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Letter to the Editor

Fighting Sarcopenia in Older Frail Subjects: Protein Fuel for Strength, Exercise for Mass

To the Editor:

Skeletal muscle has a global impact on our health not only because it permits us to stand or to move but also because of its numerous metabolic activities, including its capacities to produce energy from the mitochondrial oxidation of substrate or to deliver amino acids to the body in case of higher needs. Muscle mass loss together with alterations of muscle function, also defined as sarcopenia,^{1,2} is an important part of the frailty syndrome leading to disability, dependence, and increased mortality in the older subjects. Sarcopenia occurs not only with aging; chronic diseases are associated with loss of muscle mass and function too. Therefore, it is of major interest to understand how targeted therapeutic interventions, especially through food intake and physical exercise, are able to promote muscle mass and function in older persons through their specific impact on the regulation of muscle protein metabolism.^{3,4}

Dietary protein ingestion and the subsequent changes in plasma amino acid and hormones like insulin are key regulating signals promoting muscle protein anabolism through the induction of muscle translation initiation pathways.^{5,6} Interestingly, these intracellular signals may be also modulated by other stimulating events such as mechanical fiber contraction to promote muscle protein synthesis.⁶ During aging, a blunted response of muscle protein synthesis to nutrient intake has been reported to be one of the greatest limitations to muscle preservation by several investigators,^{4,5,7,8} suggesting an “anabolic resistance,” which may also be found in many other circumstances such as in patients with chronic obstructive pulmonary disease, with kidney disease, or in the intensive care unit.^{9–13} According to age-related anabolic resistance that may be induced by inflammation,¹⁴ insulin resistance,^{15–18} and more recently by lipotoxicity,^{19,20} the postprandial levels of plasma amino acids are crucial to reach the threshold triggering intracellular translation initiation pathways toward protein synthesis as depicted in Figure 1. This is the reason why muscle synthetic response to dietary protein or to essential amino acids has been initially reported to be preserved when adequate or high amounts of dietary proteins or amino acids were administered.^{21–24} However, when smaller intakes of essential amino acids were ingested, even though appropriate with regard to recommended dietary allowance, response of muscle protein synthesis was reduced.²⁵ Therefore, during frailty or age-related chronic diseases, postprandial stimulation of muscle protein synthesis may be restored by increasing either the anabolic stimuli (amino acids availability, hormonal responses) or the sensitivity to them

(potential role of physical activity) as schematically proposed in Figure 2. Hence, providing higher amounts of dietary proteins to frail resistant older persons together with physical activity as a “multimodal therapeutical approach” seems to be an appropriate strategy to optimize muscle anabolic response and ultimately promote gain in muscle mass and function. However, most of the studies have addressed this question in healthy older subjects not always characterized as subjects with sarcopenia, and very few have been performed on frail people. Moreover, it is of major concern to obtain simultaneous data on muscle mass and function from well designed long-term intervention trials.

Some recent studies have addressed these questions in frail subjects with sarcopenia,^{26–28} malnourished or hospitalized,²⁹ using various nutritional strategies (essential amino acids or dietary proteins supplementation) alone or together with physical exercise. The 2 recent randomized, double-blind, placebo-controlled studies from Tieland et al.^{27,28} The Journal of American Medical Directors Association determined the impact of 24 weeks of protein supplementation providing twice daily 15 g over 24 weeks alone²⁸ or in combination to resistance training²⁷ on muscle mass, strength, and physical performance in frail older adults. The protein supplement alone, consisting of protein supplementations at breakfast and lunch to spread out protein intakes throughout the 3 meals, did not increase muscle mass but promoted a significantly higher physical performance. In addition, efficiency of protein intake on muscle mass and function was amplified by resistance exercise, suggesting a synergistic impact of dietary protein and physical activity on muscle anabolism in this frail population. The results of these 2 important reports, which differ from others, raise many clinical and metabolic questions, especially regarding the requirement, the distribution, the timing, and the source of proteins together with the additive effect of different types of physical exercise.

First, at the clinical level, increasing protein intake over the recommended dietary allowance for elderly subjects (0.8 g/kg/d) in frail elderly persons to 1.3–1.4 g/kg/d was able to induce a significant improvement of muscle function: this means that current recommendations for protein only based on nitrogen balance studies may not be adequate when applied to elderly patients with chronic disease, implying that the recommendations should also be focused on specific functional outcomes (muscle performance, metabolic responses, immune functions, bone health, appetite regulation...). Then, because of an “age-related muscle anabolic resistance” in the case of frailty and/or hospitalized patients,

Fig. 1. Hypothetical temporal changes of postprandial muscle anabolism in response to meal intake: reaching the threshold is the goal!

providing more protein or essential amino acids in the diet and overcoming anabolic resistance by higher amino acid availability may improve postprandial muscle protein turnover and ultimately affect the quality of muscle proteins, which are exposed to oxidative stress attributable to their slow turnover.³⁰ Different results between studies may also be explained by the time of metabolic assessment after the start of intervention. The early postprandial stimulation of muscle protein synthesis induced by a higher protein intake may be later counteracted by an increased protein breakdown in the postabsorptive state. This remark means that interpretation of data from interventional studies should consider the duration of exposure to nutritional administrations. We may hypothesize that differences between 2 nutritional trials after 10–15 days may disappear after 3 or 6 months, suggesting that short studies, which help to understand some of the metabolic responses at the muscle level, should also be completed by long-term studies with clinical outcomes.

As previously discussed and beyond protein quantity, modifying the dietary protein distribution across the daily meals to optimize postprandial muscle protein gain is another nutritional strategy. Previous results from our group in healthy elderly women suggested that a “pulse feeding” pattern in which 80% of dietary protein was administered in 1 single meal (ie, lunch) (with equal

energy intake in all meals) was able to retain more nitrogen after 15 days than a spread diet.³¹ This concept was originally developed in a transition state of protein intake from 0.74 g/kg body wt⁻¹.d⁻¹ during the adaptive period to 1.05 g/kg body wt⁻¹.d⁻¹ in the experimental period.³¹ In the recent interventional studies performed in frail older subjects, protein distribution was rather close to a “spread diet” with equal amount across the day, because protein supplementation consisted mostly in 15g protein enrichment at breakfast and at lunch, but not at dinner to reach about 30 g protein for all meals per day (ie, 1.4 g/kg/d throughout the study period). Thus, because of the high daily protein intake, it is likely that the “timing effect” of daily protein distribution was less contributive in these investigations. However, this question is still a matter of debate because a recent randomized controlled trial indicates that malnourished and at-risk hospitalized elderly patients could benefit from the “pulse protein feeding pattern” on lean mass for 6 weeks with a target of 1.31 g protein/kg/d.²⁹

To improve postprandial muscle synthesis using dietary proteins, not only the timing but also the quality and the speed of digestion of dietary proteins are other important new options. Indeed, dietary protein amino acid composition, particularly when highly rich in essential and branched chain amino acids, has to be considered, because branched chain amino acids are specific signals to activate mTOR pathway.^{32–34} After their ingestion, these amino acids have to cross the splanchnic tissues which normally extract more than half of the dietary amino acids at first pass to be delivered up to the peripheral body tissues, especially the skeletal muscles. Because splanchnic extraction of amino acids was higher during healthy aging^{35,36} and even higher in the case of systemic inflammation for the production of acute phase proteins, a fast and ample elevation of plasma amino acid may be required to ultimately stimulate muscle protein synthesis. For this reason, the “fast/slow” protein concept initially developed at the whole body level^{37–39} has been applied in healthy aging to promote postprandial muscle protein synthesis.^{40–45} These studies confirmed that postprandial muscle protein accretion was improved by soluble milk protein (ie, whey protein ingestion in association with resistance exercise).^{42–45} From these studies, synergistic approaches are mostly required to improve muscle mass and function, but the amount, the type of protein, and the timing are

Fig. 2. Schematic representation of muscle anabolic response according to protein intake and exercise in older subjects. In situation of frailty, a lower muscle response may be restored by improving quantitative or qualitative aspects of protein consumption (box 1). Physical activity may potentiate the sensitivity of muscle protein synthesis to dietary protein (box 2).

crucial determinants to be considered in these new strategies. These nutritional concepts (protein feeding pattern, fast/slow protein, functional amino acids) and the timing together with exercise should now be tested on a practical and clinical basis in frail elderly subjects especially when protein intakes are limited. Finally, on top of nutrition and physical exercise, other strategies in future interventions focusing sarcopenia in frail older subjects could be also tested. Indeed anabolic hormones like androgens,⁴⁶ drugs targeting mitochondrial metabolism,⁴⁷ or pharmacologic enhancement of muscle perfusion during hyperinsulinemia¹⁸ are new potential tools to preserve muscle mass and function for a better quality of life during aging.

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