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How Much and What Type of Protein Should a Critically Ill Patient Receive?

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Abstract

Protein loss, manifested as loss of muscle mass, is observed universally in all critically ill patients. Depletion of muscle mass is associated with impaired function and poor outcomes. In extreme cases, protein malnutrition is manifested by respiratory failure, lack of wound healing, and immune dysfunction. Protecting muscle loss focused initially on meeting energy requirements. The assumption was that protein was being used (through oxidation) as an energy source. In healthy individuals, small amounts of glucose (approximately 400 calories) protect muscle loss and decrease amino acid oxidation (protein-sparing effect of glucose). Despite expectations of the benefits, the high provision of energy (above basal energy requirements) through the delivery of nonprotein calories has failed to demonstrate a clear benefit at curtailing protein loss. The protein-sparing effect of glucose is not clearly observed during illness. Increasing protein delivery beyond the normal nutrition requirements (0.8 g/k/d) has been investigated as an alternative solution. Over a dozen observational studies in critically ill patients suggest that higher protein delivery is beneficial at protecting muscle mass and associated with improved outcomes (decrease in mortality). Not surprisingly, new Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition guidelines and expert recommendations suggest higher protein delivery (>1.2 g/kg/d) for critically ill patients. This article provides an introduction to the concepts that delineate the basic principles of modern medical nutrition therapy as it relates to the goal of achieving an optimal management of protein metabolism during critical care illness, highlighting successes achieved so far but also placing significant challenges limiting our success in perspective. (*Nutr Clin Pract*. 2017;32(suppl 1):6S-14S)

Keywords

protein; anabolism; catabolism; protein sparing effect of glucose; amino acid imbalance; critical illness; nutritional support

Protein Loss, the Central Issue in Critical Illness

Significant, often dramatic alterations in protein metabolism are observed in virtually all critically ill patients. This reflects alterations in metabolic balance, with catabolic responses being consistently higher than those associated with protein anabolism. The magnitude of the loss of protein during illness is proportional to the severity of injury.[1] In its most severe cases, particularly in critical illness, the catabolic response associated with protein loss leads rapidly to the exhaustion of available protein contained within cells and tissues with the subsequent progression to protein malnutrition. Severe protein malnutrition is associated with poor clinical outcomes, including severe muscle deconditioning, ventilator dependency, poor wound healing, immune dysfunction, inability to maintain activities of the daily living, and ultimately death.[2]

An inordinately elevated incidence and prevalence of protein malnutrition is observed in hospitals. This poorly recognized condition is also called hospital-acquired or disease-acquired malnutrition. Up to 30% or even more of all patients in hospitals are recognized to have significant protein malnutrition. Protein malnutrition significantly increases healthcare costs and utilization of precious healthcare resources. Thus, it is an essential priority to find solutions that overcome protein malnutrition.

The main focus of nutrition interventions in all critically ill patients is how to best prevent and/or treat protein catabolism,

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improve anabolism (protein synthesis), and, through these mechanisms, curtail the progression toward protein malnutrition. In healthy individuals, progression toward protein malnutrition occurs as a result of poor intake generally due to lack of availability of adequately balanced food. And in healthy individuals, adequate provision of food prevents and/or treats protein malnutrition. One would think that by providing adequate food, one should observe similar preventative or therapeutic effects in critically ill patients. But this is not the case. Despite significant progress, medical nutrition therapy has failed to successfully and consistently achieve a balance between protein anabolic and catabolic responses during illness.[3]

Better understanding of the importance of medical nutrition therapy above that of satisfying energy requirements opens the possibility of improving outcomes in critically ill patients through increased delivery of protein. Optimal protein delivery improves anabolic responses and may result in better protection of muscle mass and immune function. We hypothesize that future research will demonstrate that in addition to obtaining physiological goals, patients will achieve better clinical outcomes as we improve the delivery of protein.[4]

Historical Perspective

Provision of protein in the diet is essential for the survival and ultimately health of all human beings. Protein has been and remains the most difficult to obtain macronutrient above that of carbohydrates (cheap and easier to obtain) and lipids. Throughout history and still today, the quantity and quality of protein in each food product determine its value and, in a modern commercial system, its price. Thus, a real challenge has been that of obtaining sufficient amounts and quality of protein to maintain health.[5]

Nutrition as a science was given one of its first challenges in the 19th century during the development of modern prison systems in England. Advances in the legal system looked at prison sentences as a time for possible rehabilitation to achieve well-adjusted, biologically healthy individuals who could be released back to society. These reforms demanded treatments for "laziness" through the imposition of heavy physical activity such as walking on treadmills for up to 10 hours at a time. Provision of food became a significant issue as it was determined that prisoners should receive just enough but not so much food or of such quality that they would feel "rewarded." Thus, the goal was to determine the minimum nutrition requirements, maximizing the amount of "cheaper" lower quality foods while minimizing high-value products, which as we now know contained the largest amount and best quality of protein.[6]

The lessons learned in prisons in the 19th century along with more modern understanding of nutrition in the first half of the 20th century were further reinforced by the realities of the Second World War, during which large amounts of the world's population were at risk for famine. Starvation experiments were done by Ancel Keys at the University of Minnesota to further understand the progression toward protein and calorie malnutrition of healthy individuals.[7] Gamble, during the so-called castaway experiments, demonstrated that a small amount of glucose would decrease protein catabolism through amino acid oxidation, otherwise necessary for the obligate generation of glucose during starvation. The concept of the "protein-sparing effect of glucose" was further studied by Francis Moore[8] and others, suggesting that even higher amounts of dextrose could further curtail protein oxidation. Once again, the focus became that of using carbohydrates to minimize provision of protein.

The advent of parenteral nutrition (PN) in 1968 permitted a route through which large amounts of calories and some protein could be delivered. The previous observations of the protein-sparing effect of glucose were applied by Long et al,[9,10] who suggested that, during critical illness, carbohydrate loads above that of normal caloric requirements would be necessary to prevent protein catabolism. This strategy was translated into clinical practices and popularized as "hyperalimentation," a technique that entailed increasing delivery of calories above and beyond that of metabolic needs. Sadly, though, hyperalimentation failed to demonstrate benefit and was abandoned due to significant metabolic side effects and complications.[11]

Disillusionment with PN opened the door for the emergence of enteral nutrition (EN) formulas. EN demonstrated superiority over PN, including a decrease in the number of side effects and a decrease in cost. Yet these formulas were overwhelmingly designed to mimic the recommendations of feeding high amounts of carbohydrates (approximately 50% of all caloric goals) with a low or moderate amount of protein. Once more, these formulas continued to focus on minimizing amino acid oxidation through the delivery of calories. In this process, it became evident that meeting nutrition goals through EN alone was challenging and, as importantly, that patients continued to progress toward protein malnutrition. Once again, it was hypothesized that the progression toward malnutrition was caused by underfeeding. A number of studies combining early use of PN along with EN followed. These recent studies demonstrate an improvement in the delivery of nonprotein calories but in general continue to deliver low amounts of protein. And more important, these studies have failed to consistently demonstrate a distinct clinical benefit as a result of meeting caloric goals. In fact, it appears that the best outcomes observed in the studies occur when only 80% of the caloric goals are met.[12]

In contrast, there is accumulating observational evidence that increasing protein delivery is associated with improved outcomes.[13] To date, at least a dozen observational trials demonstrate that increasing protein goals appears to be linked with a decrease in mortality.[14] While observational trials do not demonstrate causality, the evidence has been considered consistently sufficient so that professional societies now suggest that critically ill patients should receive an increased amount of protein above that of those recommended in the dietary guidelines for healthy individuals.[15]

Many questions still remain. Adequate prospective randomized controlled trials delivering differential amounts of protein are still pending. The proportion of nonprotein calories to protein calories is also being questioned with the use of hypocaloric high-protein regimens, which are now being considered. How much protein should be delivered? What is the upper limit? What should be the clinical end points that would validate the importance of protein delivery? These and many other questions will be determined through prospective clinical trials. The results will determine whether once and for all we will reach better success at preserving endogenous cellular protein and preventing the progression toward protein malnutrition.

Basic Protein Principles

Proteins are ubiquitously present in cells and comprise a myriad of different functions, including but not limited to enzymes, complex macromolecules involved in muscle contraction, hormones, antibodies, and many others. DNA only encodes for protein; thus, protein is the molecular expression of all DNA. In humans and higher organisms, a dietary supply of protein is necessary for survival. Protein is a small but important source of energy in human beings. Under some circumstances, cellular protein is broken down to generate glucose, an essential process for survival during starvation.

Accepted dietary requirements for protein are approximately 0.6–0.8 g/kg/d. Higher intake is observed in hunter-gatherer populations. In bodybuilders, very high-protein diets (>2.5 g/k/d) sometimes given though the safety of these practices are in question, and sports nutrition experts usually recommend 1.3–1.7 g/kg/d. Excessive amounts of protein may be poorly tolerated, and digestion and absorption may be overwhelmed. For example, Oben and colleagues[16] reported that the concomitant use of digestive proteases improved amino acid absorption significantly in healthy individuals after a single dose of 15 g whey protein concentrate, implying that there is a limit in the capacity of healthy individuals to digest and absorb higher protein loads.

All protein is constituted by 20 amino acids. Of these, 9 are considered essential, meaning that in humans, these cannot be synthesized and thus are required in the diet. Arginine is considered a "conditionally essential" amino acid in that in a healthy adult, endogenous synthesis from citrulline appears to be sufficient. However, arginine is essential for normal growth in children and can become deficient through increased destruction by arginase under certain conditions requiring dietary supplementation.

All amino acids are defined by their chemical composition sharing basic common features. Attached to a single carbon (α carbon) is an amino (NH_3+) and a carboxyl group (COO–). Each amino acid is differentiated from the other in their side chains (R) (see Figure 1). The side chains of the 20 amino acids give them specific physicochemical and ultimately biological properties. Amino acids are the largest source of nitrogen in our bodies. On average, 16% of the molecular weight of protein is formed from nitrogen. Thus, in laboratory studies to determine protein balance, measurement of nitrogen and a conversion factor of 6.25 are used to reflect the amount of protein.[17]

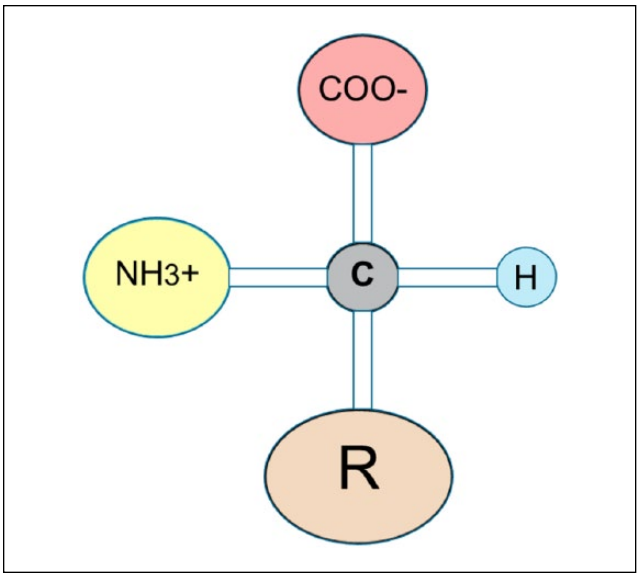

Figure 1. Common structural features of all amino acids. All amino acids share an amino group (NH_3+), carboxyl group (COO–), α carbon (C), and side chain (R). The side chain varies for each amino acid.

Protein cannot be stored in our body, and thus all protein is contained in biologically functional molecules often within cellular organelles. The amount of protein in a cell is maintained through the careful regulation of anabolism (also called protein synthesis) and catabolism (breakdown of protein back into amino acids). Protein is synthesized in the ribosome, whose function is to translate messenger RNA into new protein. The sequence of amino acids determines ultimately the physical conformation of the protein and also the biological function.

The ultimate concentration of protein macromolecules in a cell is determined by a balance between protein synthesis (anabolism) and protein breakdown (catabolism) (Figure 2). A large amount of knowledge has accumulated to understand both anabolic and catabolic processes. In the healthy individual, anabolic and catabolic processes are in balance, and thus the net synthesis of protein is zero. During critical illness, protein catabolism exceeds that of anabolic responses, and thus the net protein synthesis becomes negative.

The balance between anabolism and catabolism and, ultimately, the accumulation of protein in a cell is determined by a number of physiologic stimuli, including neurohormonal messaging and inflammation. Nutrient availability is key for protein anabolism, being severely compromised when the availability of a key nutrient such as an amino acid is decreased.

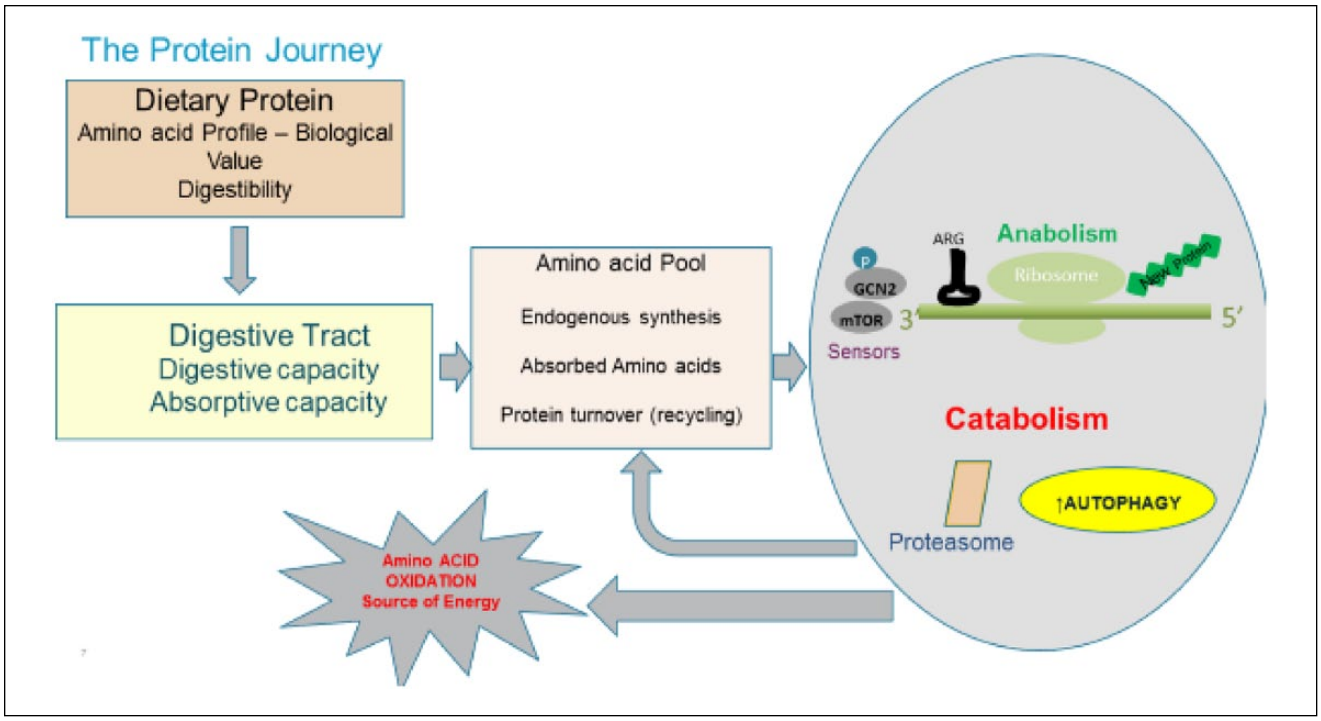

Figure 2. The protein "journey." A central goal of medical nutrition therapy is to maximize protein anabolism and minimize dietary protein loss as a source of energy. The "journey" of how dietary protein is ultimately converted into cellular protein involves a series of key steps: (1) amount and biological value of dietary protein, (2) patient's capacity to digest protein and absorb short peptides and amino acids, (3) enrichment of the amino acid pool, and (4) anabolic and catabolic processes. ARG, arginine; GCN2, general control nonderepressible 2; mTOR, mammalian target of rapamycin; P, phosphate.

Cellular mechanisms sense the availability of the amino acids necessary to make new protein. Protein synthesis proceeds as long as there are adequate amounts of amino acids and energy in the right proportion. In the absence or deficiency of 1 or more amino acids, protein synthesis ceases, setting in motion protective metabolic mechanisms aimed at defending resources and preventing cell death.

Three percent to 5% of all cellular protein is recycled (protein turnover) daily, a metabolically demanding process that may consume a significant amount of cellular energy. Lysosomal degradation and in particular autophagy are preferred mechanisms of recycling protein. Breakdown of protein also occurs through proteasomes. Liberated amino acids during protein recycling can enter into an amino acid pool and be used to make new protein, or they can be oxidized and used as an energy source.

Amino acid oxidation occurs in the cell under several circumstances:

1. When the cell is starved of glucose. In the absence of an external source of glucose, protein catabolism liberates amino acids that can be converted into glucose.
2. As part of normal protein recycling. During normal metabolic processes, approximately 10% of all amino acids are converted into energy.
3. In the presence of excess amounts of amino acids. A diet that is very rich in protein increases circulating amino acid levels. Since these amino acids cannot be stored, oxidation and degradation become the ultimate mechanism of balancing amino acid availability.
4. In the presence of amino acid imbalanced diets. Under ideal circumstances, amino acids should be in the right proportion to achieve the most efficient utilization during anabolism. However, not all protein contains the ideal balance in amino acids, and in these cases, the amino acid in the lowest concentration becomes the limiting amino acid for anabolism. Any access amino acids above the limiting amino acid are oxidized (see Figure 3).

The Protein Journey

A central goal of medical nutrition therapy is the provision of optimal amounts of dietary protein that ultimately ends up being synthesized as endogenous cellular protein. It is important that this process proceeds with maximum efficiency, minimizing amino acid loss. After all, loss of protein is seen as wasteful and metabolically expensive. Because protein sources are more costly than other nutrient sources, clinicians ordering nutrition therapy are also keen on minimizing protein loss.

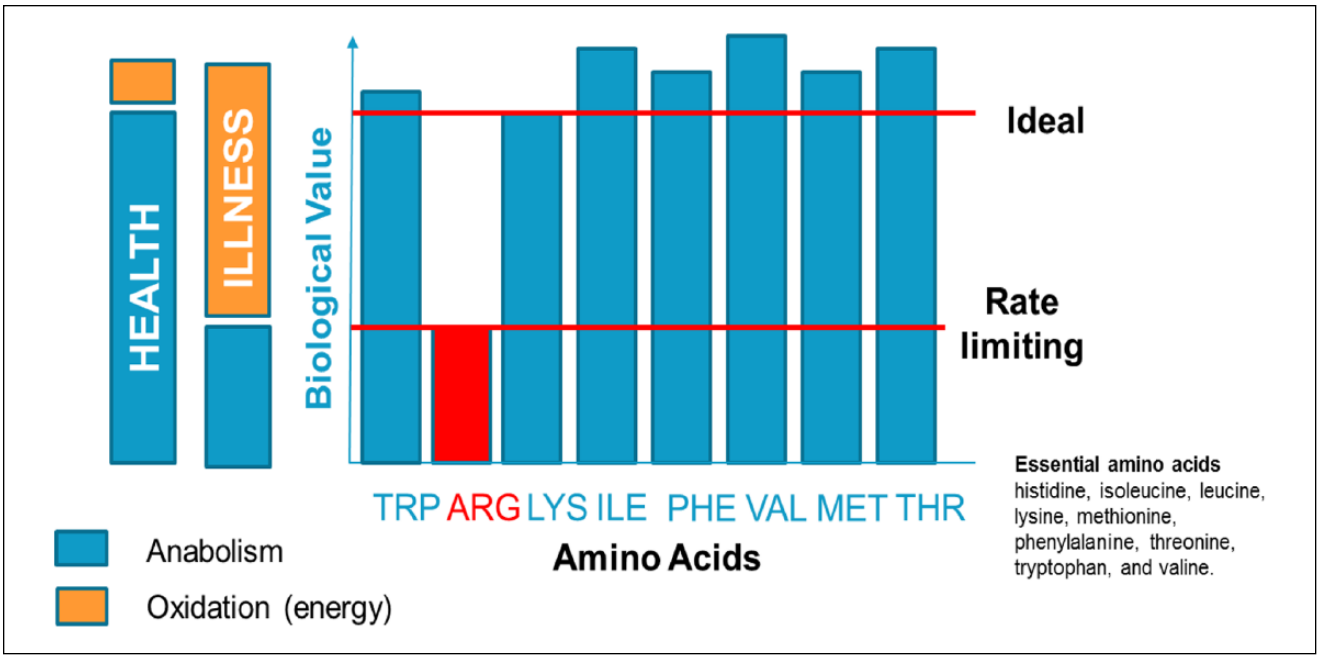

Figure 3. Anabolism is limited not only by the quantity but also by the proportion of amino acids in the pericellular environment. The lowest concentration of a specific amino acid becomes the "limiting" amino acid in that it prevents further protein anabolism. As a result, amino acids that are in higher concentrations of the limiting amino acid are oxidized. In this example, lower arginine concentrations establish the limiting amino acid and prevent further protein anabolism. ARG, arginine; ILE, isoleucine; LYS, lysine; MET, methionine; PHE, phenylalanine; THR, threonine; TRP, tryptophan; VAL, valine.

A complex number of key steps are necessary for the conversion of protein that is eaten in the diet to protein in the cell. These steps can be seen as a "journey" that starts with the decision of what to eat in the diet. This protein journey is so far incompletely studied; therefore, there are significant gaps in knowledge, particularly when it comes to critically ill patients (Figure 2). Nevertheless, significant alterations and problems have been identified, all of which can potentially and sometimes dramatically affect the efficacy of the medical nutrition therapy. These steps are as follows:

1. The amount of protein prescribed and ingested. Major professional societies and key investigators are now recommending that patients receive a significantly higher amount of protein during critical illness above that of healthy individuals. This change reflects several major observations:
   a. Increasing the amount of protein delivered exerts a favorable anabolic response (positive nitrogen balance) in critically ill patients.[18,19]
   b. Multiple studies focused on meeting caloric goals have failed to demonstrate a consistent and significant benefit associated with the delivery of higher amounts of nonprotein calories.
   c. Observational studies suggest that higher protein delivery is associated with improvement in outcomes, particularly that of decreased mortality.
   d. It is metabolically acceptable to lose some of the protein administered as an energy source.
   e. No evidence of significant toxicity has been found so far with the delivery of higher amounts of protein.

Thus, guidelines now recommend the delivery of at least 1.2 g protein/kg/d, but some investigators are suggesting delivery of 2.0 or even 2.5 g protein/kg/d.[14] It is important to say that these recommendations remain to be thoroughly tested in prospective randomized controlled trials.

2. The proportion of other macronutrients in the diet, particularly that of carbohydrates. In otherwise healthy patient populations, the use of carbohydrates minimizes amino acid oxidation and maximizes protein anabolism. This protein-sparing effect of glucose may be important, particularly under conditions of economic deprivation where by using high carbohydrate loads (which are less expensive), the cost of nutrition can be decreased. Not surprisingly, the dietary guidelines (https://health.gov/dietaryguidelines/dga2010/dietaryguidelines2010.pdf) suggest that most patients should receive between 45% and 65% of all energy in carbohydrates.
   A similar approach has been attempted in critically ill patients. Most commercial diets (be it PN or EN and

even oral nutrition supplements) underscore the paradigm of delivering high carbohydrate loads very similar to that suggested for healthy individuals. However, higher carbohydrate loads have failed to demonstrate a benefit in critically ill patients. Furthermore, increasing carbohydrate loads to minimize amino acid oxidation is associated with significant side effects, including hyperglycemia, increased metabolic demands, and increased prescription of insulin.

3. The biological value (quality) of the dietary protein. The proportion of amino acids contained in any protein delivered should, under ideal conditions, be similar to that of the amino acids required by the cellular processes occurring in the patient. Some proteins (generally reflecting those of animal origin) such as whey proteins contain the right proportion of amino acids (for healthy individuals), and thus its ingestion maximizes anabolic responses. The efficiency by which a given protein is used in anabolic responses is called "biological value." The biological value of protein has been studied in healthy individuals in proteins from multiple sources and can vary significantly. For example, the biological value of whey is significantly higher than that of protein obtained from soy. Thus, a higher amount of soy protein compared with whey would have to be fed to a patient to achieve a similar anabolic response.

   A closely related property of protein is that of its digestibility. Digestibility refers to the capacity of the protein to be broken down into short peptides and amino acids and ultimately to be absorbed into the bloodstream. To date, very few studies have focused on the importance of what is the best type of protein that should be prescribed to a patient based on the biological value or its digestibility in critically ill patients.
4. The general postulate by clinicians who prescribe EN is that the patient's gastrointestinal (GI) tract is fully functional, capable of normal digestion and absorption. However, the capacity of clinicians to diagnose and monitor GI function is limited, and thus a clear understanding on how significantly the GI tract is affected by critical illness is unknown. Recent preliminary studies suggest that exocrine pancreatic function may be severely affected in up to 18% of critically ill patients, with moderate exocrine pancreatic insufficiency being as high as 50%. This is of substantial importance, as a decrease in the production of enzymes such as trypsin and others could be associated with malabsorption of protein. In addition, there is growing evidence that there may be a limit to the amount of protein that even a normal GI tract can digest and that protein given in excess of this amount would be lost in the feces. Thus, in the future, it will be important to identify the patient populations that have a compromised GI tract and the amount of protein that can be delivered and absorbed by a given patient.[20]
5. The extracellular amino acid pool. Ultimately, the quantity and proportion of amino acids available to a cell are those that are present in the pericellular environment. The amino acid pool is a poorly defined compartment (in reality, several compartments) that is enriched by dietary amino acids, by amino acid coming from cellular protein turnover, and by endogenous amino acid synthesis.

   Critical illness can significantly alter the amino acid pool and the availability of specific amino acids. In the past 10 years, information has grown as to how the concentration of certain amino acids is governed in the pericellular environment. In 2006, Makarenkova et al[21] reported that acute injury induced the accumulation of myeloid cells expressing large amounts of arginase 1 in the marginal zones of the spleen. Similarly, in humans, physical injury (be it trauma or surgery) is associated with a significant increase in myeloid cells that express arginase 1 in the circulation and of free arginase in plasma.[22,23] Increased free arginase activity has also been observed in hemolytic reactions. These are associated with a significant decrease in arginine availability to the point that arginine can become the limiting amino acid for protein anabolism. Recently, a decrease in tryptophan availability due to induction of indoleamine dioxygenase (IDO) has been observed in septic and critically ill patients.[24,25] In this case, low tryptophan availability could also become a limiting nutrient for the accretion of protein.

   Our group has joined that of other investigators to hypothesize that decreased availability in individual amino acids in the pericellular environment can be of significant clinical consequences. In T lymphocytes, for example, arginine requirements increased dramatically upon activation. T lymphocytes are capable of "sensing" a decrease in arginine availability, and protein synthesis and ultimately immune function are severely curtailed in arginine deficiency states. Arginine deficiency, associated with increased presence of myeloid cells expressing arginase 1, is now known to cause clinically significant impaired T lymphocyte function in trauma after surgery, in certain cancers, and in certain chronic infections (such as tuberculosis or human immunodeficiency virus). Not surprisingly, arginine deficiency in these states is associated with poor prognosis.[26,27]

   Arginine-based immunonutrition is a form of medical nutrition therapy aimed at meeting the distinct nutrition requirements for patients who develop arginine deficiency states due to increased arginase 1

expression. Arginine-based immunonutrition focuses on the delivery of a diet that contains a high proportion of arginine in addition to other amino acids contained in proteins of high biological value such as casein or whey. Arginine-based immunonutrition may restore arginine levels in the amino acid pool and, through this mechanism, improve the concentration of the limiting amino acid necessary to maintain protein anabolism and normalize cellular functions. Arginine-based immunonutrition has been found to be particularly useful in patients undergoing elective surgery or after trauma, and its use is associated with a significant decrease in the risk of infection.[28]

Conclusions

Despite clear progress, clinical nutrition still faces many challenges. Among the most significant is the fact that protein loss continues unabated in critically ill patients despite the availability of medical nutrition therapy. For many years, the clinician designing and implementing medical nutrition therapy in the critically ill patient has used the principles of nutrition learned in the studies of healthy individuals, emphasizing the use of nonprotein calories to minimize protein as an energy source (protein oxidation). This approach, however, has failed in critical illness.

There is a renewed focus on increasing the delivery of protein as the best mechanism of achieving nitrogen balance. Anabolic responses in critically ill patients are proportional to the amount of protein delivered. And it appears, to observational trials, that improved protein delivery is associated with better clinical outcomes. Much needs to be learned. Many factors alter the conversion of dietary protein into cellular protein. These include the proportion of amino acids in a particular protein, the capacity of the patient to digest protein and absorb the peptides and amino acids generated, and the concentrations of limiting amino acids in the amino acid pool. Particularly interesting is the fact that significant amino acid deficiencies are now being identified in different illnesses. These are caused by the increase in cells expressing enzymes such as arginase 1 or IDO. Arginine deficiency is observed in patients after surgery or trauma, in certain cancers, and in patients with hemolytic diseases. Tryptophan deficiencies are also being described in critically ill patients. It is possible that patients with specific amino acid deficiencies have distinct nutrition requirements that are only solved with the provision of higher than normally contained concentrations to overcome specific deficiencies to restore the balance to the amino acid pool and through this mechanism reestablish protein anabolism. An example of the benefits of this approach may be observed in patients undergoing surgery or after trauma who receive arginine-based immunonutrition, where clinical benefits associated with improved T lymphocyte function are consistently observed.

Statement of Authorship

J. B. Ochoa Gautier, R. G. Martindale, S. J. Rugeles, R. T. Hurt, B. Taylor, D. K. Heyland, and S. A. McClave contributed to the conception/design of the review and critically revised the manuscript; and J. B. Ochoa Gautier drafted the manuscript. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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Discussion

Robert G. Martindale: I don't understand this exocrine pancreatic insufficiency causing nonabsorption of protein in critical care. What are the mechanisms?

Juan B. Ochoa Gautier: Indeed, there appears to be a significant incidence of occult exocrine pancreatic insufficiency from multiple causes. What we see are several things. Aging alone is a cause of exocrine pancreatic insufficiency, and that remains unrecognized and undiagnosed in critical illness. Older age alone decreases pancreatic function. Another significant cause is malnutrition. A third cause is poor organ perfusion due to shock, a frequent issue in critical illness. Even in healthy individuals, there's a maximum digestive capacity, which may limit the rate of protein absorption.

Claudia R. Morris: If we're having problems digesting, with pancreatic insufficiency and reduced enzyme secretion, should we be using pancreatic enzymes in these patients? Has anyone actually done any preliminary studies? That seems like a good first step.

Juan B. Ochoa Gautier: None that I'm aware. I do know that as critical care physicians, we have the availability of predigested diets. These formulas consist of partially digested proteins and moderately digested carbohydrates. They also may have medium-chain triglycerides (MCTs). Unfortunately, current enteral nutrition formulas in the market also contain long-chain triglycerides (LCTs), which require digestion prior to absorption. Poor absorption of LCTs is thus a potential problem in critically ill patients with occult exocrine pancreatic insufficiency. We really don't have an ideal enteral nutrition product for pancreatic insufficiency.

Claudia R. Morris: The makers of certain pancreatic enzyme brands are now starting to push the use of their product in severe critical illness.

Beth Taylor: In practice, we can't use the encapsulated form of the pancreatic enzymes. We have to use the powder form because most of our patients were feeding through a tube. When you've tried everything and you think the patient is having malabsorption, that's when I'll use pancreatic enzymes.

Juan B. Ochoa Gautier: If they look like they have diarrhea, fatty stools, and classic symptoms of malabsorption in the ICU, you should go ahead and think of adding a pancreatic enzyme.

Beth Taylor: I just add pancreatic enzymes. Aside from that, any thoughts on giving protein? How should it be delivered, by continuous infusion or by bolus infusion?

Juan B. Ochoa Gautier: The anabolic response classically was thought to be due to just a big protein load, but it depends on the type of protein that we get. There are some studies that suggest that smaller loads given several times are actually better. But it does depend on the type of protein. Whey protein will behave biologically different from the anabolic response point of view, compared with casein. They both affect anabolism and catabolism differently.

Daren K. Heyland: Those studies you're referring to are not in the context of critical illness. We really don't have any information on bolus versus continuous infusion. Jan Wernerman, though, may present some data on continuous infusion of intravenous amino acids, showing an anabolic response with that approach. But following along this line of thinking of documented problems with malabsorption and with protein digestion, I almost felt like you made an argument for giving intravenous amino acids directly to restore amino acid levels, to give more protein amino acids via the intravenous route. Can you help me think through the pros and cons of that approach versus why we still struggle with the enteral route?

Juan B. Ochoa Gautier: What would be the biological value of intravenous protein that we should be giving to different patients? Is the value of IV protein different for medically septic patients compared to surgical trauma patients? I don't know the answer to those questions. I do think that either the parenteral or enteral route is going to be possible. The data in the last 5 years open the concept that it's not one route versus the other and that we are going to have to find a balance in the use of both routes.

Frederick A. Moore: I was just going to comment on the timing of initiation of feeding after admission. We're classically taught about the ebb and the flow phase of injury. We think we're going to make the patient anabolic, when actually all the metabolic signaling is telling the skeletal muscle to break down. So you can give all the nutrients you want, if you're trying to get it in early, but it's not going to work. And there's a time in the patients' course where they actually start becoming anabolic, and you start having an effect. So the question is, when does that happen and could you actually make that

happen sooner? Do specific amino acids make that happen? Could specific amino acids such as leucine promote that anabolic response?

Juan B. Ochoa Gautier: I think the question is a little bit different. What are the metabolic requirements initially versus what are the metabolic requirements after a few days? Is one formula going to fit every patient and every condition? It would be naïve for us to think that this is the case. I think the essential goals initially are different from the long-term goals. The first thing is to control hyperglycemia and restore energy metabolism. The second one is maintaining intestinal mucosal "happiness" (physiology). The idea of becoming anabolic in the first 72 hours is naïve. I don't know when the change from ebb to flow is going to be or whether we're going to be able to determine that time point easily. I do not try to get the patients into an anabolic state within the first 72 hours or even up to a full week, depending on the patient. Thus, I am less interested in meeting caloric goals during the first week than afterward. There are some patients, however, about 3% of my patients, who present with severe classic protein and calorie malnutrition. In these cases, the goal has to change to provide both calories and protein early on.

Stuart M. Phillips: I just want to challenge you a little bit on this whole concept that oxidation is bad, and I'll bring it back to something that Dr Moore just raised by leucine being an anabolic trigger for muscle. In that situation, you actually want leucine oxidation to be high, because the Michaelis constant (Km) for the enzymes that need to bind leucine in order to trigger muscle protein synthesis is actually lower than that for the enzymes that are going to oxidize the leucine. We need to switch out of the mind-set that oxidation is wasteable. In a lot of anabolic situations, to trigger anabolism, you actually need to have oxidation of the branched-chain amino acids. There's no other amino acid that triggers muscle protein synthesis. So when you look at leucine oxidation, it has to go probably as high as you can drive it, so that you can turn on muscle protein synthesis.

Juan B. Ochoa Gautier: I agree with you completely. What I'm saying is that classically we have seen protein oxidation as an "evil" problem and that all we have to do is give more carbohydrates to block or prevent it from happening. In the classic PN studies, before we started moderating excessive carbohydrate loads, what you see are these paradoxical very high catabolic responses rather than prevention of anabolism. In fact, the highest negative nitrogen balance that you achieved in that era was by giving them PN. I do not know the exact mechanism. We were actually doing worse with the PN than we would have done starving the patient. But we don't know whether the problem was the protein formula, amino acid imbalances, or the excess carbohydrates.

Craig J. McClain: You've talked about potential malabsorption, but you haven't talked about gut bacteria. So, we look at fecal metabolomics all the time in our liver disease models, and 3 things always happen no matter what model we have. You have alteration in the short-chain fatty acids, especially butyrate, which we think are very important. There are alterations in bile acids, and there are alterations in amino acids, especially branched-chain amino acids.

Juan B. Ochoa Gautier: Frank Cerra pushed the issue of branched-chain amino acids, but it's been off the map for many years.

Craig J. McClain: I am talking about branched-chain amino acids in feces. Cerra never talked about that. You're assuming if you feed them, they will get absorbed. That's not true.

Juan B. Ochoa Gautier: The fascinating thing is how little we know. We don't even know if our patients are absorbing what we're giving them. And then downstream, what is happening? Are the amino acids being utilized?

Daren K. Heyland: Juan made the statement that we're not ready for a phase 3 trial to look at the impact of protein intake on outcomes in critically ill patients. While I may disagree with that, what I really want to press to Juan and the audience is what those critical gaps are. What are the critical gaps that we need to fill before we design and conduct a larger trial to strengthen the evidentiary basis for our clinical recommendations?