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Protein requirements, morbidity and mortality in critically ill patients: fundamentals and applications

Necessidades proteicas, morbidade e mortalidade no paciente grave: fundamentos e atualidades

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ABSTRACT

Recent evidence suggests that a negative protein balance secondary to severe disease is associated with increased morbidity. A loss of total body protein is inevitable in this scenario, even with an aggressive nutritional approach, primarily due to the catabolism of skeletal muscle fibers. The ubiquitin-proteasome system is the primary metabolic and biochemical mechanism involved in this process; paradoxically, this system consumes adenosine triphosphate as its energy source. It is possible that a neutral protein balance in these clinical situations is important for improving outcomes and achieving the caloric goals estimated or measured by indirect calorimetry. Recent studies have suggested that the use of higher protein concentrations in nutritional therapy for critically ill patients may help to reduce mortality. The purpose of this study was to review some of the nutrition therapy principles related to protein metabolism, evaluate the main assertions of the guidelines of specialty societies and review the recent studies that address these issues using critical insights from the authors' clinical experience.

Keywords: Nutrition therapy; Intensive care; Enteral nutrition; Parenteral nutrition; Dietary proteins; Nitrogen; Morbidity; Mortality

INTRODUCTION

Protein: a fundamental element of metabolism in seriously ill patients

The state of stress, which is associated with trauma, sepsis, and advanced cancer, is accompanied by multisystemic alterations, changes in macronutrient metabolism, and endocrine-metabolic activities and immunological responses. Characteristically, the stress response involves increases in energy expenditure (EE) and in the use of protein reserves, primarily in the myofibrils (actin and myosin) of skeletal muscle protein.[1,2]

The mobilization of these reserves is not a unidirectional catabolic process but rather the result of an imbalance between protein synthesis and degradation, both of which are increased compared to the equilibrium state and can become as high as 45% and 80% above normal, respectively,[3,4] depending the magnitude of the trauma. The resulting negative protein balance may be associated with immunosuppression, poor wound healing and muscle weakness, reducing the survival likelihood of critically ill patients and increasing the length of hospitalization and the accompanying costs. Preserving lean mass is one of the main goals of nutrition therapy (NT) for critically ill patients. In practice, this goal is achieved by adding adequate quantities of protein to

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the NT administered during the acute phase of disease. Skeletal muscle is used here as a synonym for "lean mass" or "cellular body mass" to refer to the tissue components of the body that exchange oxygen, are rich in potassium, oxidize glucose and perform work.[5]

The perception that the provision of dietary protein could participate in preserving lean mass is not limited to experimental settings; clinical data was published in the 1970s. Moore and Brennan[6] noted that in multiple trauma surgical patients and patients with parenteral glucose levels of 5%, protein loss could reach 1.250 g after 2 weeks, which is equivalent to 6 kg of muscle or 21% of the total body muscle mass. The administration of 3000 mL per day of a solution containing 3.5% hydrolyzed protein and 18% glucose (approximately 105 g of protein and 2580 kcal) was able to reduce this muscle loss. Although these authors did not provide the number of observations, the weights of the evaluated patients or further details about the study population, this study was one of the first to mention (recognized by the American College of Surgeons) the use of amino acids/proteins in clinical settings to conserve lean mass.

Monk et al. and Plank et al. observed similar behavior in polytrauma patients[7] and in septic patients,[8] respectively, receiving enteral nutrition and reported even greater losses, approximately 1.09 kg of protein (4.36 kg of lean mass) in 21 days. Measurements of urinary 3-hydroxyproline in these cohorts indicated that two-thirds of the nitrogen losses in the first 2 weeks following the injury were from the skeletal muscle, which constitutes an important source of nitrogen (up to 70% of total nitrogen input).

The metabolic consumption of this compartment is constant and inevitable in response to acute injury, and its intensity depends on the severity of the clinical situation (Figure 1). The consumed lean mass is not only destined for oxidation but also is used in the synthesis of acute phase proteins, i.e., proteins related to immunity and tissue repair and cellular proliferation. Clarke et al.[9] have demonstrated the compulsory aspect of non-oxidative protein fates in their study of septic (n=14) and multiple trauma (n=10) patients by analyzing the behaviors of serum levels of visceral protein markers (insulin-like growth factor 1 (IGF-1), transferrin, and prealbumin) and acute phase markers (C-reactive protein and alpha 1-antitrypsin) relative to the amount of total body protein (TBPr) measured using an *in vivo* neutron activation analysis (IVNAA). These patients received an energy intake of between 80% and 91% of their resting EE (REE), as measured using indirect calorimetry (IC) during the initial and final phases of the study, respectively, and 1.5 g ptn.kg^{-1}.d^{-1}, in the form of enteral NT (ENT) or PNT, as tolerated. The authors observed an increase in acute phase protein serum levels and a reduction in constituent proteins, which returned to normal levels after clinical-metabolic stabilization. The hepatic synthesis of constituent proteins was maintained even during massive proteolysis and was responsible for the consumption of up to 12.6% (1.31 kg) of the TBPr during the observation period (25 days).

In a study by Zhang et al.[10] using an electrical burn experimental model, the authors demonstrated that local tissue repair processes are also involved in the utilization of circulating amino acids and their commitment to non-oxidative pathways. The rates of deoxyribonucleic acid and protein synthesis were measured using tissue doses of radiolabeled leucine (synthesis) and amino acid metabolites (protein deposition) at three time points after injury. Compared to the control group, they observed that, on the 7th day after the trauma (coinciding with Cuthbertson's flow phase) the rate of local protein synthesis increased by approximately 20% (20.5±8.4% per day, $p<0.01$) compared to the baseline measurements taken immediately following the trauma. These data suggest that there is an increase in protein synthesis but no significant increase in cell proliferation in the days following an acute injury.

THE RELATIONSHIPS AMONG BODY COMPOSITION, ENERGY DEMAND, AND PROTEIN REQUIREMENTS

To preserve lean mass, nutritional protein (exogenous) should be diverted from the oxidative metabolic pathways, a goal that can be achieved with sufficient energy intake. The metabolic principle, according to which the provided protein should be accompanied by a proportional amount of calories, is consistent with the current understanding of the pathways involved in energy metabolism and is supported by experimental and observational studies in

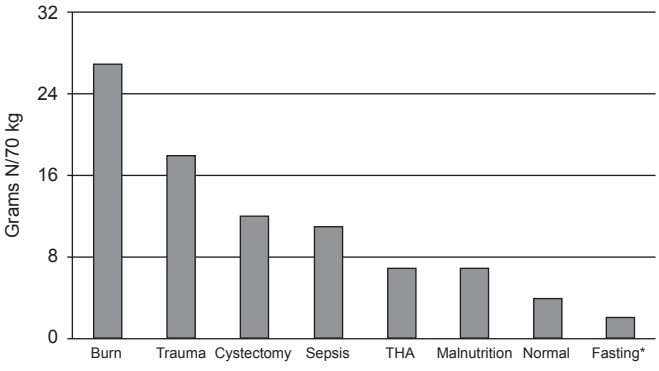

Figure 1 - Urinary excretion of nitrogen in subjects receiving intravenous infusion of glucose in different clinical contexts. Adapted from Elwyn DH. Protein metabolism and requirements in the critically ill patient. Crit Care Clin. 1987;3(1):57-69. *Fasting alone, without concomitant disease. THA - total hip arthroplasty.

healthy volunteers. This is the paradigm guiding NT today. However, it should be remembered that these postulates have not yet been tested in patients with serious diseases, and using techniques that include radioisotopes. For example, in studies of the metabolic kinetics of macronutrients labeled with radioisotopes (continuous intravenous infusion of [L-13C] (leucine) with 1.4 to 2.2 g ptn.kg^{-1}.d^{-1}), Wolfe et al.[11] and Shaw et al.[12] have demonstrated that, in severe trauma patients receiving an adequate number of calories, regardless of the type of nutritional support (enteral or parenteral), approximately one-third (33.3%) of the protein mass was directed towards protein synthesis (anabolism), and one-third was directed towards consumption (catabolism). By exclusion, the remaining one-third must become part of the plasma reserves. Thus, between the fraction destined for catabolism and the reserve fraction, approximately 66.7% of the TBPr is available for immediate consumption, if necessary, in this metabolic environment, regardless of the amount of protein that is provided by NT. This finding serves as the basis for the argument against the hypothesis that the provision of excess protein is able to preserve lean mass. To date, the optimal amount of protein required to minimize the loss of lean mass remains unknown.

Furthermore, this issue does not appear to be restricted to the amount of protein provided because the intrinsic characteristics of a disease may contribute to better or worse macronutrient utilization. The hypothesis of anabolic resistance was first postulated in the 1930s by Cuthbertson[13] and has been supported by more recent data. Anabolic resistance, which occurs during old age and in chronic diseases including liver cirrhosis and chronic obstructive pulmonary disease,[14] is also manifested during severe disease. The primary enzymatic mechanism involved in the process of anabolic resistance is the ubiquitin-proteasome system (UPS), which is responsible for increased protein consumption in cases of severe trauma, sepsis, and cancer. Other pathways, including the calcium-dependent and lysosomal pathways, induce only modest changes in lean mass. UPS is an enzyme complex that is regulated at different points by proteolytic pathways and promotes the degradation of myofibrillar proteins (actin and myosin in skeletal muscle) in the phase of organic stress. This proteolytic system is related to sarcopenia and has been extensively reviewed in the literature.[15]

ENERGY EXPENDITURES

EE is an important variable that interferes with protein balance. The first and most well known observation of this phenomenon was made in what is known as the "Minnesota experiment", which was conducted during World War II. This experiment demonstrated a substantial loss of lean mass during prolonged caloric deprivation (approximately 22 kcal.kg^{-1}.d^{-1}), even when healthy volunteers were given adequate protein (0.75 g.kg^{-1}.d^{-1}).[16] Calloway,[17,18] who was a pioneer of nitrogen balance studies in the 1950s, later demonstrated the lean mass-sparing effect that increased amounts of protein can have on the state of negative caloric balance in normal volunteers and in patients with sepsis or trauma.[19,20]

To minimize nitrogen losses in fasting subjects receiving dextrose infusion, a large supply of carbohydrates is needed, up to 3,000 kcal.d^{-1}. This sparing effect can be intensified by simply adding nitrogen to the intravenous formula. According to Bursztein et al.[2], the incorporation of nitrogen in the setting of a simple supply of carbohydrates, promotes the formation of adipose, vessel and stroma tissue but not muscle tissue. When nitrogen is introduced, fewer calories are needed to achieve a positive nitrogen balance, at the expense of muscle protein incorporation. These data provide the rationale for the use of the kcal non-protein:g N ratio in NT decision making.

PERCENT LEAN MASS IN THE BODY MASS INDEX

The EE per unit weight in subjects with a low body mass index (BMI) (e.g., <17 kg/m^2) may be different when measured using IC compared to when estimated using a formula. In theory, patients with a low BMI should have a greater fraction of metabolically active tissue, which would give this group a higher EE per unit weight, a peculiarity that is not normally expected in the formulas used to calculate EE. A 30-year-old who is 1.70 m tall and has a body weight of 70 kg (BMI=24) would have, according to the Harris-Benedict equation, a stress factor of 1.2 and an EE of 2012 kcal.d^{-1}, or 28.7 kcal.kg^{-1}. The same individual with BMI=17 (current weight of 49 kg) would have a metabolic rate of 1666 kcal.kg^{-1} and 34 kcal.kg^{-1}.d^{-1}. This approximately 20% increase in the energy expenditure per kg under reduced BMI conditions justifies, in the opinion of some authors, a 20% increase in the protein provision from 1.5 to 1.8 or 1.9 g.kg^{-1}.d^{-1}.[21-25]

A similar model was recently presented by Weijs, who proposed corrected protein estimate formulas that take into account BMI and lean mass.[26]

CALORIC INTAKE AND ANABOLIC EFFICIENCY

In addition to the variables mentioned, it is important to remember that the efficiency of nitrogen incorporation depends on an optimal range of protein and calorie provision. In studies using immobilized healthy volunteers, Biolo et al.[27,28] observed that both hyperalimentation and protein-calorie restriction were correlated with a loss of anabolic efficiency and skeletal muscle atrophy. Especially in the case of overprovision, increased fat deposition was observed, in addition to increased inflammatory activity and oxidative stress, linking skeletal muscle metabolism to systemic inflammation. Another interesting finding that highlights both the complexity of this issue and the prospects for intervention in critically ill patients is that even in situations of low calorie-protein provision, muscle work seemed to play an important role in protecting against atrophy and a reduction in localized inflammatory processes.

PROTEIN REQUIREMENTS

In a meta-analysis of 91 cohorts and 1107 patients in whom nitrogen balance was measured, Kreyman et al.[29] observed that proteolysis (measured using urea nitrogen) is exponentially related to clinical severity and that EE and is greatly increased in critically ill patients (1.2 to 3.1 $g.kg^{-1}.d^{-1}$), moderately increased in intermediate injuries (0.8 to 1.2 $g.kg^{-1}.d^{-1}$) and minimally elevated in healthy subjects (<0.8 $g.kg^{-1}.d^{-1}$). The intensity of protein loss tends to exceed the EE to the extent of the hypercatabolism of the patient. Interestingly, the nonlinear regression curves, which were very similar for both patients without supplied protein and those with NT, indicate that the urea nitrogen levels could not be explained simply by the excessive nitrogen provision. In the total sample, up to 35% of patients enrolled in these studies had protein deficits on the order of 1.5 to 2.0 g $ptn.kg^{-1}.d^{-1}$.

To meet the increased demand for nitrogen and preserve lean mass, a strategic response would be to increase amino acid and protein provision. In healthy adults, the amount of protein is considered adequate when it is sufficient to maintain protein balance, a zero-sum position (neutral balance) in which the provision is equal to loss. This model does not apply in situations of inevitable catabolism, such as in cases of severe disease when then the supply should be aimed towards maintaining a positive or minimally negative protein (and nitrogen) balance.[30]

In a classic study, Ishibashi et al.[31] sought to determine the optimal amount of protein to be provided. Serial body composition measurements made using the IVNAA and IC methods were taken in 25 polytrauma or septic patients after resuscitation and within the next 10 days. Three groups were established according to the amount of protein provided (0.9 to 1.2, 1.3 to 1.6 and 1.7 to 2.0 $g.kg^{-1}.d^{-1}$). The patient's pre-admission weight was used to calculate the protein provided, thus excluding the weight gains related to fluid retention during resuscitation. Provisions of between 1.3 and 1.6 g $ptn.kg^{-1}.d^{-1}$ were the best correlated with higher nitrogen incorporation. The authors proposed, for calculation purposes, targets of 1.2 g $ptn.kg^{-1}.d^{-1}$ (pre-admission weight) or 1.0 $g.kg^{-1}.d^{-1}$ (post-resuscitation weight, to compensate for the weight gain secondary to fluid retention) (Table 1). Protein provisions >1.7 g $ptn.kg^{-1}.d^{-1}$ did not have any additional benefit in preserving lean mass, and levels above 2 $g.kg^{-1}.d^{-1}$ in patients with BMI <30 can contribute to hyperalimentation and nitrogen retention, especially in patients with impaired renal function and elderly patients.[32] However, one cannot rule out the hypothesis that individual variation in selected clinical scenarios could benefit from provisions above the normally recommended range. For example, in traumatic brain injury (TBI), a situation in which protein oxidation can reach up to 34% of the estimated REE,[33] nitrogen balance measurement studies have shown that provisions >2 $g.kg^{-1}.d^{-1}$ were associated with a positive nitrogen balance compared with provisions of 1.5 $g.kg^{-1}.d^{-1}$.[34,35] Greater protein supplementation may also be useful in patients with excessive losses, such as those suffering from burns, fistula or peritoneostomy.[36]

Specialist societies, primarily European societies, have very similar protein provision recommendations based on the fundamental work published by Ishibashi[31] (Table 2). A protein supply within the range of 1 to 2 $g.kg^{-1}.d^{-1}$ is considered normal for critically ill patients.

Table 1 - Protein intake, corrected for fat-free mass and body weight in kg

	Group A	Group B	Group C
Corrected FFM *	1.1±0.1	1.5±0.1	1.9±0.1
Corrected BW **	0.9±0.1	1.2±0.1	1.5±0.1
Measured BW ***	0.8±0.1	1.0±0.1	1.3±0.1

FFM - fat-free mass; BW - body weight. Data are expressed as the mean ± standard deviation. *FFM on day 0 after correction for hyperhydration; ** BW on day 0 after correction for hyperhydration; *** BW measured on day 0.

Table 2 - Recommended protein provision level guidelines for critically ill patients, as reported by different societies

Society	Protein provision (g ptn.kg ideal weight^{-1}.d^{-1})	Observation
ESPEN[37,38]	1.3-1.5	+ 0.2 g ptn.kg ideal weight^{-1}.d^{-1} if trauma, obesity or nephro-replacement therapy
ASPEN[39]	1.2-2.0	If BMI < 30
	≥2	If BMI 30-40
	≥2.5	If BMI > 40
DITEN[40]	1.0-2.0	-

BMI - body mass index.

RESULTS OF RECENT CLINICAL TRIALS

The most recent evidence seems to suggest that there is an association between protein intake >1.2 g.kg^{-1}.d^{-1}, which is near the upper limit, or at least within the target range, and a reduction in morbidity and mortality. In 2009, Alberda et al.[41] conducted the first study of the association between protein and calorie provisions and patient outcomes in a multicenter study that included 2772 patients in 167 intensive care units in 37 countries. In addition to the beneficial effects of higher caloric intake, these authors observed that the provision of an additional 30 g.day^{-1} was associated with a relative risk (RR) of 0.84 (95% CI=0.74-0.96, p=0.008). This observation was not explored in more detail in the original article, but it paved the way for additional research on this topic.

Strack van Schijndel et al.[42] have reported a retrospective study that included 243 patients on mechanical ventilation. These authors evaluated the clinical impact of caloric intake determined by IC and protein provision at a target of 1.2 g.kg^{-1}.d^{-1} (pre-admission weight). They found a reduction in the 28-day mortality rate in the ICU and hospital for female but not male patients and suggested that this phenomenon was due to the lower lean body mass of female patients, which would imply a proportionally greater protein provision per kg of body weight, thus allowing the authors to more clearly observe the clinical impact of the increased provision. In a clinical trial with 886 critically ill patients on mechanical ventilation,[43] these same authors compared the clinical outcomes of patients with varying levels of success in meeting protein and calorie targets. Patients were divided into three groups: (1) no control of the protein-calorie target, (2) control of the caloric target exclusively and (3) control of both the calorie and protein targets. The average protein provisions were 0.83 g.kg^{-1}.d^{-1}, 1.06 g.kg^{-1}.d^{-1}, and 1.31 g.kg^{-1}.d^{-1} in groups 1, 2, and 3, respectively. The differences in protein provision between groups 1 and 2 and between groups 1 and 3 for a patient of 70 kg were +17.5 g and +33.6 g, respectively. The study noted significant reductions in the 28-day mortality rate and hospital mortality rate in group 3 and showed that the impact of nutritional intervention extends beyond a patient's stay in the intensive care unit. Coincidentally, the increase in the protein provided that was best associated with reduced mortality was approximately 30 g, similar to what was observed by Alberda et al.[41] Similar results were also reported in a population of patients with less severe disease who were admitted to clinical nursing units.[44] Nevertheless, the effects of increased protein provision are not well characterized and are, in part, dependent on the design of the study.

Research by Tsai et al.[45] and Franzosi et al.[46] on the clinical outcomes of patients with different protein-caloric intake after 6 days provides examples of studies that arrive at different conclusions based on the quality of the matching between groups. The control of protein targets already appears to have important implications in study design for different clinical conditions, even those that are not specifically assessing the impact of NT. This is well stated by Wischmeyer in a recent non-systematic review.[47] One example in this review was the exceptionally low mortality rate (the lowest reported to date, 16%) reported for patients who received the control nutritional formulation in the study. The study compared the effect of a nutritional formula containing eicosapentaenoic acid (EPA)/gamma-linolenic acid/antioxidants compared with a control enteral nutritional formula in patients with acute respiratory distress syndrome (ARDS). The quantity of protein in the control formula was five times higher than that in the experimental formula.[48]

Another point that should be investigated further is the mechanisms of action by which higher protein provision may be related to a better prognosis. In an observational study involving 113 patients, Allingstroup et al.[49] reported that a progressive increase in protein provision (0.79, 1.06 and 1.46 g.kg^{-1}.d^{-1}) did not linearly correlate with increased survival over 10 days (50%, 78% and 87%, respectively) but did correlate with gradually reduced benefits > 1.5 g.kg^{-1}.d^{-1}. The authors noted that this reduction in mortality was not mediated by positive protein or energy balances because they did not vary between groups. The authors suggested that the increased protein provisions could have influenced both the synthesis of skeletal muscle protein and the availability of amino acids as substrates in the synthesis of metabolic and immunological mediators and structural components.[35,50]

FINAL CONSIDERATIONS

Protein provisions guided by targets appear to be related to reduced morbidity and mortality in critically ill patients. Currently, there is strong evidence in the literature that the use of higher protein concentrations (>1.2 g ptn.kg^{-1}.d^{-1}) is associated with reduced morbidity and mortality in this population.

Further studies are needed to determine the mechanisms of action and optimal protein concentrations for nutritional formulations. Until more direct, precise, and simple methods for the measurement of body nitrogen levels and metabolic kinetics are available, the guideline recommendations from specialist societies will continue to serve as the basis for decision making. Nevertheless, a new principle seems to have been established: In addition to caloric requirements, the ideal protein provision target must be investigated, and the achievement of ideal protein levels may have clinical and prognostic impacts that are as important as or even more important than achieving caloric targets alone.

RESUMO

Evidências recentes sugerem que o balanço proteico negativo secundário à doença grave se associa ao aumento de morbidade. A perda da proteína corporal total é inevitável nesse cenário, mesmo com uma abordagem nutricional agressiva, e resulta, principalmente, do catabolismo da fibra muscular esquelética. O principal mecanismo bioquímico e metabólico envolvido nesse processo é o sistema ubiquitina-proteassoma, que, paradoxalmente, consome a adenosina trifosfatocomo fonte energética e motriz. É possível que a neutralidade do balanço proteico nessas instâncias clínicas, seja tão importante na melhora dos desfechos quanto atingir a meta calórica estimada ou medida pela calorimetria indireta. Estudos recentes apontam a utilização de concentrações mais elevadas de proteínas na terapia nutricional do paciente grave como importante para um impacto positivo na mortalidade. A proposta deste trabalho foi revisar alguns princípios da terapia nutricional relativos ao metabolismo proteico, sinalizar para as principais assertivas das diretrizes das sociedades especializadas e comentar estudos recentes, que abordam a questão em tela, sob a visão crítica da experiência clínica dos autores.

Descritores: Terapia nutricional; Terapia intensiva; Nutrição enteral; Nutrição parenteral; Proteínas na dieta; Nitrogênio; Morbidade; Mortalidade

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