Supplement Article

Update on protein intake: importance of milk proteins for health status of the elderly

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Loss of lean body mass that occurs with aging is the primary endpoint with which sarcopenia is defined. Furthermore, loss of muscle mass is central to the development of many adverse health issues in the elderly. Consequently, the response of lean body mass to nutritional interventions, particularly to dietary protein, has been a commonly measured endpoint. However, increased protein intake has been associated with improved markers for cardiovascular health, improved bone health, management of weight and metabolic diseases, and reduced all-cause mortality. Strength, rather than lean body mass, may be a more accurate indicator of health, especially in the elderly. The recommended dietary allowance for protein has been set at 0.8 g/kg/day. Because the average protein intake in the United States is approximately 1.2 g/kg/day, it appears that the average protein intake is above the recommended dietary allowance but below the low end of the acceptable macronutrient distribution range recommended by expert committees of the National Academy of Sciences and below the dietary intake levels suggested by the US Department of Agriculture in the Dietary Guidelines.

INTRODUCTION

Loss of lean body mass (LBM) that occurs with aging is the primary endpoint with which sarcopenia is defined.[1] Furthermore, this loss of muscle mass is central to the development of many adverse health issues in the elderly.[2] Consequently, the response of LBM to nutritional interventions, particularly to increases or decreases in dietary protein, has been a commonly measured endpoint in research, particularly in elderly patients. The effect of protein intake on LBM in the elderly has been extensively considered, often to the exclusion of many of the other potential health benefits of increased dietary protein. However, prospective studies that demonstrate the effect of changes in LBM on health outcomes are limited.

Historically, recommendations for protein intake have been based exclusively on measurements of nitrogen balance.[3] Presumably, nitrogen balance is taken as a surrogate for changes in LBM. However, problems exist with the nitrogen-balance approach, from technical considerations to the fact that nitrogen balance is not a physiological function. More importantly, even if nitrogen balance translates directly to short-term alterations in LBM, such results are of minimal importance in evaluating the health benefits of protein intake. This is because changes in LBM as a result of increases or decreases in dietary protein intake plateau after a few weeks and are rarely of demonstrable physiological significance. On the other hand, increased levels of dietary protein intake can translate to improvements in muscle strength and physical function, cardiovascular health, bone health, and weight management, which can affect long-term health outcomes. Determination of an optimal level of protein intake for the elderly should, therefore, take into account all of the physiological responses to varying levels of intake. The beneficial effects of increased protein intake on overall physiological

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function in the elderly and how those effects relate to health outcomes are the focus of this article.

LEAN BODY MASS AND HEALTH OUTCOMES IN THE ELDERLY

Intake of amino acids or protein increases muscle mass by shifting the balance between muscle protein synthesis and breakdown.[2] Whereas many studies have demonstrated an acute stimulatory effect of amino acids, particularly the essential amino acids (EAAs), on net muscle protein synthesis, more recent studies have confirmed that this effect may translate to increases in LBM over a period of months.[4] Results of the Health ABC study suggest that the beneficial effects on LBM observed over a few months in prospective studies is sustained over a longer period of time. For example, in that study, protein intakes for more than 2000 elderly participants were divided into 5 quintiles, and LBM among the quintiles was compared. Those in the highest quintile of protein intake lost significantly less LBM over 3 years than those in the lowest quintile.[5] However, the highest intakes were not unusually high, about 1.2 g/kg/day, but the study does provide supportive evidence that increased protein intake may spare the loss of LBM. While it is tempting to interpret numerous studies as showing a relationship between the loss of LBM with aging and outcomes from diseases such as chronic obstructive pulmonary disease[6] or cancer,[7] the currently available data do not exclude the possibility that those who are the most ill and who ultimately die are more cachectic and, therefore, lose more LBM. A more striking relationship can be demonstrated between mortality and strength than exists for mortality and LBM. All-cause mortality as well as mortality from cancer are directly impacted by the level of strength, irrespective of LBM. In a study by Ruiz et al.,[8] individuals in the lower third of strength measurements had the worst health outcomes. This led to the concept of muscle quality being the most important criterion of muscle health in the elderly.[9] Muscle strength and function are affected by the level of dietary protein as a consequence of increased turnover (i.e., synthesis and breakdown) of muscle protein. Whereas the response of net protein synthesis to increased levels of protein intake will likely plateau at some point in time, the plateau in net protein balance will occur at higher rates of both synthesis and breakdown. Presumably, this results in newly synthesized proteins replacing damaged fibers that contract less efficiently. Thus, higher dietary protein intake under completely controlled circumstances improves muscle strength and function as a result of improved single-fiber contractile properties.[10] This indicates a direct relationship exists between the turnover rate of muscle protein synthesis and strength in the elderly, even when differences in muscle mass are taken into account.[11] Studies in which protein intake[12] or amino acid intake[13] was increased over a period of months confirm that increasing dietary protein intake significantly improves muscle function in the elderly. Studies in free-living participants are supportive of the concept that stimulating protein turnover through increased protein intake improves muscle strength.[12] However, in these types of studies, it is often difficult to control dietary intakes, which may be problematic. In a study performed in elderly volunteers, participants were confined to voluntary bed rest for 10 days during which all variables, including activity, caloric intake, and protein intake, were completely controlled.[14] In the setting of controlled inactivity, increasing EAA intake above the recommended dietary allowance (RDA) significantly ameliorated the decline in a variety of functional performance measurements that would have occurred otherwise.[14] However, the more muscle loss that occurs in older individuals, the more difficult it is to accrue LBM through diet alone.[12]

PROTEIN INTAKE AND CARDIOVASCULAR HEALTH

The beneficial effects of increased protein intake on cardiovascular health have been recognized for a number of years, but these effects have not been taken into account in the formulation of dietary recommendations and guidelines for protein intake.[2] An epidemiological study documented that the relative risk of ischemic heart disease among more than 80c000 women was greatest in those with the lowest protein intake and lowest in those with the highest intake of dietary protein.[15] One explanation for this effect is the reduction in blood pressure, which has been demonstrated to respond to a single supplement of 20 g of whey protein.[16] Nitric oxide synthesis is decreased in the elderly, and the reduction in blood pressure may stem from the stimulation of nitric oxide synthesis by the arginine component of dietary protein.[17] Another aspect of dietary protein/amino acid intake relates to dietary lipids and cardiovascular disease. Supplementation of the diets of elderly individuals with EAA for 1 month significantly reduced blood and liver triglycerides.[18]

PROTEIN INTAKE AND BONE HEALTH

Dietary protein intake has been implicated in the loss of bone due to the acidification of blood. Although the major contributor to this response is thought to be the sulfur-rich proteins, even a formulation of EAAs containing a minimal amount of sulfur has been found to acidify the blood and lead to increased excretion of calcium, *n*-teleopeptide, and deoxypyridinoline in the context of bed rest.[19] However, this study, as well as others that indicated increased bone resorption in response to high protein or amino acid intake, did not consider the rate of bone formation and, thus, the net formation of bone. When net bone formation has been determined, higher rates of protein intake have been shown to have beneficial effects on bone health. For example, when 219 healthy volunteers aged 70–80 years were given either placebo or 30 g of whey protein per day for 2 years, the protein-supplemented group avoided the loss in femoral neck bone mineral density that occurred in the placebo group.[20] There may also be an indirect effect of protein intake on bone health. Bone strength is directly affected by the torque placed on the bones as a result of muscular contraction.[21] Because higher levels of protein intake increase strength in the elderly (see above), increased protein intake may have an indirect effect on bone strength by enabling the generation of greater muscular force.

BENEFITS OF PROTEIN INTAKE IN WEIGHT MANAGEMENT AND METABOLIC DISEASE

In the context of hypocaloric nutrient intake for the purpose of weight loss, the benefits of a diet in which protein comprises a relatively high proportion has been well documented in terms of maintaining LBM while fat mass is being lost. This could be explained, at least in part, by the fact that total caloric intake is reduced significantly during hypocaloric feeding, so that an increased percentage of dietary protein may be necessary just to achieve the same absolute amount of protein intake normally eaten in a conventional American diet. However, a high level of protein intake also provides beneficial effects on weight management even when caloric demands are equal to or greater than energy expenditure. A thermogenic response to protein intake, which results from the stimulation of protein turnover,[2] is one mechanism by which protein intake can benefit maintenance of energy balance. There is a metabolic cost of both protein synthesis and breakdown.[2] The energy cost of protein turnover constitutes a significant proportion of resting energy expenditure, and stimulation of protein turnover by increased protein intake increases energy expenditure via thermogenesis. If caloric intake remains constant, increased thermogenesis favors maintenance of a lower body weight. Increased protein intake may also aid in the maintenance of energy balance and weight management by having a satiating effect.[22] Increased protein and/or amino acid intake may benefit the metabolic state by improving insulin sensitivity[23] and reducing circulating lipid levels.[18] Importantly, an increase in protein intake also means a reduction in carbohydrate and/or fat intake to maintain caloric balance. Excess fat and excess carbohydrate, in particular, are linked to a variety of adverse health consequences in the elderly.[24,25] In contrast, adverse effects of high levels of protein intake have not been encountered in healthy individuals.[3] Thus, it may be that benefits of increased protein intake on weight management and metabolic disease are direct results of the increased availability of amino acids, as well as indirectly as a result of decreased intakes of carbohydrate and/or fat.

OPTIMAL PROTEIN INTAKE

A variety of recommendations for protein intake are currently available. Arguably the most well recognized is the RDA. The RDA for dietary protein was most recently considered by the Food and Nutrition Board of the National Academy of Sciences and published in the dietary reference intakes for macronutrients.[3] The RDA for protein represents 2 standard deviations above the average minimal amount of protein intake needed to maintain zero nitrogen balance (i.e., no net gain or loss of N over time). Thus, it represents the minimal amount of protein intake required to maintain nitrogen balance in approximately 98% of the population. It is important to recognize that the definition is based entirely on nitrogen balance and does not take into account any of the factors discussed above, which are impacted by the amount of protein consumed, particularly in older individuals.

The current RDA for protein (0.8 g/kg/day)[3] is a value that was first derived in 1943 in order to define the minimal amount of protein that would enable troops in World War II to avoid protein malnutrition.[26] Despite the quantity of data that have been generated since then on the topic of optimal protein intake, the value has remained unchanged. The RDA can be viewed as a reasonable minimal level of protein intake, but it was not intended to represent the optimal amount of protein intake in a circumstance of an abundance of food choices, as presently exists in the United States and other first world countries.

The optimal level of protein intake in the elderly is almost certainly greater than the RDA. There have been numerous studies in which a variety of endpoints have been used to compare the effects of consuming the RDA of protein to consuming greater amounts of protein, particularly in the elderly.[27] Although the magnitude of benefit from a higher protein intake varies among studies, depending on the specific experimental design, participants, and endpoint(s) measured, among other factors, there has never been a study in which individuals who consumed the RDA for protein experienced benefits similar to those of individuals who consumed protein in excess of the RDA.

One practical limitation in translating the RDA for protein to the formulation of a complete diet is that dietary protein is not eaten in isolation and the RDA for protein does not account for other components of the diet. The Food and Nutrition Board recognized this practical limitation of the RDA and published an additional set of recommendations termed the acceptable macronutrient distribution range (AMDR), which considers macronutrient intake in the context of a complete diet.[3] The AMDR recommends that protein intake constitute 10%–35% of total caloric intake.[3] The minimal nature of the RDA in the context of a complete diet is evident when considered in light of the AMDR. The dietary reference intakes recommend a total caloric intake of 35 kcal/kg/day.[3] Thus, the RDA for protein represents <10% of total recommended caloric intake [(0.8 g/kg/day × 4 kcal/kg/day)/35 kcal/kg/day = 9.1%). The mid-range of the AMDR recommendation for protein intake is about 2.0 g/kg/day.

The most practical expression of the recommended protein intake is found in the *Dietary Guidelines for Americans* (DGA), promulgated by the US Department of Agriculture.[28] These recommendations are intended to translate the most recent nutrition research into dietary guidelines expressed in the context of real foods and daily meal plans. When recommended food intakes from the DGA are broken down into their components, the recommended protein intake is approximately 1.5 g/kg/day.[29] Thus, recommendations for dietary protein intake in the context of a complete diet range from 1.5 to 2 g/kg/day. These values are consistent with those presented in other studies that assessed the optimal level of protein intake based on multiple endpoints.[27] Because the average protein intake in the United States is approximately 1.2 g/kg/day,[29] it appears that the average protein intake is below the amount recommended by expert committees of the National Academy of Sciences and the US Department of Agriculture.

QUANTIFYING PROTEIN QUALITY

Digestible indispensable amino acid score

The dietary recommendations referred to above specify that protein should be of "high quality" but they do not specify how protein quality should be assessed. The Food and Agriculture Organization of the United Nations developed an approach for quantifying protein quality called the protein digestibility corrected amino acid score (PDCAAS).[30] The score was derived as a means to quantify dietary protein quality based on the amino acid profile and relative amounts of dietary EAAs in the test protein, corrected for digestibility using a single value for true fecal crude protein digestibility and expressed relative to a profile of amino acid requirements. Thus, a PDCAAS of 1 means that all of the minimal requirements for EAA intake would be met if an amount of the test protein equivalent to the estimated average daily requirement for protein (0.66 g/kg/day for adult men and women) was eaten. Most high-quality proteins have a PDCAAS > 1.0. However, at the time the score was created, it was deemed that excess dietary amino acids would not be utilized and should, therefore, not be included in the PDCAAS; as a result, all scores were truncated at 1.0. The truncation of PDCAAS at 1.0 does not allow a comparison of the relative quality of high-quality dietary proteins. The Food and Agriculture Organization of the United Nations recently released a document in which the adoption of a new scoring system to quantify dietary protein quality is recommended; the system is called the digestible indispensable amino acid score (DIAAS).[31] The DIAAS is meant to supplant the use of the PDCAAS. The conceptual goal of the DIAAS is similar to that of the PDCAAS. However, with the DIAAS, the quality of a protein is based on the relative digestible content of the EAAs and the amino acid requirement pattern. In contrast to the PDCAAS, the DIAAS is not truncated, thereby theoretically enabling a ranking of all dietary proteins by quality. An accurate quantitative ranking of protein quality has great potential for clarifying many aspects of protein nutrition in a general sense and could be of value specifically in the context of dietary recommendations and the creation of meal plans.

Several DIAASs are shown in Figure 1. In general, proteins can be classified as being of high quality or lower quality. High-quality proteins provide at least 100% of all EAA requirements if 0.66 g/kg/day of the protein is ingested. For the most part, animal proteins constitute high-quality proteins, with dairy proteins among those with the highest quality. There are currently limited data to confirm that the rankings shown in Figure 1 are indicative of differences in physiological function. However, the existing evidence supports the validity of the DIASS rankings. Consistent with the respective DIAASs of milk protein or whey protein, ingestion of each stimulates muscle protein synthesis in human volunteers more than ingestion of the same amount of soy protein. Moreover, the response of muscle protein synthesis in rats to the ingestion of wheat, soy, egg, and whey proteins was found to be proportionate to the respective DIAASs. The authors attributed the effectiveness of whey protein to the relatively

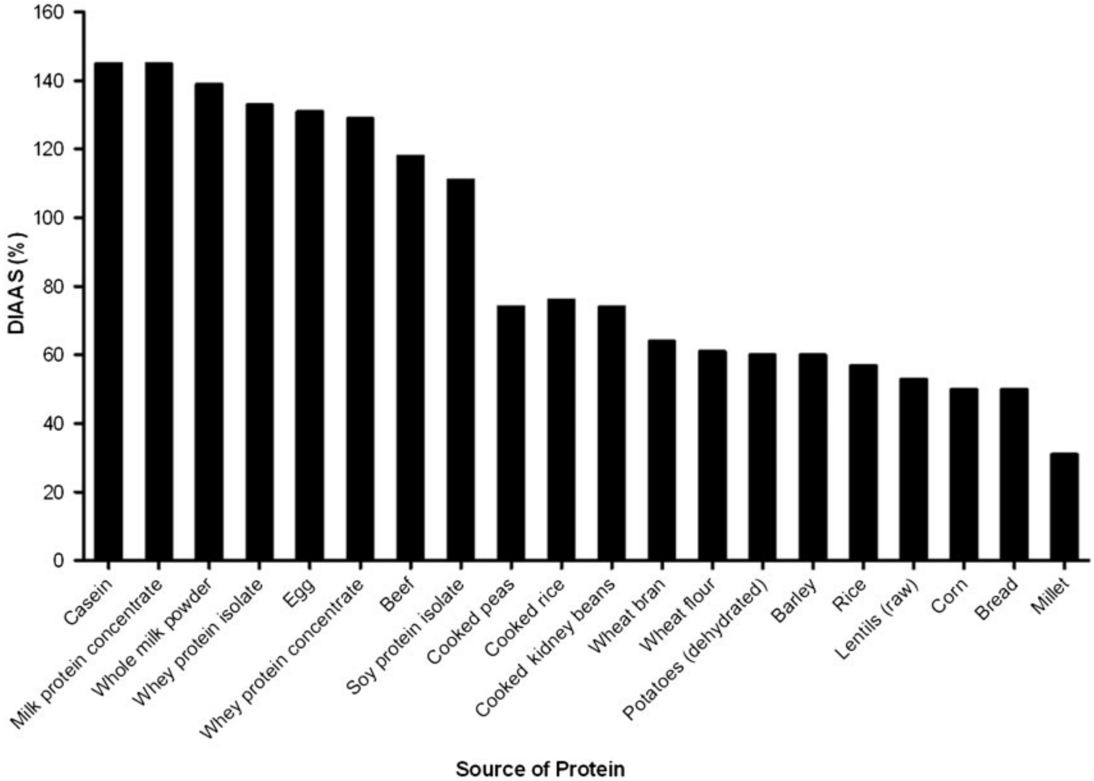

Figure 1 **Quality of common protein sources expressed as percent digestible indispensable amino acid score.** Values were calculated according to reference 31 and represent the percentage of the requirement for the most limiting essential amino acid in the test protein that will be met by ingestion of 0.66 g/kg/day of the test protein. *Abbreviation*: DIASS, digestible indispensable amino acid score.

high proportion of leucine and its affect on the increase in phosphorylation of p70 S6 kinase (p70S6K) and 4E binding protein 1 (4EBP1).[32] More measurements of protein synthetic rates following ingestion of specific proteins are important to fully understand the significance of the corresponding DIAAS.

DIAASs and milk proteins

Figure 1 shows that dairy proteins rank among the highest of the DIAASs. In addition to delivering a large amount of EAAs per gram of protein in a favorable profile relative to EAA requirements, milk proteins are absorbed at different rates, which likely further amplifies their effectiveness. Casein and whey are the principal proteins in milk. Whey protein is readily absorbed, resulting in a relatively rapid peak in plasma amino acid concentrations. In contrast, absorption of casein is prolonged due to coagulation in the stomach, resulting in a sustained but moderate increase in plasma amino acid concentrations. The rapid peak in amino acid concentrations, particularly of leucine, in response to the ingestion of milk proteins activates the process of synthesis, and the prolonged increased availability of amino acids enables sustained stimulation of protein synthesis. These aspects of milk proteins are not factored into the calculation of the DIAAS. Further, the DIAAS reflects only the ability of a test protein to meet EAA requirements, but that may not be the optimal profile of EAAs to maximally stimulate synthesis. Thus, whey protein stimulates muscle protein synthesis to a greater extent than casein, despite casein's higher DIAAS.[33] This could be due either to the more rapid absorption of whey or the fact that whey protein contains more leucine than casein. Both of these factors could have an impact on the ability of leucine to act as a "trigger" to initiate protein synthesis. According to the "leucine trigger" theory, it is necessary that intracellular initiation factors, including p70S6K and 4EBP1, be activated for protein intake to fully stimulate protein synthesis.[32] Thus, the amount of leucine in an ingested protein as well as how rapidly the amino acids in the protein are absorbed (and thus the peak leucine concentration achieved) are crucial determinants of the stimulatory effect on protein synthesis. These factors are not reflected by the DIAAS because the score is based on the most limiting amino acid in a dietary protein, and leucine is generally abundant in dietary proteins as compared to the minimal requirement for leucine. Thus, even the high DIAAS for milk proteins may underestimate their total anabolic value because of advantages that stem from the different rates of absorption of whey and casein as well as the

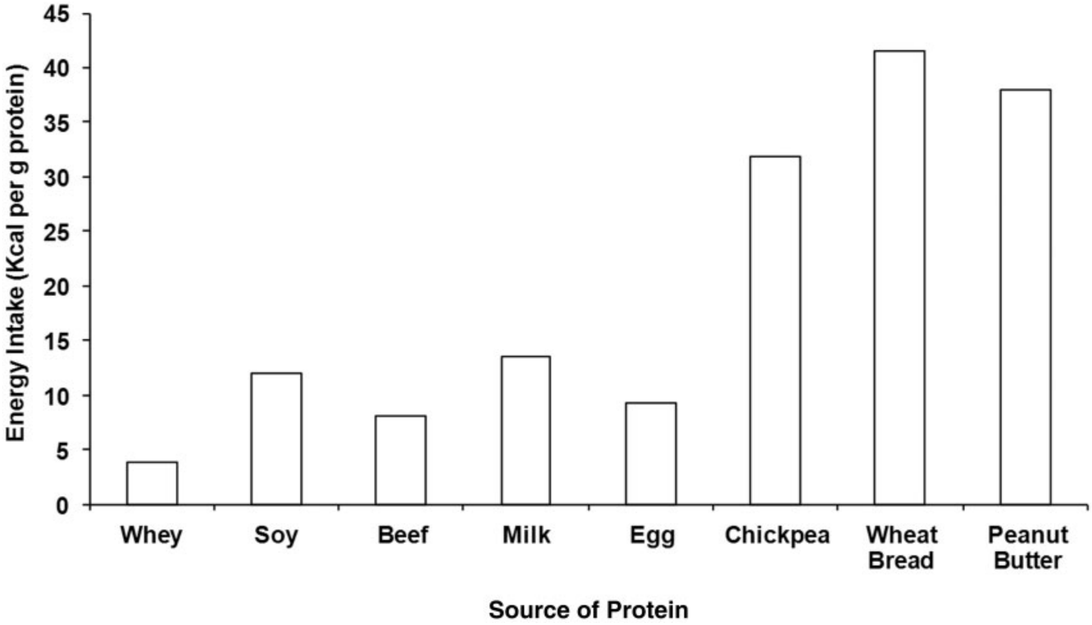

Figure 2 **Energy intake of different protein sources required to meet minimal requirements of adults for all essential amino acids.** Calculated from the US Department of Agriculture database for grams of protein per gram food source and the amount of each found source required to meet essential amino acid requirements, as derived from the digestible indispensable amino acid score.

high leucine content in whey that is not reflected by the DIAAS.

Relation of DIAAS to energy intake

Assuming that the DIAAS is substantiated by more studies that confirm the physiological relevance of its ranking of proteins, the ability to quantify protein quality has the potential for great practical significance. For example, the energy intake of particular foods required to supply enough protein to meet minimal EAA requirements could be expressed (Figure 2). The examples in Figure 2 show the wide discrepancies in the relative calorie content among various foods. Whole milk provides all of the EAA requirements, with fewer than 15 kcal of energy intake; skim milk would require significantly fewer calories. On the other hand, lower-quality proteins such as chickpea and wheat as well as foods that have a high caloric density, such as peanut butter, require that amounts in excess of the total daily caloric intake (35 kcal/kg/day) be ingested to provide the minimal requirement of EAAs.

CONCLUSION

In older individuals, protein intakes greater than the RDA promote better health outcomes by positively affecting a wide range of body systems. Rather than relying entirely on the results of nitrogen-balance studies, recommendations for protein should, therefore, take into account the impact protein has on a variety of endpoints related to health outcomes. The EAA-to-calorie ratio for high-protein foods must also be considered when comparing protein-rich foods. High-quality proteins, such as milk proteins, enable EAA requirements to be met with less caloric intake compared with lower-quality proteins. This is reflected by the scoring of their quality by the DIAAS.

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