



Protein and healthy aging^{1–5}

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ABSTRACT

Our understanding of the potential benefits and challenges of optimizing dietary protein intake in older adults continues to evolve. An overarching hypothesis generated during Protein Summit 2.0 was that consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, may delay the onset of sarcopenia, slow its progression, reduce the magnitude of its functional consequences, or all of these. The potential benefits of young and middle-aged adults adopting a diet pattern whereby adequate protein is consumed at each meal as a countermeasure to sarcopenia are presented and discussed. For example, meeting a protein threshold (~25–30 g/meal) represents a promising, yet still largely unexplored dietary strategy to help maintain muscle mass and function. For many older adults, breakfast is a carbohydrate-dominated lower-protein meal and represents an opportunity to improve and more evenly distribute daily protein intake. Although both animal and plant-based proteins can provide the required essential amino acids for health, animal proteins generally have a higher proportion of the amino acid leucine. Leucine plays a key role in stimulating translation initiation and muscle protein anabolism and is the focus of ongoing research. Protein requirements should be assessed in the light of habitual physical activity. An evenly distributed protein diet provides a framework that allows older adults to benefit from the synergistic anabolic effect of protein and physical activity. To fully understand the role of dietary protein intake in healthy aging, greater efforts are needed to coordinate and integrate research design and data acquisition and interpretation from a variety of disciplines. *Am J Clin Nutr* 2015;101(Suppl):1339S–45S.

Keywords: dietary requirements, muscle, nutrition, protein, sarcopenia

INTRODUCTION

A gradual, yet progressive loss of muscle mass and function is a common feature of aging. In the absence of a disease state or injury, sarcopenia results in a 3–8% reduction in muscle mass per decade (1, 2). A loss of muscle strength and function can be independent of changes in muscle mass but is a key determinant of disability and mortality (3). Like osteoporosis, the onset of physiologic and behavioral changes that precede sarcopenia can occur relatively early—during the fourth to fifth decade of life. Although early changes may be subtle and symptom-free, advanced sarcopenia can be profoundly debilitating, increasing the risk of falls and impairing the ability to perform routine activities of daily living (4, 5). Catabolic stressors such as acute or chronic illness, injury, and physical inactivity alone or in concert with

malnutrition or inadequate protein intake can hasten the loss of lean body mass and further increase risk of functional impairment (6, 7).

For researchers and clinicians, an overarching challenge is to identify ways to promote and guide healthy aging. Focused, mechanistic studies that seek to understand the molecular or genetic events that modulate muscle mass and influence function continue to be important. However, to fully support healthy aging, greater efforts need to be made to coordinate and integrate research design and data acquisition and interpretation from multiple and varied sources, including observational studies, clinical trials, and analyses of large data sets.

Protein Summit 2.0 explored the role of dietary protein in public health. Companion articles focusing on weight management and appetite regulation, protein, lipid and glucose metabolism, federal guidelines, and information dissemination are included in this supplement issue. There was considerable overlap and consensus across topic areas. Although all topics were relevant to an aging population, unique dietary and health needs specific to older adults were identified. These represent both an obstacle and opportunity for researchers, clinicians, and educators. Our understanding of the potential benefits and

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challenges of optimizing dietary protein intake in older adults continues to evolve. To focus our discussion and deliberations, a conceptual model that includes a general and series of specific hypotheses was developed. This model provides a framework to critically evaluate recent advances in protein and healthy aging and identifies emerging opportunities to address gaps in knowledge and application (**Figure 1**).

A PROTEIN-FOCUSED DIETARY FRAMEWORK IS NECESSARY TO COMBAT SARCOPENIA

General hypothesis: "Throughout adult life, consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, may delay the onset of sarcopenia, slow its progression, and/or reduce the magnitude of its functional consequences."

Research continues to advance our understanding of the regulation of muscle protein metabolism and the broader translational and public health consequences of manipulating dietary protein in older adults. However, a loss of muscle mass and function should not be viewed as strictly a concern for older individuals. Middle-aged adults (~40–60 y) are underrepresented in protein and nutrition research, falling between the standard "young" (20–40 y) or "older" (≥ 65 y) group assignments (8). Yet, several lines of evidence support the concept that, similar to maximizing bone mass during peak accretion years, maximizing lean body mass before the onset of sarcopenia is feasible and likely useful in slowing its progression. Although healthy middle-aged adults may display a "youthful" physiologic response to exercise and nutrition (9), catabolic stressors such as inactivity or injury may facilitate anabolic resistance and accelerated muscle loss (10–13). Although there are some age-related disparities in dietary protein digestion, absorption rate, postprandial muscle protein synthetic response, and the synergistic effects of exercise, potential differences are likely minimized by optimizing protein quantity and quality (14–17). A recent meta-analysis that examined the adaptive response of skeletal muscle to resistance exercise training and protein supplementation noted a similar positive effect on fat-free mass in healthy younger (23 ± 6 y) and older (62 ± 6 y) adults (18). Collectively, recent data suggest that, whereas general protein intake and exercise recommendations to promote optimal health may not vary dramatically as an individual ages, increased vigilance is needed to ensure that middle- and older-aged adults do not experience prolonged periods of net muscle catabolism during times of stress, injury, or inactivity.

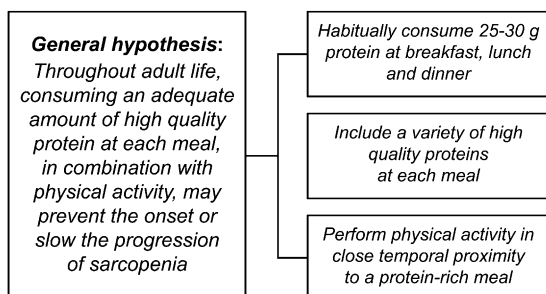


FIGURE 1 Conceptual model used to generate hypotheses and to guide discussion.

Several recent review and opinion articles highlighted the growing consensus among protein and sarcopenia experts (1, 4, 19–22). General areas of consensus were as follows:

- 1) Sarcopenia is a complex, multifactorial condition influenced by nutrition, physical activity, comorbidities, and psychosocial factors.
- 2) Although acute, mechanistic studies continue to yield promising results, managing sarcopenia and promoting healthy aging is more than a "protein synthesis" challenge.
- 3) Postprandial assessment of muscle protein breakdown is methodologically challenging, invasive, and often neglected.
- 4) Many of the negative outcomes associated with sarcopenia, such as falls, slow gait, and nursing home mortality, can be attributed to muscle weakness. Muscle mass is important, but integrating and optimizing strategies to preserve muscle strength and protect functional capacity to allow a more active, independent lifestyle should be a priority.
- 5) A deliberate and coordinated dietary-protein and exercise prescription may be particularly important for middle-aged and older adults experiencing catabolic stressors such as illness, inflammation, physical inactivity, or injury. In circumstances in which the ability to exercise is compromised, nutrition, and protein consumption in particular, represents one of the few opportunities to positively influence muscle protein anabolism and ultimately protect muscle mass and function.

PROTEIN QUANTITY: HOW MUCH PROTEIN DO OLDER ADULTS NEED?

In recent years, multiple consensus statements and opinion articles have argued that protein intakes between 1.0 and $1.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ may confer health benefits for aging adults beyond those afforded by the current Recommended Dietary Allowance (RDA)⁶ for protein (i.e., $0.8 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (4, 22–25). The RDA for protein is based on whole-body nitrogen equilibrium and provides an estimate of the minimum daily average dietary intake that meets the nutrient requirements of 97–98% of all healthy individuals (23, 26). Although the RDA for protein is quantitatively the same for all adults (male and female, young and old, sedentary and physically trained), older adults tend to consume less protein than younger adults, primarily due to reduced energy needs (22). Approximately one-third of adults >50 y of age fail to meet the RDA for protein, whereas an estimated 10% of older women fail to meet even the Estimated Average Requirement for protein ($0.66 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (23, 27). Although a discussion on protein requirements and the adequacy of the current RDA was a prominent theme throughout Protein Summit 2.0, discussion of protein requirements for older adults took a more prescriptive approach, focusing on optimizing protein intake at specific meals or eating opportunities, and netted the following:

⁶ Abbreviations used: AMPK, AMP-activated protein kinase; eEF2, eukaryotic elongation factor 2; mTOR, mammalian target of rapamycin; RDA, Recommended Dietary Allowance; S6K1, ribosomal protein S6 kinase $\beta 1$; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1.

Specific hypothesis 1: “Habitually consuming 25–30 g protein at breakfast, lunch, and dinner provides sufficient protein to effectively and efficiently stimulate muscle protein anabolism and may delay the onset of sarcopenia, slow its progression, and/or reduce the magnitude of its functional consequences.”

Meeting a protein threshold (~ 25 – 30 g/meal) represents a promising, yet relatively unexplored dietary strategy to help maintain muscle mass and function in older adults (28, 29). The majority of clinical trials and observational studies that consider protein consumption and issues such as adequacy and health outcomes focus on total daily protein consumption. The distribution of protein across ≥ 3 daily meals is seldom discussed despite the fact that NHANES data demonstrate that adults in the United States skew protein (and energy) consumption toward the evening meal (30) (**Figure 2**).

Acute muscle metabolism studies that explore exercise or dietary interventions occasionally draw criticism if they fail to accurately predict longer-term phenotypic, functional, or clinically relevant health changes (31, 32). Nevertheless, acute studies are often predictive and provide important prerequisite insight into mechanisms that regulate changes in muscle mass and function, which are needed to justify longer-term or larger-scale trials. Mamerow et al. (33) recently completed a 7-d crossover feeding study to measure changes in 24-h muscle protein synthesis in response to isonitrogenous diets with an even or skewed protein distribution. Over 24-h periods, muscle protein synthesis was 25% higher when the same quantity of protein was evenly distributed across breakfast, lunch, and dinner compared with a more common/typically skewed protein consumption pattern (**Figure 3**), an observation that favors conscious distribution of protein across daily meals.

The protein quantity/meal threshold concept was supported by a recent investigation that examined ingestion of 10, 20, and 35 g of whey protein during a continuous intravenous infusion of labeled L-phenylalanine and tyrosine in healthy older men (73 ± 2 y). The investigators found that amino acid absorption and subsequent stimulation of de novo muscle protein synthesis were limited after ingestion of 10 g of protein but increased substantially after the 20-g protein meal and was highest after ingestion of 35 g of protein (34).

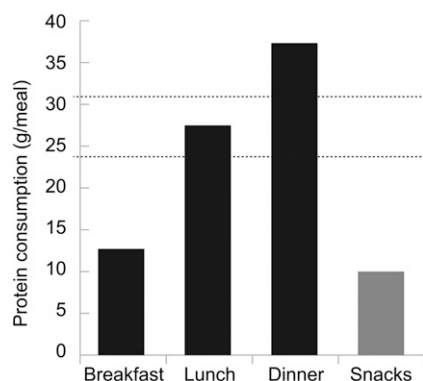


FIGURE 2 Protein consumption per meal for adults (aged ≥ 19 y) in the United States shows a skewed intake pattern. Data were adapted from NHANES 2001–2008 (30). The dotted line approximates the amount of protein required per meal to maximally stimulate muscle protein synthesis (59).

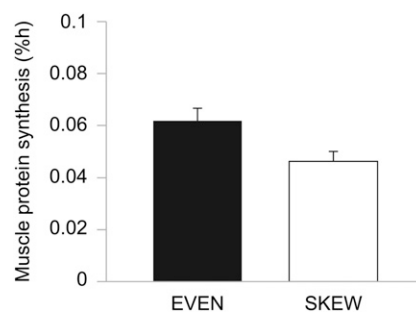


FIGURE 3 Twenty-four-hour mixed muscle protein fractional synthesis rates in healthy adults in response to diets with protein at breakfast, lunch, and dinner distributed evenly ($n = 8$; EVEN) or skewed (SKEW). EVEN: 31.5 ± 1.3 , 29.9 ± 1.6 , and 32.7 ± 1.6 g; SKEW: 10.7 ± 0.8 , 16.0 ± 0.5 , and 63.4 ± 3.7 g at breakfast, lunch, and dinner, respectively. Values are means $\pm$ SEMs. $P < 0.05$. Adapted from reference 33 with permission.

Most studies that examined the eating patterns of healthy older adults also support the hypothesis that daily protein consumption should focus on individual meals or specific eating opportunities, with breakfast providing the greatest opportunity to more evenly distribute the protein available that day (33). A recent clinical trial highlighted the importance of considering both the distribution and quantity of protein consumed over the course of a day (35). During a 6-wk randomized trial in hospitalized older adults, patients consumed diets that followed a “spread/distributed” protein intake pattern (0800 h: 12.2 g; 1200 h: 21 g; 1600 h: 13.5 g; 1900 h: 21.2 g) or a “pulsed/skewed” protein intake pattern (0800 h: 4.5 g; 1200 h: 47.8 g; 1600 h: 2.3 g; 1900 h: 10.9 g). Somewhat surprisingly, the “pulsed/skewed” pattern facilitated a modest, but significant improvement in lean mass compared with the “spread/distributed” protein diet. However, in this hospitalized and potentially anabolic-resistant older population, the quantity of protein consumed at each meal in the “spread/distributed” protein group (i.e., 12–21 g/meal) may have been insufficient to optimally stimulate postprandial muscle protein synthesis rates. This observation is consistent with a recent retrospective analysis that concluded that, compared with younger adults, older men require a greater relative protein intake to maximally stimulate muscle protein synthesis (36). To this end, a recent cross-sectional study in healthy adults (>60 y) reported a positive relation between daily protein distribution and appendicular skeletal muscle mass (37). Appendicular skeletal muscle mass was significantly higher in men and women consuming >25 g of protein/meal vs. those consuming less. Although this association was diminished after adjustment for body weight, sex, and height, the findings are intriguing and further study in a cohort setting may be worthwhile.

The distribution of protein throughout the day may also influence functional outcomes associated with frailty and quality of life, such as exhaustion and slow walking speed (38). Specifically, researchers noted that even though a cohort of frail, prefrail, and nonfrail elderly individuals consumed a similar absolute and relative amount of protein each day (dietary protein consumption of all study participants exceeded the RDA), the nonfrail individuals evenly distributed protein intake across their daily meals, whereas frail and prefrail individuals skewed their protein consumption toward the noon meal (38). In healthy, community-dwelling elderly individuals, protein intake at breakfast is consistently reported to be <20 g (37–39) and often composed

primarily of plant-based proteins and bread (40). These findings indicate that there is potential benefit for incorporating ~25–30 g protein into meals throughout the day to optimize postprandial skeletal muscle protein synthesis, an approach suggested by earlier work of Paddon-Jones and others (28, 29).

Snacking behaviors among older adults also warrant consideration when evaluating protein intake and distribution patterns (41). Although snacking may influence satiety and (positively or negatively) affect protein and energy consumption at subsequent meals, older adults who exhibit snacking behavior consume, on average, 6 g more protein daily than do their nonsnacking counterparts (41). Although small amounts of protein consumed during a snack are unlikely to acutely influence protein anabolism, there may be health benefits via mechanisms associated with blood glucose regulation, optimized total micronutrient and energy intake, and satiety (8) (see companion articles in this supplement). Recent cross-sectional study data also suggest that snacking may improve physical function among adults aged ≥ 60 y (42). Specifically, snacking frequency and percentage of energy from snacking were positively associated with gait speed among older adults participating in the 1999–2002 NHANES (43). Randomized trials designed to investigate the benefits or potential negative consequences of increased protein consumption at breakfast and the role of snacking on protein intake at meals are needed to more clearly define the role of meal frequency and protein distribution in maximizing muscle protein synthesis and functional outcomes for older adults. In total, these findings not only provide a rationale for consuming more protein in a prescribed pattern throughout the day but for consideration of protein source and quality.

PROTEIN QUALITY: DOES PROTEIN QUALITY AT EACH MEAL MATTER?

The essential amino acid profile, digestibility, and amino acid bioavailability of protein are critical determinants of its anabolic potential and quality (44–46). A recent FAO expert panel recommended “that dietary amino acids be treated as individual nutrients and that wherever possible data for digestible or bioavailable amino acids be given in food tables on an individual amino acid basis” and recommended the use of the Digestible Indispensable Amino Acid Score to be used to assess protein quality (47). The use of these amino acid profiles and scores for dietary prescription typically involves decisions on the proportion of animal and plant-based proteins in a diet.

Specific hypothesis 2: “Including high-quality protein at each meal improves postprandial muscle protein synthesis and may delay the onset of sarcopenia, slow its progression, and/or reduce the magnitude of its functional consequences.”

The 2010 *Dietary Guidelines for Americans* note that although animal-based proteins provide a better quality of protein, individuals consuming plant-based diets are still able to meet essential amino acid requirements (26). Relatively few studies directly compared the ability of animal vs. plant-derived proteins to chronically influence muscle mass or function (48, 49). Acute comparative studies are more common; however, until quite recently the majority of muscle metabolism studies favored the use of isolated amino acid cocktails (12, 50–52), whey (47, 53), or soy protein supplements (47, 53–55). Yang et al.

(55) reported a reduced ability of soy protein isolate to stimulate myofibrillar protein synthesis both at rest and after resistance exercise compared with whey protein isolate in older men (aged 71 y) fed a 20-g dose of protein. Differences were largely attributed to a lower postprandial increase in plasma leucine concentration after ingestion of soy protein. The branched-chain amino acid leucine plays a key role in translation initiation and is the focus of a considerable amount of ongoing research. In a recent study in older men (74 y), coingestion of 2.5 g leucine with 20 g casein resulted in a 22% higher muscle protein synthetic rate compared with ingestion of casein alone (56). A chronic improvement in muscle protein synthesis was also observed when leucine was added to the moderate-protein meals habitually consumed by older adults (4 g leucine/meal, 3 meals/d for 2 wk) (32).

Although enthusiasm for leucine’s anabolic potential continues to increase, there is clearly a concomitant message of moderation/saturation that needs to be considered. For example, in studies in which habitual protein intake exceeded $1.0\text{--}1.1\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ and included a moderate/high proportion of (higher leucine-containing) dairy protein, prolonged leucine supplementation ($3 \times 2.5\text{ g}$ daily) did not increase muscle mass or strength in healthy type 2 diabetic older adults (31, 57).

In recent years, an increasing number of studies have adopted a practical dietary approach by focusing on the ability of protein-rich foods (e.g., milk, beef, eggs) to stimulate protein anabolism (58–62). In general, the results of these studies are consistent with earlier trials that used specialized protein supplements and isolated amino acids. They confirmed that a variety of high-quality dietary protein foods are capable of enhancing muscle protein anabolism in both young and older adults.

The quality of protein was also demonstrated to have an effect on protein digestion, absorption, and whole-body and muscle anabolism in older subjects. For example, in older adults (72 ± 2 y), the ingestion of amino acids in a liquid form resulted in a greater postprandial plasma amino acid concentration compared with the same amino acids provided in solid form (63). In a somewhat similar study in a cohort of healthy older men (74 ± 2 y) that used a crossover design and stable isotope methodology, researchers noted that whereas minced beef was more rapidly digested and absorbed than whole steak and resulted in an enhanced whole-body protein balance, the difference did not translate to greater postprandial muscle protein synthesis rates (61). Data such as these provide a foundation for future trials to evaluate the importance not only of the biological quality but the

Meal	Appearance of amino acids in blood	Meal timing to hit peak anabolic window
Amino Acids Isolated Proteins (whey, soy, etc.)	10-20 minutes	Consume meal 0-60 minutes post exercise
Intact Proteins: beef, eggs, dairy	120+ minutes	Consume meal ~90 minutes before exercise

FIGURE 4 The timing of protein ingestion and exercise to optimize the potential for muscle protein anabolism should also consider practical issues such as exercise performance, satiety, gastric comfort, and hunger.

physical quality of protein and the matrix in which the protein is consumed on muscle mass preservation in older adults.

THE EFFECT OF PHYSICAL ACTIVITY AND PROTEIN

The combination of exercise and protein ingestion has a positive, often synergistic effect on skeletal muscle protein synthesis (16, 64). Recent analysis of NHANES data from Americans aged ≥ 50 y reinforces the synergistic relation between dietary protein intake, physical activity, and appendicular skeletal muscle mass. These data suggest that strength and aerobic-type exercise preserve muscle in older adults when combined with a dietary protein intake that meets or exceeds the current RDA (65). Creating an effective framework to maximize the synergistic effect of physical activity and protein intake in older adults requires consideration of not only protein quantity and type of physical activity but also how timing of ingestion may stimulate net muscle protein accretion.

Specific hypothesis 3: "Performing physical activity in close temporal proximity to a high-quality protein meal enhances muscle anabolism and may delay the onset of sarcopenia, slow its progression, and/or reduce the magnitude of its functional consequences."

Although the benefits of resistance and aerobic exercise training are unequivocal, any habitual physical activity is clearly preferable to no activity at all (1, 66–68). Even moderate amounts of walking or axial loading may impart a protective effect on muscle mass and metabolic health (69, 70). In a cohort of healthy older adults (72 ± 1 y), Breen et al. (70) recently demonstrated that a 76% reduction in total daily step count for 2 wk had a significant negative effect on postprandial muscle protein synthesis, insulin sensitivity, and systemic inflammatory markers. In longer-duration trials in healthy and frail older adults, consistent improvements in muscle mass and function most often occur in response to the combination of protein supplementation and exercise training (65, 71–75). However, if an older adult's habitual protein is already adequate (more than ~ 1.0 g protein $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$, evenly distributed), providing even more protein may confer limited or no additional benefits on skeletal muscle mass and function (18, 31).

Optimizing the timing of protein ingestion and exercise is a relatively simple strategy to maximize the potential for muscle protein anabolism. Acute cell signaling and stable isotope studies suggest that resistance exercise temporarily inhibits protein synthesis via increased AMP-activated protein kinase (AMPK) activation and reduced phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and other key regulators of translation initiation (12, 26, 28). However, ~ 60 min postexercise, the capacity for maximal muscle protein synthesis is restored and potentially increased via the activation of protein kinase B, mammalian target of rapamycin (mTOR), ribosomal protein S6 kinase $\beta 1$ (S6K1), and eukaryotic elongation factor 2 (eEF2) (75, 76). It remains to be seen if increasing plasma and intracellular amino acid availability at the onset of this rebound/recovery period offers an anabolic advantage (Figure 4). For older adults, consuming a moderate amount of protein at breakfast, lunch, and dinner could provide the necessary amino acid precursors and flexibility to allow at least some protein-exercise anabolic synergy, irrespective of

when the exercise session or activity of daily living is performed (15, 72, 77, 78).

CONCLUSIONS

The loss of muscle mass and function associated with sarcopenia has debilitating effects on older men and women. Skeletal muscle mass, function, and quality of life are influenced by a variety of modifiable behaviors. For all adults, optimizing the potential for muscle protein anabolism by consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, represents a promising strategy to prevent or delay the onset of sarcopenia. Research efforts continue to show great promise. Moving forward, multidisciplinary research combining human clinical trials and molecular biology, animal model, and cellular investigations is needed to continue to enhance our understanding of the role of protein in the regulation and maintenance of muscle mass and function during aging.

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