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Perspective: Protein Supplementation in Frail Older Persons: Often Necessary but Not Always Sufficient

To the Editor:

Since 1838, when Gerardus Johannes Mulder first described proteins and used the name derived from the Greek word πρωτεϊός (*proteios*), meaning “primary,” the importance of proteins in human physiology has incessantly expanded.¹ The demonstration that

muscle contraction is the result of the interaction of 2 proteins with ATP signed the beginning of a new era in physiology.² Because proteins are key nutrients for every cell in the human body, their role in the maintenance of cellular function during aging is unquestionable. The human body is unable to repair, regulate, and especially to move without these vital macronutrients. Essential amino acids cannot be synthesized in the body, whereas proteins are the only macronutrient without inactive reservoir, hence they might be taken with food. Even if skeletal muscle mass preservation during aging is influenced by multiple factors,^{3,4} the content of amino acids in the diet is a requisite for muscle protein synthesis.^{5,6}

Frailty and age-related sarcopenia are closely interconnected. Frail older persons are sarcopenic by definition,⁷ whereas advanced age-associated sarcopenia may lead to frailty, risk for falls, and loss of independence.⁸ However, other features characterize frailty together with the loss of muscle mass and function. The concept of frailty is so complex and heterogeneous that in the past decade, various interpretations of its notion have been proposed. These include, among others, a definition according to the presence of few biological and functional characteristics identifying a specific phenotype⁹; a progressive accumulation of deficits (a scale of up to 70 items)¹⁰; an integrated approach including physical, psychological, and social domains¹¹; and a multidimensional concept where multiple domains aggregate together and interact.^{12,13} Such a complex condition varies widely among populations and among individuals in the same population, hence it is not surprising that results from trials conducted in frail persons with extensive heterogeneity may not agree, even if a plausible intervention is examined, that is, protein supplementation in frail older persons, who are at high risk for undernutrition.¹⁴ Several studies have shown positive effects for such intervention,^{15–20} but there are also negative results.^{17,21} Moreover, even if protein deficiency or a blunted anabolic response to dietary nutrients could be overcome with a protein supplement, other mechanisms proposed as mediators of age-associated sarcopenia and frailty, such as mitochondrial dysfunction,²² calcium transport alterations,²³ intramyocellular lipids,²⁴ and/or inflammation²⁵ may add to the uneven response to protein supplements. The presence of other deficits that may exacerbate sarcopenia and alter ATP availability, that is, vitamin D²⁶ or magnesium,²⁷ may also help to explain the lack of response in some frail persons to the added protein intervention, in addition to the variability in study design, dose, composition, and schedule of protein supplementation.

The role of physical inactivity in the genesis of sarcopenia and frailty is compelling, as shown consistently by studies demonstrating a rescue of muscle performance with resistance strength training.²⁸ Thus, it is plausible that multi-intervention approaches, such as combining protein supplementation with resistance exercise training,¹⁵ among other integrated strategies, are necessary to overcome the muscle protein anabolic resistance associated with old age.²⁹ Insulin resistance may affect protein synthesis,³⁰ which can be ameliorated with physical exercise^{15,20,31} or other strategies.³² Supplementing proteins without considering total caloric intake may be misleading, because a positive nitrogen balance to increase protein synthesis cannot occur if there is an energy deficit, which is frequently associated with frailty.³³ Furthermore, a high-protein diet with a low or an inadequate caloric intake has a higher thermogenic effect and may induce satiety,³⁴ which may worsen anorexia and undernutrition in a frail person.

Demonstrating a clear benefit of protein supplementation on frail persons may be challenging because of the many confounding factors involved. One single strategy may not be completely successful in the treatment of sarcopenia and frailty because of the complexity of the pathogenesis and symptoms of these syndromes. Thus, multicomponent interventions, such as those proposed in

other geriatric strategies,³⁵ might be implemented. Frail persons living in long term care facilities are often undernourished, hence protein supplementation as a regular practice seems to be indicated, but a single correction is probably not sufficient to impact general health, quality of life, or survival. Cost-effectiveness analysis issues may arise if protein supplements for frail persons would be universally implemented on a regular basis. Assessment of renal function, frequently compromised in frail older persons, is needed before a higher protein diet as part of a multi-intervention approach is initiated and in the course of the intervention, as well as a comprehensive geriatric assessment to help in the decision whether such intervention is most likely beneficial on an individual basis.

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Perspective: Exercise and Protein Supplementation in Frail Elders

To the Editor:

In the October 2012 issue of this journal, Michael Tieland and colleagues^{1,2} present two studies exploring longer duration protein supplementation in older adults. It is easy to be enthusiastic about these studies. The choice of study population (frail elders) is compelling, and the interventions (protein supplementation and exercise) are clinically and intuitively desirable. Dietary protein intake and physical activity are the key modifiable means of stimulating muscle protein anabolism.^{3–5} However, one of the lingering problems facing muscle metabolism researchers is the tenuous link between highly controlled, acute, mechanistic studies and longer duration, outcome-focused trials.^{6–8} In their articles, Tieland et al^{1,2} clearly demonstrate that making the translational leap from a successful acute, mechanistic result to longer term improvement in outcomes such as muscle mass and function is possible but should not be an automatic expectation.

The two articles presented in the October issue use a traditional “protein supplementation/exercise training” experimental design: Expose volunteers to a resistance exercise or protein supplementation regimen, or both, for 24 weeks and closely monitor outcomes.^{1,2} However, instead of being formulaic, the authors have incorporated several novel design elements in their work. Notably, the investigators specifically target breakfast and lunch, two traditionally lower protein meals, as the times to provide protein supplementation. This represents a more thoughtful, meal-driven approach to protein supplementation, which aims to optimize muscle anabolism by delivering a moderate amount of high-quality protein at each meal, rather than dumping the bulk of the day’s protein in a single meal.^{9,10}