Nutritional Support in Intensive Care Unit (ICU) Patients

Topic 18

Module 18.2

Protein Requirements in the ICU

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Learning Objectives

- To understand the catabolism occurring during critical illness;
- To assess protein and muscle loss;
- To learn how to administer protein orally, enterally or parenterally;
- To learn when and how much to administer protein.

Contents

Key Messages

- Higher protein intake increases whole protein content in the body;
- No strong evidence for high protein administration (more than 1.3 g/kg/d) in ICU patients;
- Disease specific protein therapy for trauma, renal or frail and elderly patients: messages.

1. Protein Metabolism in the Whole Body

1.1 In the Normal Subject

Free Amino Acids (70 g/day) are provided every day by oral intake (70g/day) and oxidized in the same amount. The body is able to synthesize and to transform these amino acids for specific functions. There is a perpetual exchange between the amino acid pool and the body reserves exchanging around 300 g/day in synthesis or proteolysis (1). The result is a zero nitrogen balance (see **Fig. 1**).

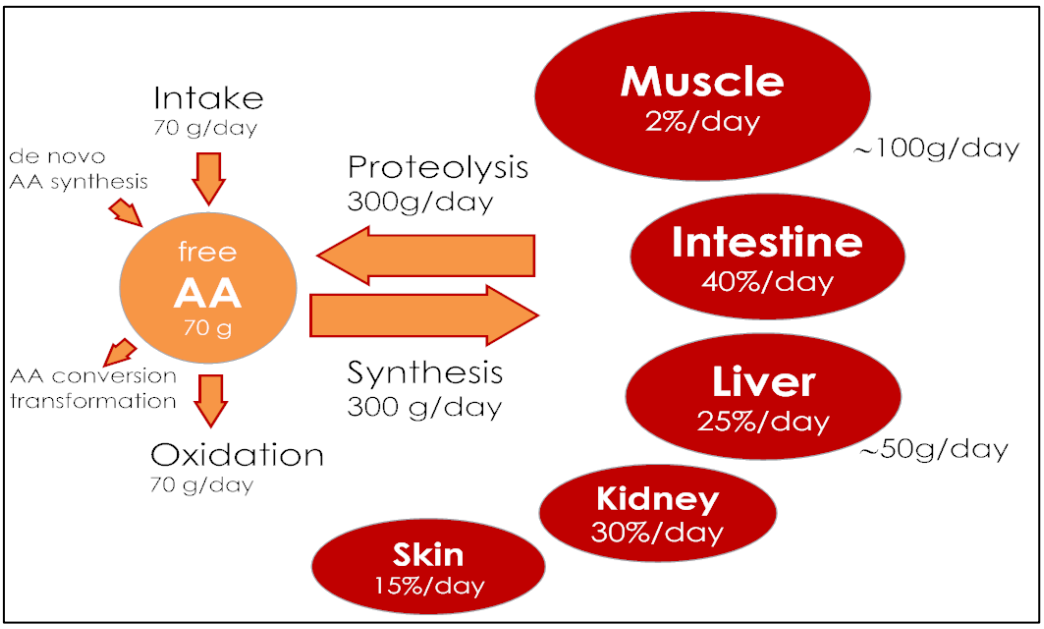

Fig. 1 Protein metabolism in the all body

1.2 In the Critically Ill Patient

The critically ill patient is highly catabolic, losing significant amounts of protein and muscle (2). First, proteolysis occurs to provide amino acids for endogenous substrate production and gluconeogenesis. Second, ubiquitinisation is triggered and results in an extensive destruction of muscle using actin and myosin. Third, the bedridden condition is a pro-inflammatory phenomenon that increases IL6 and CRP as well as IL10, and results in weight loss. Finally, the hormones and mediators produced by the body after stress also have a catabolic effect. All of these together result in a substantial loss of muscle and lean body mass that can be evaluated by measuring nitrogen excretion in the urine, muscle

mass using bioimpedance, CT or ultrasound, or in specific studies using biopsies or stable isotopes (3). In these conditions, protein synthesis is increased but protein breakdown is even more elevated resulting in a strong negative nitrogen balance. The body is resistant to any protein administration and this status has been defined as anabolism resistance (4).

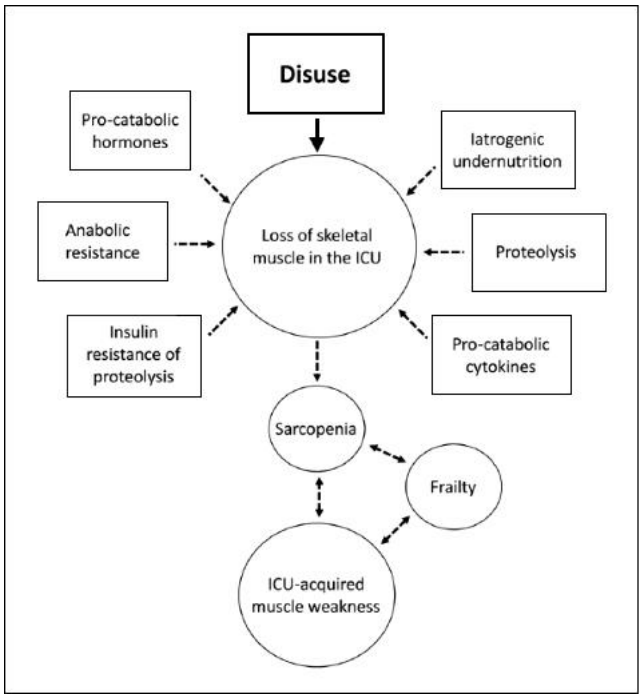

Fig. 2 Protein Turnover. From Phillips et al, Protein turnover and metabolism in the eldery intensive care patient. Nutr Clin Pract 2017; 32: 112S-120S

Only later (after 10 to 30 days), may protein synthesis increase and the patient could enjoy positive nitrogen balance (5).
The clinical consequences of this loss of muscle and lean body mass are seen in the short- and the long-term. Patients with severe negative nitrogen balance have increased infection rates, longer length of ventilation and ICU stay and higher hospital mortality (6). The survivors suffer from ICU acquired weakness which is associated with 1 and even 5 years of severe disabilities and decreased quality of life (7).

2. Assessment of Protein Breakdown and Loss of Muscle

2.1 Nitrogen Loss

Urea nitrogen is lost in the urine and this loss can vary between 8 and 35 g nitrogen a day (8). The total daily nitrogen loss is the sum of the urinary nitrogen and the faecal losses (around 3-4 g/d). It has to be remembered that 1g Nitrogen relates to 2 g urea, 6,25 g protein and 30 g muscle. In the case of renal failure, increase in BUN should be taken into account. The following equation (9) can be used. The protein equivalent of nitrogen appearance (PNA) was calculated by the Bergstron formula:

PNA (g/day) = 15.1 + 6.95 (UNA) + dialyzate and
urinary protein los per day

where

UNA (g/day) = urinary urea nitrogen (g/day)
+ dialyzate urea nitrogen (g/day)
+ change in blood urea nitrogen (g/day)*
The PNA normalized to body weight (nPNA)
was calculated by the following formulas:
nPNA(g/kg/day) = PNA/weight
Negative protein in balance (g/kg/day)
= nPNA —protein intake(g/kg/day)

2.2 Bio-impedance

This technique described elsewhere (body composition module) allows evaluation of the phase angle, an indicator of nutritional status. In addition, if the patient is stable and without large fluid shifts, an evaluation of the fat mass and the fat free mass can be performed and followed during the hospitalization. This method is not invasive and is reproducible, and therefore very helpful in the ICU setting. Phase angle has been considered as a valuable tool to predict mortality (10, 11).

2.3 Ultrasound, CT or MRI

No validated tool is available but lean body mass evaluated by ultrasound (12), or computerized tomography (CT) scan (13) might be performed to evaluate muscle loss. Such loss in muscle is associated with a prolonged hospital stay and interferes with quality of life and functional capacity (14). CT scan has been used in the ICU to assess lean body mass and may be a promising tool for patients already undergoing abdominal CT for other clinical reasons. A very recent study (15) showed that patients with low muscle mass found at admission have a higher length of stay and higher mortality. Sarcopenia (16) is defined as a decrease in muscle loss and/or function and is frequent in undernourished patients admitted to the ICU. Muscle function may also be assessed by various tools such as the handgrip dynamometer (17) if the patient is conscious, being an especially good prognostic factor in conscious patients with Adult Respiratory Distress Syndrome (ARDS) (**Fig. 3**).

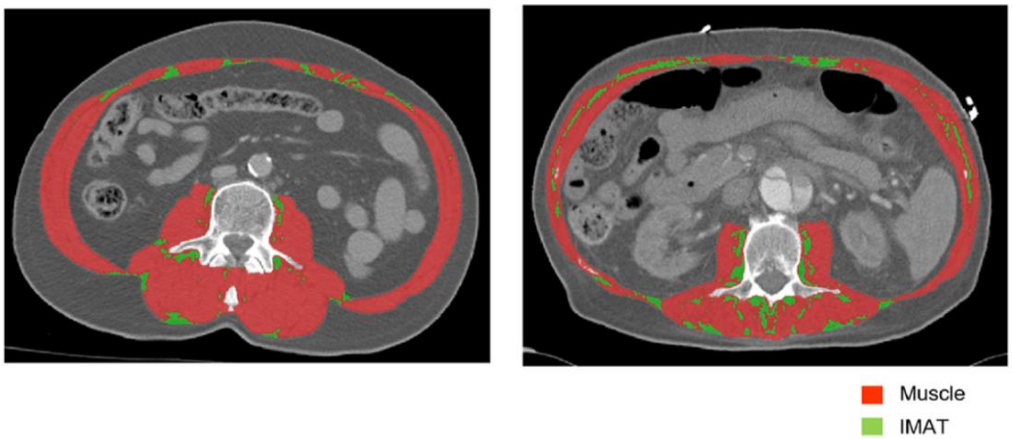

Fig. 3 Abdominal CT evaluating muscle mass (15).

2.4 Stable Isotopes

According to a method described by Deutz et al (18), calculations for whole body protein metabolism during the fed state have been described. Under steady state conditions the rate of appearance (Ra) of amino acids in the plasma pool is equal to the rate of disappearance (Rd; flux or Q). In the fed state Ra equals the sum of the rate at which the amino acid is released from whole body protein breakdown (WbPB) and the rate at which the amino acid enters the blood pool from the nutrition source. In case of enteral nutrition this is the rate of enteral intake, corrected for the proportion of the amino acid intake that is retained in the splanchnic area during first pass (splanchnic extraction, SPE). Rd equals the sum of the rate of oxidation or hydroxylation (in case of phenylalanine: PheOH) and the rate at which the amino acid is used for whole body protein synthesis (WbPS). This experimental technique allows evaluation of protein synthesis and protein breakdown in the critically ill patient.

2.5. Biopsy

Puthucheary et al (3) showed that taking serial muscle biopsies could confirm the significant loss of muscle mass. The loss of types I, IIa and IIb fibres could lead to significant muscle atrophy after 10 days. This technique is only used experimentally.

3. Route of Administration

Protein sources can be administered orally, enterally or/and parenterally. In the last case, only balanced amino acid (AA) solutions can be used. With the oral and enteral routes, protein sources can be administered as whole or partially hydrolyzed protein or as a powder of amino acids. It is important to remember that 100 g of protein hydrolyzate produces only 83 g of amino acids (19). Critically ill patients lose more protein that they receive and therefore are in a negative nitrogen balance. This is due to the severe catabolic state and the inappropriate content of protein in the commercial products which are usually proportionately richer in energy. The optimal amount of protein to administer is developed in the next chapter.

3.1 Oral Administration

This intake can be reached using oral nutritional supplements (ONS) with high protein content. These products can reach 1 g of nitrogen for 80 to 100 kcal. However, many of the ONS are not sufficiently enriched in protein. Another possibility is to use supplemental amino acid powders that could be added to the oral nutritional regimen and administered as boluses of 30g 2 to 4 times a day. These formulas are enriched in leucine and are based on whey as the source of protein.

3.2 Enteral Administration

This route is an excellent tool to administer the required amount of protein if the gastrointestinal tract is preserved. Formulas with various protein compositions can be chosen and amino acid powders can be administered in addition if needed. Most of the ICU population is currently not provided with enough protein (below 0.7 g/kg/day) according

to the NutritionDay® ICU audit (20). New enteral formulas are now providing better protein content without increased energy intake (21).

3.3 Parenteral Nutrition

When the gastrointestinal system is not functioning, parenteral nutrition can be used (22). Amino acid hydrolysates are a pivotal component of parenteral nutrition and have a balanced composition with essential and non-essential amino acids. The concentration of AA varies from 5% to 10 and even 15%. The prescription should be adapted to the patient's needs. Glutamine can be included in special amino acid solutions and administered according to guidelines (23).

4. How Much Protein?

According to the ESPEN guidelines (23), at least 1.3 g/kg ideal body weight/day should be progressively administered to critically ill patients. These recommendations are based on large observational studies, some randomized prospective studies, and stable isotope studies. Outcome can be improved: nitrogen balance, protein synthesis, whole protein content in the body, improved length of stay, and decrease in mortality (24, 25, 26). However, most of the meta-analyses (27) have failed to demonstrate that higher protein administration is improving survival. Improvement in muscle strength has been shown by some authors. The explanation may be anabolic resistance, such that the protein administered cannot be integrated into the muscle. Recently it has been shown that the association of muscular exercise with protein administration may overcome ubiquitinisation and improve muscle mass (fibres type I, II a and b) (28).

4.1 According to the Disease

4.1.1 Older, Frail Patients

Effectiveness of protein administration depends of the type of disease. Frail (29) and sarcopenic (16) ICU patients have better survival when receiving 1.2g/kg/day in comparison to 0.8 g/kg/d (15), while septic patients seem to be resistant to protein intake (30). Sarcopenia can be defined from CT scan examination at the level of L3 using specific software. Severe weight loss and decrease in appetite before hospitalization can also be a diagnostic tool for malnutrition.

4.1.2 Obese Patients

This population is becoming more and more frequent in the world. The recent TARGET study (31) included around 50% of obese patients. It has been suggested (32, 33) that high protein administration (2g/kg/day and more) together with hypocaloric regimens could be helpful in improving outcome in obese patients. However, the evidence behind these recommendations is not strong. ESPEN (23) suggests measuring energy expenditure using indirect calorimetry, and nitrogen balance using urinary urea nitrogen losses to better evaluate these patients. It is difficult to know the precise requirements of a severely obese patient without these tools. The current ESPEN recommendations do not distinguish between obese and non obese patients: 1.3 g/kg/day.

4.1.3 Renal Failure Patients

There are numerous studies comparing lower versus higher protein administration in acute kidney injury patients. Sheinkestel et al (34) showed a positive influence on patients on Continuous Renal Replacement Therapy (CRRT). Doig (35) and Singer (36) found an improvement in glomerular filtration rate but without other improvement. Fluid balance and creatinine clearance may be improved. In CRRT patients it is recommended to add 10 to 20 g of protein to the prescribed regimen to compensate for amino acids lost through the membrane to ultrafiltration (37). There is no indication to reduce protein administration in fear of increased urea. This increase may be controlled by dialysis if it occurs.

4.1.4 Trauma and Burn Patients

There is a strong body of evidence that enteral glutamine at the dose of 0.3g/kg/day is improving outcome in the patient with burns or trauma (38). The ESPEN guidelines declare (23) that: "In critically ill trauma, additional EN doses of GLN (0.2-0.3 g/kg/d) can be administered for the first five days with EN. In case of complicated wound healing it can be administered for a longer period of ten to 15 days. Grade of recommendation: 0 – strong consensus (91 % agreement)". Glutamine was described to have beneficial effects in major burn injuries, reducing infectious complications (mainly Gram negative infections) and also mortality (38). This has been confirmed in the latest meta-analysis (39). Protein losses in patients with an open abdomen have been evaluated to be around 2-4 g/day (40), suggesting an additional protein prescription in these patients. Burns patients are also suffering from an excessive loss of protein.

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4.2 According to the Progression of the Disease

Administration of protein can be to reach the target within the first 24-72 hours after admission or more progressive across the first 7 days to reach the target. Ferrie et al (41) administered 1.2 g/kg/day of protein from day 1 and showed functional muscle improvement while Allingstrup et al (42) failed to find functional improvement giving 1.4 g/kg/day from day 1. Retrospective studies also found different outcomes. Bendavid et al (20) observed an association between 1g/kg/day at day 3 and an improvement in 60 days survival, while Keokeok et al (43) found that 0.8g/kg/d during the first days followed by 1.2 g/kg/day after 5 days formed the best progression to reach better outcomes. It has been suggested by Casaer et al (44) in a post analysis that early administration of protein - at day 3 -may be associated with a decrease in discharge alive from the hospital. These findings may be hypothesis generating.

4.3 According to Energy Administration

The association between protein and energy intake is crucial. However, due to limitations of industry products, reaching the protein goals might lead to overfeeding in terms of energy administration. This load in energy may be deleterious and even lead to increase in mortality. Therefore, additional commercial products have recently been proposed to prevent an increase in calories secondary to increase in protein load (45). These products are currently under investigation. Calorie provision should be guided by indirect calorimetry (23) measurement while protein administration should follow the recommendation of 1.3

g/kg/day administered progressively. In stabilized patients energy administration may be increased as well as the daily protein load. Rooyakers's team (6) have found in a stable isotope study that after 20-30 days protein synthesis was significantly increased, encouraging a higher prescription.

5. Type of Amino Acids/Protein

5.1 Glutamine

The amino acid GLN is a normal component of proteins, representing around 8% of all amino acids, and is present in standard commercial enteral feeds. GLN for parenteral use has been available since 1994, after its synthesis by Fürst (38). Previously unstable in parenteral nutrtion, glutamine became available as a parenteral product. GLN transports nitrogen between cells and/or organs and serves as a metabolic fuel in rapidly proliferating cells (38). Under physiological conditions, sufficient endogenous GLN stores are maintained by daily nutritional intake (80 g of mixed protein contains approximately 10 g GLN) and by endogenous synthesis (skeletal muscle and liver).
Plasma GLN levels have repeatedly been shown to be low during critical illness, and low values to be associated with poor outcome (38). However, not all critically ill patients are GLN depleted. Patients with acute liver failure typically have very high plasma GLN concentrations for example (46). As GLN is one of the most potent gluconeogenic and ureogenic amino acids, liver failure reduces the normal removal of ammonia produced from GLN metabolism. In the REDOXS trial (45), some patients exhibited high levels of plasma GLN. If glutamine is indicated enterally in trauma and burns as described previously, there is no evidence to recommend it in other conditions requiring enteral feeding. The REDOXS study (45) has shown that administration of a high dosage of glutamine parenterally was associated with a higher mortality in ICU patients suffering from multi organ failure, mainly renal and hepatic failure. Therefore there is a strong recommendation not to administer glutamine in these patients (23). In stable patients without multiorgan failure, administration of IV glutamine has been considered safe and associated with improvement in morbidity (47).

5.2 Source of Protein

Differences in the source of protein may lead to different protein efficiency. Whey protein has been proposed as the best source, because of its high content in leucine. Whey protein is a strong GI hormone and insulin stimulator, improving anabolism (48). Whey proteins contain all the essential amino acids in higher concentrations than vegetable protein sources and also have a high concentration of branched-chain amino acids (BCAAs) – leucine, isoleucine, and valine – important factors in tissue growth and repair. Leucine is a key amino acid in protein metabolism. Whey proteins are also rich in the sulfur-containing amino acids cysteine and methionine, which enhance immune function. The digestion and absorption of whey and casein differ in that casein, unlike whey, coagulates in the stomach due to its precipitation by gastric acid. As a result, overall gastric emptying time for casein is longer and there is a smaller postprandial increase in plasma amino acids compared with the noncoagulating whey proteins. They are considered to be 'fast proteins', as they reach the jejunum quickly, but after reaching the small intestine, hydrolysis is slower than that of casein, allowing greater absorption over the length of the small intestine. Whey's rapid

absorption patterns are superior for postprandial protein utilization and overall nitrogen balance in elderly women (49).

6. Conclusions

Protein requirements have to be reached in the critically ill. The target of 1.3 g/kg/day should be reached progressively and should be adapted to the clinical conditions. Special attention should be given to the patient's disease, the route, the progression and the type of the formula administered. Energy administration should be appropriate. Exercise has been recently suggested to be an excellent adjuvant to protein load.

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