Protein Turnover and Metabolism in the Elderly Intensive Care Unit Patient

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Abstract

Many intensive care unit (ICU) patients do not achieve target protein intakes particularly in the early days following admittance. This period of iatrogenic protein undernutrition contributes to a rapid loss of lean, in particular muscle, mass in the ICU. The loss of muscle in older (aged >60 years) patients in the ICU may be particularly rapid due to a perfect storm of increased catabolic factors, including systemic inflammation, disuse, protein malnutrition, and reduced anabolic stimuli. This loss of muscle mass has marked consequences. It is likely that the older patient is already experiencing muscle loss due to sarcopenia; however, the period of stay in the ICU represents a greatly accelerated period of muscle loss. Thus, on discharge, the older ICU patient is now on a steeper downward trajectory of muscle loss, more likely to have ICU-acquired muscle weakness, and at risk of becoming sarcopenic and/or frail. One practice that has been shown to have benefit during ICU stays is early ambulation and physical therapy (PT), and it is likely that both are potent stimuli to induce a sensitivity of protein anabolism. Thus, recommendations for the older ICU patient would be provision of at least 1.2–1.5 g protein/kg usual body weight/d, regular and early utilization of ambulation (if possible) and/or PT, and follow-up rehabilitation for the older discharged ICU patient that includes rehabilitation, physical activity, and higher habitual dietary protein to change the trajectory of ICU-mediated muscle mass loss and weakness. (Nutr Clin Pract. 2017;32(suppl 1):112S-120S)

Keywords
anabolic resistance; leucine; protein turnover; sarcopenia; intensive care unit; aged; skeletal muscle

A number of evidence-based guidelines form the basis of protein provision for critically ill patients in the intensive care unit (ICU).1-4 In this short review, the focus is on the older patient (defined here as someone aged >60 years) for whom there are also general recommendations regarding protein provision.5,6 As opposed to the younger patient, the older ICU patient represents a far greater challenge in terms of protein provision. The challenge is due to the fact that on admittance to the ICU, older patients can be assumed to be losing muscle mass,7 to be impaired in terms of their ability to recover muscle mass due to muscle disuse,8,9 to be at risk of the development of frailty on discharge from the ICU,10 and to be “anabolically resistant,” meaning that they will have a lower skeletal muscle protein synthetic response to the normally anabolic effects of hyperaminoacidemia.11,12 In all ICU patients, there is likely a catabolic hormone profile (hypercortisolemia and potentially hypogonadism) and hypercytokinemia (ie, interleukin-6 [IL-6] and tumor necrosis factor–α [TNF-α]).13,14 Such a pro-catabolic/anianabolic state creates a “perfect storm” for loss of body protein in even the most “robust” ICU patient, but it may be even more profound in terms of muscle loss and a poor prognosis for recovery for an older patient. The loss of muscle mass in the ICU is not a trivial occurrence since evidence shows that muscle mass (or proxies such as creatinine excretion, ultrasound thickness) and sarcopenic status are independent predictors of mortality in the ICU.15-18 In addition, more patients are now, due to technical advances, surviving the ICU. Thus, concern about quality of life and physical function is important for ICU patients in general but is of particular importance on discharge from the ICU, a point underscored when considering that older patients are at a greater risk of becoming frail.19,20 Muscle weakness in the ICU is, for example, associated with delayed cessation of ventilation, extended length of stay, worse long-term physical function and quality of life, greater hospital costs, increased death 1 year after ICU admission, and increased caregiver burden.19,20

One stimulus that we know is markedly anabolic, at any age, is physical activity and particularly resistive activity.7 A growing body of evidence shows that physical therapy (PT) in the ICU can result in improvements in physical function, ventilator-free days, and length of stay in both the ICU and hospital20-22; however, admittedly improved outcomes with exercise therapy are not a universal finding.23,24 Nonetheless, that there is lack of harm with delivering PT and the potential benefit would make its implementation in the ICU, if feasible, prudent. In addition, the documented enhancements of muscle anabolism imparted by exercise7 provide a further rationale for implementation of PT in the ICU.20-22 It needs to be...
emphasized that PT can take a variety of forms in the ICU, varying from simply sitting up at the bedside, to walking, cycling (in and/or out of bed), resistive work using elastic bands, and neuromuscular electrical stimulation (NMES). While these forms of exercise may seem relatively “mild” and perhaps not able to impart much benefit, the opposite would be true given the extremely low level of function that patients in ICU settings would have.20–22

The goal of this short review is to examine what mechanism might underpin lean mass loss in the ICU and whether enteral and/or parenteral feeding can alleviate muscle loss. The relative merits of parenteral nutrition (PN) vs enteral nutrition (EN) in mitigating muscle mass loss are not discussed here, but the reader is referred to a recent evidence-based analysis and review on this topic.25 In particular, where data are available, the focus is on the older ICU patient. In addition, this study provides a brief exploration of the evidence underpinning PT as an important aspect in the promotion of lean mass retention and improved muscle function for the older ICU patient.

**Protein Turnover**

Protein turnover describes the simultaneous synthesis and breakdown of body proteins. When lean body mass (or skeletal muscle) is lost, it means there has been an imbalance in protein turnover that has shifted the balance of synthesis and breakdown to result in muscle retention (protein synthesis has exceeded breakdown) or muscle loss (atrophy). In the ICU, there is evidence to show that muscle atrophy occurs early and rapidly (Figure 1). Such rapid loss of lean mass is highly unlikely to be due to a stimulation of muscle protein breakdown (MPB) or suppression of muscle protein synthesis (MPS) but is likely the result of a simultaneous reduction in the rates of MPS and a concomitant rise in MPB.26 To lessen muscle loss in the ICU, there needs to be an aggressive and early intervention.

A multitude of factors contribute to the shift in muscle protein turnover to favor catabolism and rapid muscle loss seen in the ICU, and this may be particularly marked in the older patient. First, older patients (ie, aged >60 years) will be losing muscle mass (albeit slowly) before they enter the ICU as a result of the normal age-related decline in muscle mass (sarcopenia).7 Age-related sarcopenic muscle loss is estimated to proceed, beginning in the fifth decade of life, at ~0.8% annually.27 The sarcopenic loss of muscle may have a multifaceted etiology, but the predominant mechanism is now thought to be a phenomenon termed *anabolic resistance.*28–29 Anabolic resistance describes a relative degree of refractoriness of MPS to feeding-induced hyperaminoacidemia in older vs younger persons.28,29 The exact etiology of anabolic resistance is unclear and likely involves some biological aspect of aging, a reduction...
in levels of physical activity with aging, increased sedentarism, inflammation, or reductions in nutritive blood flow.\textsuperscript{30} Regardless of the etiology of this phenomenon, older persons require relatively higher protein (leucine) intakes than their younger counterparts to stimulate MPS to the same degree.\textsuperscript{28,31} Even nonpathologic muscle disuse (bedrest, immobilization) induces a profound and rapid loss of muscle mass.\textsuperscript{32,33} A rapid loss of muscle mass has been observed in patients in the ICU (Figure 1).\textsuperscript{26} However, the decline is likely more rapid in the ICU than in simple bedrest likely due to a number of factors that result in not only a reduction in MPS, due to aging per se and a disuse-induced accompanying anabolic resistance, but also an increase in MPB. In fact, muscle disuse induces a reduction in fed-state MPS.\textsuperscript{34,35} The reduction in fed-state MPS induced by muscle disuse\textsuperscript{34,35} is similar in magnitude to the anabolic resistance seen with aging.\textsuperscript{28,29} Thus, in line with observations from ICU patients, there is a reduction in MPS\textsuperscript{26} and also an increase in protein breakdown.\textsuperscript{26,29} When these factors are considered in an older person in whom muscle mass is already decreasing and for whom, we propose, it would be much more difficult to recover lost muscle mass,\textsuperscript{8} the problem in the older ICU patient is recognizable as one of tremendous relevance.

Proteolysis in skeletal muscle is regulated by a number of systems (for reviews, see Friedrich et al\textsuperscript{14} and Egerman and Glass\textsuperscript{37}). In brief, proteolysis in skeletal muscle is mainly regulated by the ubiquitin-proteosomal system that cannot degrade intact myofibrils but is responsible for the bulk of proteolysis in catabolic situations.\textsuperscript{14} In addition, the lysosomal autophagic pathway is also upregulated in the ICU.\textsuperscript{14} The upshot is that increased amino acids being released as a result of proteolysis are not being nearly as efficiently recycled into protein via MPS in ICU patients as they are in healthy persons.\textsuperscript{14} The main factors that contribute to an elevation in MPB in the ICU, and possibly even more so in an older ICU patient,\textsuperscript{14,15,18} are inflammation,\textsuperscript{38} insulin resistance of proteolysis,\textsuperscript{39} and muscle disuse per se.\textsuperscript{40} While an in-depth discussion of these mechanisms is not warranted here, suffice to say that reductions in MPS and resistance to the normal hyperaminoacidemia-induced stimulation of MPS, combined with elevations in MPB, create an environment in which muscle mass would be rapidly lost. Thus, a culmination of factors (Figure 2)\textsuperscript{26} likely contributes to a profound wasting of muscle mass (Figure 1).\textsuperscript{26,41}

In the absence of pharmacologic intervention to prevent muscle loss that occurs in the ICU, the 2 most potent nonpharmacologic stimuli are muscle loading (exercise), particularly resistive/weight-bearing exercise, and protein ingestion (for reviews, see Churchward-Venne et al\textsuperscript{7} and Phillips\textsuperscript{42}). Briefly, exercise serves to stimulate MPS, but there is no net protein accretion unless there is delivery of amino acids that result in a more positive net protein balance than when amino acids are provided alone.\textsuperscript{7,42} The mechanisms underpinning an exercise-induced sensitization of MPS to amino acids are not entirely clear and are not discussed here, but it is worth noting that the effect of exercise can be quite long-lasting.\textsuperscript{41,44} Whether such a long-lasting impact of activity can be extended from these findings\textsuperscript{43,44} to older ICU patients is not known, but as a viable means of overcoming the factors that result in muscle wasting (Figure 1), exercise holds promise.

### Protein Requirements in the Older ICU Patient

Protein requirements in the ICU have been recommended in a number of guidelines.\textsuperscript{3,45} An important question is whether the requirement for protein is different for older ICU patients.\textsuperscript{5,6,46} Hoffer and Bistrian\textsuperscript{47,48} have hypothesized that protein consumption/infusion at levels significantly higher (up to 2.5 g/kg normal body weight/d) than those suggested\textsuperscript{3,45} would be safe and potentially better for patients in ICU. And Dickerson et al\textsuperscript{6} have shown that older ICU patients show improved (sometimes positive) protein balance but only at higher protein intakes. Given what we know about protein turnover in older patients (see above) and the multitude of antianabolic and pro-catabolic factors older ICU patients face (Figure 2), a reasonable thesis is that early delivery of sufficient protein and/or amino acids would be recommended. The balance of enteral to parenteral delivery cannot be made at the present time, but meta-analyses provide some framework.\textsuperscript{25} For example, a recent trial showed that early PN spared lean mass and resulted in less invasive ventilation but did not reduce mortality.\textsuperscript{49} As Hoffer and Bistrian\textsuperscript{50} point out, “Only certain ICU patients..."
would be strongly predicted to benefit from early high-protein provision. They are patients whose protein requirement is increased by catabolic critical illness and patients with preexisting muscle atrophy when admitted to the ICU.” The recommendation for early and higher intakes of enteral protein would likely require reformulation of certain commercial feeding products, and a potential solution is to parenterally deliver amino acids in older persons in the ICU; such an approach is at least biologically plausible for the reasons outlined.6,43,50

Recent consensus guidelines from several expert groups51,52 have outlined a rationale for why protein intakes beyond the recommended dietary allowance (RDA) of 0.8 g/kg/d are likely optimal for healthy older persons. The bases for recommending protein intakes higher than the RDA, which is the minimal protein intake required to meet needs for 98% of the population, have been discussed recently.51 Some of the rationale for why protein intakes greater than the RDA might be optimal for older persons is focused on the preservation of lean mass that is observed in older persons with higher total protein intakes54 but also higher per-meal protein intakes,55,56 which are associated with improved muscle function.55 Appreciating that the arguments provided here only provide corollary evidence and do not constitute proof that older ICU patients need more protein, there is at least a credible framework on which to base a thesis of greater than recommended levels of protein for older ICU patients. Regrettably, as Hoffer and Bistrian47,48 have highlighted, we do not have data from appropriately designed clinical trials to answer this question. Nonetheless, an interesting analysis performed by Dickerson et al46 comparing nitrogen balance in younger to older patients is worth highlighting. These authors concluded, “Improvement in nitrogen accretion was blunted at lower protein intakes in critically ill, older patients compared with younger patients.”46 These authors46 observed that the relationship between protein intake and nitrogen balance in younger patients was sensitive and easily saturable, whereas in older patients, it was less sensitive to lower protein intakes and yet rose asymptotically with increasing protein intake. Interestingly, this “blunted” response of older persons to lower protein intakes in terms of muscle protein synthesis vs younger individuals has also been observed in healthy older persons.28 The encouraging conclusion, however, is that older patients in the ICU were able to achieve nitrogen balance and MPS in younger persons and lower sensitivity and improved response only at higher protein loads in older persons provide a reasonable rationale for why older patients may require more protein in or outside of the ICU.

An important issue with higher protein intakes in older ICU patients is the potential for ureagenesis and azotemia and impairments in renal function. An issue is whether the normal age-related decline in renal function is an issue for concern in the ICU with a recommendation for higher (2–2.5 g/kg/d) protein intakes. While beyond the scope of this brief review, an extensive and very thorough discussion on this topic has been undertaken by Dickerson.7 The point made is that observational studies suggest that protein intakes ≥1.2 g/kg usual/d during critical illness improve ICU survival compared with those given lower protein intakes,57–59 and combined with the potential to achieve a positive nitrogen balance with much higher intakes in older ICU patients, Dickerson7 states, “The limitation of protein intake on a short-term basis is unwarranted in the patient without overt acute kidney failure and contraindication for hemodialysis.” The point made by Dickerson is that it is moot to consider a negative impact of added protein/amino acid provision on renal function if the patient is not given enough protein to survive the ICU.5 Thus, while monitoring of renal function is encouraged, the potential for harm, unless the ICU patient has marked renal insufficiency, seems low and needs to be balanced against potential benefits of higher protein intakes.

Of relevance to the discussion of protein intakes in older persons is the recognition that all proteins are not equal in their capacity to stimulate MPS and possibly to suppress MPB.60 While extensive discussion of this topic is not warranted here, several reviews discuss how protein quality (reflected in the indispensable amino acid [IAA] content and digestibility of a protein) affects MPS and can have ramifications for preservation of lean mass with aging.60,61 Importantly, it is only the IAA that are important in driving MPS,62 and evidence shows that it is primarily, if not exclusively, the branched-chain amino acid (BCAA) leucine that is the trigger for switching on MPS as well as being a substrate for protein synthesis (for review, see Drummond and Rasmussen63). In sum, leucine binds to a protein, sestrin2,64 that allows the mechanistic target of rapamycin-complex 1 (mTORC1).63 The mTORC1 is the nexus for protein synthesis, and thus, leucine binding allows the process of MPS to become active. Thus, as a recommendation to stimulate MPS in older persons, it may be more prudent to focus on total protein delivery but in particular on the leucine content of proteins or amino acid mixtures. Of relevance to the ICU, it is acknowledged that data show the ineffectiveness of BCAA supplementation in various ICU patient groups,65–67 which has been reviewed.68 However, as pointed out by De Bandt and Cynober,69 the rationale for using BCAA as a mixture was based on preclinical observations without consideration of the individual effects of the amino acids themselves and ignored the relative contribution of leucine per se over and above valine and isoleucine. These authors state, “Positive results were most frequently observed with AA solutions containing a higher molar ratio of leucine . . . while data supports the notion of a relative decrease in the antiproteolytic effect of leucine in stress situations, it preserves part of its effectiveness. This leucine concept deserves to be evaluated in
large, randomized, controlled trials in patients receiving truly adequate nutritional support.™

Physical Therapy

Practice of PT in the ICU has been shown to be associated with a number of beneficial outcomes, including physical function, quality of life, respiratory muscle strength, ventilator-free days, and length of hospital and ICU stay.21,22 Despite the demonstrated positive impact of PT, point of prevalence estimates show that mobility practice is not a priority for a number of ICUs (for reviews, see Cameron et al70 and Hodgson et al71). The reasons for low rates of PT practice were recently reviewed and classified as being patient-related (50%), structural (18%), ICU cultural (18%), and process-related (14%) barriers.72 These authors stated, ‘‘To overcome the identified barriers . . . [the authors recommended] implementation of safety guidelines; use of mobility protocols; interprofessional training, education, and rounds. . . . Systematic efforts to change ICU culture to prioritize early mobilization using an interprofessional approach and multiple targeted strategies are important components of successfully implementing early mobility in clinical practice.‘‘72 Of relevance to the focus of the current review, it is posited that aside from the positive outcomes associated with early mobilization of ICU patients,70,71 PT and early mobilization could also result in a small but measurable sensitization of skeletal muscle to aminoacidemia. The sensitization of skeletal muscle to amino acids would be important in highly immobile patients. There are certainly ICU patient groups—trauma, brain injury, burns—in whom ambulation and PT will be difficult and perhaps impossible. However, even very low levels of contractions in older inactive patients73 and NMES74,75 can increase MPS. In the ICU, NMES has some promise as documented in a meta-analysis.76 These authors76 reported that NMES can maintain or increase muscle mass, as well as reduce time on mechanical ventilation and weaning time, and a significant effect in favor of NMES on strength in 2 studies has been shown. Thus, PT, ambulation, and NMES represent promising treatment not only for improving ICU outcomes21 but also as an adjunctive therapy to adequate protein to prevent excessive muscle loss.

Conclusions and Recommendations

Skeletal muscle is becoming recognized as a critical independent predictive factor for survival in the ICU and possibly for quality of life and physical function post-ICU. The 2 normally robust anabolic stimuli for maintenance of skeletal muscle are contraction (loading) and protein/amino acid delivery. The older ICU patient presents a challenge from a protein provision perspective for a number of reasons. One primary reason is that in older patient, an ICU stay superimposes profound antianabolic (muscle disuse, protein undernutrition) and procatabolic (inflammatory cytokinemia) stimuli in a person who is already experiencing (~0.8% per year) muscle loss and in whom muscle is anabolically resistant to protein/amino acids. Thus, the normally rapid and early loss of muscle seen in the ICU is not surprising and may well be even more rapid in older vs younger patients. What is encouraging is that older patients, who appear resistant to hyperaminoacidemia at low(er) protein doses, can achieve nitrogen balance and, it is hypothesized, increased MPS but only at protein close to ~2 g/kg/d.46 Importantly, older patients will likely have a much harder time recovering from the catabolic insult of an ICU stay. Hence, long-term quality of life, physical function, and risk for frailty may be permanently affected in the older patient following a period in the ICU. What is quite clear is that PT has a positive impact on a number of relevant ICU-related outcomes: physical function, ventilator-free days, ICU stay, and hospital stay. It may also be the case that PT and NMES impart a similar anabolic sensitizing effect to aminoacidemia that helps retain muscle mass. Based on the review of evidence, it seems prudent to explore the following recommendations for older ICU patients:

- early provision of protein/amino acids by enteral and/or parenteral means, potentially with a focus on higher leucine-containing proteins or amino acid mixtures;
- early PT, NMES, and/or ambulation in concordance with established protocols; and
- on discharge from the ICU, older patients should receive intensive rehabilitation in combination with increased consumption of protein, of high quality (high leucine), to maximize the anabolic synergism of these 2 stimuli to promote recovery and reduce risk for sarcopenia and frailty.

Clearly, more research is needed in this area. Given the increasing age of the population globally and the advances in ICU treatments, the proportion of older patients surviving the ICU is going to increase. Thus, the most efficacious in-unit and postdischarge nutrition and physical activity strategies are needed, particularly for older patients.

Statement of Authorship

S. M. Phillips, R. N. Dickerson, F. A. Moore, D. Paddon-Jones, and P. J. M. Weijs contributed to conception of the manuscript, drafted and critically revised the manuscript, gave final approval of the content, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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**Discussion**

Roland N. Dickerson: We published a paper in 2015 looking at 50 older patients versus 200 younger patients and protein intake. We examined the range from zero protein intake to 2.5 g/kg/d and attempted to characterize the change in nitrogen balance that occurred. One of the surprising things that we found was that the younger patients had a highly variable convex relationship with nitrogen balance. As protein intake increased, nitrogen balance went up and tended to plateau around 1.7–2.2 g/kg/d. You got small increases in nitrogen balance after that, but not a whole lot. The older patients coincide with the data you presented in that they didn’t seem to respond very well. They were kind of plateau in the beginning until we got somewhere around 1.3–1.5 g/kg/d. Then it started, the nitrogen balance started going up linearly all the way up to 2.5 g/kg/d. I don’t know if anyone else has looked at that kind of information or tried to evaluate that, but we were kind of shocked by that.

Stuart M. Phillips: I agree young people are very sensitive to amino acids at low doses and then plateau off, whereas the older people are not as sensitive and they require larger doses of protein/amino acids to get up to the same nitrogen balance. Our data for muscle protein synthesis in older persons look a lot like what you’re describing.

Douglas Paddon-Jones: Exercise alone has an energy cost associated with it and could increase muscle breakdown. In ICU patients, is there any anabolic advantage to physical activity if they don’t have sufficient amino acids precursors on board? Or do we really need to try and time the PT to
correspond with when you’re going to provide the feedings and protein delivery?

**Stuart M. Phillips:** I think that there’s no question in my mind that the physical therapy, exercise, or at the bare minimum neuromuscular electrical stimulation sets the muscle up to become more sensitive. It turns on the right factors to get good nutritive flow to the muscle, so then the protein delivery timing should always be after that. It appears that the sequential events should be therapy/loading/stimulation, followed by provision of amino acids to take advantage of the sensitivity that’s imparted by the exercise.

**Beth Taylor:** We never know when physical therapy is going to come in the ICU. This is why we have an early mobility program. I have a question about timing. If PT or we get the patient up and walking, how close to the exercise should we deliver a bolus of protein?

**Stuart M. Phillips:** In the sports nutrition world, this is a principle they call the anabolic window. The bottom line is for healthy young people who are exercising 5 days a week, the anabolic window is always open, so timing really doesn’t matter. For your ICU patients, I think the anabolic window becomes critical, because they get probably a limited amount of PT. When it occurs in the day, I would plan some type of delivery of nutrients, particularly protein, right after the exercise. Whether it is an enteral or parenteral source, I would say definitely within the first hour.

**Stephen A. McClave:** What about the benefit of stimulating protein synthesis with intermittent versus continuous feedings? There are well-known clinicians that want us to feed for 20 minutes, then stop and come back 2 hours later and do it all over again. This goes against what happens in the vast majority of patients who are continuously fed.

**Stuart M. Phillips:** What are we talking about is the refractory period. We’re not exactly clear on how this is defined, but the system seems to like to be pulsed with amino acids. Individuals who consume a high amount of high-quality protein every day like chicken breasts because the feedback in the system the muscle is full. You can’t cram any more amino acids into the muscle. I think you are getting some sort of negative feedback with anabolic signaling markers such as mTOR being turned off. So, in short, yes a pulse feeding-type pattern would seem preferable.

**Peter J. M. Weijs:** I love the meal fed bolus feeding model and studies that evaluate muscle anabolism. How do these studies translate to 24-hour continuous feeding in the ICU patients?

**Stuart M. Phillips:** Coming back to the previous comment, the most appropriate feeding pattern that I would suggest is this sort of cyclical pattern. I can’t explain why the muscle responds better when amino acids are provided in that manner. I am not sure that continuous provision of food in the ICU is a bad thing, but if you were to pulse amino acids and create periodic hyperaminoacidemia, I think that would have a greater anabolic effect in the long run. This is based on data we have in healthy older adults.

**Peter J. M. Weijs:** If you pulse nutrition including amino acids, as you suggested, spike the leucine concentration in the muscle where it could actually have an effect, could we then lower the total amount of protein you would suggest?

**Stuart M. Phillips:** Leucine is the anabolic trigger, and if you could pulse leucine, maybe that would be one way of doing it. There is a growing piglet model that demonstrates if you just have enough baseline amino acids, it is the spikes in leucine that really determine and drive the protein synthetic response. Translation of this into the clinical practice may be a long way off.

**Frederick A. Moore:** I’ve been interested in sepsis for about the last decade. The problem is that sepsis is a disease of the elderly. If you look at sepsis rates when you hit 65, you’re on that downward curve. The frustration is I deal with a bunch of young trauma patients, and they go through this same thing. Three to 6 months after discharge from the ICU, they come back versus the old patients do not. I’m very skeptical about this feeding early idea and whether or not we will have a positive impact. My question is, what can you do to really kick-start these people? There’s a bunch of anabolic agents, but is leucine more potent of these anabolic agents? Exercise, obviously, is a big deal, but I’m trying to figure out, what do you think is the most important thing I could tell my patients? Go exercise and eat leucine?

**Stuart M. Phillips:** I talked about long-term data, which demonstrate that as people get older, their changes in muscle mass are strongly predictable by total protein intake and even better so by total leucine intake. I think leucine is potent and you can choose leucine-enriched foods such as soy, dairy-based sources. I completely agree with the point that the young people recover and bounce back after a hospital stay while old people do not. To attempt to limit this, it takes aggressive targeted physical therapy with a strong emphasis on mobility combined with a higher protein diet with high leucine content and potentially other anabolic agents.

**Saúl J. Rugeles:** Do you have some comments about HMB or β-hydroxy β-methylbutyric acid use in older people?

**Stuart M. Phillips:** Given the potency of leucine, HMB, which is a metabolite of leucine, will have an anabolic and antica
tabolic effect. In fact, we were involved in the one and only trial to show that it is anabolic and antica
tabolic. Leucine does exactly the same thing, I think that every HMB trial has been compared with a “strawman” placebo, and when you compare
something that’s anabolic and anticatabolic to placebo, you’re going to see an effect. I think if you compared leucine to HMB in isomolar quantities, you’d see no difference.

**Jan Wernerman:** There are lots of data showing that in the ICU, the muscle protein synthesis is not lower than normal, but the degradation rate is much higher. Do these data also interfere with the degradation rate?

**Stuart M. Phillips:** Absolutely, I think that it’s fair to say that if you put someone in disuse, there’s no doubt that their resting and fed-state rates of protein synthesis are lower. I don’t think that’s equivocal at all. I disagree that there’s no effect on protein synthesis. I do agree that at the same time, there is likely an increased rate of protein degradation. Balance has shifted toward loss of muscle mass. There’s no doubt about that, but I agree with the sentiment that was made, that blocking proteolysis in that situation is perhaps not a good idea. I think you need to let protein proteolysis proceed. Protein breakdown in that situation probably gets rid of a lot of damaged or misfolded or somehow nonfunctional proteins that you need to get rid of. I would focus on anabolic as opposed to anticatabolic solutions.

**Jan Wernerman:** The synthesis rate is not lower in the ICU? What do you suggest then?

**Stuart M. Phillips:** Synthesis rates in all situations of disuse are lower. It’s either from a reduction in protein synthesis or rampant proteolysis that is responsible for muscle loss, and I think, at least in part, it is from a reduction in protein synthesis.

**Jan Wernerman:** Is that the intracellular leucine concentration in the ICU is at least 2 times that of healthy individuals? Please comment on that.

**Stuart M. Phillips:** Because amino acids aren’t being used for synthesis. That’s one interpretation of those data.

**Jan Wernerman:** The synthesis rate is normal.

**Stuart M. Phillips:** Well, and again, we’d have to agree to disagree.

**Robert G. Martindale:** This is the synthesis from the protein, total protein, not from muscle. Total protein synthesis in the body doesn’t change.

**Jan Wernerman:** If you look at the study you have cited extensively in your talk, it shows an unaltered protein synthesis and a higher degradation rate. It was in the small subset of patients in that particular study.