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Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group

Jürgen Bauer MD^{a,*}, Gianni Biolo MD, PhD^b, Tommy Cederholm MD, PhD^c, Matteo Cesari MD, PhD^d, Alfonso J. Cruz-Jentoft MD^e, John E. Morley MB, BCh^f, Stuart Phillips PhD^g, Cornel Sieber MD, PhD^h, Peter Stehle MD, PhDⁱ, Daniel Teta MD, PhD^j, Renuka Visvanathan MBBS, PhD^k, Elena Volpi MD, PhD^l, Yves Boirie MD, PhD^m

^a Geriatric Centre Oldenburg, Oldenburg, Germany

^b University of Trieste, Trieste, Italy

^c Uppsala University, Uppsala, Sweden

^d Université de Toulouse III Paul Sabatier, INSERM UMR1027, Toulouse, France

^e Hospital Universitario Ramón y Cajal, Madrid, Spain

^f Saint Louis University School of Medicine, St Louis, MO

^g McMaster University, Hamilton, Ontario, Canada

^h Friedrich-Alexander-University Erlangen-Nürnberg, Nürnberg, Germany

ⁱ University of Bonn, Bonn, Germany

^j Centre Hospitalier Universitaire Vaudois, Service de Néphrologie, Lausanne, Switzerland

^k University of Adelaide, Adelaide, Australia

^l University of Texas Medical Branch, Galveston, TX

^m Université d' Auvergne, INRA, CRNH, Centre Hospitalier Universitaire, Clermont-Ferrand, France

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New evidence shows that older adults need more dietary protein than do younger adults to support good health, promote recovery from illness, and maintain functionality. Older people need to make up for age-related changes in protein metabolism, such as high splanchnic extraction and declining anabolic responses to ingested protein. They also need more protein to offset inflammatory and catabolic conditions associated with chronic and acute diseases that occur commonly with aging. With the goal of developing updated, evidence-based recommendations for optimal protein intake by older people, the European Union Geriatric Medicine Society (EUGMS), in cooperation with other scientific organizations, appointed an international study group to review dietary protein needs with aging (PROT-AGE Study Group). To help older people (>65 years) maintain and regain lean body mass and function, the PROT-AGE study group recommends average daily intake at least in the range of 1.0 to 1.2 g protein per kilogram of body weight per day. Both endurance- and resistance-type exercises are recommended at individualized levels that are safe and tolerated, and higher protein intake (ie, ≥ 1.2 g/kg body weight/d) is advised for those who are exercising and otherwise active. Most older adults

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* Address correspondence to Jürgen Bauer, MD, Department of Geriatric Medicine, Klinikum Oldenburg, Geriatrics Centre Oldenburg, Rahel-Strauss-Straße 10, 26133 Oldenburg, Germany.

E-mail address: bauer.juergen@klinikum-oldenburg.de (J. Bauer).

who have acute or chronic diseases need even more dietary protein (ie, 1.2–1.5 g/kg body weight/d). Older people with severe kidney disease (ie, estimated GFR <30 mL/min/1.73m²), but who are not on dialysis, are an exception to this rule; these individuals may need to limit protein intake. Protein quality, timing of ingestion, and intake of other nutritional supplements may be relevant, but evidence is not yet sufficient to support specific recommendations. Older people are vulnerable to losses in physical function capacity, and such losses predict loss of independence, falls, and even mortality. Thus, future studies aimed at pinpointing optimal protein intake in specific populations of older people need to include measures of physical function.

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Guidelines for dietary protein intake have traditionally advised similar intake for all adults, regardless of age or sex: 0.8 grams of protein per kilogram of body weight each day (g/kg BW/d).^{1–3} The one-size-fits-all protein recommendation does not consider age-related changes in metabolism, immunity, hormone levels, or progressing frailty.⁴

Indeed, new evidence shows that higher dietary protein ingestion is beneficial to support good health, promote recovery from illness, and maintain functionality in older adults (defined as age >65 years).^{5–10} The need for more dietary protein is in part because of a declining anabolic response to protein intake in older people; more protein is also needed to offset inflammatory and catabolic conditions associated with chronic and acute diseases that occur commonly with aging.⁵ In addition, older adults often consume less protein than do young adults.^{11–13}

A shortfall of protein supplies relative to needs can lead to loss of lean body mass, particularly muscle loss.¹⁴ As a result, older people are at considerably higher risk for conditions such as sarcopenia and osteoporosis than are young people.^{15–17} In turn, sarcopenia and osteoporosis can take a high personal toll on older people: falls and fractures, disabilities, loss of independence, and death.^{4,16–18} These conditions also increase financial costs to the health care system because of the extra care that is needed.¹⁹

With the goal of developing updated evidence-based recommendations for optimal protein intake by older people, the European Union Geriatric Medicine Society (EUGMS), in cooperation with other scientific organizations, appointed an International Study Group led by Jürgen Bauer and Yves Boirie, and including 11 other members, to review dietary protein needs with aging (PROT-AGE Study Group). Expert participants from around the world were selected to represent a wide range of clinical and research specialties: geriatric medicine, internal medicine, endocrinology, nutrition, exercise physiology, gastroenterology, and renal medicine. This PROT-AGE Study Group reviewed evidence in the following 5 areas:

1. Protein needs for older people in good health;
2. Protein needs for older people with specific acute or chronic diseases;
3. Role of exercise along with dietary protein for recovering and maintaining muscle strength and function in older people;
4. Practical aspects of providing dietary protein (ie, source and quality of dietary proteins, timing of protein intake, and intake of protein-sparing energy);
5. Use of functional outcomes to assess the impact of age- and disease-related muscle loss and the effects of interventions.

PROT-AGE Methods

The PROT-AGE Study Group first met in July 2012, followed by numerous e-mail contacts. The group followed a Delphi-like process for consensus decision making: structured discussions,

evidence-based reasoning, and iterative steps toward agreement. The PROT-AGE Study Group represented the EUGMS, the International Association of Gerontology and Geriatrics (IAGG), the International Academy on Nutrition and Aging (IANA), and the Australian and New Zealand Society for Geriatric Medicine (ANZSGM). The recommendations developed by the PROT-AGE Study Group and represented here have been reviewed and endorsed by these participating organizations.

Recommended Protein Intake for Healthy Older People: Current Recommendations and Evolving Evidence

PROT-AGE recommendations for dietary protein intake in *healthy* older adults

- To maintain and regain muscle, older people need more dietary protein than do younger people; older people should consume an average daily intake in the range of 1.0 to 1.2 g/kg BW/d.
- The per-meal anabolic threshold of dietary protein/amino acid intake is higher in older individuals (ie, 25 to 30 g protein per meal, containing about 2.5 to 2.8 g leucine) in comparison with young adults.
- Protein source, timing of intake, and amino acid supplementation may be considered when making recommendations for dietary protein intake by older adults.
- More research studies with better methodologies are desired to fine tune protein needs in older adults.

Existing guidelines for dietary protein intake specify the same recommended dietary allowance (RDA) for all adults: 0.8 g/kg BW/d.^{1–3} In the view of the PROT-AGE working group, this recommendation is too low for older people. Evolving evidence supports the concept that lean body mass can be better maintained if an older person consumes dietary protein at a level higher than the general RDA.^{6–10,14,20,21} Recent research results also suggest other specific nutritional strategies to promote protein absorption and its efficient use in older people; such strategies deal with protein source, timing of intake, and specific amino acid content or supplementation.^{22–31}

The current dietary reference intake (DRI) for protein is based on nitrogen balance studies.³² The concept underlying nitrogen balance studies is that protein is the major nitrogen-containing substance in the body. Therefore, gain or loss of nitrogen from the body represents gain or loss of protein; the amount of protein required to maintain nitrogen balance reflects the amount of protein required for optimal health.¹ A nitrogen-balance study uses careful documentation of nitrogen intake, a diet adjustment period of 5+ days for individuals for each test level of intake, and a precise accounting of all nitrogen excreted. There are several limitations to nitrogen-balance studies, including the difficulty of quantifying all routes of nitrogen intake and loss, and the practical challenge of managing research studies with extended adaptation times; such limitations are likely to result in underestimation of protein requirements.⁶ In addition, a neutral nitrogen balance may not

reflect subtle changes in protein redistribution (eg, shifts between muscle and splanchnic tissues in older subjects).³³ Moreover, given the relatively slower rate of protein turnover in muscle, it is unlikely that significant changes in muscle mass, particularly in older persons, could be detected in short-term balance studies. These limitations underscore the challenges of determining protein intake requirements for all adults, as well as the difficulty in differentiating needs for men versus women or for older adults versus younger adults.³² Although other methods, including carbon balance³⁴ and amino acid indicator studies,^{35–37} have been used to estimate protein requirements, they are still not currently considered as robust as the nitrogen balance method.¹

Protein Intake and Utilization Affect Functionality in Older Adults

Determining the appropriate protein intake for older adults is important because inadequate intake contributes to increased risk for common age-associated problems, such as sarcopenia, osteoporosis, and impaired immune responses.^{15–17,38} The following 3 factors variously influence protein use in older individuals: inadequate intake of protein (eg, anorexia or appetite loss, gastrointestinal disturbances), reduced ability to use available protein (eg, insulin resistance, protein anabolic resistance, high splanchnic extraction, immobility), or a greater need for protein (eg, inflammatory disease, increased oxidative modification of proteins), all of which point to a need to understand the role of dietary protein in maintaining functionality in older people (Figure 1).

Benefits of Higher Protein Intake for Older Adults

Epidemiological studies and clinical trials support the need for higher protein intake by older adults. Several epidemiological studies have found a positive correlation between higher dietary protein intake and higher bone mass density^{39–41}; slower rate of bone loss⁴²; and muscle mass and strength.⁴³ One epidemiological study showed a positive association between higher dietary protein intake and fewer health problems in older women.⁴⁴

With data from the Health, Aging, and Body Composition (Health ABC) Study, Houston et al¹⁴ were able to assess the association between dietary protein intake and changes in lean body mass (LBM) over a 3-year period in healthy, older adults ($n = 2066$). In this study, dietary protein intake was assessed by using a food-frequency questionnaire; changes in LBM were measured using dual-energy x-ray absorptiometry (DEXA). After adjustment for potential confounders (eg, demographic characteristics, smoking

status, alcohol consumption, physical activity), energy-adjusted protein intake was associated with 3-year changes in LBM ($P = .004$); participants in the highest quintile of protein intake lost approximately 40% less LBM than did those in the lowest quintile of protein intake. These results remained significant even after adjustment for changes in fat mass. Although causality cannot be established, these results do suggest a close relationship between higher protein intake and maintenance of skeletal muscle mass in older adults.

Several short-term metabolic studies investigated the differences in protein synthesis and breakdown (both whole-body and skeletal muscle) between younger and older adults.^{45–47} Given the complex nature of the aging process,⁴⁸ it is not surprising that the combined results of these studies are inconclusive, and sometimes contradictory, for the fasted state. In the fed state, however, most researchers now agree that there is an impairment of the muscle protein anabolic response to meal intake in older adults,^{46,49,50} although some studies found no difference between older and younger adults, especially when high amounts of amino acids or proteins were administered. Abnormal muscle protein anabolism may result from inadequate nutritional intake (lower anabolic signal) or from impaired response to nutrients and hormones (lower sensitivity), that is, anabolic resistance.⁵ For such anabolic resistance, several new strategies aim to improve postprandial anabolic signaling or sensitivity to nutrients. These include providing sufficient protein/amino acid intake to maximize muscle protein anabolism and/or using exercise to improve sensitivity to nutrients and hormones (particularly insulin).^{51–53} Additionally, supplementation of anabolic nutrients, such as specific amino acids (eg, leucine), different distribution of the protein intake over the daily meals, or selection of proteins with different digestion profiles (“slow” and “fast” proteins concept), are new strategies. These innovative strategies, especially those combining nutritional and physical preventive strategies, are discussed later in this article.

Longer-term protein intake studies in older adults are scarce. In one intervention study of intermediate length, Campbell et al²¹ found that consuming the RDA for protein resulted in the loss of mid-thigh muscle area over a 14-week period in healthy older adults ($n = 10$). Although whole body composition (% body fat, fat-free mass, and protein + mineral mass) and weight did not change over the course of the intervention, mid-thigh muscle area was significantly decreased ($P = .019$), suggesting that metabolic adaptation may have occurred and the RDA for protein was not adequate to meet the metabolic and physiological needs of these individuals. These findings highlight how

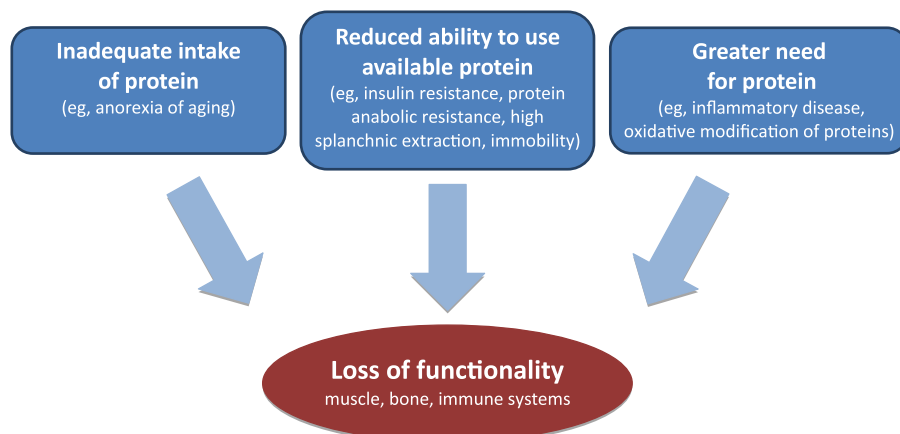


Fig. 1. Aging-related causes of protein shortfall. Such protein deficits have adverse consequences, including impairment of muscular, skeletal, and immune function.

changes in muscle tissue are not always reflected at the whole-body level.

Concerns are frequently raised regarding the impact of high-protein diets on renal function, particularly in older persons. However, reviews of research studies reveal little or no evidence that high-protein diets cause kidney damage in healthy individuals, including those who are older.^{6,54,55} Given the available data, a recommendation of protein intake at 1.0 to 1.2 g/kg BW/d is expected to help maintain nitrogen balance without affecting renal function, especially until results of additional studies are available.⁶

Protein intake recommendations for individuals with kidney disease are presented later in this article.

Specific Nutritional Strategies to Achieve Optimal Protein Utilization

Specific feeding strategies represent advancing refinement in our understanding of protein synthesis in older adults. Strategies include feeding to optimize protein digestion and absorption by specifying the type of protein, addition of specific amino acids or fatty acids to enhance protein synthesis, and specifying per-meal protein quantity and timing of intake (Table 1).

For timing and amount of intake, older individuals appear to have a higher per-meal protein threshold to promote anabolism (ie, 25 to 30 g protein per meal containing about 2.5 to 2.8 g leucine).⁵⁰

This evidence suggests benefits to even distribution of protein at breakfast, lunch, and supper; however, recent studies have also shown anabolic benefits from pulse feeding (ie, a main high-protein meal, usually at midday).^{56,57} Additional clinical studies are needed to determine whether both feeding patterns are effective or whether one is clearly favored over the other. Such strategies should be tested in both long- and short-term clinical interventions.

Specific Recommendations on Dietary Protein Intake by Healthy Older People

Current guidelines for protein intake in older adults are identical to those for younger adults. In particular, the most commonly used benchmark for dietary recommendations, the RDA, is defined by the minimum amount of daily protein necessary to prevent deficiency in 97% of the population. However, present recommendations (0.8 g/kg BW/d), are based on adult studies and do not take into account the many body changes that occur with aging, so they may not be adequate to maintain, or help regain, muscle mass in the older population. Although longer-term studies are needed, research to date supports increasing this recommendation from the current 0.8 g/kg BW/d to a range of at least 1.0 to 1.2 g/kg BW/d (Table 2). Although this change represents a significant increase,

Table 1
Some Examples of Nutritional Strategies to Enhance Optimal Protein Synthesis

Strategy	Reference	Outcomes
Protein source: animal-based vs vegetable-based protein	Pannemans 1998 ²⁷ Luiking 2011 ⁵⁸	Net protein synthesis was lower with a high vegetable-protein diet than with a high animal-protein diet. Moderate-nitrogen casein and soy protein meals affected leg amino acid uptake differently but without significant differences in acute muscle protein metabolism.
Protein source: whey vs casein	Boirie 1997 ⁵⁹ Dangin 2002 ⁶⁰ Pennings 2011 ⁶¹	The speed of protein digestion and amino acid absorption from the gut had a major effect on whole body protein anabolism after one single meal. "Slow" and "fast" proteins thus modulate the postprandial metabolic response. A "fast" protein was more effective than a "slow" protein for limiting body protein loss in older subjects. Whey protein stimulated postprandial muscle protein accretion more effectively than either casein or casein hydrolysate in older men.
Protein source & exercise: whey vs casein	Burd 2012 ³⁰	Ingestion of isolated whey protein supported greater rates of myofibrillar protein synthesis than micellar casein both at rest and after resistance exercise in healthy older men.
Protein feeding pattern	Paddon-Jones 2009 ²³ Arnal 1999 ³¹ Bouillane 2013 ⁵⁶	Review article proposes a dietary plan that includes 25–30 g of high-quality protein per meal (spread feeding) in order to maximize muscle protein synthesis. A protein pulse-feeding pattern (most protein at midday) was more efficient than a spread-feeding pattern in improving whole-body protein retention in older women. A protein pulse-feeding pattern (midday) had a positive and greater effect on lean mass in malnourished and at-risk hospitalized elderly patients than a protein spread-feeding pattern.
Amino acid supplementation: essential amino acids	Volpi 2003 ⁴⁵	Essential amino acids were primarily responsible for the amino acid-induced stimulation of muscle protein anabolism in older adults.
Amino acid supplementation: leucine	Wall 2012 ²⁵ Katsanos 2006 ²⁸ Rieu 2006 ⁶²	Co-ingestion of leucine with a bolus of pure dietary protein further stimulated postprandial muscle protein synthesis rates in older men. Increasing the proportion of leucine in a mixture of essential amino acids reversed an attenuated response of muscle protein synthesis in older adults, but did not result in further stimulation of muscle protein synthesis in young subjects. Leucine supplementation during feeding improved muscle protein synthesis in older adults independently of an overall increase of other amino acids. It is not known whether high leucine intake can limit aging-related loss of muscle protein.
Fatty acid supplementation: omega-3 fatty acid & insulin sensitivity of protein synthesis	Smith 2011 ²⁶	Omega-3 fatty acid supplementation augmented the hyperaminoacidemia-hyperinsulinemia-induced increase in the rate of muscle protein synthesis, which was accompanied by greater increases in muscle mTOR (mammalian target of rapamycin) ($P = .08$) and p70s6k ($P < .01$) phosphorylation.
Timing of protein and exercise	Jordan 2010 ²⁹ Esmark 2001 ⁶³ Cermak 2012 ⁵³	Older individuals were better able to maintain nitrogen balance by consuming a high-quality protein source following exercise as opposed to consuming the identical protein several hours before exercise. Immediate intake of an oral protein supplement after resistance training increased muscle mass as well as dynamic and isokinetic strength in older men, whereas delayed intake improved only dynamic strength. Protein supplementation increases muscle mass and strength gains during prolonged resistance-type exercise training in both younger and older subjects

this value, which is approximately 13% to 16% of total calories, is still well within the acceptable macronutrient distribution range (AMDR) for protein (10%–35% of total daily calories) according to the Institute of Medicine.⁶

Protein Recommendations in Acute and Chronic Diseases

PROT-AGE recommendations for protein levels in geriatric patients with specific acute or chronic diseases

- The amount of additional dietary protein or supplemental protein needed depends on the disease, its severity, the patient's nutritional status prior to disease, as well as the disease impact on the patient's nutritional status.
- Most older adults who have an acute or chronic disease need more dietary protein (ie, 1.2–1.5 g/kg BW/d); people with severe illness or injury or with marked malnutrition may need as much as 2.0 g/kg BW/d.
- Older people with severe kidney disease (ie, estimated glomerular filtration rate [GFR] < 30 mL/min/1.73m²) who are not on dialysis are an exception to the high-protein rule; these individuals need to limit protein intake.

Protein Needs and Recommendations in Older Populations With Disease or Injury

Many healthy older adults fail to eat enough dietary protein, but the situation is worsened when they are sick or disabled. When older adults have acute or chronic diseases, their activities are more limited, they are less likely to consume adequate food, and they fall farther behind in energy and protein intake.^{67,68} As a result, malnourished older people recover from illness more slowly, have more complications, and are more frequently admitted to hospitals for longer stays than are healthy older adults.^{67,68}

Most experts agree that when a person has an acute or chronic disease, his or her needs for protein increase. Guidelines for critically ill adults^{69–71} advise that adequate energy should be provided along with protein for a protein-sparing effect. Energy requirements are preferably determined by indirect calorimetry. When calorimetry is unavailable, an estimation (eg, 25 kcal/kg/d) or appropriate predictive equation taking into account resting energy expenditure plus factors for activity level and stress is recommended.

The American Society for Parenteral and Enteral Nutrition (ASPEN) standards for critically ill adults call for adjusting both protein and energy level for obese patients.⁷⁰ In the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, Weijs et al⁷² propose using “ideal body weight” to more accurately estimate protein requirements for underweight (body mass index [BMI] <20 kg/m²) and obese (BMI >30 kg/m²) patients. Some recommendations are specific to protein, whereas others recommend protein as part of an oral nutrition supplement (ONS) or enteral nutrition formula.

With increased protein intake, older people may experience improved bone health, cardiovascular function, wound healing, and recovery from illness.⁷³ These benefits also have the potential to help older people meet the health challenges of illness. The latest Cochrane update from 2009 indicates that protein-energy supplementation reduces mortality, especially in older, undernourished subjects and in patients with geriatric conditions.⁷⁴

Table 3 summarizes studies and recommendations for protein intake in older people who are hospitalized in ward or critical care settings.

Hospitalized older adults

Results of a retrospective study of undernourished older people in a Dutch hospital (n = 610) showed that only 28% met protein targets (n = 172).⁷⁸ For the study, subjects were identified by nutrition

screening on admittance. Of those screened, 15% were malnourished and included in the study; 40% of patients older than 65 had multiple diseases. Energy targets were determined with the Harris-Benedict equation, then adjusted by +30% for activity or disease; protein targets were 1.2 to 1.7 g protein/kg BW/d.

In a French study, the sickest patients in a group of older adults in short- or long-stay care settings were found to be the most undernourished, and fell particularly short of protein targets (intake of 0.9 g protein/kg BW/d, compared with 1.5 g/kg BW/d goal). Patients categorized to be at a nutritional “steady state” were able to meet their energy and protein goals (25–30 kcal/kg BW/d and 1.0 g protein/kg BW/d).⁷⁹

Frailty

The frailty syndrome has a place on the continuum between the normal physiological changes of aging and the final state of disability and death.^{4,80} Frailty worsens age-related changes in protein metabolism, further increasing muscle protein catabolism and decreasing muscle mass.⁸¹ Higher protein consumption has been associated with a dose-responsive lower risk of incident frailty in older women.⁸² Incorporating more protein into the diet is thus a rational strategy for frailty prevention.

Hip fracture

Older adults (average age 84) with hip or leg fracture who entered the hospital undernourished did not meet estimated energy or protein targets. Individual energy requirements were estimated by age, gender, activity level, and disease-related metabolic stress; protein requirements were estimated at 1.0 g protein/kg BW/d. With diet alone, patients were able to meet only 50% of energy and 80% of target protein intake.⁸³ Considerable evidence supports the concept that supplemental protein or higher dietary protein intake by older people hospitalized for hip fracture could reduce risk for complications,^{74,84,85} improve bone mineral density,^{86,87} and reduce rehabilitation time (Table 4).⁸⁶

Osteoporosis

In older people with osteoporosis, findings from a systematic review,⁸⁸ several prospective cohort studies,^{89,90} and a randomized, controlled trial⁹¹ (RCT) all found higher bone mineral density when protein intake was at levels higher than 0.8 g/kg BW/d or was 24% of total energy intake (Table 4).

Stroke

In patients with stroke (69.0 ± 11.3 years), Foley et al⁹² found that the actual intake failed to meet energy or protein targets, reaching just 80% to 90% of either target in the first 21 days of hospitalization. Energy targets were set using measured energy expenditure (plus 10% for bedridden or 20%–40% for ambulatory patients); protein targets were 1.0 g/kg BW/d, above the healthy adult level to allow for the additional physiological demands of stroke. Enterally fed patients in the study, unlike patients on regular or dysphagia diets, were able to meet or exceed energy or protein goals at some of the 5 evaluation points.

Pressure ulcer

Results of an observational study in a small group of older patients (71 ± 10 years) hospitalized for surgical repair of chronic pressure ulcers, showed that intake from normal hospital meals covered only 76% of patients' energy requirements. Oral nutrition supplements were necessary to achieve both energy and protein requirements.⁹³ A report from Health Quality Ontario (2009) indicated that protein supplementation improved healing score when compared with a placebo.⁹⁴

Table 2
Summary of Recommendations for Dietary Protein Intake in Healthy Older Adults

Reference	Recommendation	Authors' Comment
Paddon-Jones 2012 ⁵⁰	1.0–1.3 g/kg BW/d	... we argue that while a modest increase in dietary protein beyond the RDA may be beneficial for some older adults (perhaps 1.0–1.3 g/kg per day), there is a greater need to specifically examine the quality and quantity of protein consumed with each meal.
Wolfe 2012 ⁶⁴	>0.8 g/kg BW/d, but no specific value given	Since there is no evidence that a reasonable increase in dietary intake adversely affects health outcomes, and deductive reasoning suggests beneficial effects of a higher protein intake, it is logical to recommend that the optimal dietary protein intake for older individuals is greater than the recommended dietary allowance of 0.8 g protein/kg/d.
Volpi 2012 ⁶⁵	>0.8 g/kg BW/d, but no specific value given	Although the RDA of protein is probably sufficient for most sedentary or low-active adults to avoid protein inadequacy, it may not provide a measure of optimal intake to maintain health and maximize function in older adults. Avoidance of net nitrogen losses may be an inadequate outcome for older sarcopenic individuals, for whom net lean mass gains are desirable.
Morley 2010 ¹⁰	1.0–1.5 g/kg BW/d	As 15% to 38% of older men and 27%–41% of older women ingest less than the recommended daily allowance for protein, it is suggested that protein intake be increased.
Gaffney-Stomberg 2009 ⁶	1.0–1.2 g/kg BW/d	Given the available data, increasing the RDA to 1.0 to 1.2 g/kg per day (or approximately 13%–16% of total calories) would maintain normal calcium metabolism and nitrogen balance without affecting renal function and still be well within the acceptable range according to the IOM. ² Therefore, increasing the RDA to 1.0 to 1.2 g/kg per day for elderly people may represent a compromise while longer term protein supplement trials are still pending.
Morais 2006 ⁶⁶	1.0–1.3 g/kg BW/d	Data from published nitrogen balance studies indicate that a higher protein intake of 1.0–1.3 g/kg/d is required to maintain nitrogen balance in the healthy elderly, which may be explained by their lower energy intake and impaired insulin action during feeding compared with young persons.

A Japanese cross-sectional nitrogen balance survey of older adults with pressure ulcers (n = 28) found that the average daily protein requirement for these subjects to achieve nitrogen balance was 0.95 g/kg BW/d, but protein requirements varied according to an individual's condition and wound severity and ranged from 0.75 to 1.30 g/kg BW/d.⁹⁵

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) presents multiple nutritional challenges. People with COPD have a need for greater supplies of energy and protein to meet higher energy expenditure, in part from the increased work of breathing and the inflammatory process of the disease, and, when also insulin-resistant, decreased protein anabolism.^{96,97} In the face of these challenges, patients with COPD are generally underweight, and several studies show they have a lower fat-free mass than healthy people.⁹⁶ Aniwidyansih and

colleagues⁹⁶ recommended high-protein ONS with 20% kcal from protein. However, evidence is limited, so further studies are necessary, especially in older people with COPD.

Cardiac disease

Guidelines from Spain recommended protein intake at 1.2 to 1.5 g/kg ideal BW/d for all adult critically ill patients with cardiac disease who are hemodynamically stable.⁹⁸ They also recommended adequate energy, 20 to 25 kcal/kg/d.

In addition, Aquilani et al⁹⁹ found that cardiac patients given supplemental amino acids had improved exercise capacity and shortened postexercise recovery time. The RCT involved 95 community-living patients with chronic heart failure (74 ± 5 years) who received supplemental amino acids twice a day (8 g amino acids per day) for 30 days along with standard pharmacologic therapy.

Table 3
Summary: Recommendations and Evidence on Dietary Protein Intake in Older Adults With Illness or Other Complicating Medical Conditions

Reference	Protein Recommendation	Description
General		
Cawood 2012 ⁷³	High protein ONS: >20% kcal from protein	<ul style="list-style-type: none"> • Meta-analysis of 11 RCTs in community patients aged 65 years and older with hip fracture, leg and pressure ulcers, and acute illness • High protein given as part of multinutrient ONS • Significant reduction in the incidence of complications
Gaillard 2008 ⁷⁵	1.06 ± 0.28 g/kg BW /d (minimum requirement) so that 1.3–1.6 g/kg/d as safe protein intake	<ul style="list-style-type: none"> • Mean safe protein intake needed to reach neutral nitrogen balance in 36 older patients (age 65–99) hospitalized in short-stay geriatric wards and rehabilitation care units
Morais 2006 ⁷⁶	>1.0–1.3 g/kg BW/d	<ul style="list-style-type: none"> • Nitrogen balance studies indicate that healthy older people require 1.0–1.3 g/kg BW/d; even higher protein-intake levels may help restore muscle and function for older people who have become frail.
Critical illness		
Wejls 2012 ⁷⁷	1.2–1.5 g/kg preadmission BW/d	<ul style="list-style-type: none"> • Study of 886 critically ill patients with various medical or surgical conditions who required extended mechanical ventilation; average age, 63 ± 16 years • 245 patients who reached predefined protein and energy targets experienced nearly a 50% decline in 28-day mortality
Singer 2009 ⁷¹ Fürst 2011 ⁶⁹ All adults	1.3–1.5 g/kg ideal BW/d	<ul style="list-style-type: none"> • ESPEN Guidelines for parenteral nutrition for all adults in intensive care—not specific to older adults • Provide energy adequate to meet the patient's measured expenditure (without indirect calorimetry, use 25 kcal/kg/d)
McClave 2009 ⁷⁰ All adults	1.2–2.0 g/kg BW/d	<ul style="list-style-type: none"> • ASPEN Guidelines for patients with BMI <30; may be higher in patients with burns or multiple traumas • Provide energy adequate to meet the patient's measured expenditure (without indirect calorimetry, use predictive equations unless patient is obese) • Critically ill obese adult: reduced energy and higher protein is recommended; refer to guideline for details

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index; BW, body weight; ESPEN, European Society for Clinical Nutrition and Metabolism; ONS, oral nutrition supplement; RCT, randomized controlled trial.

Table 4
Summary: Recommendations and Evidence on Dietary Protein Intake by Older People With Hip Fracture or Osteoporosis

Reference	Protein Recommendation	Description
Hip fracture		
Avenell 2010 ⁸⁴	Not specified	<ul style="list-style-type: none"> Review of patients recovering from hip fracture; most were > 65 years old Based on 4 studies addressing protein intake, protein supplementation may reduce the number of long-term complications
Botello-Carretero 2010 ⁸⁵	1.4 g/kg BW/d compared to 1.0 g/kg BW/d	<ul style="list-style-type: none"> RCT of 60 normal or mildly undernourished older patients (age 85.0 ± 4.4 years) undergoing surgery for hip fracture High protein given perioperatively as part of multivitamin ONS Tendency for fewer complications in the supplemented group
Milne 2009 ⁷⁴	Not specified	<ul style="list-style-type: none"> Review of 62 trials of protein-energy supplementation in older people (≥ 65 years old) 24 studies looked at morbidity; meta-analysis found there may be a reduced risk of complications with supplementation for hip fracture patients (RR 0.60; 95% CI 0.40 to 0.91)
Tengstrand 2007 ⁸⁷	20 g extra/d	<ul style="list-style-type: none"> RCT for 6 months in lean women after hip fracture showing improved BMD with protein supplementation
Schurch 1998 ⁸⁶	20 g extra/d	<ul style="list-style-type: none"> RCT with 82 patients with recent hip fracture, 20 g proteins day for 6 months increased IGF-1, decreased loss of BMD and reduced hospital stay.
Osteoporosis		
Darling 2009 ⁸⁸	Not specified	<ul style="list-style-type: none"> A systematic review indicating a small positive effect of protein supplementation on lumbar spine BMD
Meng 2009 ⁹⁰	1.6 g/kg BW/d vs 0.85 g/kg BW/d	<ul style="list-style-type: none"> 5-year prospective cohort study showing higher BMD with higher protein intake
Devine 2005 ⁸⁹	>0.84 g/kg BW/d vs <0.84 g/kg BW/d	<ul style="list-style-type: none"> 1-year prospective cohort study showing higher BMD with higher protein intake
Dawson-Hughes 2004 ⁹¹	High protein diet (24% of energy) vs low protein diet (16% of energy)	<ul style="list-style-type: none"> RCT in 32 old subjects for 9 weeks, BMD increased in the higher protein group

BMD, bone mass density; BW, body weight; CI, confidence interval; IGF-1, insulin-like growth factor 1; ONS, oral nutrition supplement; RCT, randomized controlled trial; RR, relative risk.

Diabetes

For older people with diabetes, dietary recommendations, including protein recommendations, depend on the individual's nutritional status, as well as on comorbid conditions. However, diabetes is associated with a faster loss of muscle strength and a higher rate of disability. An older person with diabetes and sarcopenic obesity may benefit from increased dietary protein intake, whereas someone with diabetes and severe kidney nephropathy may need to follow a protein-restricted diet. In developed countries, diabetes is the leading cause of chronic kidney disease, and in the United States, accounts for nearly half of all kidney failure.¹⁰⁰ Recent guidelines from the American Geriatrics Society stress the importance of an individualized treatment approach for diabetic adults who are frail or have multiple comorbid conditions.¹⁰¹ Table 5 summarizes protein recommendations and study results for older people with diabetes.

Diabetes without kidney disease

The American Diabetes Association recommends normal protein intake (15%–20% of daily energy) as long as kidney function is normal. Not enough is known about the effect of high-protein diets

(>20% of daily energy) to evaluate their safety.¹⁰⁴ However, a recent study of older patients (upper age limit: 75 years) with moderate Type 2 diabetes (HbA_{1c} about 7.9%) but no kidney disease, showed that those who ate a high-protein diet (about 30% kcal from protein) tended to require fewer glucose-lowering medications after 1 year, compared with their baseline medication levels.¹⁰⁵

Diabetes with kidney disease

Robertson et al¹⁰³ conducted a systematic review of the effects of low-protein diets in people with Type 1 or 2 diabetes and diabetic nephropathy (very few older adults included). When possible, RCT results were combined for meta-analysis. In 7 studies of Type 1 diabetes, a low-protein diet appeared to slow the progression of diabetic nephropathy, but not significantly. A review of 4 studies among people with Type 2 diabetes again noted small but insignificant reductions in the rate of declining kidney function in 3 of them. Accordingly, the Kidney Disease Outcomes Quality Initiative of the American National Kidney Foundation (KDOQI) guidelines call for adults with chronic kidney disease (CKD) and diabetes to follow the same low-protein diets (0.8 g protein/kg BW/d) as people with CKD, although there is little evidence for adults older than 75.¹⁰⁰

Table 5
Summary: Recommendations and Evidence Supporting Dietary Protein Intake in Older Adults With Diabetes

Reference	Protein Recommendation	Description
Diabetes without nephropathy		
Larsen 2011 ¹⁰²	High-protein diet (30% of kcal from protein)	<ul style="list-style-type: none"> RCT of 99 older adults (≥60 years old) with type 2 diabetes, HbA_{1c} 7.9% Those who ate a diet with about 30% of kcal from protein required 8% fewer diabetes medications (primarily insulin and sulfonylurea therapies) after 1 year, compared to baseline medication levels
Diabetes with nephropathy		
Robertson 2007 ¹⁰³	Low-protein diet (0.8 g/kg BW/d)	<ul style="list-style-type: none"> Systematic review of low protein diets in adults with Type 1 or 2 diabetes and diabetic nephropathy (few were ≥65 years). Results of 7 studies of Type 1 diabetes were combined in a meta-analysis; a low protein diet appears to slow the progression of diabetic nephropathy, but not significantly 4 studies of Type 2 diabetes noted small but nonsignificant reductions in the rate of kidney function decline in 3 of them

RCT, randomized controlled trial.

Other experts argue that low-protein diets may not be appropriate for all people with Type 2 diabetes. Koya et al¹⁰⁶ conducted a clinical trial in 88 people (average age approximately 57 ± 8 years) with Type 2 diabetes and nephropathy, randomizing patients to follow a diet with low protein (0.8 g/kg BW/d) or higher protein (1.2 g/kg BW/d) for 5 years. Findings showed that the low-protein diet did not appear to slow the rate of progression of nephropathy. Researchers noted it was extremely difficult for patients to maintain the low-protein diet,^{107,108} and they concluded that uncertain renal protection may not be worth the risk of malnutrition.¹⁰⁷

For older adults with diabetes and mid- to late-stage CKD, some experts¹⁰⁹ argue that the effect of the modest delay in progression of diabetic CKD is too small, with a benefit that accrues across a term that may be longer than an older patient's available time horizon. Furthermore, people frequently reduce their protein intake spontaneously as they age.

Kidney Function and Kidney Disease

Increased protein intake can help improve muscle health and functionality in older people. However, aging is associated with decline in kidney function; thus, clinicians are concerned that high-protein diets will stress kidney function. The key question is, "At what level of kidney impairment does higher protein intake do more harm than good?"

Recent evidence from a large, 5-year prospective cohort study found that older women (most older than 60, but not older than 79) with normal or slightly impaired kidney function and consuming higher protein than the RDA (an average of 1.1 g protein/kg BW/d), did not experience a reduction in renal function.¹¹⁰ Similarly, among older women in the Nurses' Health Study (56.0 ± 6.6 years at start of study, but not older than 68) who had normal renal function, protein intake was not associated with declining GFR over 11 years.¹¹¹ However, among women with mild kidney insufficiency at the start of the study, high protein intake (particularly nondairy animal protein) was associated with more rapid GFR decline than expected.¹¹¹

In patients with nondiabetic CKD stages 3 and 4 (moderate to severe) up to age 70, there is evidence that low-protein diets can slow the progression of CKD.^{112–114} Compared with a non-protein-limited diet, a low-protein diet of 0.6 g/kg BW/d can prevent a decline in GFR of approximately 1 mL/min per year per 1.73 m² and is associated with a 30% decrease in reaching a dialysis-dependent stage.^{114,115} However, there are concerns about the safety of low-protein diets, in particular when patients are not adequately monitored regarding nutritional indicators. In patients with well-controlled CKD enrolled in an RCT, a small but significant decline in nutrition indicators, essentially muscle mass, has been observed.¹¹⁶ When a low-protein diet is prescribed, nutritional counseling advocating an energy intake of 30 kcal/kg

BW/d is necessary to maintain a neutral nitrogen balance. In addition, a regular nutritional follow-up by a renal dietician is recommended to detect early signs of malnutrition. Under those conditions, the development of malnutrition during a low-protein diet is an extremely rare event.¹¹⁵ As a safety precaution, malnourished patients and patients under stress conditions (eg, hospitalization or surgery) should not follow a protein-restricted diet.

An Italian RCT of older (≥70 years) patients with CKD who were close to starting dialysis¹¹⁷ showed that a very low protein diet with 0.3 g/kg BW/d, supplemented with keto-analogues, amino acids, and vitamins, delayed the start of dialysis by approximately 11 months compared with a control group who followed a nonrestricted protein diet and immediately started dialysis. Compared with the control group, patients who were prescribed a very low protein diet had similar mortality rates and their nutritional status was maintained. It is important to mention that patients enrolled in the study were not malnourished at baseline, and that they received nutritional counseling and follow-up nutritional care to maintain intake at 35 kcal/kg BW/d.

In a retrospective Dutch study of older patients (average age 65) with uncomplicated advanced CKD, a diet of 0.6 g protein/kg BW/d with nutritional counseling helped delay the start of dialysis by 6 months, with no difference in mortality compared with a control group not receiving a low-protein diet.¹¹² Nonetheless, some experts remain concerned about prospects for survival in older patients with CKD with sarcopenia, or depleted muscle mass. These experts call for 0.8 g protein/kg BW/d as a measure to help maintain fat-free mass and improve survival prospects (Table 6).^{113,118}

The International Society of Renal Nutrition and Metabolism (ISRNM) has recently developed new dietary recommendations for people with CKD, including patients not on dialysis as well as those on peritoneal or hemodialysis.¹¹⁹ Because patients with kidney disease are at risk of protein-energy wasting, 30 to 35 kcal/kg BW/d is recommended. In patients not on dialysis, protein intake of 0.6 to 0.8 g/kg BW/d is recommended for people who are well and 1.0 g/kg BW/d for those with disease or injury. Once maintenance dialysis begins, a diet with higher protein is necessary to overcome nutritional depletion of the dialysis procedure. Experts currently recommend more than 1.2 g/kg BW/d to compensate for the spontaneous decline in protein intake and the dialysis-induced catabolism.¹¹⁹ It is recommended that more than 50% of the protein consumed be of high biological value (ie, complete protein sources containing the full spectrum of amino acids).

PROT-AGE recommendations for older people reflect the ISRNM guidelines, providing as much protein as possible for patients not on dialysis based on actual kidney function (measured as GFR).¹¹⁹

In a recent year-long study of older people with CKD (65 ± 14 years) on hemodialysis, patients were offered high-protein,

Table 6
Recommended Energy and Protein Intakes for Patients With CKD

Nondialysis CKD		Hemodialysis	Peritoneal Dialysis
PROT-AGE recommendations for older people with kidney disease	<ul style="list-style-type: none"> • Severe CKD, GFR <30*: Limit protein intake to 0.8 g/kg BW¹/d • Moderate CKD, 30 <GFR <60: Protein >0.8 g/kg BW¹/d is safe, but GFR should be monitored 2x/year • Mild CKD, GFR >60: Increase protein intake per patient needs 	>1.2 g/kg BW ¹ /d or, if achievable, 1.5 g/kg BW ¹ /d [‡]	>1.2 g/kg BW ¹ /d or, if achievable, 1.5 g/kg BW ¹ /d [‡]

BW, body weight; CKD, chronic kidney disease; GFR, glomerular filtration rate.

*GFR is measured in mL/min/1.73 m².

¹Recommendations are based on ideal body weight. Regular follow-up supports compliance.

[‡]Prospective studies targeting these high protein intakes in older hemodialysis/peritoneal dialysis patients are not available.

multinutrient ONS during their thrice-weekly dialysis sessions.¹⁰² The “as-treated” patients receiving ONS had a 34% reduced risk of 1-year mortality (hazard ratio 0.66; 95% confidence interval [CI] 0.61–0.71), a significant and important improvement.

Combining Protein Intake and Exercise in Older People

The anabolic effects of insulin and amino acids on protein synthesis are enhanced by physical activity and some nutrients (omega-3 fatty acids, vitamin D) and are impaired by sedentary lifestyle, bed rest, or immobilization (Figure 2).^{53,120,121} With aging, the normal balance between muscle protein synthesis and degradation is shifted toward net catabolism, the body’s anabolic response to dietary protein or amino acids is limited,^{46,120,122,123} and the normal antiproteolytic response to insulin is impaired.^{46,124,125} At the same

PROT-AGE recommendations for exercise and protein intake for older adults

- Endurance exercise is recommended at 30 minutes per day or at individualized levels that are safe and tolerated. Include progressive resistance training when possible; consider 2 to 3 times per week for 10 to 15 minutes or more per session.
- Increase dietary protein intake or provide supplemental protein, as needed, to achieve total daily intake of at least 1.2 g protein/kg BW; consider prescribing a 20-g protein supplement after exercise sessions.
- Protein or amino acid supplementation is recommended in close temporal proximity of exercise; some evidence supports protein consumption after the exercise/therapy session.

time, older people lead a less-active lifestyle, sometimes because of limitations imposed by chronic illnesses.¹²⁶ As a result, aging is associated with a progressive loss of skeletal muscle mass and strength, which leads to reduced functional capacity.^{120,122,127} Evidence shows that age-related muscle loss can be counteracted by exercise training¹²⁸ and by increased intake of protein or amino acids.^{5,120}

Physical Activity

The amounts of physical activity and exercise that are safe and well tolerated depend on each individual’s general health. For all

adults, physical activity can be accumulated as activities of daily living (ADLs); exercise is structured and repetitive. For older people, structured exercises are recommended to target health-associated physical benefits: cardiorespiratory fitness, muscle strength and endurance, body composition, flexibility, and balance.¹²⁹ The American Heart Association (AHA) and the American College of Sports Medicine (ACSM) encourage older adults to accumulate 30 to 60 minutes of moderate intensity aerobic exercise per day (150–300 minutes per week) or 20 to 30 minutes per day of vigorous intensity (75–150 minutes per week).¹²⁹ In addition, to counteract muscle loss and increase strength, resistance exercises are strongly recommended for 2 or more nonconsecutive days per week. For healthy older adults, exercise of 10 to 15 minutes per session with 8 repetitions for each muscle group is a reasonable goal.

Considerable evidence shows that exercise, both as aerobic activity and as resistance training, is beneficial to older people.^{130–132} With exercise, frail older people can gain muscle strength and function into their 9th and 10th decades of life, as shown in resistance-training studies.^{133–135} When their opinions were surveyed, older people reported positive perceptions of exercise, even during hospitalization.¹³⁶

Protein or Amino Acid Supplementation

Dietary protein or amino acid supplementation promotes protein synthesis in older people¹³⁷ and can enhance recovery of physical function in older individuals. Tieland et al¹³⁸ showed that muscle strength and physical function improved when frail older people were given supplemental protein daily (15 g at breakfast, 15 g at lunch) for 24 weeks; such improvement occurred in the absence of measurable changes in muscle mass. These results suggest that protein feeding alone may improve muscle strength and function more readily than muscle mass.¹³⁸

Synergistic Effects of Exercise and Protein or Amino Acids

In young and old people alike, protein ingestion together with exercise training increased synthesis of skeletal muscle^{24,30,52,53,139}; effects were evident for both aerobic exercise^{51,52} and resistance exercise.^{24,30,139} Exercise consistently reduced the difference between muscle protein breakdown and synthesis; net positive protein balance (ie, synthesis greater than breakdown) was achieved only when protein or amino acid intake was supplemented.^{140,141} In a clinical study, frail older people who engaged in resistance training and consumed supplemental dietary protein for 24 weeks showed significant muscle hypertrophy, together with increases in muscle strength and performance; study researchers concluded that protein intake was necessary for training-associated gains in muscle mass.¹⁴²

In addition, the quality of the protein consumed may exert an influence on the protein synthetic response. High-leucine-containing and rapidly digested whey proteins showed an advantage over isolated casein and soy proteins,^{24,30,61,139} which was particularly evident in short-term experiments.^{62,143} As for the combination of protein and exercise, a recent RCT in 175 community-dwelling women with sarcopenia showed that the combination of exercise twice weekly and 3 g of leucine twice daily for 3 months was superior compared with either intervention alone.¹⁴⁴ In another study, blends of whey and soy protein stimulated muscle protein synthesis after exercise to a similar extent as did whey protein alone.¹⁴⁵ Yet another trial compared resistance training in mobility-limited older adults in subgroups who received either whey protein supplementation or an isocaloric diet over 6 months; no statistically different changes were seen in lean body mass, muscle cross-sectional area, muscle strength,

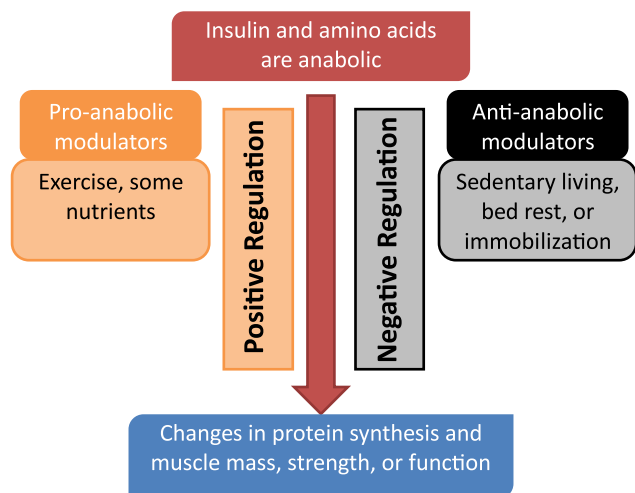


Fig. 2. Anabolic effects of insulin and amino acids on protein synthesis are enhanced by physical activity and some nutrients and are impaired by sedentary lifestyle, bed rest, or immobilization.

or stair-climbing.¹⁴⁶ More long-term studies are needed to confirm potential benefits of whey protein.

When, How Much, and How?

With combination exercise-protein therapy, the timing of protein or amino acid intake relative to exercise is central to muscle anabolism. Exercise enhances muscle protein synthesis by sensitizing muscle to insulin- or amino acid-mediated anabolic actions, an effect that appears to peak in the first 3 hours after exercise¹⁴⁷ and may persist 18 to 24 hours after an exercise bout.^{52,148} Such findings suggest that protein should be consumed close after exercise (or physical therapy) to take advantage of its sensitizing effect. The short-term complementary effects of exercise and protein supplementation were underscored in long-term studies as well. Results of a meta-analysis of 22 RCTs involving 680 young and old subjects demonstrated that prolonged resistance training (>6 weeks) combined with cotemporal protein supplement consumption led to significant muscle mass gains, which were associated with significant strength gains.⁵³ During and following hospitalization, a rehabilitation specialist usually makes individualized recommendations for duration and intensity of exercise. There is no global standard or recommendation, but physical activity during hospitalization and in posthospitalization rehabilitation sessions has reported benefits.^{1–3,5–10,69,70,149–152}

Total daily dietary protein intake seems to influence the anabolic effects of exercise. In a study of body composition changes in 50- to 80-year-old adults who followed resistance training regimens for 3 months, net positive effects of protein occurred when protein intake was greater than 1.0 g protein/kg BW/d.¹⁵¹

Specific Patient Populations

Evidence supports the combination of exercise and protein/amino acid supplementation for prevention and treatment of muscle loss in certain debilitating clinical conditions, including bed rest for acute critical illness or injury^{153–160} and also for chronic diseases, such as COPD^{161–165} and congestive heart failure (CHF).^{99,163,166}

The loss of muscle mass and strength associated with bed rest per se can be partly offset by protein or amino acid supplementation.^{158,167} Exercise is recognized to provide a potent anabolic stimulus to muscle, even among patients who are mostly limited to bed rest.^{153,157,168} For patients with COPD, results of 2 studies clearly showed benefits from exercise training along with protein supplementation^{162,164}; whey protein served as an effective protein source. People with CHF likewise experienced benefits when treated with exercise and amino acid supplementation.⁹⁹ Thus, a small number of trials have shown that modest physical activity is possible in people with chronic illnesses or those recovering from critical illness,^{169–171} but more and larger trials are needed to demonstrate the safety and efficacy of such strategies, especially because protein supplementation alone may not be sufficient to rescue very old people or those with severe muscle loss.¹⁶⁰

Other Dietary Supplements for Muscle Maintenance in Older People

Several dietary supplements have been tested in combination with exercise in older adults, namely creatine^{160,172–175} and beta-hydroxy-beta-methylbutyrate (β -HMB).^{176–180} In general, these agents have positive effects on lean body mass and strength, but the effects tend to be small and are not consistent. Some authors have championed the benefits of creatine for outcomes other than skeletal muscle synthesis, including bone health and cognitive function.^{181–183} However, at this

time, it is not possible to state definitively whether creatine or β -HMB can enhance exercise responses in older people, as these agents have been shown to do in younger people.^{184,185} Clearly this is an area for more clinical trials.

Exercise and Protein Recommendations for Older People

Because older people are at high risk for muscle loss and disability when immobilized, and because exercise has known prevention and recovery benefits for physical health, the PROT-AGE group recommends a combination of higher protein intake and exercise for older people. A usual intake of 20 g protein at least, probably just after physical exercise, is recommended as muscle sensitivity to amino acids may be increased after exercise.²⁴ Another aspect is the amino acid content of the protein source, as leucine has been reported as an interesting stimulating factor for muscle protein synthesis. From the available studies, it is accepted that 2.0 to 2.5 g of leucine intake should be contained in the amino acid mixture.^{24,25}

Some individuals may not be able to tolerate exercise (eg, those with acute myocardial infarction, unstable angina, uncontrolled arrhythmia) or very high protein/amino acid supplementation (eg, nondialyzed late-stage kidney patients). As always, all treatment decisions are guided by clinical judgment and a full perspective of the patient's health condition. In these situations, muscle electrical stimulation may be an effective therapy to help alleviate muscle loss.^{186–188}

Protein Quality and Specific Amino Acids

PROT-AGE recommendations on dietary protein and amino acid quality for older people

- The list of indispensable amino acids is qualitatively identical for young and old adults.
- There is no evidence that protein digestion and absorption capacities change significantly with aging.
- "Fast" proteins may have some benefits over "slow" proteins in muscle protein metabolism.
- Dietary enrichment with leucine or a mixture of branched-chain amino acids may help enhance muscle mass and muscle function, but further studies are needed to support specific recommendations.
- β -HMB may attenuate muscle loss and increase muscle mass and strength in older people, but further studies are needed to support specific recommendations.
- Creatine supplementation may be justified for older people, especially those who are creatine-deficient or at high risk of deficiency.

For older people, a high-quality protein is one that has a high likelihood of promoting healthy aging or improving age-related problems and diseases. Protein quality was traditionally defined by amino acid composition, as measured by an essential amino acid score or by the ratio of essential to nonessential nitrogen. It was believed that a high-quality protein supplied all needed amino acids in quantities sufficient to satisfy demands for ongoing protein synthesis in the human body; however, the definition of protein quality has evolved in recent years. Protein quality still considers amino acid content but also includes new concepts: digestibility and absorption of the protein, as well as newly recognized roles of specific amino acids in regulation of cellular processes.^{147,189} The following section reviews state-of-the-art understanding of protein quality and relates these concepts to practical aspects of protein intake by older adults.

Indispensable, Dispensable, and Conditionally Dispensable Amino Acids

Nutritive amino acids were originally classified as essential (no endogenous synthesis pathway in humans possible) or non-essential (endogenous enzymatic synthesis possible). This simple classification did not take all physiological situations into account, so the classification was revised.^{190,191} Dispensable amino acids can be synthesized by the human body in sufficient amounts for all physiological situations. Indispensable amino acids are never synthesized in humans because enzymatic pathways are lacking; supplies must be provided from dietary sources. Conditionally-indispensable amino acids are synthesized by the human body under normal physiological conditions but must be supplied in part from dietary sources when needs are unmet. Unmet needs occur when protein synthesis increases, enzymatic pathways are limited by genetic factors, or endogenous supplies are insufficient due to decreased availability of precursor supplies.

Using novel methodologies (eg, stable isotopes, long-term metabolic studies), metabolism and function of amino acids can be evaluated objectively. To date, research has not shown that aging has a significant impact on endogenous synthesis of amino acids. There is, thus, no scientific evidence to make a separate amino acid classification for older people. Consequently, there is no reason at this time to change indispensable amino acid requirements compared to those published for young adults.¹⁹²

Protein Digestibility—Corrected Amino Acid Score

Recent scoring systems, such as the Protein Digestibility—Corrected Amino Acid Score (PDCAAS), consider not only the chemical composition of a protein but also its digestibility rate.¹⁹³ The score is based on a comparison between the quantities of single indispensable amino acids in 1 g of a test protein with the quantities of these amino acids in the same amount of reference protein. The lowest ratio (first limiting indispensable amino acid) determines the quality of the protein. This calculated value is then corrected for the true fecal/ileal digestibility, which is evaluated by measuring the endogenous losses of amino acids after protein consumption *in vivo*. The PDCAAS is now widely used¹⁹³; it has been adopted by the Food and Agriculture Organization/World Health Organization as the preferred method for the measurement of protein quality in human nutrition.

Although some age-related anatomical and physiological changes have been described in the gastrointestinal tract,¹⁹² these changes are relatively small and do not substantially impair amino acid availability from food.¹⁹⁴ Consequently, there is no reason at this time to change amino acid requirements compared with those published for young adults.¹⁹²

“Fast” and “Slow” Proteins

After protein intake and digestion, the magnitude and duration of changes in amino acid availability have been shown to regulate protein gain.^{59,60} The concept of “fast” proteins means a faster, higher, and more transient elevation of postprandial plasma amino acid appearance from dietary protein than for “slow” proteins, even when the amino acid content is similar.¹⁹⁵ Such different kinetic patterns influence the subsequent amino acid metabolism.⁵⁹

In older men, whey protein (a “fast” milk-derived protein) stimulated postprandial muscle protein accretion more effectively than casein (a “slow” milk-derived protein), an effect that is attributed to a combination of whey’s faster digestion and absorption kinetics and

possibly to its higher leucine content.^{30,61,143} However, because ingestion of 15 g of whey protein appeared to be better than ingestion of its equivalent in essential amino acids (6.72 g),¹⁹⁶ whey protein does appear to have some anabolic benefit beyond its essential amino acid content.

The whey/casein difference has not been found universally. When taken in immediately after resistance exercise, whey and casein resulted in equally increased protein synthesis despite temporal differences in postprandial insulin and amino acid concentrations.¹⁹⁷ Milk-derived proteins (whey, casein) were both more efficient for improving muscle protein anabolism than soy proteins.¹⁹⁸ Studies are therefore needed to ascertain whether such benefits are characteristic of milk proteins or are more generally related to animal versus plant differences.

Taken together, research findings generally suggest that “fast” proteins provide greater benefit to muscle protein accretion than do “slow” proteins. However, evidence from small experimental trials needs to be confirmed in larger patient populations before precise recommendations can be made on the choice of “fast” versus “slow” proteins.^{29,63}

Enrichment of Diet With Branched-Chain Amino Acids

Based on the concept of “rate-limiting” amino acids, the idea was born to enrich the daily diet or specific food with amino acids. Furthermore, branched-chain amino acids (BCAA), including leucine, are now thought to have specific positive effects on signaling pathways for muscle protein synthesis.²⁸ The addition of a mixture of BCAA to the nutritional support of severely ill patients increased muscle protein synthesis in different settings.^{28,199,200} Although the BCAA leucine has been proposed as a promising pharmacutrient for prevention and treatment of sarcopenia, results of nutritional intervention studies are not consistent regarding the clinical efficacy of leucine in healthy, active older men.^{24,28,201,202} Moreover, no data are available today for older people who are inactive or ill.

Supplementation With Amino Acid Derivatives/Metabolites

β -HMB is a metabolite of leucine with multiple modes of action. β -HMB has been widely used by athletes to improve performance.²⁰³ Combining exercise training with β -HMB supplementation leads to increased muscle mass and strength in young persons, but this has not been shown in older persons. A recent review stated that β -HMB may attenuate muscle loss and increase muscle mass and strength in older people and in specific clinical populations (AIDS and cancer).¹⁷⁷ Although the number of β -HMB studies in older people remains limited, results of a recent study demonstrated that β -HMB supplementation preserved muscle mass during 10 days of bed rest in healthy older adults (age range 60 to 75 years).²⁰⁴

Creatine Supplementation

Creatine is a guanidine-derived compound naturally synthesized in the human body using several amino acids (arginine, glycine, methionine) as precursors. Creatine is also sourced from meat in the diet; dietary creatine intake depends on daily food choices. In the body, creatine is mostly stored in skeletal muscle because it is needed to synthesize and maintain adenosine triphosphate (ATP) levels for muscle contraction.

Results of several interventional studies in older adults suggest that high amounts of exogenous creatine may support muscle mass and function.²⁰⁵ Whether creatine can be classified as an “indispensable” nutrient in older people is a current topic of discussion.

Some^{173,206} but not all^{172,207} studies show a muscle strength benefit with the use of creatine supplements in older people. This effect may be related to timing and dosage of creatine supplementation; long-term benefits of different strategies are not yet known.²⁰⁵ Creatine supplementation may be justified in older people who are creatine-deficient or at high risk of deficiency.

body.^{73,74,84,208–212} Clinicians, policy makers, and health care administrators must therefore seek to identify interventions that can prevent, delay, or reverse age-related loss of functionality. For this reason, measures of physical function should always be considered when determining the cost-effectiveness of interventions.

Relationship Between Dietary Protein Intake and Physical Function Outcomes

PROT-AGE recommendations for use of functional outcomes in studies of older people

- An older person's physical function capacity can predict important outcomes such as loss of independence, onset of dementia, falls, and even mortality.
- To date, relatively few studies of dietary protein supplementation in older people have used measures of physical function as primary outcomes. However, available evidence from comprehensive reviews, meta-analyses, and recent clinical trials suggest some beneficial effects.
- To assess cost effectiveness of nutritional interventions in practical terms, new studies should be designed to explore functional outcomes. Studies are needed to assess the effectiveness of nutritional interventions to prevent disability for at-risk populations, or reverse it in those with mild disability.

What Are the Best Measures of Physical Function?

There is no consensus on the best measure of an older person's physical function; the choice largely depends on what the assessor needs to know or predict. A measure (including those assessing physical function) is useful if it captures effects of interventions, correlates with modifications of risk, or is associated with cost-effectiveness parameters.²⁰⁸ Physical function measures may support clinical decisions, for example suggesting whether an individual is capable of living alone, needs health and social services (eg, assisted living), or needs the full support of a nursing home or hospital.^{210,212} In older people, physical function can be measured in terms of mobility, endurance, and ability to perform ADLs (Table 7).

Does Nutritional Supplementation With Protein Improve Physical Function Outcomes?

Reduced mortality risk has been reported in undernourished, hospitalized geriatric patients where supplementation (at least 400 kcal/d) may assume a therapeutic role.⁷⁴ Furthermore, more recently, nutritional supplementation has been linked to reduced complications and readmission to hospitals.⁷³ However, the ability to live at home as opposed to being institutionalized is very important to most people and to support achievement of this goal, good physical function is essential.

To date, relatively few studies of dietary protein for older people have used physical function measures as outcomes. However, findings from 3 comprehensive reviews/meta-analyses^{73,74,84} and 2 recently published clinical trials^{227,228} may suggest some beneficial effects, especially in individuals who are older, malnourished, frailer, and with interventions used for at least 3 months (Table 8).

In older people, loss of muscle strength is associated with reduced functional capacity and increased health care costs.¹⁶ In addition to the amount of skeletal muscle, other conditions also affect functional outcomes: muscle quality, total body fat, neurologic function, cardiovascular and pulmonary function, and other comorbid conditions.^{16,208} Nutrition, especially dietary protein intake, is known to affect overall function of the

Systematic reviews and meta-analyses

Cawood et al⁷³ conducted a systematic review of the effects of high-protein, multinutrient ONS in community patients older than 65 years. When possible, RCT results were combined for meta-analysis. In terms of functional outcomes, hand-grip strength improved significantly in patients who received multinutrient, high-protein ONS compared with control patients who did not receive ONS

Table 7
Examples of Physical Function Measures

Measure of Function	References	Comments
Physical performance		
Short Physical Performance Battery (SPPB)	Guralnik 1994 ²¹³	Practical tests to measure balance, gait, strength, and endurance
Usual gait speed	Guralnik 2000 ²¹⁴	Assessment of timed usual gait speed on a short track (ie, 8 or 15 feet, 4 or 6 meters) course
6-minute walk	Wise 2005 ²¹⁵	Reflects physical function, exercise tolerance, and endurance for generally high-functioning adults
400-meter walk	Newman 2006 ²¹⁶	The incapacity to complete a 400-meter walk indicates mobility disability, an early stage of the disabling process
Stair Climb Power Test	Bean 2007 ²¹⁷	Measure of leg power function
Timed Get-up-and-go Test (TGUG)	Mathias 1986 ²¹⁸	Balance measured as time for patient to stand up from a chair, walk a short distance, turn around, return, and sit down again
Activities of daily living		
Barthel Index	Mahoney 1965 and others ^{219–221}	Measures 10 functional motor items
Activities of daily living (ADL)	Katz 1963 ^{209,222}	Scale assessing independence for 6 functions: bathing, dressing, toileting, transferring, continence, and feeding
Instrumental activities of daily living (IADL)	Lawton 1971 ²²³	Scale measuring independence for 8 "complex" functions of daily living
Frailty		
FRAIL scale	Woo 2012 and others ^{80,224,225} Rodríguez-Mañas 2013 ²²⁶	Scale measures fatigue, ability to climb 1 flight of stairs, ability to walk 1 block, more than 5 illnesses, and 5% or more weight loss in 6 months. Experts discussed but did not achieve consensus on specific diagnostic criteria for frailty.

Table 8
Summary of Evidence About Effects of Supplemental Protein on Functional Outcomes

Reference	Study Population and Functional Measure	Benefits of Supplemental Protein
Reviews and meta-analyses		
Avenell 2010 ⁸⁴	<ul style="list-style-type: none"> Review of patients recovering from hip fracture; most were > 65 years old Based on 4 studies addressing protein intake, no significant benefits were evident for strength, mobility, or activities of daily living 	–
Milne 2009 ⁷⁴	<ul style="list-style-type: none"> Review of 62 trials of protein-energy supplementation in older people (>65 years old) Only some studies looked at functional outcomes, and few found positive effects Benefits of protein-energy supplementation were found in subgroups of malnourished patients 	–/+
Cawood 2012 ⁷³	<ul style="list-style-type: none"> Meta-analysis of 4 RCTs in community patients >65 years old with chronic obstructive pulmonary disease, gastrointestinal disease, and hip fracture High protein concentration as part of multinutrient ONS Significant improvement of hand-grip strength 	+++
Research papers		
Neelemaat 2012 ²²⁷	<ul style="list-style-type: none"> RCT of hospital-admitted, malnourished older patients (>60 years old) who were assigned to receive nutritional intervention and counseling (n = 105) or usual care (control; n = 105); outcomes assessed 3 months after discharge Functional limitations decreased significantly more in the intervention group than in the control group 	++
Kim 2013 ²³⁸	<ul style="list-style-type: none"> RCT of community dwelling, at nutritional risk (Mini Nutritional Score <24), older people who were assigned to receive two 200-mL cans of nutritional supplementation (additional 400 kcal energy, 25.0 g protein, 9.4 g essential amino acid) or no supplementation for 12 weeks; outcome was assessed at 3 months Physical functioning improved but not significantly in the intervention group; no deterioration in SPPB scores compared with the control group Intervention group performed better on both gait speed and Timed Get Up and Go time compared to the control group 	++

ONS, oral nutrition supplement; RCT, randomized controlled trial; SPPB, Short Physical Performance Battery.

Key: + benefit; ++ strong benefit; +++ very strong benefit; - no apparent benefit; -/+ mixed benefit.

(4 RCTs; strength +1.76 kg; n = 219; $P = .014$ with a random effects model).^{73,229–232} Of 7 RCTs exploring modifications of ADLs, most found no significant differences between high-protein ONS groups and controls, whereas one trial found improvement for people in the ONS group.^{86,230}

Milne et al.⁷⁴ reviewed a total of 62 studies on protein and energy supplementation in older people. Overall results showed that the risk of complications was reduced in 24 trials (relative risk [RR] 0.86, 95% CI 0.75–0.99), but few supported functional benefits from supplementation. Only some of the studies reported findings in terms of physical function measures: mobility (n = 14 studies), walking distance or speed (n = 4 studies), ADL (n = 11 studies), or hand-grip strength (n = 13 studies). Overall, there was little support for functional benefits of protein-energy supplementation, but some positive effects were still reported.^{74,233–237} Avenell and Handoll⁸⁴ reviewed studies of nutritional interventions for people recovering from hip fractures. A higher intake of protein reduced the length of time spent in a rehabilitation hospital and numbers of complications. The authors found weak evidence that including high protein in the supplement shortened the time needed for rehabilitation.

Recent trials targeting physical function outcomes

In 2012, Neelemaat and colleagues²²⁷ reported effects of an intervention that included protein-energy-enriched diet, ONS, and nutrition counseling in comparison with usual care. Malnourished older patients were enrolled during hospitalization and treated for 3 months after discharge. At the end of the follow-up, functional limitations more significantly decreased in the intervention compared with the control group (mean difference at the Longitudinal Aging Study Amsterdam questionnaire of -0.72 , 95% CI 1.15 to -0.28).

A very recent RCT conducted in South Korea investigated 87 nutritionally-at-risk, community-dwelling, frail older adults with gait speed less than 0.6 m/s. The intervention of two 200-mL cans of commercial liquid formula providing 400 kcal additional energy (25.0 g protein, 9.4 g essential amino acid) was compared with no supplementation. Compared with the control group, the

participants randomized to the intervention group performed better in both gait speed and Timed Get Up and Go test. Also, there was no change in the Short Physical Performance Battery (SPPB) score in the intervention group, whereas a decrease was seen in the control group.²³⁸

Future studies of nutritional interventions need to measure functional outcomes. Protein supplementation may serve as an important preventive and therapeutic intervention against functional decline, especially when implemented in frail older people with malnutrition.^{73,227,238} When older people experience functional decline and lose their independence, health care costs significantly rise.²³⁹ For these reasons, it is important that studies investigating functional outcomes are undertaken when assessing efficacy and cost-effectiveness of specific interventions. To ensure appropriate care, it is likewise important to quantify functional capacity in relationship to needs for supportive social services. Vulnerable populations, such as those living in residential care or with dementia, should also not be excluded a priori from studies on the topic.

Take-Home Messages

For this article on protein nutrition for older people, members of the PROT-AGE Study Group reviewed an extensive medical literature

Key PROT-AGE recommendations for dietary protein intake in older adults

- To maintain physical function, older people need more dietary protein than do younger people; older people should consume an average daily intake at least in the range of 1.0 to 1.2 g/kg BW/d.
- Most older adults who have an acute or chronic disease need even more dietary protein (ie, 1.2–1.5 g/kg BW/d); people with severe illness or injury or with marked malnutrition may need as much as 2.0 g/kg BW/d.
- Older people with severe kidney disease who are not on dialysis (ie, estimated GFR < 30 mL/min/1.73m²) are an exception to the high-protein rule; these individuals need to limit protein intake.
- Protein quality, timing of intake, and amino acid supplementation may be considered so as to achieve the greatest benefits from protein intake, but further studies are needed to make explicit recommendations.
- In combination with increased protein intake, exercise is recommended at individualized levels that are safe and tolerated.

and compiled evidence to show that getting adequate dietary protein is important to maintaining functionality. We found that optimal protein intake for an older adult is higher than the level currently recommended for adults of all ages.^{1–3} New evidence shows that higher dietary protein ingestion is beneficial to support good health, promote recovery from illness, and maintain functionality in older adults.^{5–10} Based on our findings, we made updated recommendations for protein intake.

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