

Role of dietary protein in the sarcopenia of aging¹⁻⁴

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ABSTRACT

Sarcopenia is a complex, multifactorial process facilitated by a combination of factors including the adoption of a more sedentary lifestyle and a less than optimal diet. Increasing evidence points to a blunted anabolic response after a mixed nutrient meal as a likely explanation for chronic age-related muscle loss. There is currently insufficient longer-term research with defined health outcomes to specify an optimal value for protein ingestion in elderly individuals. However, there is general agreement that moderately increasing daily protein intake beyond $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ may enhance muscle protein anabolism and provide a means of reducing the progressive loss of muscle mass with age. The beneficial effects of resistance exercise in aging populations are unequivocal. However, research has not identified a synergistic effect of protein supplementation and resistance exercise in aging populations. There is little evidence that links high protein intakes to increased risk for impaired kidney function in healthy individuals. However, renal function decreases with age, and high protein intake is contraindicated in individuals with renal disease. Assessment of renal function is recommended for older individuals before they adopt a higher-protein diet. *Am J Clin Nutr* 2008;87(suppl):1562S–6S.

INTRODUCTION

Sarcopenia is a complex, multifactorial process facilitated by a combination of voluntary and involuntary factors including the adoption of a more sedentary lifestyle and a less than optimal diet (1–3) (**Figure 1**). Advanced sarcopenia is synonymous with physical frailty and is associated with an increased likelihood of falls and impairment in the ability to perform routine activities of daily living (1). Some loss of muscle is viewed as a largely inevitable yet undesirable consequence of aging. After reaching a peak in early adult years, skeletal muscle mass declines by $\approx 0.5\text{--}1.0\%\cdot\text{y}^{-1}$ beginning at about 40 y of age. In its early stages, a gradual loss of lean muscle mass may be masked by a concurrent increase in fat mass along with subtle lifestyle adaptations. However, a breakpoint can occur when a previously asymptomatic individual experiences an injurious event or is acutely/temporarily disabled (4). In such instances, the loss of skeletal muscle is accelerated and may rapidly facilitate a debilitating loss of functional capacity.

Chronic muscle loss is estimated to affect 30% of people older than 60 y and may affect >50% of those older than 80 y (5). Sarcopenia is associated with a 3- to 4-fold increased likelihood of disability, which in turn is associated with substantial socioeconomic and health care spending. One analysis estimated that in 2000, sarcopenia was responsible for \$18.5 billion in health care costs (6). As the number of people older than 65 y continues

to increase, sarcopenia will become an increasingly important public health concern. According the Census Bureau, by the year 2025, the elderly population in the United States is expected to be $\approx 80\%$ greater than the number in 2000 (7).

PREVENTION AND TREATMENT

To combat the progression of sarcopenia, several intervention strategies including the provision of replacement or even supplemental doses of hormones, meant to reestablish or exceed youthful concentrations of testosterone (8–12), growth hormone (13), insulin-like growth factor-1 (14), and dehydroepiandrosterone (15), have been assessed in clinical trials with mixed results (11, 16, 17). There are compelling data supporting the efficacy of physical activity and resistance exercise in particular in maintenance of muscle mass and function in aging populations (18–28). However, whereas the health benefits of physical activity are undeniable, in many older populations the ability to exercise is compromised by physical disability, frailty, or disease (4). In such instances, targeted control of daily protein consumption and dietary derived amino acids represents one of the few remaining alternatives to slow or prevent muscle protein catabolism (29, 30). Unfortunately, protein intake and efficiency of use appears to decrease with age (31–34). This may be due to a combination of factors including greater expense, increased satiety, dentition/chewing difficulties, and changes in digestion, gastric emptying, splanchnic uptake, and peripheral use.

Between 15% and 38% of adult men and 27% and 41% of adult women have dietary protein intakes below the current Recommended Dietary Allowance of $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, which itself may

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² Presented at the conference “Protein Summit 2007: Exploring the Impact of High-Quality Protein on Optimal Health,” held in Charleston, SC, May 24, 2007.

³ Support for “Protein Summit 2007: Exploring the Impact of High-Quality Protein on Optimal Health” and this supplement was provided by the Egg Nutrition Center, National Dairy Council, National Pork Board, and The Beef Checkoff through the National Cattlemen’s Beef Association.

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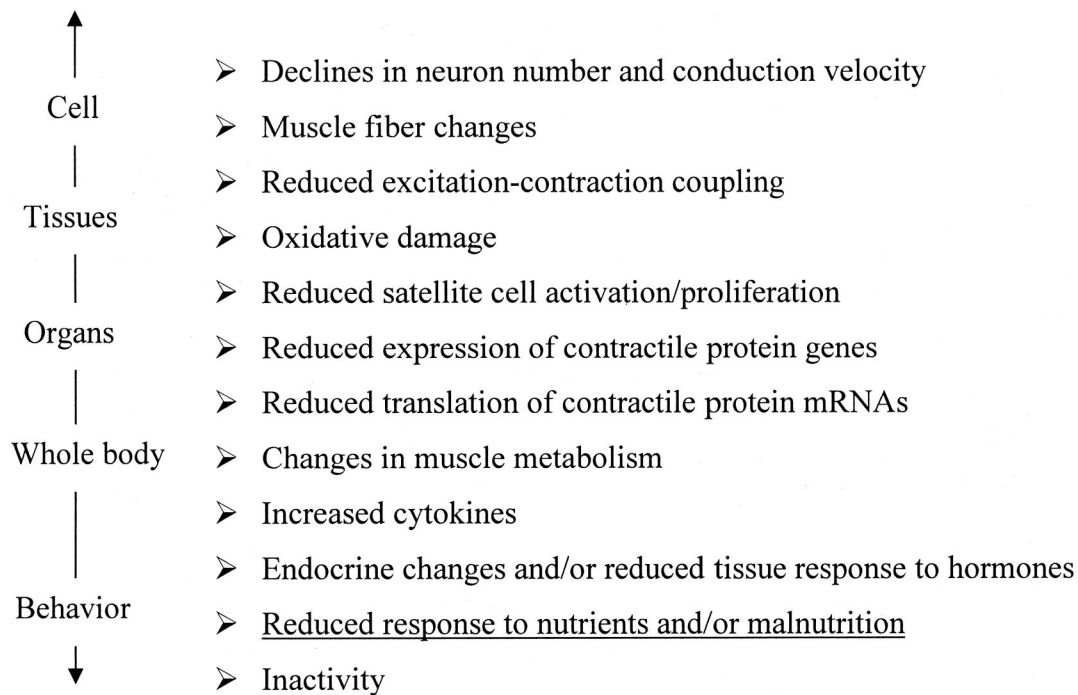


FIGURE 1. A partial list of mechanisms/consequences of sarcopenia.

represent a minimal requirement for populations such as the elderly (35). Moderately increasing dietary protein intake above the Recommended Dietary Allowance may enhance muscle protein anabolism and reduce the progressive loss of muscle mass with age (35, 36). As noted, the beneficial effects of resistance exercise in aging populations are unequivocal. However, the interactive effects of protein supplementation and resistance exercise on muscle mass and function in aging populations are less clear (37–39). In a recent study by Iglay et al (38), 36 older men and women underwent 12 wk of resistance training in association with a lower protein ($0.9 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) or higher protein ($1.2 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) intake. Although all outcome measures improved (eg, increased strength, greater whole-body protein accretion, and reduced fat mass), there were no significant differences between the lower-protein and higher-protein groups. Similarly, Andrews et al (37) suggested that total daily protein intake (1.35 versus $0.72 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) does not affect lean mass gains in the context of postexercise protein supplementation. Nevertheless, it has been demonstrated that mixed macronutrient supplementation in frail elderly individuals can result in a compensatory reduction in voluntary food intake and without concomitant resistance exercise may not improve muscle mass or strength (18).

Muscle deposition occurs in response to a complex interplay among stimuli such as physical activity and hormonal signaling. However, in all circumstances the prerequisite for muscle protein synthesis is dietary derived amino acids (40). Several studies have demonstrated an acute increase in muscle protein synthesis with no compensatory change in muscle protein breakdown after protein (34, 41) or amino acid ingestion (42, 43) in both young and elderly individuals. Insufficient or ineffectual protein intake in elderly individuals may facilitate the loss of muscle by blunting muscle protein synthesis and thus promoting net muscle protein catabolism (33, 44, 45). Although there are some reports

that basal muscle protein synthesis declines with age (46, 47), several other studies disagree (34, 43, 48), and current opinion is that in most healthy older people, muscle protein synthesis in the postabsorptive state is similar to that of younger people. Increasing evidence points to a blunted anabolic response after a mixed nutrient meal as a likely explanation for muscle loss over time (33, 34, 49). In a recent study examining myofibrillar and sarcoplasmic protein synthesis in young and elderly volunteers after amino acid ingestion, postabsorptive rates of protein synthesis were the same in both age groups, although the elderly demonstrated less anabolic sensitivity to the amino acids. The authors suggested that this result may be due to decreased intramuscular expression and phosphorylation of signaling proteins (eg, mammalian target of rapamycin, p70 S6 kinase, and eukaryotic initiation factors 4BP-1 and 2B) (33).

In addition to insufficient protein intake, reduced sensitivity to the anabolic action of insulin and amino acids may precede overt changes in skeletal muscle mass (33, 49–51). Furthermore, the reduced vasodilatory response of older muscle to insulin may reduce anabolism by decreasing nutritive blood flow and precursor availability. Whereas there is clear evidence that ingestion of a relatively large amount of protein or free-form essential amino acids increases muscle protein synthesis in both younger and older people (30, 41–43, 52–56), it has been demonstrated that during concomitant hyperglycemia (50) or when carbohydrate is added to an amino acid supplement (49), elderly individuals respond with a diminished anabolic response compared with that of their younger counterparts. For example, Volpi et al. (49) demonstrated that after ingestion of an amino acid–glucose mixture, muscle protein synthesis increased in the young (61 ± 17 to $133 \pm 30 \text{ nmol}\cdot\text{min}^{-1}\cdot 100 \text{ mL}^{-1}$ leg volume), but remained unchanged in the elderly (62 ± 9 to $70 \pm 14 \text{ nmol}\cdot\text{min}^{-1}\cdot 100 \text{ mL}^{-1}$ leg volume). In practical terms, these findings suggest that aging may be associated with reduced anabolic efficiency in

response to a normal mixed nutrient meal (33, 49, 50). Ultimately, these data indicate the need to identify nutritional strategies that maximize the stimulation of muscle protein synthesis in elderly individuals. In all likelihood, any such recommendation would take into account the interactive effects of hyperinsulinemia and hyperaminoacidemia and address the amount and quality of protein ingested during each meal rather than the total daily protein intake.

DIETARY PROTEIN REQUIREMENTS

Currently there is no consensus on whether dietary protein needs change with advancing age. The current recommendation for protein intake for all men and women aged 19 y and older is $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, established by the Institute of Medicine and based primarily on data from short-term nitrogen balance studies in young adults (57, 58). A concern about the broad scope of this recommendation is that the original data set used for the estimate was derived from nitrogen balance studies performed on young men. Although several studies support the $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ recommendation (59–61), others have suggested that a moderately higher protein intake of $1.0\text{--}1.3 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ may be required to maintain nitrogen balance and offset a potentially lower energy intake, decreased protein synthetic efficiency, and impaired insulin action in elderly individuals (33–35, 62, 63). Such recommendations should be weighed against any potential increase in the risk of toxicity or impaired renal function (see Renal Function). Very-high-protein diets (>45% energy) have been associated with a host of adverse events, including nausea, diarrhea, increased calcium excretion from diets high in sulfur-containing amino acids, and increased morbidity (64, 65). However, diets containing a moderate amount of protein (20–35% energy) do not appear to be associated with negative health outcomes (66, 67). Furthermore, in human clinical trials, apart from isolated cases of intolerance or hypersensitivity, there have been no reports of toxicity associated with amino acid administration (66).

Inherent difficulties in the assessment of nitrogen balance notwithstanding (68), there are a number of common arguments offered to support or refute the validity of the current Recommended Dietary Allowance for protein. Many contend that nitrogen balance studies may not be the best indicator of protein requirements, nor may they be the best method for setting recommendations for optimal protein intake and health. However, with appropriate experimental control, the technique can produce reliable and consistent data and has several practical advantages over alternatives such as stable isotope methodology. Nevertheless, although nitrogen balance studies may be appropriate for establishing the nitrogen or amino acid requirements to prevent deficiency, the question of whether they are an appropriate means of establishing optimal intakes for maintenance of muscle mass, strength, and metabolic function remains.

QUALITY OF PROTEIN

In addition to the quantity of protein ingested, there appears to be subtle inherent differences in the ability of different protein sources to promote muscle protein synthesis. These differences appear to be governed by 2 key determining factors. First, and perhaps most important, is the essential amino acid content of a protein, in particular leucine, that serves as the primary determinant of its anabolic potential (41, 55, 69). Specifically, in terms

of muscle protein synthesis, the addition of nonessential amino acids to an essential amino acid supplement does not provide an additional stimulatory effect. Second, differences in digestibility and bioavailability of certain protein-rich foods may influence muscle protein synthesis (52, 70, 71). For example, the combination of fast (whey) and slow (casein) proteins found in milk may provide a greater increase in muscle protein synthesis than an isonitrogenous soy beverage after resistance exercise in young individuals (71, 72). In such a specific context, any additional nutrition-derived increase in muscle protein anabolism is certainly advantageous and desirable. However, in the context of a typical meal, which contains a variety of proteins and macronutrients, subtle inherent differences in the ability of individual protein sources to stimulate muscle protein anabolism are likely to be minimized. Nevertheless, the key point is that, irrespective of the source, meals should contain a moderate amount of high-quality protein.

There have been a large number of proof of concept studies indicating that free-form essential amino acids and whey protein supplements promote muscle protein synthesis in healthy younger and older people (41–43, 54, 55, 73). Of greater practical importance, however, is determining whether common protein-rich foods can stimulate muscle protein anabolism in older people. Recent data suggest that a moderate 113 g (4 oz) serving of an intact protein (ie, lean beef) contains sufficient amino acids (30 g total; 10 g essential amino acids) to increase mixed muscle protein synthesis by $\approx 50\%$ in both young and elderly men and women (34).

Promoting muscle anabolism with a protein-rich food has several advantages over supplementation with products such as free-form amino acids. Many plant- and animal-based protein-containing foods are readily accessible, relatively inexpensive, and palatable, whereas supplements such as essential amino acids frequently are not. In addition, whereas some forms of supplementation have been shown to acutely stimulate net protein synthesis in both elderly and young individuals (16, 17), their use does not address the fundamental need to examine dietary interventions that may be implemented in a realistic context. Furthermore, energy-dense supplements have the potential to act as a meal replacement, especially in elderly individuals, resulting in little or no change in daily protein, energy or essential nutrient intake (15). Although targeted amino acid supplementation may indeed be beneficial in cases involving accelerated protein catabolism (eg, advanced sarcopenia, cachexia, and trauma) (74), for the majority of older adults the most practical means of increasing skeletal muscle protein anabolism is to include a moderate serving of protein of high biological value during each meal.

RENAL FUNCTION

There is little evidence to link high protein intakes (up to $2 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) to increased risk for impaired kidney function in healthy, physically active men and women (75–77). However, there is evidence that a higher protein intake may facilitate a greater decline in renal function in those with modestly impaired renal function (75). In patient populations, high-protein diets may lead to glomerular hyperfiltration and hyperemia, acceleration of chronic kidney disease and various associated metabolic alterations (77). In higher-risk groups, including those with existing renal disease, high-protein diets should be avoided (78).

The initial onset and progression of chronic kidney disease are often symptomless. Consequently, initial screening (serum creatinine and urinary dipstick for proteinuria) and subsequent monitoring of renal function and creatinine clearance may also be prudent in older individuals before commencing a higher-protein diet as both lean body mass and renal function decline with age (77).

CONCLUSION

There are compelling data to support the ability of dietary protein to acutely stimulate muscle protein synthesis in aging individuals. However, there is insufficient longer-term research with defined health outcomes to specify an optimal value for protein ingestion. There is general agreement that moderately increasing daily protein intake beyond $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ may enhance muscle protein anabolism and provide a means of reducing the progressive loss of muscle mass with age. However, current research has not identified a synergistic or additive effect of protein supplementation and resistance exercise on muscle protein anabolism in aging populations. There is little evidence to link high protein intakes to increased risk of impaired kidney function in healthy men and women. However, renal function decreases with age and a high protein intake is contraindicated in individuals with renal disease. Assessment of renal function is recommended for older individuals before they adopt a higher-protein diet.

The authors' responsibilities were as follows—DP-J, KRS, WWC, EV, and RRW: contributed to the conception, drafting, and revision of this manuscript.

Reimbursements of travel costs and lodging were provided to DP-J, KRS, WWC, EV, and RRW by the Protein Summit sponsors. The Summit sponsors provided DP-J and RRW an honorarium for efforts on the Steering Committee for organization of the meeting and preparation of manuscripts, and KRS and EV received an honorarium for participation in a working group that reviewed and compiled the relevant published literature on this topic. DP-J, KRS, WWC, EV, and RRW have received compensation for speaking/consulting engagements with The Beef Checkoff through the National Cattlemen's Beef Association. WWC has received grant funding from the National Pork Board, the American Egg Board/Egg Nutrition Center, and the US Whey Consortium. DPJ has received grant funding from The Beef Checkoff through the National Cattlemen's Beef Association and has received compensation for speaking engagements with the National Dairy Council.

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