenia, and cachexia. Starvation is a pure protein-energy deficiency, thus forcing a reduction in both fat and fat-free mass. The key physiological sign of starvation is that it is reversed solely by the replenishment of nutrients.[30] Observed age-related decline in muscle mass has been termed sarcopenia. Sarcopenia was coined from the Greek ''sarx,'' or ''flesh,'' and ''penia,'' or ''loss.'' The term was first introduced by Irwin Rosenberg[31] in 1988, and the first Sarcopenia Workshop held by the National Institute on Aging in 1994. Severe wasting of both fat and fat-free mass is termed cachexia. Cachexia is from the Greek ''kak'' or ''cac,'' meaning ''bad,'' and ''hexis,'' or ''condition.'' Cachexia is widely recognized as severe wasting accompanying disease states such as cancer or immunodeficiency disease, but does not have a widely accepted definition.

The key clinical question is whether these descriptions of change in body composition are distinct entities or represent an interdependent continuum. Failure to distinguish among these causes of skeletal muscle loss often results in frustration over the clinical response to therapeutic interventions.

In the most simplistic view, all skeletal muscle loss is seen as resulting from an inadequate intake of nutrients. Under this paradigm, hypercaloric feeding should result in repair of the nutritional deficit and weight gain. However, in most studies of hypercaloric feeding, it has been difficult to produce a significant gain in body weight. This suggests that factors other than pure starvation are operational, since a response to refeeding is the hallmark of starvation. Skeletal muscle loss due to sarcopenia and especially cachexia has been remarkably resistant to nutritional therapy.

Sarcopenia

Sarcopenia is characterized subnormal amounts of skeletal muscle. The ability to easily measure body composition by dual-emission X-ray spectrometry, or bioelectrial impedence has led to intensive research on skeletal muscle mass in aging.[32,33]

Sarcopenia is operationally defined as an appendicular skeletal muscle mass divided by height in meters of more than two standard deviations below the young normal mean. Using this definition, Baumgartner found that 14%, 20%, 27%, and 53% of men aged less than 70, 70–74, 75–80 years, and over 80 years, respectively, met this definition. In women, 25%, 33%, 36%, and 43% in the same age groups had sarcopenia. Cultural effects confound this observation, showing that Hispanic men and women have relatively higher rates of sarcopenia.[34]

Although a decrease of muscle mass is the hallmark of sarcopenia, not all sarcopenic persons have a low body mass. At a BMI cut point of approximately 27, 13.5% of men less than 70 years old and 29% of men older than 80 years were sarcopenic and obese, and 5.3% of women less than 70 years old and 8.4% of women older than 80 years were sarcopenic and obese. Although the decline in muscle mass should be reflected in body weight, an increase in fat mass may obscure the body weight loss. Therefore, a relatively small proportion of sarcopenic persons do not exhibit a loss in body weight.[35]

The decline in skeletal muscle mass is greater in men than women. The mechanisms leading to greater losses of muscle mass with aging in men compared with women are unknown but have been postulated to relate to hormonal factors, including growth hormone, insulin-like growth factor, testosterone,[33] and dehydroepiandrosterone sulfate (DHEAS)[36] A genetic component has also been postulated. Birth weight is associated with sarcopenia in men and women, independently of adult height and weight.[37] Birth weight and prepubertal height gain have been associated with midlife grip strength, independently of later weight and height gain and other determinants.[38] The term sarcopenia has also been used to describe the decrease in skeletal muscle mass accompanying severe dieting, hormonal deficiency syndromes, and extreme inactivity.

The critical component of sarcopenia is its link to impaired functional status. In men with sarcopenia, an approximately four-fold increase in the risk of disability in at least three of the instrumental activities of daily living, a two to three-fold increase in the risk of having a balance disorder, and a two-fold greater likelihood of having to use a cane or walker was observed. In women, an approximately four-fold increase in the risk of disability in at least three of the instrumental activities of daily living has been reported.

In the InChianti study, participants with sarcopenia defined by age and gender T-scores, calf muscle cross-sectional area in both men and women had an almost linear relationship with knee extension, handgrip strength, and lower extremity muscle power.[39] Janssen found a significant association for the lowest tertile of skeletal muscle mass divided by the square of height and the presence of any disability in the study subjects, after adjustment for age, race, health behaviors, comorbidity, and fat mass.[40]

The definition of sarcopenia continues to evolve. The reduction of muscle mass and strength that occurs with aging may be independent of body mass as measured by body weight.[39] The recognition of impairment in muscle strength and functional status with sarcopenia has focused the inclusion of function in the definition. Sarcopenia is therefore defined as the loss of muscle protein mass, function and muscle quality that accompanies advancing age.[41]

Mechanisms of sarcopenia

Various mechanisms have been put forth to explain the change in total muscle mass (see Table 2). Proposed mechanisms generally include a lack of regular physical activity (sedentary lifestyle), alterations in endocrine function ((insulin, testosterone, growth hormone /insulin-like growth factor-1, cortisol), a loss of neuromuscular

Table 2 Potential causes of age-related loss of muscle mass.

Sedentary lifestyle
Reduced levels of and responsiveness to trophic hormones
Growth hormone
Androgens (testosterone)
Insulin-like growth factor 1
Dehydroepiandrosterone sulfate (DHEAS)
Estrogens (estrone, estradiol)
25-hydroxy ergocalciferol (vitamin D)
Decrease or imbalance in protein metabolism
Neurodegenerative process
Muscle fiber atrophy
Increased prevalence of disability
Decreased functional capacity
Decreased basal metabolic rate
Alteration in gene expression

function (denervation or reinnervation), a change in protein metabolism (a deficit between protein synthesis versus degradation), nutrition (primarily amino acids), apoptosis, and disease or trauma. There is also a clear genetic influence.

Insulin acts as an anabolic hormone by inhibiting muscle protein breakdown when stimulated by either amino acids or carbohydrate feeding. Although hormones other than insulin (testosterone, cortisol, and possibly growth hormone via insulin-like growth factor-1) may result in muscle protein turnover with feeding, their physiological importance relative to insulin is minor, except in the presence of deficiencies or excess of these hormones. The effect of insulin on muscle protein synthesis is less clear and somewhat controversial. Muscle protein synthesis increases variably in response to oral or intravenous feeding and a major component of this increase results from stimulation by amino acids. The effect of insulin on muscle protein synthesis is due to stimulation by amino acids.[42] An ongoing debate centers around whether the changes in basal protein synthesis changes with age or is due to this post-prandial effect.

Regardless of the exact mechanism, muscle atrophy occurs when protein breakdown exceeds synthesis. Aging is associated with a lower fractional synthetic rate of mixed muscle protein,[43,44] myofibrillar protein (actin/myosin),[45–47] and mitochondrial proteins. This reduced basal muscle synthetic rate is associated with a reduction in mRNA responsible for myofibrillar protein gene expression.[48]

The observed age-related decrease in muscle cross-sectional area appears to be due to a decrease in size of Type II muscle fibers compared to Type I muscle fibers[49,50] and also from loss of muscle fiber number.[51] In addition to Type II atrophy, fiber type grouping, fiber atrophy, and increased coexpression of myosin heavy chain isoforms in the same fiber has been observed. This process is thought to be consistent with a progressive denervation and reinnervation process secondary to a chronic neuropathic process.[52–54] This age-associated loss of motoneurons may be an important contributing factor to reduced muscle fiber number and muscle mass.[49] It is not known whether physical activity or hormonal or genetic factors potentially influence the extent or rate of motor unit loss.

The result of an imbalance between the rates of muscle protein synthesis and muscle protein breakdown in sarcopenia results in a net negative muscle protein balance. After an overnight fast, the in-vivo rates of mixed muscle (myofibrillar+mitochondrial+sarcoplasmic) and myosin heavy chain protein synthesis were reduced in 60–70- and 78–92-year-old men and women in comparison to 20–32-year-old adults.[55] Both mixed and myofibrillar protein synthetic rates were found to be approximately 30% lower in 60–70-year-old than in men and women under 35 years of age.[44]

The decline in estrogen in women associated with menopause may also have anabolic effects on muscle, possibly as a result of its conversion to testosterone. Estrogen and testosterone may also inhibit the production of IL-1 and IL-6, suggesting that decreased levels of these hormones may have an indirect catabolic effect on muscle.[56]

Cachexia

Although there is no widely accepted definition, cachexia is best viewed as the cytokine-associated wasting of protein and energy stores due to the effects of disease.[57] Systemic inflammation mediated through cell injury or activation of the immune system triggers an acute inflammatory response. Persons with cachexia lose roughly equal amounts of fat and fat-free mass, while maintaining extracellular water and intracellular potassium. The loss of fat-free mass is mainly from the skeletal muscle.

Specific disease states are frequently associated with cachexia. Persons with cachexia due to cancer may deplete up to 80% of their muscle mass.[58] More than 80% of persons with upper gastrointestinal cancer have cachexia at diagnosis and more than 60% of lung cancer patients develop cachexia. HIV/AIDS,[59] rheumatoid arthritis,[60] chronic renal insufficiency and chronic uremia[61] have been associated with cachexia. A list of conditions that have been associated with cachexia are shown in Table 3.

On the other hand, proinflammatory cytokines have been found in apparently healthy older persons as a function of age. Age greater than 70 years is associated with increased circulating plasma levels of interleukin-6 (IL-6) independent of disease states and disorders of aging.[62] The difference in

Table 3 Conditions associated with cachexia.

Infections, e.g. tuberculosis, AIDS
Cancer
Rheumatoid arthritis
Congestive cardiomyopathy
End stage renal disease
Chronic obstructive pulmonary disease
Cystic fibrosis
Crohn's disease
Alcoholic liver disease
Elderly persons without obvious cause

levels of IL-6 in randomly selected older persons compared with strictly selected healthy older persons suggests that inflammatory activity may be a marker of health status.[63]

Increased levels of circulating inflammatory components including tumor necrosis factor-alpha, IL-6, IL-1 receptor antagonist, soluble tumor necrosis factor receptor, C-reactive protein, serum amyloid A, and high neutrophil counts have been observed in older adults. These age-related changes in immune function are associated with progressively increased levels of glucocorticoids and catecholamines and decreased growth and sex hormones, a pattern reminiscent of that seen in chronic stress.

However, the increase in circulating inflammatory parameters in healthy elderly humans is small and far less than levels seen during acute infections. Increased cytokine production with aging is inconsistent, resulting in uncertainty whether changes in cytokine levels are due to age itself or to underlying disease.[64] The observed increase in levels of IL-6 with age may occur as the result of catecholamine hypersecretion and sex-steroid hyposecretion.[65] In addition, numerous other conditions (visceral obesity, smoking, stress, etc.) also trigger IL-6 release.[66] Subclinical infections such as Chlamydia pneumoniae or Helicobacter pylori, or dental infections and asymptomatic bacteriuria have been postulated to play a role in the observed increase in proinflammatory cytokine levels.[67]

Cytokines have a direct negative effect on muscle mass, and increased concentrations of inflammatory markers have been associated with a reduced lean mass.[68–70] This direct effect also has been associated with a decline in muscle strength in older adults. A combination of elevated tumor necrosis factor and IL-6 was found in 31% of white males and 29% of black males, and in 24% of white women and 22% of black women. For each standard deviation increase in tumor necrosis factor, a 1.2–1.3 kg decrease in grip strength was observed, after adjusting for age, clinic site, health status, medications, physical activity, smoking, height, and body fat. For each standard deviation of IL-6, a 1.1–2.4 kg decrease in grip strength was observed.[68]

In women followed for 3 years, the baseline level of IL-6 predicts walking limitations and knee strength, diminished activities of daily living.[71] In a study population of persons at high risk for cardiovascular disease, an inverse relationship was found between fat-adjusted appendicular lean mass and both C-reactive protein and IL-6, and also between appendicular lean mass and C-reactive protein.[72] In a sample of older persons with a mean age 71 years and no mobility or Activities of Daily Living deficit at baseline, levels of IL-6 predicted mortality at 4 years.[73]

Proinflammatory cytokines lead to a decrease in nutrient intake. However, this effect appears to contribute to, but not directly cause, the loss of body mass. Cytokines directly result in feeding suppression and lower intake of nutrients and cachexia is nearly always accompanied by anorexia. IL-1 beta and tumor necrosis factor act on the glucose-sensitive neurons in the ventromedial hypothalamic nucleus (a ''satiety'' site) and the lateral hypothalamic area (a ''hunger'' site).[74] This response is the most common cause of anorexia observed in the acute care setting.[75]

Mechanisms of cachexia

Patients with cachexia experience progressive severe loss of skeletal muscle with relative preservation of visceral protein reserves. The loss of skeletal muscle mass is due to a combination of reduced protein synthesis and increased protein degradation. While reduced protein synthesis plays a role, protein degradation is the major cause of loss of skeletal muscle mass in cachexia.

Lysosomal protease cathespins B probably play a role in early protein breakdown, as they are elevated in skeletal muscle biopsies from patients with lung cancer and minimal weight loss.[76] In more established cachexia, the ubiquitin-proteasome dependent proteolytic pathway is upregulated and is the predominant pathway for protein degradation.[77] The underlying mechanism(s) appears to involve the induction of muscle-specific ubiquitin ligases by catabolic hormones, such as the glucocorticoids, but also the inhibition of anabolic pathways as those controlled by insulin-lide growth factor-1, phosphatidylinositol-3-kinase/Akt, and mammalian target of rapamycin.[78]

Several cytokines, including tumor necrosis factor-alpha, IL-6, IL-1-beta and gamma interferon, reproduce symptoms of cachexia in animal models, although individually they have not be shown to produce full-blown cachexia syndrome.[79] Direct infusion of IL-6 into a mouse muscle decreased myofibrillar protein by 17% at 14 days, suggesting a direct effect on muscle.[80]

In addition to the effect of cytokines on skeletal muscle, cytokines act in the hypothalamus to cause an imbalance between the orexigenic and anorexigenic regulatory pathways. In anorexia-cachexia syndrome, the peripheral signals for an energy deficit reaching the hypothalamus fail to produce a response, which propagates the cachectic process.

This same cachexia process is thought to occur in cardiac and pulmonary conditions, chronic infection, inflammatory myopathies, liver disease, malabsorptive syndromes, and perhaps in normal aging.[81]

Differentiating sarcopenia from cachexia

A decline in muscle mass, muscle strength, and muscle quality is common in older adults. Epidemiological data demonstrates that sarcopenia is the most frequent cause (Fig. 1). Cachexia is the next most common cause of loss of muscle mass, occurring in a number of disease states. In the extreme, starvation can lead to cachexia but is usually not as common, at least in developed countries where access to food is not a factor. Although starvation, cachexia, and sarcopenia can be defined as distinct clinical syndromes, our understanding of the process is complicated by a certain degree of overlap.

Starvation, from whatever cause, will ultimately lead to a loss of muscle mass and strength indistinguishable from that produced by cachexia or sarcopenia. In cachexia, proinflammatory cytokines have a direct effect on muscle mass, leading to a loss of muscle mass indistinguishable from sarcopenia. On the other hand, sarcopenia alone has not been shown to lead to a decrease in appetite or to loss of fat mass similar to that associated with cachexia. Whether

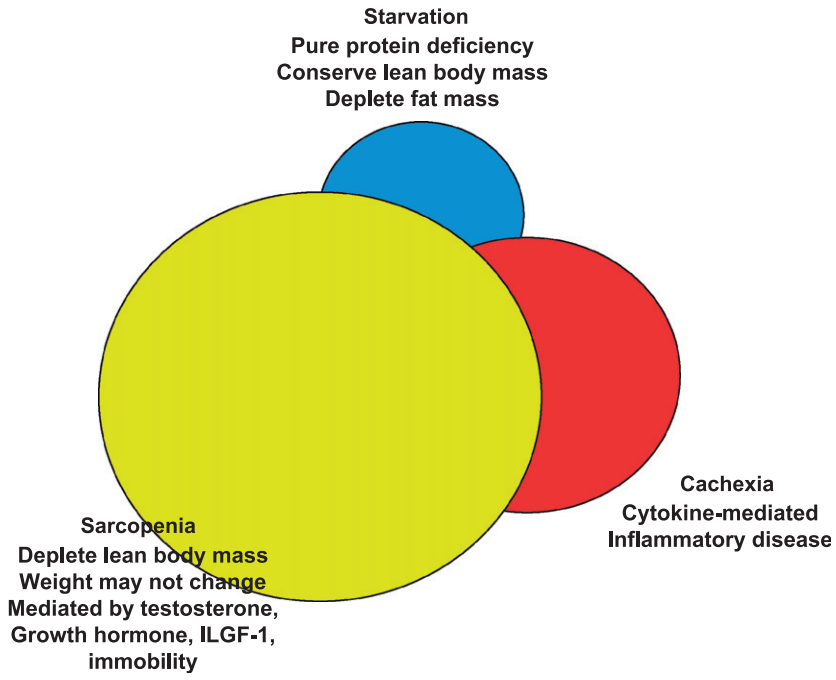

Figure 1 Causes of body weight loss.

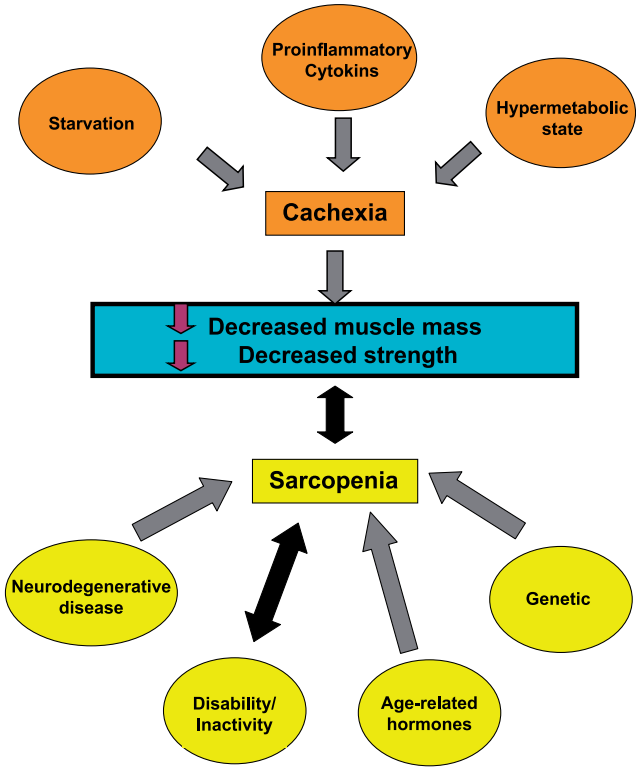

Figure 2 Mechanisms of muscle wasting.

aging itself in some persons, in the absence of any defined inflammatory disease, is associated with elevated proinflammatory cytokines that lead to sarcopenia is not clear.

A summary of the proposed mechanisms for age-related decline in muscle mass and strength is shown in Fig. 2. Sarcopenia is mediated by a number of factors, including an age-related decline in hormonal status, degeneration of muscle innervation, genetic factors, activity levels, or coexisting disability. Cachexia defines a distinct clinical syndrome where the activation of proinflammatory cytokines have a direct effect on muscle metabolism and anorexia. The anorexia resulting from the effect of proinflammatory cytokines can initiate a vicious feedback loop leading to starvation. Starvation resulting from an inability to eat due to mechanical problems, or a hypermetabolic state can directly lead to cachexia. Distinguishing sarcopenia from cachexia can be difficult, since there can be an overlap between hormonal deficiency and disease activation causes. Some guidelines are suggested in Table 4.

Table 4 Distinguishing sarcopenia from cachexia.

	Sarcopenia	Cachexia
Appetite	Not affected	Suppressed in early phase
Food intake	Not affected	Decreased
Body weight	May remain normal	Decreased
Body mass index	Predictive of mortality	Predictive of mortality
Fat-free mass	Decreased	Greater decrease
Serum albumin	Normal	Low in early phase
Serum cholesterol	May remain normal	Low
Cortisol	May remain normal	Increased
Cytokines	Little data	Increased
Inflammatory disease	Not present	Present
Response to refeeding	Resistant	Resistant
Pathway	Does not lead to cachexia	May lead to sarcopenia

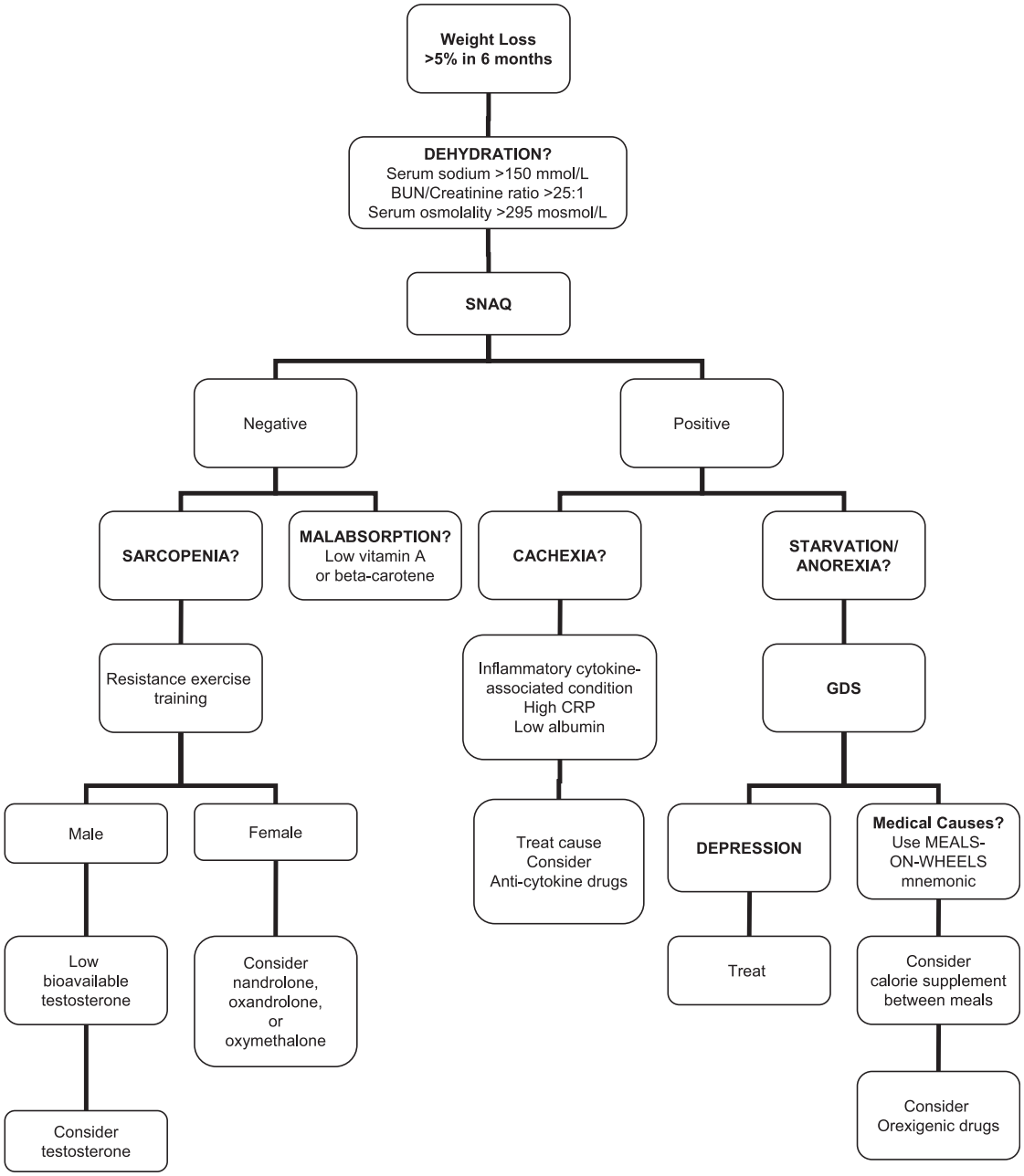

Figure 3 Approach to the management of age-related weight loss. CRP: C-reactive protein; GDS: Geriatric Depression Scale; SNAQ: simplified nutrition assessment questionnaire.

The importance of defining the distinction lies in developing a therapeutic approach to skeletal muscle loss and muscle strength in older persons. In all persons, the first consideration should be an evaluation of nutritional intake. A helpful instrument is the Simplified Appetite Nutritional Questionaire (SNAQ). Based on the assessment of appetite, this instrument accurately predicts weight gain in the ensuing 6 months.[82] Deficits in intake should be corrected whenever possible. However, the failure of appetite associated with cachexia may limit the success of the nutritional interventions. A proposed approach to the management of sarcopenia and cachexia is shown in Fig. 3.

Interventions for sarcopenia

For persons with sarcopenia, the primary intervention should include resistance exercise interventions. Progressive resistance exercise training increases muscle protein mass and strength in men and women. The increase in muscle protein mass is attributable to an acute and chronic increase in muscle protein turnover resulting in the rate of muscle protein synthesis exceeding muscle proteolysis. Coincident with the increase in muscle protein are increases in maximum voluntary muscle strength and muscle fiber hypertrophy.[83] An improvement in muscle mass[84] and strength[85] has been demonstrated with resistance exercise, even in the very old.

Targeting the hormonal changes with aging is an attractive intervention. Serum levels of both testosterone and the adrenal androgens decline with age and there are epidemiological data supporting the relationship between the fall in testosterone and the decline in muscle mass, strength, and functional status.[34,86] Clinical trials have demonstrated that the administration of testosterone in older individuals modestly increased both muscle mass and upper arm strength, as well as bone density and grip strength.[87–89] However, testosterone replacement in elderly hypogonadal men has demonstrated only modest increases in muscle mass and strength. There appears to be a dose-dependent effect, but studies of higher doses have been limited by concern for accelerating prostate cancer.[90]

Dehydroepiandrosterone administration has shown conflicting data regarding improvement in muscle mass and strength. The results are more promising in males than in females.[85,91] Several studies suggest a potential benefit of creatine, especially when combined with exercise to increase stores of phosphocreatine in the muscle and replenish phosphocreatine and adenosine triphosphate, but more studies are needed to confirm these findings.[92,93] No positive effects have been demonstrated for chromium picolinate on body composition and muscle function.[94]

Levels of both growth hormone and insulin-like growth factor-I decline with age and has stimulated interest in their potential therapeutic benefit to counter sarcopenia based on their known anabolic effects.[23] In a study of the chronic administration of growth hormone and insulin-like growth factor-1 to elderly women (aged 66–82 years) anabolic effects of each could be observed in whole body composition and in muscle.[95] In general, studies have shown that growth hormone administration in pharmacological doses increases muscle mass but not strength.[96,97] Unfortunately, growth hormone has many side effects in older adults, including fluid retention, gynecomastia, and orthostatic hypotension. The incidence of adverse effects is high in older persons and no augmentation of muscle strength with resistance training has been demonstrated.[87]

Nutritional supplementation for sarcopenia has been controversial. High protein meals have not been shown to enhance the myofibrillar protein synthesis rate following resistance exercise in 62–75-year-old men and women.[98] Conversely, other studies have shown an increased rate of mixed muscle synthesis with intravenous infusion of amino acids (10% Travasol+glutamine) in healthy 69–73-year-old men,[99] and with oral supplementation with essential amino acids in 69–73-year-old men and women.[100] Whether this translates into improvement in sarcopenia is not known.

A combination of strength training and protein calorie supplementation in very old persons was more likely to increase calories consumed than protein calorie supplementation alone, although this trend did not reach statistical significance.[85]

Bed rest reduces muscle protein synthesis and induces a loss of lean body mass, a model that simulates sarcopenia due to inactivity. Essential amino acids supplementation has been shown to stimulate muscle protein synthesis in healthy volunteers to a greater extent than meals, intact proteins, or similar energy intake. Continued stimulation of muscle anabolism positively affects the preservation of lean body mass and the amelioration of functional decrement throughout inactivity. However, the loss of lean body mass is exacerbated when coupled with the persistent hypercortisolemia that accompanies trauma. Although essential amino acids promote muscle anabolism during hypercortisolemia, it is unlikely that a nutritional intervention alone would be effective in maintaining lean body mass during severe stress or prolonged hypercortisolemia.[101]

A number of amino acids have unique organ-specific functions, especially in patients with sepsis, trauma, and critical illness. Several studies have evaluated the metabolic response of muscle to individual amino acids in healthy athletes. In summary, branched-chain amino acids do not improve endurance performance, glutamine supplements do not prevent the downregulation of the immune system in the period after exercise, and commercial arginine supplements contain too little arginine to increase growth hormone levels and muscle mass. No studies have been performed to evaluate whether tyrosine supplements can improve exercise function.[102]

Nutritional supplementation of glutamate or its precursors (glutamine, ornithine, alpha-ketoglutarate and branched-chain amino acids) may influence muscle glutamate status. However, few specific intervention studies have been conducted to investigate the effect of supplementation on muscle glutamate turnover and related metabolic and functional consequences in either healthy individuals or in patients with acute or chronic diseases.[103] Supplementation of the diet with branched chain amino acids has been shown to increase nitrogen balance in the free amino acid pool, but has not been effective in promoting protein synthesis.[104] More studies are needed to evaluate the impact of a combination of strength training and anabolic hormones and/or strength training and nutritional supplementation on muscle mass.

For persons with sarcopenia, the primary intervention should include resistance exercise interventions. An improvement in muscle mass[84] and strength[85] has been demonstrated with resistance exercise, even in the very old. Targeting the hormonal changes with aging is an attractive intervention. Clinical trials have demonstrated that the administration of testosterone in older individuals increased both muscle mass and upper arm strength.[87–89] However, testosterone replacement in elderly hypogonadal men has demonstrated only modest increases in muscle mass and strength. There appears to be a dose-dependent effect, but studies of higher doses have been limited by concern for accelerating prostate cancer.[90] Administration of growth hormone in pharmacological doses increases muscle mass but not muscle strength.[96] The incidence of adverse effects is high in older persons and no augmentation of muscle strength with resistance training has been demonstrated.[87]

Interventions for cachexia

In contrast to starvation, cachexia is remarkably resistant to hypercaloric feeding. Trials of both enteral and parenteral feeding in cancer cachexia have consistently failed to show any benefit in terms of weight gain, nutritional status, quality of life, or survival.[77] Pharmacological treatment of anorexia with agents that modulate cytokine production may produce weight gain in cachexia states.[105] Steroids and

hormonal agents such as megesterol acetate are currently widely used in the treatment of cachexia and anorexia.[106] They act through multiple pathways, such as increasing neuropeptide-Y levels to increase appetite, and down-regulating pro-inflammatory cytokines. Thalidomide significantly attenuated both total weight loss and loss of lean body mass in patients with cancer and acquired immunodeficiency syndrome.[107] The action is linked to inhibition and degradation of tumor necrosis factor-alpha. Eicosapentaenoic acid can halt weight loss in cancer cachexia and may increase lean body mass at high doses.[108] The effect is postulated to result from its ability to down-regulate pro-inflammatory cytokines and proteolysis-inducing factor. The results of these pharmacological trials suggest that improvement in cachexia results from a common effect of these agents on proinflammatory cytokines.

Conclusion

A therapeutic approach to the loss of skeletal muscle mass and strength in older persons depends on correct classification. The term sarcopenia should be reserved for age-related decline in muscle mass not attributable to the presence of proinflammatory cytokines. Cachexia may be a better term for a decline in muscle mass associated with known inflammatory disease states. While starvation due to protein energy undernutrition is widely regarded as the primary cause of loss of fat and fat-free mass in older persons, a failure to improve with nutritional replacement should trigger a consideration of other causes.

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