How Many Nonprotein Calories Does a Critically Ill Patient Require? A Case for Hypocaloric Nutrition in the Critically Ill Patient

Saúl J. Rugeles, MD[1]; Juan B. Ochoa Gautier, MD, FACS, FCCM[2]; Roland N. Dickerson, PharmD[3]; Jorge A. Coss-Bu, MD[4]; Jan Wernerman, MD, PhD[5]; and Douglas Paddon-Jones, PhD[6]

Abstract

Calculation of energy and protein doses for critically ill patients is still a matter of controversy. For more than 40 years of nutrition support, the total amount of nutrients to be delivered to these patients has been calculated based on expert recommendations, and this calculation is based on the administration of nonprotein calories in one attempt to ameliorate catabolic response and avoid the weight loss. New evidence suggests protein delivery is the most important intervention to improve clinical and metabolic outcomes. This article describes the metabolic rationale and the new evidence supporting a change in the approach of metabolic support of the critically ill, proposing a physiological-based intervention supported by the recognition of ancillary characteristics of the metabolic response to trauma and injury. A moderate dose of calories around 15 kcal/kg/d with a delivery of protein of 1.5 g/kg/d appears to be the new recommendation for many hypercatabolic patients in the first week following injury. (*Nutr Clin Pract*. 2017;32(suppl 1):72S-76S)

Keywords

enteral nutrition; protein; hypocaloric nutrition; critical illness; intensive care unit; nutritional support

Critically ill patients exhibit severe and unique metabolic abnormalities, making them unable to use nutrients in the same way that a healthy or fasting human does.[1] Healthy individuals are capable of using carbohydrates, lipids, or protein in different proportions to obtain energy and structure. Different cultures around the world eat diets with a wide variation in the proportion of micronutrients from which energy is derived, and the human metabolism adapts well to these variations. During fasting, individuals adapt their metabolism to spare protein and use lipids as the preferred source of energy, thus preserving structure and functional proteins as long as possible. Soon after a meal, normal metabolism resumes, with the return of normal protein turnover within minutes after receiving a meal. In contrast, critically ill patients have metabolic changes that cannot be reversed by feeding.

The challenge to nutrition support must be to interpret the changes in biochemical routes produced in response to injury and design a nutrition regimen that adapts to these special needs, maintaining homeostasis while improving the capacity to adapt to conditions of stress. In this article, we will discuss the metabolic response to injury with an emphasis on nitrogen metabolism, abnormal energy utilization, and the evidence supporting hypocaloric and hyperproteic nutrition support in the critically ill patient.

The Metabolic Response to Injury

The metabolic response to injury (trauma) was described in detail more than 50 years ago. Progress has continued, and in recent decades, better understandings of the mechanisms and metabolic derangements that occur as a result of illness have been achieved. We are able to obtain a more exact metabolic diagnosis of each patient.

In this new scenario, the following characteristics of the response must be recognized:

From [1]Pontificia Universidad Javeriana School of Medicine, Hospital Universitario San Ignacio, Bogota, Colombia; [2]Nestlé Health Science Institute, Lausanne, Switzerland; [3]University of Tennessee Health Science Center, Memphis, Tennessee, USA; [4]Director of Research, Section of Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Intensive Care Service, Texas Children's Hospital, Houston Texas, USA; [5]Department of Clinical Science Interventional Technology, Karolinska Universitetssjukhuset, Stockholm, Sweden; and the [6]Department of Nutrition and Metabolism, The University of Texas Medical Branch, Galveston, Texas, USA

Corresponding Author:
Saúl J. Rugeles, MD, Pontificia Universidad Javeriana School of Medicine, Hospital Universitario San Ignacio, Calle 106 # 21 95 apto 301, Bogota 110111, Colombia.
Email: saul.rugeles@gmail.com

1. The metabolic response is observed in all injured patients, no matter the cause of the illness.
2. The characteristics of the response are similar in all patients; the intensity of this response is different and depends on the severity of injury.
3. The main metabolic event is the increase in protein catabolism, with a high nitrogen loss from somatic and visceral protein. The magnitude of nitrogen loss has a linear relationship with morbidity and mortality.[2]
4. The tolerance to nitrogen loss is limited and depends on the severity of injury and nitrogen reserves of each individual. Indeed, undernourished individuals have a limited reserve and higher mortality rates after injury.
5. The oxidation rates of glucose are low because inflammatory mediators (such as tumor necrosis factor [TNF] and certain interleukins) affect intra-mitochondrial conversion of pyruvate to acetyl CoA, thus preventing glucose oxidation and an efficient production of energy from glucose.[3] This occurs through an enzymatic blockade of pyruvate dehydrogenase, which is proportional to the magnitude of the inflammatory response and consequently to the magnitude of the injury.
6. The altered glucose oxidation does not improve with insulin administration because insulin has no effect on the function of pyruvate dehydrogenase.
7. Hyperglycemia is very frequent and is associated with increased risk of mortality and morbidity. Therefore, a strategy to control glucose levels must be developed.
8. Although insulin administration in this setting improves glucose control, it is associated with at least 3 undesirable effects:
   a. Inhibition of lipolysis and low levels of free fatty acids available for peripheral oxidation
   b. Induction of lypogenesis and increased CO_2 production with a need of increased tidal volume and respiratory work
   c. Induction of anaerobic glycolysis, with conversion of pyruvate to lactate and increased intracellular and extracellular metabolic acidosis
9. Therefore, it is logical to hypothesize that a better alternative to the use of excessive amounts of insulin is that of controlling glucose levels by decreasing exogenous glucose delivery.
10. Lipid oxidation is variable and depends on the intensity of inflammatory response and carnitine availability in the mitochondrial membrane.

In summary, the injured patient has a very intense protein catabolism with a variable ability to oxidize glucose and fatty acids. The metabolic needs of acutely/critically ill patients must be carefully calculated to achieve a better match between metabolic requirements and the nutrients that should be administered. Overfeeding must be avoided as it increases metabolic stress, infections, and probably mortality.[4,5]

Nutrition Needs of the Catabolic Patient

Historically, clinicians have assumed that the metabolic requirements of acutely/critically ill patients are similar to those observed in healthy individuals. This is particularly telling in the calculation of the caloric requirements where the calculation of basal energy expenditure (BEE) is done using different formulas (designed for healthy individuals) along with an assumption of "stress factors" to increase caloric requirements. In one equation, total energy expenditure (TEE) linearly increases with the severity of injury.[4] In this model, for example, many patients receive very high caloric loads, with burn patients receiving 200% of BEE. The consequences of attempting to meet caloric loads with medical nutrition therapy are the induction of hyperglycemia, hyperosmolarity, and immunosuppression with a high incidence of infectious morbidity, particularly as a result of parenteral nutrition (PN) support.[5,6]

In recent years, there has been unanimity in recommending adjusting caloric needs near to 25–30 kcal/kg/d, based on expert consensus. Recent guidelines of the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN) recommend this amount of calories for most patients in the intensive care unit (ICU).[7–9] However, a growing number of observations reveal that maintaining a provision of 25 kcal/kg/d in most critically ill patients can be excessive as these patients often exhibit high blood glucose concentrations.

The Hypocaloric Theory

Patiño et al[10] proposed in 1999 a hypocaloric high-protein support for the acutely/critically ill patient, describing the hypothetical rationale of this therapy from the metabolic point of view; however, high-level clinical evidence in support of his proposal was missing. Recent studies have shown that BEE in the critically ill is generally <25 kcal/kg/d, approaching 22 kcal/kg/d—surprisingly, the same amount as calculated with the Harris-Benedict equation for more than 100 years.[11] The question about how many calories must be delivered to critically ill patients simply remains to be answered.

New Evidence

Since 2010, at least 8 trials have been published addressing the question of how many calories must be delivered to the critically ill.[12–19] Analyzing the data of these trials, there is no evidence to suggest that permissive underfeeding is more harmful than feeding following the goal of 25–30 kcal/kg/d.

Our research team in Bogotá, Colombia, has conducted 2 of these trials. The first one was designed to test the hypothesis that hypocaloric high-protein nutrition (15 kcal/kg/d and 1.5 g

protein/kg/d) improved clinical and metabolic outcomes in critically ill patients compared with a traditional caloric delivery of 25 kcal/kg/d, using 20% of the calories as protein.[14] The results of this trial supported our hypothesis; we found a benefit from the hypocaloric hyperproteic regimen, as demonstrated with an improvement at 48 hours of the delta Sequential Organ Failure Assessment (SOFA) score. This score has been suggested to be an indicator of therapy effectiveness and has been positively correlated with good clinical outcomes and lower mortality.[20–23] In our study, we guaranteed the protein load with an exogenous protein, soy isolate, and whey protein, complementing commercial nutrition formulas used in clinical practice. The average amount of caloric intake in both groups was similar, lower than the caloric goals recommended by current clinical guidelines (and the amounts actually prescribed). The real difference between the 2 groups was in protein intake (<1 vs 1.5 g protein/kg).

The results support the hypothesis that poor outcomes in acutely ill/critically ill patients are due to an accumulated protein debt rather than a caloric debt and that the success of medical nutrition therapy is predicated upon increasing the delivery of protein. However, that trial did not answer the question of the safety of the hypocaloric regimen, because the difference in caloric delivery between groups was not significant.

In our second trial, we therefore compared outcomes of a hyperproteic normocaloric regimen with that of a hyperproteic hypocaloric nutrition in the ICU setting.[18] In this recent trial, both groups of patients received 1.4 g/kg/d of protein, but the hypocaloric group received 12 kcal/kg/d while the control group received 19.2 kcal/kg/d. We did not find differences in clinical outcomes, but we did find a significant difference in hyperglycemic events, number of patients requiring insulin, and total dose of insulin required. We speculate that hyopocaloric hyperproteic medical nutrition therapy, by achieving better glucose control and decreasing insulin utilization, will eventually demonstrate improved clinical outcomes.

Recommendations regarding protein requirements in critically ill patients have changed over the past decades, leading to a consensus among the experts. In 1983, Apelgren and Wilmore[2] suggested that high-protein PN (1.5–2 g/kg/d) reduced mortality in severe trauma patients. Implementing these recommendations at the bedside met with significant problems. Attempts at delivering increased protein was done simultaneously with an increase in the delivery of nonprotein calories (mainly carbohydrates) mainly through the use of PN. Hypercaloric hyperproteic PN, however, was associated with significant side effects, prompting clinicians to shift to enteral nutrition (EN) (1990–2000). Importantly, though, most commercial enteral formulations are designed to meet the nutrition requirements of healthy individuals, which maximize the delivery of nonprotein calories and have a lower protein content. Consequently, most enteral commercial formulations are inadequate at delivering the increased protein recommendations suggested by the new guidelines.

As far as we know, our trial is the only one that has maintained a high provision of protein in both groups and compared 2 levels of caloric delivery in EN in the ICU, freeing protein delivery from caloric delivery. The results are consistent with the altered metabolic response to injury. Increased delivery of protein should improve nitrogen balance and clinical outcomes.

In this order of ideas, current evidence supports the use of low caloric loads along with an increase in protein delivery. This concept changes the distribution of caloric loads between carbohydrates, lipids, and proteins.

Final Remarks and Recommendations

The metabolic response of the injured patient is characterized by severe protein catabolism and nitrogen loss associated with a limited capacity to oxidize carbohydrates and lipids. In this context, the need for nitrogen is high, and metabolic support through medical nutrition therapy must guarantee high protein delivery during a catabolic state. The delivery of carbohydrates and lipids must follow a careful evaluation of the oxidation capacity of the patient to support the catabolic state, avoiding nutrient toxicity. Hyperglycemia is a consequence of intramitochondrial defects in glucose oxidation and is associated with increased mortality and morbidity. Insulin does not improve glucose oxidation and may inhibit lipolysis, as well as increase lypogenesis and lactate production. The best physiological strategy to control hyperglycemia and overfeeding is hypocaloric nutrition. New evidence suggests the use of this strategy, with a goal of 15 kcal/kg/d, with a protein dose between 1.4 and 2.0 g/kg/d for many hypercatabolic patients during the first week following injury. After that time, a normocaloric approach seems reasonable.

Statement of Authorship

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Discussion

Jan Wernerman: I think you performed an interesting study, but I would interpret the results slightly differently. You compared 15 to 25 kcal/kg/d and you got the 2 groups separated, which some earlier studies didn't do. Your clinical outcome was a delta SOFA score and there wasn't a significant difference. But there was a difference in insulin intake. Was it a good or bad thing to decrease the amount of insulin when it didn't have an effect upon the primary outcome?

Saúl J. Rugeles: The study was designed to compare 25 with 15 kcal/kg/d, to demonstrate a noninferiority effect of hypocaloric nutrition versus normal caloric nutrition. We found noninferiority. But the sample size was 60 patients in each group. Maybe if we repeated the study with a larger size, with more power, we could find differences in clinical outcomes. The primary outcome was delta SOFA and the sample size was calculated with delta SOFA, not with any other clinical outcome.

Jan Wernerman: Okay, point taken. I think in general terms, you made an adequate recommendation of 1.5 g/kg/d of protein, which makes your study more solid than the other studies in your expose. When we discuss this and we have a manipulation or a difference in nutrition intake, in calories or in protein, then we have mortality. Now we have an intermediate end point in terms of delta SOFA. When we discuss the protein, we hope to preserve lean body mass or something like that. We need to take this stepwise. You do a nutrition manipulation, you achieve something in terms of, say, lean body mass, and then you will have an effect of an outcome. I think the jump from nutrition and manipulation all the way to mortality is a very huge step. I think that we need to have some type of measure of the nutrition effect in between. If you give glutamine, you would look to normalize glutamine concentration. If that is the issue, then you take serial computed tomography scans and look upon the lean body mass as estimated by that. This wasn't particular to your study, but I think in general terms, it's important not to take the large step from the amount of protein in the study to mortality.

Saúl J. Rugeles: Yes, I agree with you that it is important to make measurements relative to the effect of protein, for example, in lean body mass or the protein catabolic or anabolic process. I personally think that nowadays it is impossible to reverse the catabolic response of the patient. It's impossible to avoid muscle lost during critical illness. We must support the catabolic response, giving enough protein to prevent the patient from consuming his own body protein. But it is very difficult if not impossible to avoid muscle catabolism in this kind of patient. In other words, the nutrition intervention must affect clinical outcomes in the ICU. To show any effect of protein intervention, the study should be an evaluation of short clinical outcomes. But Heyland showed this morning long-range clinical outcomes in his studies. This is also very important from the economic and efficiency point of view for nutrition support in the ICU.

Juan B. Ochoa Gautier: We need intermediate steps to understand physiology before we try to jump into big studies. I have one question for Saúl. Do you think what you're really

showing is that we are giving a toxic substance—and I'm being provocative when I say that—when we give carbohydrate to patients who cannot tolerate it?

Saúl J. Rugeles: Yes. I think one of our most important findings from our study is about carbohydrate metabolism. The patient in the ICU does not have the capacity to oxidize glucose in a good way as do healthy people. And the other side, as you showed minutes ago, insulin administration is not good for all the patients. Insulin administration increases CO_2 production. The best way to control hyperglycemia is to moderate the amount of carbohydrate that we give to the patient.

Jorge A. Coss-Bu: From what you said, do you think that you should do a larger trial? Do you think that there is a biological link between giving less calories and seeing better short-term outcome effects? Or should you look more at long-term effects, like 14 days, or 60-day mortality?

Saúl J. Rugeles: We analyzed 28-day mortality in these patients and we found no difference. But the power of the study was not enough to detect smaller differences in mortality. If we increased the sample size in this kind of study, maybe we could find a small difference in mortality.

Roland N. Dickerson: I noticed in your study design that it was 7 days. My question is, should we be titrating calorie provision according to metabolic response of the patient, if they're no longer insulin resistant or no longer hyperglycemic? Can we then introduce more calories at that point?

Saúl J. Rugeles: The design of the study was determined by several clinical factors. The first factor is our length of stay. The mean length of stay in our ICU is 5.0–6.5 days. The study must be limited to the average length of stay in our ICU. The metabolic evolution of the patient may indicate the point at which to increase calories during the care of the patient. One of the difficulties of this study was to make the nutrition support similar in all patients. But this is not real life. Real life is that I evaluate the patient each day and maybe make a change in caloric or protein delivery in accordance to the tolerance of the patient.

Roland N. Dickerson: I asked that question because in our trauma ICU, for those who require specialized nutrition support, the average duration of stay is about 20 days.

Douglas Paddon-Jones: Just a quick observation from our bedrest studies in healthy adults. We find that within 3 or 4 days, they start to become insulin resistant. And from an efficiency point of view, just the simple provision of leucine really reduces the postprandial hyperglycemia quite dramatically. The protection from leucine lasts over that 14-day period. I'm wondering if there is any translation into a clinical setting, perhaps with something like whey protein or another high-quality source?

Saúl J. Rugeles: Immobilization in this patient population is the rule. The kind of protein that we use is about 80% whey protein and 20% soy protein. But we didn't use any kind of physical stimulation or something like that to improve insulin resistance.

Douglas Paddon-Jones: I'd like to come back to the glucose issue. Jean Charles Prieser talks a lot about endogenous glucose production. He says you can't measure it, but he says he estimates that 40% of your glucose needs are met in the first day or two by this endogenous production. My question for the panel, maybe for you "pound 'em hard enthusiasts," is that a real phenomenon? And is this a reason to back off on calories as long as our protein is covered?

Jan Wernerman: I'm a strong supporter of indirect calorimetry to measure energy expenditure. Mark my word, it's not energy need, it's energy expenditure. With respect to your question, how much endogenous supply of this energy expenditure is there? This is an extremely important question that we need to address. As we plan these studies, this is a real black hole. We must put into proof that we can suppress this endogenous mobilization or at least that we have taken it into account.