Role of Skeletal Muscle in Health

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Skeletal muscle plays a major role in health. Loss of skeletal muscle has been associated with weakness, fatigue, insulin resistance, falls, fear of falling, fractures, frailty, disability and death. All the components of frailty, as shown in Table 1, are related to skeletal muscle function.[1]

Table 1. Components of Frailty: The Cardiovascular Health Study[1]

- The Cardiovascular Health Study enrolled 5317 men and women ≥65 years of age
- Frailty was defined as a clinical syndrome in which ≥3 of the following were present:
  - Unintentional weight loss (10 lb in past year)
  - Exhaustion (self-reported)
  - Weakness (grip strength, lowest 20%)
  - Walking speed (15 feet, slowest 20%)
  - Low physical activity (kcal/week, lowest 20%)

By this definition, nearly 7% of the participants were frail

This article summarizes the causes and outcomes of skeletal muscle loss, as well as current recommended nutritional interventions in the treatment of muscle loss.

Muscle disease related to aging can lead to loss of mass (sarcopenia), loss of strength, loss of power (dynapenia), fatigue, pain, and cramps. We need to recognize, however, that loss of strength and power are not directly related to loss of muscle mass. In particular, we need to recognize that, with age, collagen infiltration into the tendons leads to loss of the angle of pennation (angle formed by pennate muscle fibers with the line of action of the muscle), which results in a decline in the ability to generate power.[2]

Weight loss can be caused by loss of muscle, fat, and/or bone. Whatever the type of loss, multiple studies have shown that weight loss in people older than 60 years of age increases mortality and morbidity, including in patients with diabetes mellitus.[3,4]

One study found that women older than 60 years of age who lost weight, intentionally or unintentionally, had a 2.5 times greater risk for hip fracture than those who had not.[5] Because of the increased morbidity associated with weight loss in older adults, their risk for institutionalization also is increased.

Prevalence of protein energy malnutrition (PEM) also is increased in populations with certain diseases and in certain health care settings. For instance, PEM occurs in 10% to 50% of people with diseases such as renal failure, chronic obstructive pulmonary disease, congestive heart disease, and HIV. Forty percent of people in subacute care are malnourished, as are 5% to 20% of those in nursing homes.[6]

The major causes of muscle wasting are anorexia, sarcopenia (age-associated muscle loss), and cachexia (disease-related muscle loss). Although these conditions all are characterized by loss of muscle, they differ in their impact on several anthropometric and laboratory parameters, as shown in Table 2.

Table 2. Comparison of Three Major Causes of Muscle Wasting

	Anorexia	Sarcopenia	Cachexia
Body mass	––	–	–––
Fat-free mass	–	––	–––
Body fat	–––	0	––
RMR	–	–	++
Physical activity	–	–	–
Food intake	–––	0	––
Proteolysis	–	+	++
Cortisol	+/–	+/–	++
Triglycerides	0	0	++
Cytokines	+/–	+	+++
Anemia	+	0	+++
Insulin resistance	0	0 (+ in sarcopenic obesity)	+

RMR=resting metabolic rate
+ and – symbols indicate the direction and strength of the impact of these conditions on the anthropometric and laboratory parameters listed at left

Anorexia and Aging

Physiologic anorexia of aging can lead to weight loss. Age-related loss of appetite and reduction of food intake are caused by changes in taste and smell, alterations in the rate of filling of the antrum of the stomach, increased levels of the satiating hormone cholecystokinin, and in males, high leptin levels stemming from declining testosterone. In older people, numerous reversible causes of weight loss occur, as shown in the mnemonic device in Table 3.[7] Depression is the most common cause of weight loss in older adults.[8]

Table 3. Causes of Weight Loss

Medications

Emotions (depression)

Alcoholism, anorexia, abuse (elder)

Late life paranoia

Swallowing problems

Oral problems

Nosocomial infections, no money (poverty)

Wandering/dementia

Hyperthyroidism, hypercalcemia, hypoadrenalism

Enteric problems (malabsorption)

Eating problems (eg, tremor)

Low-salt, low-cholesterol diet

Shopping and meal preparation problems, stones (cholecystitis)

Clinicians can screen patients for anorexia with the Simplified Nutritional Appetite Questionnaire (SNAQ), shown in Table 4.[9]

Table 4. Simplified Nutritional Appetite Questionnaire (SNAQ) To Predict Weight Loss in Older People[9]

1. My appetite is
   A. Very poor
   B. Poor
   C. Average
   D. Good
   E. Very good

2. When I eat
   A. I feel full after eating only a few mouthfuls
   B. I feel full after eating about one third of a meal
   C. I feel full after eating over half a meal
   D. I feel full after eating most of the meal
   E. I hardly ever feel full

3. Food tastes
   A. Very bad
   B. Bad
   C. Average
   D. Good
   E. Very good

4. Normally I eat
   A. Less than one meal a day
   B. One meal a day
   C. Two meals a day
   D. Three meals a day
   E. More than 3 meals a day

Instructions: Complete the questionnaire by circling the correct answers and then tally the results based on the following numerical scale:
A=1, B=2, C=3, D=4, E=5

Scoring: If the score is less than 14, the risk of weight loss is significant

Physiologic anorexia of aging puts older adults at high risk for developing PEM when they develop either psychologic or physical disease processes. Screening for anorexia and early nutritional and/or pharmacologic intervention can reduce this risk.

Sarcopenia

Nearly 3.6 million people in the United States have sarcopenia and are at increased risk for physical disability and frailty. In one study of 4504 adults 60 years of age and older, those with severe sarcopenia had a two to three times greater likelihood of functional impairment and disability than those without sarcopenia.[10] People who are obese but who nonetheless are losing muscle mass (sarcopenic obesity) can develop severe disability and have an increased death rate.[11]

Muscle is normally in a balanced state of anabolism and catabolism. While protein synthesis plays an important role in this process, repair of muscle cells requires the constant generation of satellite cells.[12] Satellite cells are small mononucleated myogenic cells found in skeletal muscle fibers. They are normally quiescent, but they proliferate in response to injury and help in repair and maintenance of skeletal muscle.

Nutrition intervention in sarcopenia typically has focused on dietary supplementation with protein and/or specific amino acids. While a total protein intake of 0.8 g/kg/day is normally recommended, the International Cachexia Society recommends an intake of 1-1.5 g/kg/day for older people to prevent sarcopenia. Protein synthesis is best maintained by a mixture of leucine-enriched essential amino acids. These act not only as building blocks for protein synthesis but also activate mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that drives protein synthesis. Essential amino acids act synergistically with exercise to increase muscle strength. Oral amino acids slow muscle loss that occurs with bed rest, reverses sarcopenia, and increases walk speed.

Supplementation with other nutrients such as creatine and vitamin D have shown some positive effects in people with sarcopenia. Creatine supplementation is shown to increase muscle power, if not mass, in older people, especially when combined with exercise. People with 25(OH) vitamin D levels below 30 ng/mL show declines in muscle strength and increases in disability, falls, hip fracture, and mortality.[13] Levels of 25(OH) vitamin D decline with aging. Vitamin D supplementation can decrease or reverse these changes.

Hormonal treatments also have been used with sarcopenic men. Testosterone replacement increases muscle mass, strength, and function in hypogonadal males. Testosterone in combination with a protein supplement decreased hospitalizations in people living in assisted living.[14] Selective androgen receptor molecules are being developed as potent anabolic steroids for use in treating sarcopenia.

At present, treatment of sarcopenia and frailty consists of supplementation with essential amino acids and creatine, together with resistance exercise. Some studies show that giving essential amino acid and/or calorie supplements between meals results in optimum efficacy.

Cachexia

Cachexia occurs in 10% to 35% of chronically ill older people.[15-17] The International Cachexia Society has defined cachexia as "a complex metabolic syndrome associated with underlying illness and accompanied by loss of muscle with or without [loss of] fat mass. The prominent clinical feature of cachexia is weight loss."[18] Table 5 describes the diagnostic criteria for cachexia.

Table 5. Diagnostic Criteria for Cachexia

- Weight loss (nonedema) of at least 5% in 12 months or less
- BMI (<20 kg/m^2) in the presence of underlying illness
- Plus three of the following:
  - Decreased muscle strength
  - Fatigue
  - Anorexia
  - Low fat-free mass index
  - Abnormal biochemistry
    - Elevated inflammatory markers (eg, CRP, TNF, IL-6)
    - Anemia (<12 g/dL)
    - Low serum albumin (<32 g/L)

BMI=body mass index, CRP=C reactive protein, TNF=tumor necrosis factor, IL-6=interleukin-6

The central pathophysiologic factors in cachexia are cytokines such as tumor necrosis factor alpha, interleukin-1, and interleukin-6.

Some evidence indicates that a balanced calorie supplement improves outcomes in critically ill patients, older hospitalized patients, patients with hip fracture, and those with liver disease. Thus, it is strongly recommended that people with cachexia receive a balanced calorie supplement of 300–600 kcal between meals, given preferably by the enteral route. People with cachexia should receive between 1.5–2.0 g/kg/day of protein. On admission to a hospital, patients with cachexia should receive 50,000 IU of vitamin D.

Omega-3 fatty acids decrease death and hospitalization in cardiac-failure patients and thus, all heart-failure patients should receive them.[19] Omega-3 fatty acids also have positive outcomes and minimal side effects in subgroups with cancer.

Conclusion

Muscle plays a key role in health. The three major causes of muscle wasting—anorexia, sarcopenia, and cachexia—are compared in Table 2. At present, treatment of muscle loss includes resistance exercise, protein supplements (leucine-enriched essential amino acids and creatine) between meals, and vitamin D supplementation (1000-2000 IU/day). Emerging evidence indicates that anabolic steroids also may enhance muscle power. Improving muscle function reverses frailty, increases walking speed, and decreases disability.

References

1. Fried L, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M134-M135.
2. Narici MV, Maffulli N, Maganaris CN: Ageing of human muscles and tendons. *Disabil Rehabil* 2008;30:1548-1554.
3. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al: Risk factor paradox in wasting diseases. *Curr Opin Clin Nutr Metab Care* 2007;10:433-442.
4. Morley JE: Is weight loss harmful to older men? *Aging Male* 2006;9:135-137.
5. Ensrud KE, Ewing SK, Stone KL, et al: Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc* 2003; 51:1740-1747.

6. Thomas DR, Zdrodowski CD, Wilson MM, et al: A prospective, randomized clinical study of adjunctive peripheral parenteral nutrition in adult subacute care patients. *J Nutr Health Aging* 2005;9:321-325.
7. Morley JE, Silver AJ: Nutritional issues in nursing home care. *Ann Intern Med* 1995;123:850-859.
8. Morley JE: Weight loss in the nursing home. *J Am Med Dir Assoc* 2007; 8:201-204.
9. Wilson MM, Thomas DR, Rubenstein LZ, et al: Appetite assessment: Simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr* 2005;82:1074-1081.
10. Janssen I, Heymsfield SB, Ross R: Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;50:889-896.
11. Baumgartner RN, Wayne SJ, Waters DL, et al: Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;12:1995-2004.
12. Morley JE: Weight loss in older persons: New therapeutic approaches. *Curr Pharm Des* 2007;13:3637-3647.
13. Brose A, Parise G, Tarnopolsky MA: Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol A Biol Sci Med Sci* 2003;58:11-19.
14. Chapman IM, Visvanathan R, Hammand AJ, et al: Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. *Am J Clin Nutr* 2009;89:880-889.
15. Yeh SS, Blackwood K, Schuster MW: The cytokine basis of cachexia and its treatment: Are they ready for prime time? *J Am Med Dir Assoc* 2008;9:219-236.
16. Morley JE, Anker SD, Evans WJ: Cachexia and aging: An update based on the Fourth International Cachexia Meeting. *J Nutr Health Aging* 2009;13:47-55.
17. Morley JE, Thomas DR, Wilson MM: Cachexia: Pathophysiology and clinical relevance. *Am J Clin Nutr* 2006;83:735-743.
18. Evans WJ, Morley JE, Argilés J, et al: Cachexia: A new definition. *Clin Nutr* 2008;27:793-799.
19. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomized, double-blind, placebo-controlled trial. *Lancet* 2008; 372:1223-1230.