The 110th Abbott Nutrition Research Conference: Selected Summaries

June 23–25, 2009
Columbus, Ohio

The Role of Nutrition in the Accretion, Retention, and Recovery of Lean Body Mass

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Welcome

We are pleased to provide you with Selected Summaries from the Proceedings of the 110th Abbott Nutrition Research Conference, entitled “The Role of Nutrition in the Accretion, Retention, and Recovery of Lean Body Mass.”

The 110th Abbott Nutrition Research Conference is one of a series of conferences designed to connect the latest in science and research with the practice of clinical nutrition. We strongly believe that advancing therapeutic nutrition into clinical practice will play a vital role in the future of healthcare.

The subject of the 110th conference was the impact of nutrition on lean body mass and overall health. The purpose of this conference was to explore the underlying mechanisms controlling muscle quality and quantity that could be affected by nutrition. This publication highlights 4 of the 16 presentations, which focused on the clinical consequences of loss of skeletal muscle mass due to sarcopenia, disuse, and the effects of metabolic stress brought on by acute and chronic disease. These topics and others will be addressed in detail in the full conference report, which will be available in 2010. We hope you find these summaries insightful and that they inspire changes in the way you view the role of nutrition in skeletal muscle health.

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The Role of Nutrition in the Accretion, Retention, and Recovery of Lean Body Mass

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October 2009

Abbott Nutrition
Columbus, Ohio 43215
Division of Abbott Laboratories, USA

The Role of Nutrition in the Accretion, Retention, and Recovery of Lean Body Mass

The 110th Abbott Nutrition Research Conference was held in Columbus, Ohio, on June 23–25, 2009. This Report contains summaries of presentations given by the following contributors:

Keynote Address

Important Role of Skeletal Muscle in Overall Health

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Presentation Summaries

Lean Body Mass Loss With Age

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Nutrition, Muscle Mass, and Muscular Performance in Middle Age and Beyond

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Measurement of Lean Body Mass Using CT Scans

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Contents

Acronyms and Abbreviations

BMI . . . . . body mass index
CRP . . . . . C reactive protein
CT . . . . . computed tomography
EAAs . . . . . essential amino acids
HMB . . . . . beta-hydroxy-beta-methylbutyrate
IL-6 . . . . . interleukin-6
LBM . . . . . lean body mass
MRI . . . . . magnetic resonance imaging
mTOR . . . . . mammalian target of rapamycin
NFκB . . . . . nuclear factor κB
PEM . . . . . protein-energy malnutrition
RDA . . . . . recommended dietary allowance
RMR . . . . . resting metabolic rate
SNAQ . . . . . Simplified Nutritional Appetite Questionnaire
TNF . . . . . tumor necrosis factor

Role of Skeletal Muscle in Health

John E. Morley, MB, BCh

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.

Lean Body Mass Loss With Age

Douglas Paddon-Jones, PhD

Sarcopenia is an age-related, multifactorial process characterized by the progressive loss of lean tissue mass. The onset of sarcopenia is insidious, but its progression may be accelerated by physical inactivity and poor nutrition. Research continues to focus on the mechanisms contributing to sarcopenia, including changes in protein metabolism and cell signaling, voluntary or imposed reductions in physical activity, malnutrition, and reduced anabolic efficiency to protein ingestion.

Elderly individuals are at increased risk of becoming physically incapacitated or placed on bed rest for an extended period. The loss of lean body mass is dramatically increased during inactivity and is driven by a chronic imbalance between muscle protein synthesis and breakdown and facilitated by decreased activation of nutrient signaling pathway.[1-3] In recent studies examining changes in protein synthesis and muscle mass in healthy adults subjected to bed rest, older subjects experienced an approximate three-fold greater loss of lean leg muscle mass compared to a cohort of younger individuals confined to bed for 28 days (Figs 1 and 2).[2,4]

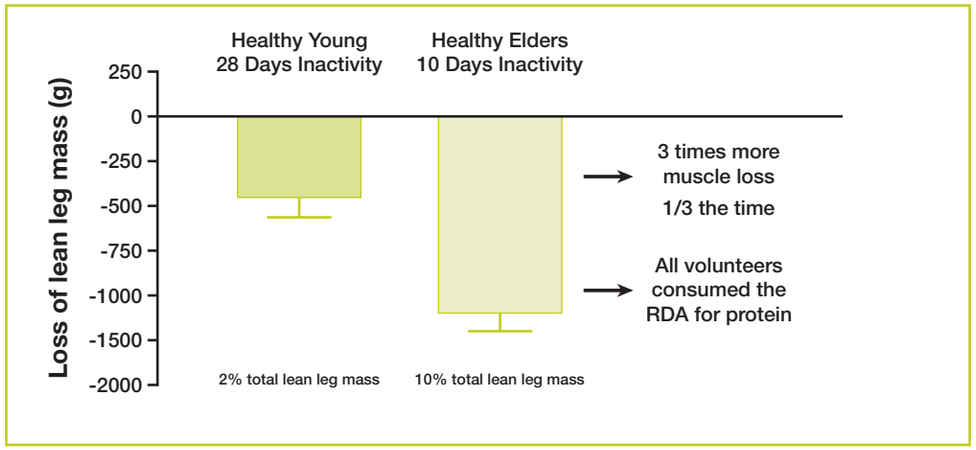

Fig 1. Inactivity and aging muscle. After 10 days of inactivity, older healthy subjects experienced an approximately three-fold greater loss of lean leg muscle mass than a cohort of younger individuals confined to bed for 28 days.[2,4] (1000 g=2.2 lb muscle loss)

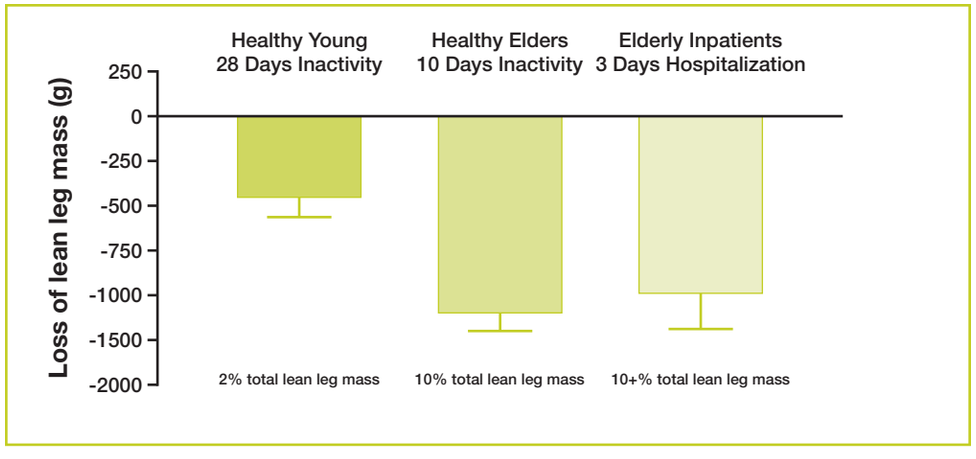

Fig 2. Muscle loss in hospitalized elders. After 3 days of hospitalization, elderly inpatients lost approximately the same amount of lean leg muscle mass as healthy older subjects experienced in 10 days of inactivity—approximately three-fold greater loss of lean leg muscle mass than a younger cohort confined to bed for 28 days.[2,4]

General consensus exists that a moderate-to-large serving of protein or amino acids increases muscle protein synthesis similarly in both young and elderly.[4-12] Unlike earlier *proof of concept* studies using free-form amino acid supplements, several recent studies have adopted a more practical approach and sought to examine the ability of protein-rich foods (eg, milk and beef) to stimulate protein anabolism. These studies are important as they more closely reflect responses to actual dietary practices and provide information on how meal choices may influence accrual of muscle mass and ultimately functional capacity. In one study directly comparing young and elderly, Symons et al[13] reported that a moderate 113 g (≈4 oz) serving of an intact protein (ie, lean beef) contains sufficient essential amino acids (EAAs) (30 g total; ≈12 g EAAs) to increase mixed-muscle protein synthesis by 50% in both young and elderly men and women (Fig 3).

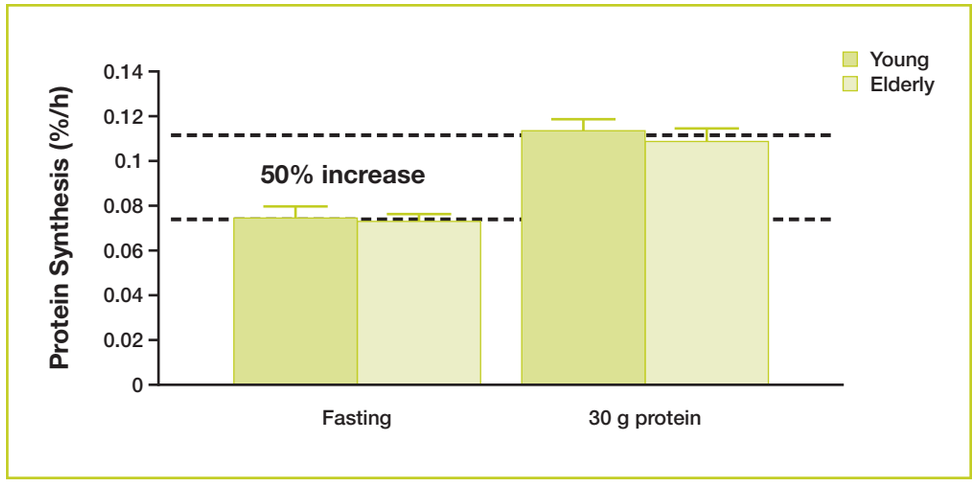

Fig 3. Aging does not impair the ability to increase muscle protein synthesis following ingestion of 113 g of lean beef (30 g protein). h=hour

The adequacy of the recommended dietary allowance (RDA) for protein has recently been the subject of renewed debate.[14-19] The current recommendation for protein intake for adults is 0.8 g/kg^{-1}/day^{-1}. While a modest increase in protein intake beyond 0.8 g/kg^{-1}/day^{-1} is likely to be beneficial for many elders, there is a greater need to specifically examine the dose and distribution of protein across each meal. For a 75 kg individual, the RDA represents 60 g protein/day, or if distributed evenly across three meals, 20 g protein/meal. A 20-g serving of most protein contains 5–8 g of EAAs, which are primarily responsible for stimulating muscle protein synthesis.[10] This is important because aging appears to be associated with an inability of skeletal muscle to respond to low doses of protein (<20 g) or EAAs (<8 g), whereas higher doses (protein >25 g; EAAs 10–15 g) are capable of stimulating muscle protein synthesis in older adults to a similar extent as in the young (Fig 4).[7,20]

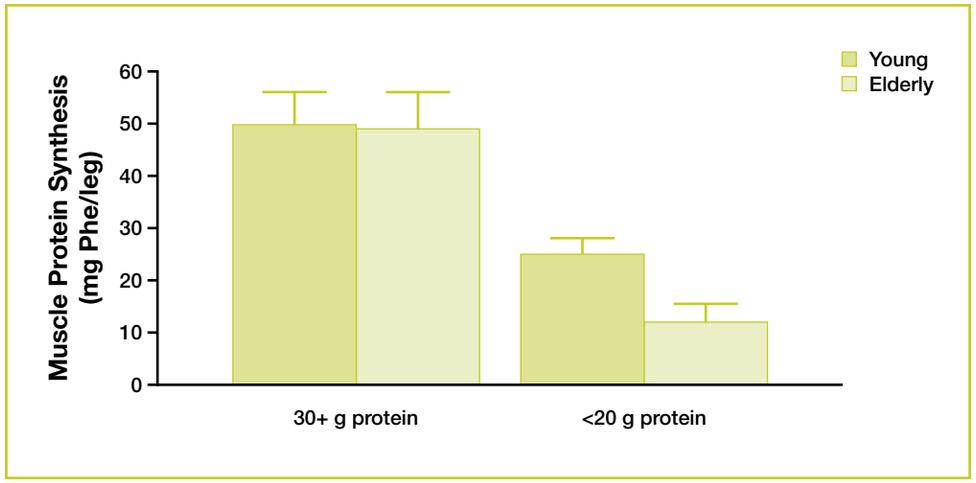

Fig 4. Older adults exhibit a blunted anabolic response to a lower "subthreshold" dose of amino acids or protein measured by the uptake of phenylalanine (mg Phe) per leg (adapted from Katsanos et al[20]).

To examine the effect of protein dose on muscle protein synthesis using a high-quality, protein-rich food, we demonstrated that a large single 340-g (≈12 oz) serving of lean beef (90 g protein) does not elicit a greater anabolic response in healthy young and elderly people than a serving one third the size.[21] This suggests that, despite the additional protein and energy content, ingestion of more than 30 g of protein in a single meal may be an energetically inefficient means of stimulating muscle protein synthesis. If we accept that 25–30 g of high-quality protein (≈10 g EAAs) are necessary to maximally stimulate skeletal muscle protein synthesis, then it seems reasonable to suggest that ingestion of this amount of high-quality protein at each meal could be a useful strategy to maintain muscle mass in the elderly (Fig 5).

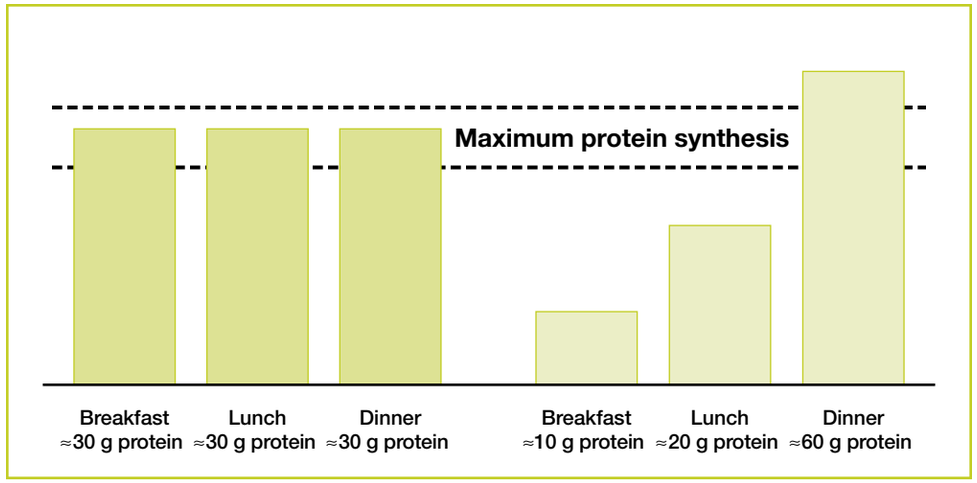

Fig 5. Ingestion of 90 g of protein, distributed evenly over three meals is more likely to provide a greater 24-hour protein anabolic response than an unequal protein distribution.

Thus, research indicates that ingestion of protein, consumed in adequate amounts over the course of a day, can ameliorate the effects of sarcopenia in older adults.

References

1. Dreyer HC, Glynn EL, Lujan HL, et al: Chronic paraplegia-induced muscle atrophy downregulates the mTOR/S6K1 signaling pathway. *J Appl Physiol* 2008; 104:27-33.
2. Kortebein P, Ferrando A, Lombeida J, et al: Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007;297:1772-1774.
3. Paddon-Jones D, Sheffield-Moore M, Cree MG, et al: Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. *J Clin Endocrinol Metab* 2006;91:4836-4841.
4. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al: Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab* 2004;89:4351-4358.
5. Paddon-Jones D, Sheffield-Moore M, Aarsland A, et al: Exogenous amino acids stimulate human muscle anabolism without interfering with the response to mixed meal ingestion. *Am J Physiol Endocrinol Metab* 2005;288:E761-E767.

6. Paddon-Jones D, Sheffield-Moore M, Katsanos CS, et al: Differential stimulation of muscle protein synthesis in elderly humans following isocaloric ingestion of amino acids or whey protein. *Exp Gerontol* 2006;41:215-219.
7. Paddon-Jones D, Sheffield-Moore M, Zhang XJ, et al: Amino acid ingestion improves muscle protein synthesis in the young and elderly. *Am J Physiol Endocrinol Metab* 2004;286:E321-E328.
8. Paddon-Jones D, Wolfe RR, Ferrando AA: Amino acid supplementation for reversing bed rest and steroid myopathies. *J Nutr* 2005;135:1809S-1812S.
9. Volpi E, Ferrando AA, Yeckel CW, et al: Exogenous amino acids stimulate net muscle protein synthesis in the elderly. *J Clin Invest* 1998;101:2000-2007.
10. Volpi E, Kobayashi H, Sheffield-Moore M, et al: Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *Am J Clin Nutr* 2003;78:250-258.
11. Volpi E, Lucidi P, Cruciani G, et al: Contribution of amino acids and insulin to protein anabolism during meal absorption. *Diabetes* 1996;45:1245-1252.
12. Volpi E, Mittendorfer B, Wolf SE, Wolfe RR: Oral amino acids stimulate muscle protein anabolism in the elderly despite higher first-pass splanchnic extraction. *Am J Physiol Endocrinol* 1999;277:E513-E520.
13. Symons TB, Schutzler SE, Cocke TL, et al: Aging does not impair the anabolic response to a protein-rich meal. *Am J Clin Nutr* 2007;86:451-456.
14. Campbell WW, Trappe TA, Wolfe RR, Evans WJ: The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. *J Gerontol A Biol Sci Med Sci* 2001;56:M373-M380.
15. Wolfe RR: The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;84:475-482.
16. Wolfe RR, Miller SL: The recommended dietary allowance of protein: A misunderstood concept. *JAMA* 2008;299:2891-2893.
17. Leidy HJ, Carnell NS, Mattes RD, Campbell WW: Higher protein intake preserves lean mass and satiety with weight loss in pre-obese and obese women. *Obesity* (Silver Spring) 2007;15:421-429.
18. Thalacker-Mercer AE, Fleet JC, Craig BA, et al: Inadequate protein intake affects skeletal muscle transcript profiles in older humans. *Am J Clin Nutr* 2007; 85:1344-1352.
19. Millward DJ, Layman DK, Tomé D, Schaafsma G: Protein quality assessment: Impact of expanding understanding of protein and amino acid needs for optimal health. *Am J Clin Nutr* 2008;87:1576S-1581S.
20. Katsanos CS, Kobayashi H, Sheffield-Moore M, et al: Aging is associated with diminished accretion of muscle proteins after the ingestion of a small bolus of essential amino acids. *Am J Clin Nutr* 2005;82:1065-1073.
21. Symons TB, Sheffield-Moore M, Wolfe RR, Paddon-Jones D: A moderate serving of high-quality protein maximally stimulates skeletal muscle protein synthesis in young and elderly subjects. *J Am Diet Assoc* 2009;109:1582-1586.

Nutrition, Muscle Mass, and Muscular Performance in Middle Age and Beyond

Catherine D. Johnson, PhD, RD, LD

Aging is associated with many changes in body composition, including reduction of lean body mass with a concomitant increase in fat mass.[1] These changes often have a negative impact on overall health and functional capacity.

Sarcopenia is the degenerative loss of skeletal muscle and strength, beginning as early as age 30, and accelerating with advancing age. Advancing sarcopenia is associated with increased risk of fall and fractures, decreased ability to complete activities of daily living, and increase in fatigue, which all lead to dependency and disability.[2]

A lifestyle behavior that positively affects muscle mass is consumption of dietary protein. Longitudinal studies have shown that older people who consume higher amounts of protein lose less lean muscle mass over 3 years than those who eat lower amounts (eg, 91 g/day vs 57 g/day).[3] Protein quality, quantity, and timing of consumption throughout the day and in conjunction with physical activity are all important to maintenance of muscle mass. Protein sources of high biologic value, namely those from animal sources, will provide the highest concentration of branched-chain amino acids such as leucine, which stimulate muscle protein synthesis.[4,5]

Milk proteins, whey and casein, are shown to stimulate muscle protein synthesis. Both are high-quality proteins and should be consumed daily. However, they produce a different response in young people than they do in older people. Whey, for instance, is digested faster than casein and produces a relatively better response on protein balance in older people. Casein has the opposite effect and has a better response in younger people.[6,7]

The goal of protein consumption and lean body mass gains is to optimize muscle protein synthesis. The quantity of essential amino acids (EAAs) is critical to elicit muscle protein synthesis. Elderly people may require 20–30 g of high-quality protein containing at least 8 g of EAAs, including leucine, three or four times a day.[4,8] Another strategy to maximize muscle protein synthesis is consumption of protein-rich meals more frequently, every 2 or 3 hours.[9]

Leucine is the primary amino acid regulator that "turns on" protein synthesis in the cells, signaling that quality protein is available for protein synthesis. Research shows that adding leucine to a meal that combines carbohydrate and protein is not necessary to get a response in protein synthesis in younger people, but it is necessary to get the same response in older people.[10] These results suggest that the protein-synthesis response is blunted in older people when a meal combines carbohydrate with protein. Reducing simple carbohydrates may be an advantageous strategy to maximize protein synthesis, because this also is shown to reduce loss of lean tissue for people with a negative caloric intake.[9-12]

A minor metabolite of L-leucine, beta-hydroxy-beta-methylbutyrate (HMB), is a precursor of cholesterol synthesis in skeletal muscle and plays a role in the control of protein homeostasis (Fig 1).[13]

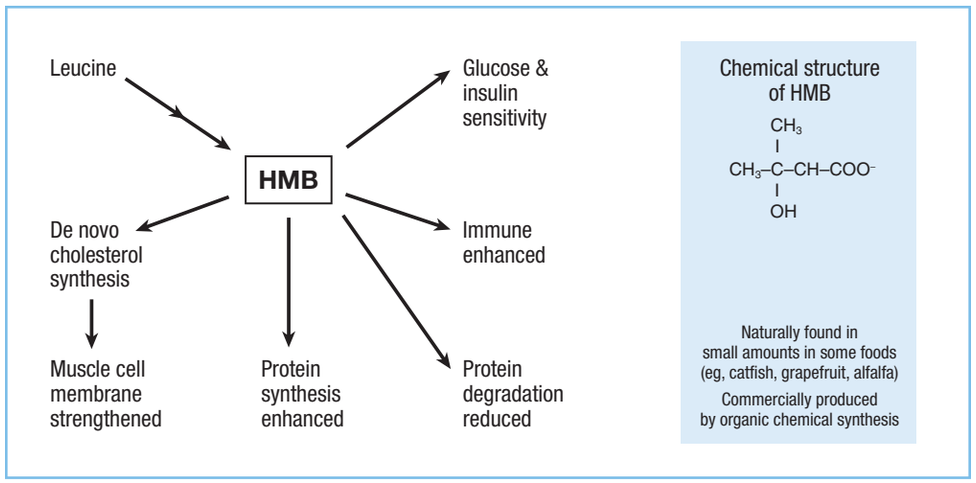

Fig 1. Sources and functions of HMB.[13]

HMB is shown to decrease protein degradation by downregulation of the ubiquitin-proteasome system (Fig 2).[14] It also is shown to stimulate protein synthesis by activation of mammalian target of rapamycin (mTOR), a serine/threonine protein kinase.[15,16]

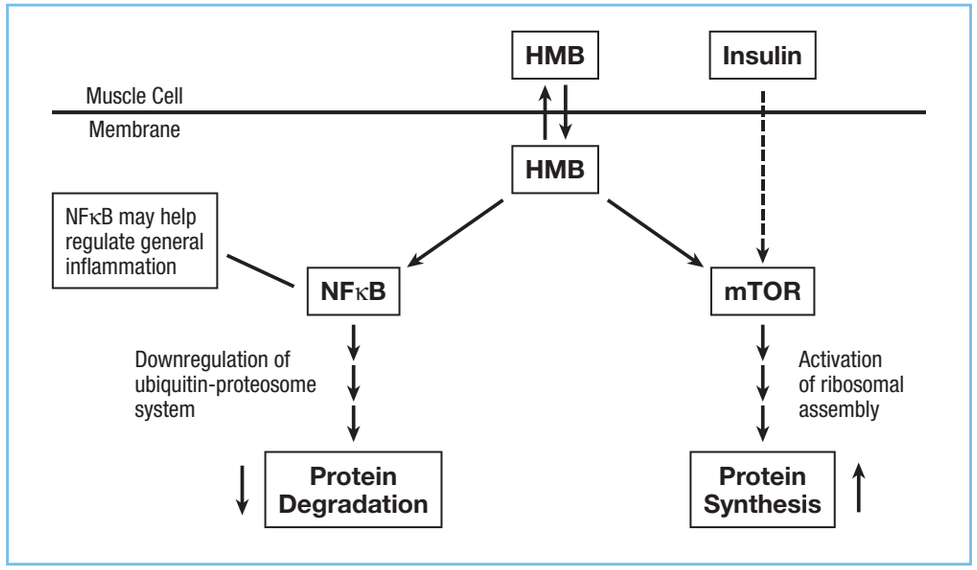

Fig 2. Role of HMB in protein synthesis and degradation. NFκB=nuclear factor κB

Oral administration of HMB is strongly associated with increased strength and lean body mass (LBM) and with decreased fat mass in young- to middle-aged people when combined with resistance exercise. HMB has also been shown to have clinical benefit in a number of muscle wasting/cachectic conditions and in limb immobilization.[14,17,18] These mechanisms appear to be relevant to older people, and clinical studies have demonstrated decreases in body fat percentage, gains in lower- and upper-body strength, increases in limb circumference, leg and handgrip strength, and increases in "get-up-and-go" performance with HMB.[13,19,20] The get-up-and-go functionality assessment involves measuring the time it takes a person to rise from a chair, walk a specified distance, and then return to the chair.

Fig 3 shows the improvements in functionality that resulted when 50 elderly women were supplemented with 2 g HMB, along with arginine and lysine, daily for 12 weeks.[19]

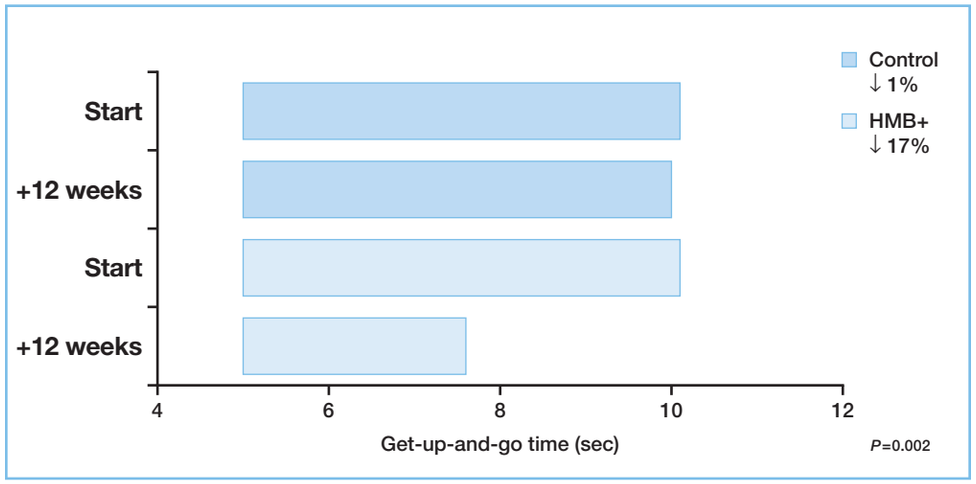

Fig 3. Changes in functionality after 12 weeks of supplementation with HMB+ (HMB, arginine, and lysine) compared to controls.[19] sec=seconds

After 12 weeks of supplementation, the "get-up-and-go" functionality test results improved by 17% in the experimental group (2.3 +/- 0.5 seconds), but did not change in the placebo group (P=0.002). Improved functionality also was reflected in increased limb circumference, leg strength, and handgrip strength (each P<0.05).

The current recommended dosage for HMB is 3 g/day.[13] This recommendation is based on the finding that increasing HMB from 1.5 g to 3 g increases strength and LBM, while doses greater than 3 g/day do not have an additional effect.[13]

Exercise also is known to increase muscle mass. Muscle mass gains can be maximized by combining the consumption of protein, amino acids, or HMB in close proximity to a session of resistance exercise. An increase in muscle protein synthesis can last up to 36 to 48 hours after a bout of intense exercise. Providing amino acids immediately before or after exercise can increase muscle protein synthesis approximately 2.5 times greater than the effect from exercise alone.[21,22] In the elderly, consumption of protein has to occur immediately after exercise to realize the benefits.[21-23]

In summary, several lifestyle strategies are recommended to promote optimal muscle protein synthesis, including consumption of the following:

- Adequate amounts of high-quality protein, essential amino acids/branched-chain amino acids/leucine, and supplemental HMB
- Protein-rich meals and snacks every 2–3 hours to maximize muscle protein balance
- Moderate amounts of carbohydrate for energy (insulin secretion) and to spare protein from being used for energy
- Foods containing a mixture of protein and carbohydrates 40–120 minutes before exercise and immediately after exercise to increase strength and hypertrophy

References

1. Kyle UG, Genton L, Hans D, et al: Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *Eur J Clin Nutr* 2001;55:663-672.
2. Hunter GR, McCarthy JP, Bamman MM: Effects of resistance training on older adults. *Sports Med* 2004;34:329-348.
3. Houston DK, Nicklas BJ, Ding J, et al: Dietary protein intake is associated with lean mass change in older, community-dwelling adults: The Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2008;87:150-155.
4. Symons TB, Schutzler SE, Cocke TL, et al: Aging does not impair the anabolic response to a protein-rich meal. *Am J Clin Nutr* 2007;86:451-456.
5. Paddon-Jones D, Rasmussen BB: Dietary protein recommendations and the prevention of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2009;12:86-90.
6. Dangin M, Boirie Y, Guillet C, Beaufrère B: Influence of the protein digestion rate on protein turnover in young and elderly subjects. *J Nutr* 2002; 132:3228S-3233S.
7. Dangin M, Guillet C, Garcia-Rodenas C, et al: The rate of protein digestion affects protein gain differently during aging in humans. *J Physiol* 2003; 549:635-644.
8. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al: Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab* 2004;89:4351-4358.
9. Solerte SB, Gazzaruso C, Bonacasa R, et al: Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. *Am J Cardiol* 2008;101:69E-77E.
10. Koopman R, Verdijk L, Manders RJ, et al: Co-ingestion of protein and leucine stimulates muscle protein synthesis rates to the same extent in young and elderly lean men. *Am J Clin Nutr* 2006;84:623-632.

11. Koopman R, Wagenmakers AJ, Manders RJ, et al: Combined ingestion of protein and free leucine with carbohydrate increases postexercise muscle protein synthesis in vivo in male subjects. *Am J Physiol Endocrinol Metab* 2005;288:E645-E653.
12. Layman DK: The role of leucine in weight loss diets and glucose homeostasis. *J Nutr* 2003;133:261S-267S.
13. Wilson GJ, Wilson JM, Manninen AH: Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: A review. *Nutr Metab* (Lond) 2008;5:1.
14. Smith HJ, Mukerji P, Tisdale MJ: Attenuation of proteasome-induced proteolysis in skeletal muscle by beta-hydroxy-beta-methylbutyrate in cancer-induced muscle loss. *Cancer Res* 2005;65:277-283.
15. Kornasio R, Riederer I, Butler-Browne G, et al: Beta-hydroxy-beta-methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways. *Biochim Biophys Acta* 2009;1793:755-763.
16. Eley HL, Russell ST, Tisdale MJ: Attenuation of depression of muscle protein synthesis induced by lipolysaccharide, tumor necrosis factor, and angiotensin II by beta-hydroxy-beta-methylbutyrate. *Am J Physiol Endocrinol Metab* 2008;295:E1409-E1416.
17. Hsieh LC, Chien SL, Huang MS, et al: Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation in chronic obstructive pulmonary disease patients in intensive care unit. *Asia Pac J Clin Nutr* 2006;15:544-550.
18. May PE, Barber A, D'Olimpio JT, et al: Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg* 2002;183:471-479.
19. Flakoll P, Sharp R, Baier S, et al: Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. *Nutrition* 2004; 20:445-451.
20. Vukovich MD, Stubbs NB, Bohlken RM, et al: Body composition in 70-year old adults responds to dietary beta-hydroxy-beta-methylbutyrate (HMB) similarly to that of young adults. *J Nutr* 2001;131:2049-1935.
21. Biolo G, Maggi SP, Williams BD, et al: Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. *Am J Physiol* 1995;268:E514-E520.
22. Biolo G, Tipton KD, Klein S, Wolfe RR: An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. *Am J Physiol* 1997;273:E122-E129.
23. Esmarck B, Andersen JL, Olsen S, et al: Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. *J Physiol* 2001;535:301-311.

Baracos

Measurement of Lean Body Mass Using CT Scans

Vickie Baracos, PhD

Body Mass Index (BMI) and Weight Loss: Conventional Elements of How Cachexia and Nutritional Status Have Been Defined in Cancer Patients

Our understanding of cancer cachexia in the past has focused on losses of body weight. Since ancient times, the relationship between loss of body weight over time and poor cancer outcomes has been known. Even though measures such as loss of lean body mass may be better predictors of patient outcomes, weight loss remains firmly entrenched as a criterion for identification of malnutrition and cachexia. Body weight loss, for instance, still is used as a major criterion of inclusion and also as a principal endpoint in randomized clinical trials for various forms of cachexia treatment, including nutritional support. In a review of 55 clinical trials looking at the effect of appetite stimulants on cancer cachexia, Yavuzsen et al[1] reported that 91% of studies examined used overall body weight change as an outcome.

Progressive loss of weight is conventionally viewed as culminating in a cachectic (ie, emaciated) state. Current demographics of cancer patients, however, are progressively affected by increasing rates of obesity, as well as by an increasing prevalence of cancer in obese people. As a result, patients with advanced disease are reported to have a high prevalence of obesity in spite of ongoing weight losses.[2]

Despite considerable weight loss in some of these patients, the classic image of cachexia (ie, emaciation) is becoming less common. We conducted population-based profiling of BMI and weight loss history in a cohort (n=2695) of patients with gastrointestinal cancer. Patients were newly referred to medical oncology clinics in a regional cancer center. A computerized database of all cancer cases in the province (Alberta Cancer Registry) was used to capture disease site and morphology, along with biological, clinical, and demographic information. Analysis of BMI reveals an

average BMI clinical, and demographic information. Analysis of BMI reveals an average BMI >26 kg/m^2 and a preponderance of overweight and obese patients, with only 5% presenting with a BMI <18.5 kg/m^2. A history of weight loss was common, with an average loss of 8.6±8.9%. The population quartiles of 6 month weight loss were -19.3%, -10.6%, -4.5%, and +2.4%. In the following Table, the data are stratified by time to death.

Table. BMI Distribution (%) and 6-Month Weight Loss at Different Times From Death in Patients With Advanced Solid Tumors (n=2695)

	Days to Death				
	<90 (n=509)	90 to 180 (n=312)	181 to 360 (n=346)	361 to 540 (n=396)	>540 (n=1132)
BMI <20.0 (%)	23	22	15	12	8
BMI 20.0 to 24.9 (%)	39	44	37	38	38
BMI 25.0 to 29.9 (%)	28	25	36	35	36
BMI ≥30.0 (%)	10	9	12	15	18
BMI (Mean±SD)	23.9±5.3	23.7±4.6	24.9±5.0	25.5±5.4	26.0±5.0
6 month weight loss (%, Mean±SD)	11.7±9.0	9.3±8.8	7.8±8.8	7.0±7.5	5.5±7.9

Despite a mean weight loss of about 12%, the mean BMI of patients within 90 days of death was high at 23.9 kg/m^2. Owing to high body weights, many patients remained obese or overweight in spite of considerable weight loss. These data appear to reflect the generally heavier body weights in Westernized countries.

A Reconceptualization of Cancer Cachexia

Skeletal muscle wasting can hide within the bulk of body weight and body weight change, and recognition of sarcopenia (age-related muscle wasting) as a clinically important phenomenon is emerging. The term *sarcopenia* denotes a reduced quantity of skeletal muscle (ie, >2 standard deviations below that typical of healthy adults).[3] Sarcopenia is associated with loss of physical function, disability,[2-4] risk of fractures and of falls,[3] increased length of hospital stay,[5] nosocomial infections,[6] and decreased survival[7] in nonmalignant diseases. Sarcopenia is not restricted to people who are thin or wasted.[2,8] The aging process is often paralleled by decreases in muscle and increases in fat mass, which may culminate in *sarcopenic obesity*.[9,10] Recent studies[11,12] point to an increasing prevalence of sarcopenic obesity in elderly people in North American and Europe.

Experts are starting to acknowledge the independent behavior of muscle and adipose tissues on wasting syndromes. A recently convened consensus conference on the definition of cachexia[13] notably made a distinction between the behavior of skeletal muscle and adipose tissue: “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….” This perspective acknowledges the possibility of a persistent muscle loss in the absence of any change in fat mass.

The Use of Diagnostic Images To Assess Body Composition Changes and Sarcopenia in Cancer Patients

A highly differentiated understanding of human body composition has evolved in tandem with image-based technologies such as computed tomography (CT) and magnetic resonance imaging (MRI). These methods enjoy a high degree of specificity for the separate discrimination of many organs and tissues (Fig 1).

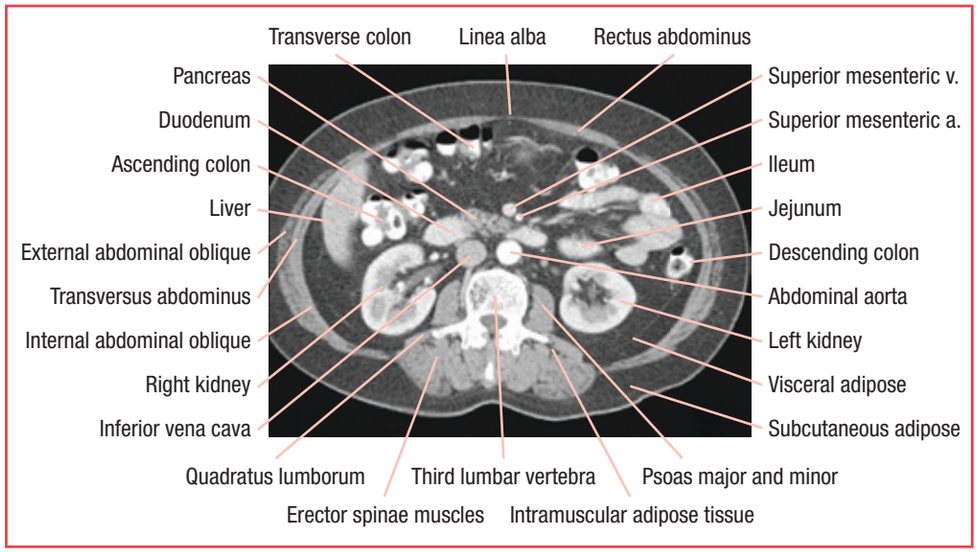

Fig 1. Structures present in a computerized tomography image at the 3rd lumbar vertebra.

CT is considered a gold standard method used to assess body composition[14]; however, its use in noncancer populations is limited.

Cancer patients undergo frequent routine scans for diagnosis and to monitor disease progression. Although these patients are routinely evaluated by high-resolution diagnostic imaging, the information content of these images is barely exploited, in part owing to lack of deployment of relevant methods and concepts in a cancer care setting. We have proposed the opportunistic use of these high-quality images, which are readily available in the medical records of these patients, to provide accurate and practical studies of body composition across the cancer trajectory.[15] These images are a considerable resource and are now in many institutions stored and accessible in a digitized format. For example, our large cohort of patients with solid tumors of the lung and gastrointestinal tract typically undergo imaging four times a year during active treatment. An extensive reliance on diagnostic imaging gives specialists in cancer care an unprecedented ability to evaluate their patients' body composition, including repeated measures over time.

The premise of CT scans for body composition research has been described in detail elsewhere.[14,15] It is important to note that these methods are accessible. Image analysis software is commercially available, and the quantification can be done by any qualified person with appropriate knowledge of human anatomy, the nature of the images, and the capacities of the software.

Diagnostic images taken in cancer care do not usually encompass the whole body; this requires that patients be evaluated at a standardized location. Specific skeletal landmarks in the lumbar region appear in a majority of work in non-malignant disease as well as in cancer.[2,15] As illustrated in Fig 1, this region contains visceral, subcutaneous, and intermuscular adipose tissue, *psoas* and paraspinal muscles (*erector spinae* and *quadratus lumborum*), as well as *transversus abdominus*, external and internal oblique abdominals, and *rectus abdominus*. Since the cross-sectional areas of tissues in single images in the lumbar area are strong correlates of whole-body adipose tissue, muscle, and lean tissue mass,[15-17] we make use of the 3rd lumbar vertebra (L3) in our characterization of cancer patients. Individuals may be compared directly on this basis; however, these quantities may be translated to approximate whole-body tissue masses using regression equations from earlier work.[15-17] Specific tissues are identified based on their anatomical features (Fig 1) and then demarcated and quantified (Fig 2) based on pre-established thresholds of Hounsfield units (units of radiation attenuation) using commercially available imaging analysis software.

Cross-sectional areas (cm^2) are computed automatically by the program once the desired tissues are demarcated. Demarcated images (Fig 2) illustrate body composition changes in a lung cancer patient over time; this person lost skeletal muscle during progressive disease.

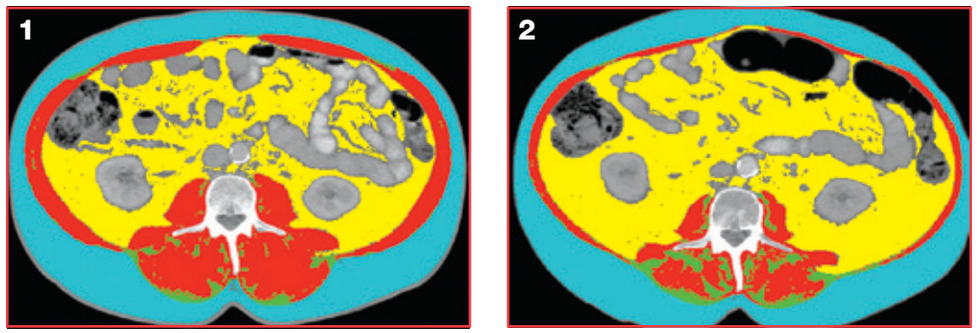

Fig 2. Skeletal muscle loss in a patient with lung cancer. Segmented CT images for a male lung cancer patient at two separate timepoints. Number 1 was taken 390 days before death, and 2 was taken 58 days before death. Segmented tissues of interest: ■ is skeletal muscle, ■ is visceral adipose tissue, ■ is subcutaneous adipose tissue, and ■ is intramuscular adipose tissue. During this 332-day period, skeletal muscle area decreased from 173 cm^2 to 86.7 cm^2.

Conclusions

Current demographics of weight and body composition suggest a need to reconceptualize cancer cachexia. Substantial depletion of skeletal muscle is a widespread abnormality of body composition in patients with advanced solid tumors, which is present in people at any BMI and strongly related to outcome. Valid and convenient approaches for determining muscularity are required to evaluate this feature in cancer patients, and the secondary analysis of CT images is an accessible means of making this evaluation.

References

1. Yavuzsen T, Davis MP, Walsh D, et al: Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005;23:8500-8511.
2. Prado CM, Lieffers JR, McCargar LJ, et al: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. *Lancet Oncol* 2008;9:629-635.
3. Baumgartner RN, Koehler KM, Gallagher D, et al: Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755-763.

4. 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.
5. Pichard C, Kyle UG, Morabia A, et al: Nutritional assessment: Lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr* 2004;79:613-618.
6. Cosqueric G, Sebag A, Ducolombier C, et al: Sarcopenia is predictive of nosocomial infection in care of the elderly. *Br J Nutr* 2006;96:895-901.
7. Metter EJ, Talbot LA, Schrager M, Conwit R: Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci* 2002;57:B359-B365.
8. Baumgartner RN: Body composition in healthy aging. *Ann N Y Acad Sci* 2000;904:437-448.
9. Zamboni M, Mazzali G, Fantin F, et al: Sarcopenic obesity: A new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis* 2008;18:388-395.
10. Roubenoff R: Sarcopenic obesity: Does muscle loss cause fat gain? Lessons from rheumatoid arthritis and osteoarthritis. *Ann N Y Acad Sci* 2000; 904:553-557.
11. Bouchard DR, Dionne IJ, Brochu M: Sarcopenic/obesity and physical capacity in older men and women: Data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec Longitudinal Study. *Obesity* (Silver Spring) 2009. [Epub ahead of print].
12. Rolland Y, Lauwers-Cances V, Cristini C, et al: Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: The EPIDOS (EPIDemiologie de l'OSteoporose) Study. *Am J Clin Nutr* 2009;89:1895-1900.
13. Evans WJ, Morley JE, Argilés J, et al: Cachexia: A new definition. *Clin Nutr* 2008;27:793-799.
14. Ross R, Janssen I: Computed tomography and magnetic resonance imaging, in Heymsfield S, Lohman T, Wang Z, Going S (eds): *Human Body Composition*, ed 2. Champaign, Ill: Human Kinetics, 2005, p 523.
15. Mourtzakis M, Prado CMM, Lieffers JR, et al: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;33:997-1006.
16. Shen W, Punyanitya M, Wang Z, et al: Visceral adipose tissue: Relations between single-slice areas and total volume. *Am J Clin Nutr* 2004;80:271-278.
17. Shen W, Punyanitya M, Wang Z, et al: Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004;97:2333-2338.

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