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Protein Catabolism and Requirements in Severe Illness

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Abstract: Reduced total body protein mass is a marker of protein-energy malnutrition and has been associated with numerous complications. Severe illness is characterized by a loss of total body protein mass, mainly from the skeletal muscle. Studies on protein turnover describe an increased protein breakdown and, to a lesser extent, an increased whole-body protein synthesis, as well as an increased flux of amino acids from the periphery to the liver. Appropriate nutrition could limit protein catabolism. Nutritional support limits but does not stop the loss of total body protein mass occurring in acute severe illness. Its impact on protein kinetics is so far controversial, probably due to the various methodologies and characteristics of nutritional support used in the studies. Maintaining calorie balance alone the days after an insult does not clearly lead to an improved clinical outcome. In contrast, protein intakes between 1.2 and 1.5 g/kg body weight/day with neutral energy balance minimize total body protein mass loss. Glutamine and possibly leucine may improve clinical outcome, but it is unclear whether these benefits occur through an impact on total body protein mass and its turnover, or through other mechanisms. Present recommendations suggest providing 20–25 kcal/kg/day over the first 72–96 hours and increasing energy intake to target thereafter. Simultaneously, protein intake should be between 1.2 and 1.5 g/kg/day. Enteral immunonutrition enriched with arginine, nucleotides, and omega-3 fatty acids is indicated in patients with trauma, acute respiratory distress syndrome (ARDS), and mild sepsis. Glutamine (0.2–0.4 g/kg/day of L-glutamine) should be added to enteral nutrition in burn and trauma patients (ESPEN guidelines 2006) and to parenteral nutrition, in the form of dipeptides, in intensive care unit (ICU) patients in general (ESPEN guidelines 2009).

Key words: Stress, severe illness, total body protein mass, protein turnover, protein requirements

Introduction

Proteins are stored in visceral tissue and muscle, mainly skeletal muscle. Along with water, minerals, and glycogen, protein mass is often grouped under the term of fat-free mass, as opposed to fat mass. A low protein or fat-free mass is a marker of protein-energy malnutrition (PEM). Since PEM has a high prevalence among hospitalized patients and has been associated with numerous complications, methods to prevent or limit PEM and the associated loss of protein mass are suitable.

The literature describes several types of PEM; i. e. cachexia, starvation, and/or sarcopenia, which frequently overlap in severely ill patients. Cachexia represents a complex metabolic syndrome associated with underlying illness, characterized by an accelerated loss of muscle mass with or without loss of fat mass and often associated with anorexia, inflammation, insulin resistance, and increased muscle protein breakdown. In contrast, starvation results from a pure deficit of all macro- and micronutrients, as seen for instance in hunger strikers and persons with anorexia. Sarcopenia describes the depletion of skeletal muscle mass occurring mostly in older or immobilized subjects but it is

not quite sure whether it reflects a third type of PEM, as it is associated with increased plasma concentrations of inflammatory cytokines.

Since there is no universal definition of "severe illness" and studies use various severity scores, if any, to describe their patients, we decided to define arbitrarily severely ill patients as intensive care, burned, septic, or trauma patients.

This article reviews the impact of acute severe illness and nutritional intake on protein mass and turnover and the subsequent protein requirements in human adults.

Protein mass in severe illness

Protein mass can be evaluated *in vivo* by measurements of body composition. *In vivo* neutron activation (IVNA) is usually considered the gold standard but available only at a small number of centers worldwide and relies on administration of radioisotopes to humans. It measures directly the nitrogen content of the body and allows calculation of total body protein mass (TBP) by the relationship: protein (g) = 6.25 x nitrogen (g). The other methods determine fat-free mass directly or indirectly. Bedside methods are of limited accuracy in case of overhydration, as is often seen in intensive care unit (ICU) and critically ill patients.

Studies reporting TBP changes in severe illness are summarized in Table 1. Four of them showed an important loss of TBP. Two of them found that TBP can be maintained in severe illness but likely included subjects who were less ill. Indeed, Chandrasegaram *et al.* performed the measurements of TBP and started parenteral nutrition at different stages of illness and not specifically on the day of diagnosis, and thus patients may already have been in their recovery phase [1]. In the study by Sevette *et al.*, the authors had excluded patients who became septic or required admission to the intensive care unit [2].

Protein is mainly lost from skeletal muscle. In patients with severe sepsis, the protein loss originates by 67 % from skeletal muscle mass during the first 10 days and later on predominantly from viscera [3]. Patients with blunt trauma lose 70 % of their protein mass as skeletal muscle mass during the first 15 days [4]. In contrast, cardiac mass and function do not decrease 21 days after critical surgical illness despite massive nitrogen loss [5].

The changes of total body protein mass over 3 weeks are similar between patients with severe sepsis and major trauma [6]. Similarly, energy and macronutrient balances during 7 days did not differ between septic (APACHE III score of 70 ± 11) and non-septic patients who received a similar amount of daily parenteral nutrition, providing an energy supply of 25 % above the measured resting energy expenditure [7]. Reeds *et al.* even showed that the kinetics of nitrogen loss after an insult and the peak of nitrogen loss were similar between numerous stressors [8].

These studies demonstrate the loss of protein mass during severe illness. This loss of protein mass cannot be overcome by nutritional support in case of severe sepsis or trauma and occurs mainly in skeletal muscle and is similar between patients with a variety of stressors.

Protein turnover in severe illness

The understanding of mechanisms underlying protein catabolism requires insight into protein turnover, which is a dynamic process. It is ideally measured by incorporation of isotope-labeled tracer amino acids into protein or dilution of tracer amino acids in the free amino acid pool by protein breakdown and performing tissue or limb balances. During severe illness, there is an increased protein breakdown (25–127 %) and, to a lesser extent, an increased whole-body protein synthesis (16–47 %) (acute phase response, wound repair, immune response, etc.) [9], leading to a negative protein balance, and an increased flux of amino acids from the periphery to the liver.

The accelerated protein breakdown results from a generalized stress response associated with complex neuronal, inflammatory, and hormonal interactions (Figure 1). It occurs mainly in skeletal muscle, as mentioned earlier, and involves the activation of the ubiquitin-proteasome proteolytic pathway. The protein breakdown is likely not disease-specific since an animal study showed that muscle atrophy could be related to multiple systemic diseases share a common set of transcriptional adaptations [10]. The resulting amino acids can be either used for protein synthesis or for non-protein physiological and metabolic functions (peroxidative protection, lymphocyte proliferation, energy production, etc.). Noteworthy is the fact that there is a mismatch between the amino acids provided by muscle protein breakdown and the amino acids needed for protein synthesis during the acute phase response. Indeed, 2.6 g of muscle protein must be catabolized to synthesize 1 g of fibrinogen. Thus, the type of amino acids needed for the acute phase response may determine the severity of muscle catabolism.

Table I: Studies on the impact of severe illness on total body protein mass measured by *in vivo* neutron activation.

Authors	Patients (n)	Severity Score	Duration of follow-up	ΔTBP	Nutrition during follow-up
Plank LD *et al.* 1998	Generalized peritonitis (12)	Mean APACHE II Score = 21 ± 7	21 days	–13 %	Energy balance: –318 ± 264 kcal/day during first 10 days
Streat SJ *et al.* 1987	Postoperative sepsis (8)	Acute Physiology Score 22 ± 5	10 days	–12.5 %	Energy intake: 43 non protein kcal/kg FFM/day and 2.3 g/kg FFM/day
Monk DN *et al.* 1996	Blunt trauma (10)	Mean Injury Severity Score = 36 ± 6	15 days	–16 %	Energy balance: –1293 ± 695kcal/day
Finn PJ *et al.* 1996	Blunt trauma (9), severe sepsis (11)	Not available	21 days	–15 %	Not available
Chandrasegaram MD *et al.* 2005	Severe acute pancreatitis (15)	Atlanta criteria met in 13 patients	14 days	+ 2 %*	Energy prescription: 40 kcal/kg/day with calorie to nitrogen ratio of 150:1 Energy balance: not available
Sevette A *et al.*2005	Surgery for upper GI malignancy (15)	Not available	14 days	–3.5 %*	Energy intake: 26.5 ± 1.4 kcal/kg/day and 0.25 ± 0.04 g N/kg/day

ΔTBP: change of total body protein mass compared to baseline
*non-significant compared to baseline

Figure 1: The decreased fat-free mass occurring in severe disease originates from the complex association of neuronal, inflammatory, and hormonal interactions.

Although whole-body protein synthesis is increased in severe illness, protein synthesis varies between individual tissues. Muscle protein synthesis decreases in severely ill patients, which results from impairments at the transcriptional and post-transcriptional levels. In contrast, as shown in animal models of sepsis, protein synthesis increases in numerous other tissues. Liver contributes mainly by an increased synthesis of secreted proteins as part of the acute phase response. In humans, studies have described an increased synthesis of specific proteins, originating mainly from the liver (Table 2) or an increased protein synthesis of specific tissues during severe illness. For instance, studies have shown an increased protein synthesis in circulating blood lymphocytes of critically-ill patients [11], in the colonic mucosa of patients with a benign or malignant colorectal tumor, or inflammatory bowel disease [12], or of phenylalanine in wounds of burned patients [13].

The transport of amino acids is altered in severely ill patients. In skeletal muscle of 19 severely burned patients, at 14 ± 5 post-burn days, Biolo *et al.* studied transmembrane transport by calculating the rate of net movement of the essential amino acids phenylalanine, leucine, and lysine from the muscle to the vein. When comparing the results to healthy controls, they found that outward transmembrane transport of these amino acids is higher in patients, presumably to promote the export of amino acids to other tissues such as liver, spleen, kidney, skin, or digestive tract. In contrast, inward transport to the muscle is impaired relatively to the increased delivery of circulating amino acid to skeletal muscle secondary to accelerated blood flow [14]. Noteworthy also is that intensive care patients have lower plasma amino acid concentrations in their basal state, defined as a state where patients receive glucose infusion but no nutritional support for at least 12 hours, compared to volunteers, which in view of the

Table II: Human studies comparing fractional synthesis rate (turnover rate) of specific proteins or glycoproteins between severely ill patients and healthy controls.

Authors	Patients (n)	Isotope used	Mean fibrinogen FSR	Mean albumin FSR	Mean fibronectin FSR
Essen *et al.* 1998	ICU patients (15)	$^{2}H_{5}$-L-phenylalanine		12.8*	
Preston *et al.* 1998	Pancreas cancer (6) Controls (7)	$^{2}H_{5}$-L-phenylalanine	39.3 21.9	– –	– –
Mansoor *et al.* 1997	Head –injury (8) Controls (5)	[^{13}C]leucine	28.1 15.1	11.4 1.0	– –
Thompson *et al.* 1989	Burn + trauma (6) Controls (9)	[^{15}N]glycine	32.8 10.8	– –	22.0 14.7
Moshage *et al.* 1987	Inflammatory disease (4) Controls (20)	[^{14}C] arginine	– –	16.8 16.2	– –

FSR: fractional synthesis rate (%/24 hours)
*Compared to a reported control value of 6.7 %/24 hours

negative protein balance is probably due to increased amino acid oxidation [15].

Albumin synthesis in severe illness

The effect of severe illness on albumin synthesis is unclear. Moshage *et al.* found a decrease in absolute albumin synthesis in 4 patients with inflammatory diseases, compared to healthy controls [16]. The patients were fed orally with about 1800 kcal/day (60 g protein/day). The authors of this study examined the possible molecular mechanisms in rats and found a reduced concentration of albumin mRNA in the liver. This contrasts with the results of two more recent studies, which both found an increase in the absolute synthesis rate of albumin in their patients compared to healthy controls. Essen *et al.* had included ICU patients between day 2 and 30 after ICU admission, who received parenteral nutrition (~1800 kcal/day, 58 g protein/day) and albumin (32 ± 10 g) the day before and glucose the night before measurement of albumin synthesis [11]. Mansoor *et al.* had included 6 head-injured patients on day 8 after admission, fed by continuous enteral nutrition (~39 kcal/kg/day, 1.5 g protein/kg/day) [17]. The latter authors hypothesized two mechanisms for the increased albumin synthesis. First, they suggest a biphasic pattern in acute inflammation, where albumin synthesis is first decreased and later increased, as described in animal models. Second, they suggest that high leucine concentrations resulting from accelerated proteolysis may stimulate albumin synthesis. Indeed, branched-chain amino acid formulas were shown to stimulate albumin synthesis in cancer patients. The reason why these two studies show contradictory results with the one of Moshage *et al.* is unclear. It may be related to different severity of inflammation diseases or energy balances. High-energy infusions, for instance, have been shown to increase albumin synthesis in postoperative patients. In any case, the hypoalbuminemia related to acute severe illness is in all likelihood not related to decreased albumin synthesis but rather to transcapillary escape as demonstrated earlier by Fleck *et al.* [18].

Impact of energy intake on protein mass and turnover

Energy and protein intakes may limit muscle catabolism in severe disease (Figure 2) As mentioned in the section "Protein mass in severe illness," studies lasting several days or weeks showed that energy intake did not prevent the loss of total body protein mass in patients with severe sepsis or major trauma. For obvious ethical reasons, none of these studies compared patients with and without nutritional intakes. However, one study looked at the impact of energy provision by nutritional support on *in vitro* neutron activation (IVNA)-derived TBP. In patients after major upper gastrointestinal surgery, the administration of full-strength parenteral nutrition (26.5 ± 1.4 kcal/kg/day and 0.25 ± 0.04 g N/kg/day) compared to ½ parenteral nutrition (20.2 ± 1.5 kcal/kg/day and 0.14 ± 0.03 g N/kg/day) preserved TBP [2].

With regard to protein turnover, it is unclear whether short-term nutritional support promotes protein

synthesis. In 6 burned patients, Wolfe *et al.* measured protein turnover by leucine kinetics and nitrogen excretion and described a stimulation of protein synthesis through feeding, as compared to a 10- to 12-hour fast [19]. Shaw *et al.* compared the rates of net protein catabolism in 18 septic patients receiving either glucose (3.8 ± 0.6 mg/kg/minute) or parenteral nutrition (glucose 3.8 ± 0.3 mg/kg/minute, fat 20 %: 9.8 ± 0.6 ml/kg/day, protein 1.5 ± 0.3 mg/kg/minute) over 6 hours. Patients who received parenteral nutrition and thus higher amount of calories and protein showed a lower rate of net protein catabolism than those treated with glucose infusions [20]. In contrast, in patients undergoing laparoscopic cholecystectomy, total parenteral nutrition infused over 8.6 ± 1.0 hour and providing 17.5 nonprotein kcal/kg compared to no nutritional support did not influence the fractional synthesis rate of total liver protein [21].

Only a few human studies have looked at the impact of nutritional support over several days on protein kinetics. Frankenfield *et al.* randomized 30 trauma patients into 3 groups; i. e. 1) non-protein calorie intakes corresponding to measured energy expenditure; 2) total calorie intakes corresponding to measured energy expenditure; 3) or hypocaloric intakes. On day 4 of nutritional support, they measured urinary urea, nitrogen production, and 3-methylhistidine excretion over 24 hours. They showed that achievement of energy balance did not attenuate the negative nitrogen balance [22]. A more recent study allocated patients after gastrointestinal surgery to four different types of parenteral nutrition, administered for 7 days after surgery [23]. The authors determined protein kinetics preoperatively and at days 2, 4, and 7 after operation. Already on the second postoperative day, the group fed with total parenteral nutrition (TPN) showed decreased protein breakdown and synthesis compared with those on a hypocaloric TPN formula and those receiving only carbohydrates and amino acids. Protein synthesis and breakdown rates in the TPN group remained in the preoperative range and were in favor of positive net protein synthesis.

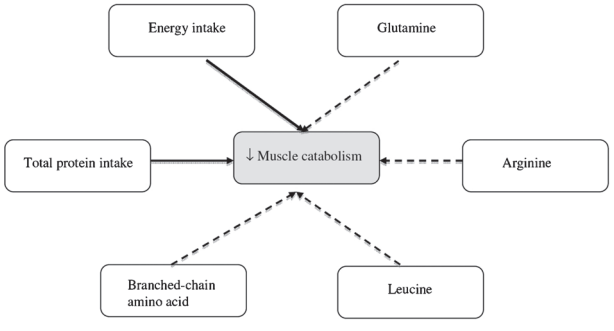

Figure 2: Nutritional elements which limit muscle catabolism (——) or are under investigation for prevention of muscle catabolism (----).

A negative energy balance exerts a negative effect on outcome in ICU patients. It was correlated with a higher rate of infectious complications [24]. More studies focused on the effect of early vs. delayed enteral nutrition. Early enteral nutrition resulted in higher mean calorie intakes the days after the insult. One metanalysis found that early enteral nutrition was associated with a lower risk of infections, a reduced length of hospital stay in patients with severe illness [25], but another study was inconclusive [26].

Noteworthy is the fact that studies evaluating the impact of energy intake on protein mass and turnover vary with regard to the type of disease, nutritional state, and type of feeding, which precludes comparisons between studies. Furthermore, a thorough study on the impact of energy intake necessitates taking into account energy expenditure. However, measurements of energy balance in patients with severe illness are not easy to perform and may not be accurate. Energy expenditure is generally measured by indirect calorimetry, but this method extrapolates 24-hour energy expenditure from short periods of measurements and may give false results due to gas leaks through endotracheal or chest tubes and high O_2 requirements. Some studies extrapolate total energy expenditure from body composition changes but this requires at least two measurements, is performed retrospectively, and consequently cannot be used for everyday practice. Thus, these studies have to be interpreted with caution as they include numerous confounding factors.

To summarize, it seems that nutritional support may limit but not stop the loss of total body protein mass occurring in acute severe illness. Its impact on protein kinetics is so far controversial. Maintaining calorie balance the days after an insult does not clearly show an advantage for the clinical outcome of the patient.

Impact of protein intake on total body protein mass and turnover

In many studies, the impact of protein intakes on total body protein is obscured by energy balance. Ishibashi *et al.* studied 18 trauma and 5 sepsis patients who were hemodynamically stable [27]. They measured fat-free mass by dual-energy x-ray absorptiometry and allocated them to enteral intakes of 1.1, 1.5, or 1.9 g protein/kg fat-free mass/day with similar non-protein

calorie content relative to fat-free mass (FFM). They measured changes in TBP over 10 days by IVNA. While the average loss of TBP was 10 %, the loss was significantly higher in the group receiving only 1.1 g protein/kg fat-free mass/day (–1.8 ± 0.8 kg) than the groups who received 1.5 (–0.8 ± 0.6) or 1.9 g/kg FFM/day (–1.0 ± 0.5 kg).

With regard to whole-body protein turnover, Shaw *et al.* included 18 septic patients and separated them into three groups who received intravenously 1.1, 1.5, or 2.2 g protein/kg body weight/day with similar total calorie intakes relative to body weight over a 6-hour period [20]. They found that the optimal protein-sparing effect was lowest with an infusion of about 1.5 g protein/kg/day. Similarly, another study in septic patients receiving parenteral nutrition for 6 days described no advantage in nitrogen balance between patients who received 1.2 vs. 2.3 g protein/kg /day [28]. In 6 burned patients submitted in a crossover study to either a 1.4 or a 2.2 g protein/kg/day isocaloric regimen over a three-day period, intravenously or enterally, there was no benefit of a higher N provision on whole-body protein balance [19]. Finally, in trauma patients who were randomized into five groups receiving from 0 to 1.9 g protein/kg body weight/day intravenously, as well as fat and glucose in isocaloric amounts, the negative nitrogen balance improved with intakes up to 1.3 g protein/kg/day compared to the no nitrogen group [29].

The protein synthesis rate in response to nutritional support likely varies between individual tissues. Rittler *et al.* compared, in two different studies, the effect of a 4-hour amino acid infusion (1.6 g/kg/day) containing glutamine vs. saline in 16 patients recovering from major abdominal operations. They showed that the amino acid infusion increased small-bowel protein synthesis but not albumin [30] or colon protein synthesis [31]. They explain that the low synthesis rate in the colon may be related to a lower percentage of proliferative cells and metabolic turnover than in the small bowel, making the colon less sensitive to parenteral substrates.

Protein intake affects circulating free amino acids. In healthy volunteers, an infusion of amino acids at a rate of 0.2 g N/kg/day is sufficient to switch net outflow to inflow of amino acids into peripheral tissues as skeletal muscle. Interestingly however, this amount of N does not seem sufficient to increase arterial concentrations of amino acids and reverse the flow in severe illness, as suggested by Iresjö *et al.* [15]. They compared 3 types of amino acid formulations in ICU patients who received parenteral nutrition providing 20 kcal/day of non-protein calories and 0.2 g N/kg/day for 3 days. The infusion of these formulas increased the overall arterial amino acids concentrations only to the level of fasting healthy subjects. They concluded that the composition of the available amino acid formulations may not be optimal to increase arterial amino acid concentrations and promote amino acid inflow.

Diminished FFM loss and improved nitrogen balance may ameliorate outcome in acute severe illness, although it is unknown whether achievement of a neutral nitrogen balance is desirable. In burned patients, growth hormone and insulin, considered as anabolic hormones, decreased mortality [32] and hospital length of stay, respectively [33], but in critically ill patients in general, growth hormone worsened outcome [34]. In an interesting review, Stroud *et al.* hypothesized that anorexia and limitation of food and protein intake accompanying catabolism in severely ill patients may even exert a protective effect. Indeed, provision of high amounts of protein leads to increased amino acid oxidation and formation of urea. This can be problematic in severely ill patients as high levels of urea may aggravate renal failure and reduce the capacity of salt and water elimination in patients with edema. A high level of protein supply could also stimulate protein synthesis, but since it may not provide the amino acids needed for the acute phase response, it could force the metabolism away from pathways maximizing survival [35].

Consequently, administration of amino acids or of protein improves total body protein mass and protein turnover in severe illness. The effect seems to be maximal at doses of around 1.2 and 1.5 g/kg body weight/day, but most of the studies did not detail how they measured body weight. It is variable according to individual tissues. It is not clear whether forcing the body toward preservation of muscle mass in severely ill patients improves outcome.

Impact of specific Amino acids on total body protein mass and turnover

There is growing interest in the role of specific amino acids on total body protein mass and protein turnover. In 2006, De Bandt *et al.* carefully reviewed the utility of branched-chain amino acids (BCAA) in burn, trauma, and sepsis [36]. They found 7 studies performed in trauma and ICU patients, among which 3 claimed an improvement in muscle protein balance, and 2 in septic patients, which showed an improvement in prealbumin, retinol-binding protein, and a reduction of muscle catabolism and mortality with BCAA. They concluded that BCAA did not show any clear benefit

in these medical conditions. They mentioned however that leucine-supplemented amino acid solutions deserve further attention, as they showed anti-catabolic effects in animal studies. Since 2006, one published study included intensive care patients after radical cancer surgery [37]. Patients received intravenously, in a crossover design, isonitrogenous amino acid solutions over 3 hours (246 mg/kg) with a ratio of leucine to total amino acids of 0.09 (22 mg/kg) or 0.22 (54 mg/kg) on the first two post-operative days. The solution with the higher leucine content stimulated protein synthesis and increased glutamine release from skeletal muscle.

Conditionally essential amino acids, as glutamine and arginine, also received considerable attention in severe illness. In a metanalysis including critically ill patients, high arginine-content enteral formulas led to a decreased length of hospital stay, a trend toward a reduction in infectious complications, but no effect on mortality compared with other immunonutrition formulas [38]. However, the authors recognized that these effects of arginine relied on speculations as all high arginine-content enteral formulas contained more than one specific nutrient. Noteworthy is the fact that the authors found a higher mortality with immunonutrition when considering studies with high methodological scores.

Surgical, trauma, and sepsis patients show low plasma and intramuscular glutamine levels [39], which have been related to high severity illness scores and hospital mortality. In ICU patients who randomly received for five days increasing doses of intravenous glutamine (0, 0.3, 0.6, 0.9 g/kg/day) as part of an isocaloric, isonitrogenous parenteral nutrition, plasma glutamine normalized in a dose-dependent manner but free-muscle glutamine, muscle protein synthesis, and muscle protein content did not change [40]. Similarly, in critically ill patients, parenteral nutrition with glutamine (0.4 g/kg/day) vs. without glutamine for 3 days did not affect protein balance [41]. Regarding outcome, two metanalyses found that supplementation of glutamine in enteral and parenteral nutrition reduced infectious complications and lengths of stay in surgical patients as well as complications and mortality in critical illness [42 ,43]. Possible mechanisms of these beneficial effects are decreased oxidant damage and inflammatory cytokine production, reduction of gut bacterial translocation, and improvement of nitrogen balance.

Thus, glutamine and potentially leucine are important for clinical outcome, but it is unclear whether these benefits occur through an impact on TBP and turnover or through other mechanisms.

Protein requirements in severe illness

The essential role of nutritional support in severe disease is to protect lean tissue mass and function. In ICU patients, the adequate amount of protein supply is still debated but intakes between 1.2 and 1.5 g/kg ideal body weight/day are usually advised [44, 45].

According to the ESPEN guidelines, if enteral nutrition is indicated, it should be given at a dose of 20–25 kcal/kg body weight/day during the first 72–96 hours and then up to 25–30 kcal/kg/body weight/day during stabilization and recovery [46]. They do not mention protein requirements by enteral nutrition. There is no advantage of using a peptide-based formula compared to whole-protein formula. Immunonutrition enriched with arginine, nucleotides, and omega-3 fatty acids should be given to patients with trauma, ARDS, and mild sepsis (APACHE II<15), but not to patients with severe sepsis and those who do not tolerate more than 700 mL of enteral nutrition per day. No position is taken for immunonutrition in burned patients. Glutamine should be added in burned and trauma patients but there is insufficient data to support its use in surgical or heterogeneous, critically ill patients.

If parenteral nutrition is indicated in ICU patients, a balanced mixture of amino acids should be infused at about 1.3 to 1.5 g/kg ideal body weight/day with 0.2–0.4 g/kg/day of glutamine (ESPEN guidelines) [44]. Energy should be supplied at a dose of 25 kcal/kg/day in the absence of indirect calorimetry and increased to target over the following 2–3 days. It remains unclear whether actual or anamnestical weight should be taken into account since these patients are often overhydrated. In addition, energy requirements may be affected by sex and age. In ICU patients, glutamine should be added as 0.2–0.4 g/kg/day of L-glutamine.

In obese patients, the weight to be used seems to be the actual rather than the ideal body weight [47]. In these patients, several studies support the use of hypocaloric (11–14 kcal/kg actual body weight/day or 22–25 kcal/kg ideal body weight/day), hyperproteinic (≥1.5 g protein/kg actual body weight/day) parenteral nutrition, but so far no specific nutritional guidelines have been provided for them. Noteworthy is however that hypocaloric, hyperproteinic feeding is contraindicated in patients with renal insufficiency, hepatic encephalopathy, diabetic ketoacidosis, hypoglycemia, age greater than 60 years, or severe immunocompromise [48].

In undernourished patients, the resting energy expenditure is 25 % higher than predicted by the Harris-

Benedict formula [49]. In the absence of clinical data, and based on mathematical approximations, Hoffer *et al.* estimated that protein requirements may be higher by 25 %, thus at 1.9 g/kg/day, in neutral or positive energy balance, in undernourished patients [50]. Studies including specifically underweight patients with acute severe illness are needed to confirm these estimations before recommendations on requirements can be given.

Conclusions

Severe illness is characterized by increased protein turnover leading eventually to loss of total body protein mass, mainly in the skeletal muscle. Energy and protein intakes limit muscle catabolism and improve outcome. Current guidelines suggest the administration of 20–25 kcal/kg body weight/day during the acute phase (e. g., 1–3 days after ICU admission) and 25–30 kcal/kg body weight/day once the condition is stabilized. The optimal protein requirement has been set at 1.2–1.5 g/kg body weight/day.

However, these recommendations rely on two types of study design, which have to be interpreted with caution. In the first study design, study groups have received different protein intakes (in g/kg) and similar amounts of glucose or fat and, in this case, the highest protein supply led also to the highest calorie supply. In the second study design, patients have received different protein intakes with isocaloric diets and consequently the subjects with the lowest protein supply received more calories as glucose or fat. Consequently, it is impossible to study the impact of protein intakes alone on total body protein mass and protein turnover. Nutritional supply of study groups differ in either energy or macronutrient composition.

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