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High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: A randomized clinical trial

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ABSTRACT

Purpose: Appropriate caloric intake in critically ill patients receiving enteral nutrition is controversial. This study evaluates the impact of different caloric regimens on severity of organ failure measured with Sequential Organ Failure Assessment (SOFA).
Materials and methods: We conducted a randomized prospective controlled trial. Study population included adult intensive care unit (ICU) patients expected to require enteral nutrition for more than 96 hours. Goals in the intervention group were hypocaloric (15 kcal/kg per day) enteral nutrition compared to normocaloric (25 kcal/kg per day) enteral nutrition, both with hyperproteic intake (1.7 g of protein/kg per day). Primary end point was change in SOFA score (ΔSOFA) from baseline at 48 hours. Secondary end points were ΔSOFA at 96 hours, insulin requirements, hyperglycemia or hypoglycemic episodes, length of ICU stay, days on ventilator, and 28-day mortality.
Results: After screening 443 patients, 120 patients were analyzed. There were no differences between groups in baseline characteristics. We did not find a statistically significant difference in ΔSOFA at 48 hours. Patients in the hypocaloric group showed lower average daily insulin requirements and percentage of patients requiring any insulin.
Conclusions: Hyperproteic, hypocaloric nutrition did not show different outcomes compared to normocaloric nutrition, except lower insulin requirements. Hypocaloric nutrition could provide a more physiologic approach with lower need for care and metabolic impact.

1. Introduction

Daily energy requirements may vary from 1200 kcal during rest to 14 000 kcal in individuals undergoing high-performance activities [1,2]. In critically ill patients receiving enteral nutrition (EN), the question of what is the appropriate caloric intake is still unanswered. Current guidelines recommend EN over parenteral nutrition because of its lower risk of infectious complications, fistulas, and bacterial translocation, reducing length of stay [3–6]. Several studies suggest that EN is the preferred choice in most intensive care unit (ICU) patients [7–12] and should be initiated within the first 24 to 48 hours [5,6]. However, there is no consensus on the optimal caloric requirement in critically ill patients using EN. Different predictive equations are commonly used [13,14].

A recent clinical trial performed by our research group compared hypocaloric EN (12 kcal/kg per day) with a protein intake of 1.4 g/kg per day, with a normocaloric scheme defined as 25 kcal/kg per day and 20% protein. However, for several reasons, the latter group ended up receiving only 14 kcal/kg per day, with a protein intake of 0.76 g/kg per day. As such, groups received similar caloric intake and only differed in protein intake. The former (hyperproteic) group showed better outcomes in terms of Sequential Organ Failure Assessment (SOFA) score progress, lower blood sugar levels, and a tendency to decrease days on mechanical ventilation and ICU length of stay [15].

Therefore, we believe that, to evaluate the optimal caloric intake in critically ill patients, it is necessary to compare 2 regimes with high protein intake, but with different energy supply. A trial comparing a normocaloric high-protein scheme (25 kcal/kg per day) and a hypocaloric high-protein scheme known as a controlled starvation (low doses of carbohydrates and high-protein intake) [16] would allow physicians to choose a caloric scheme, given a protein intake between 1.5 and 2 g/kg per day in catabolic patients [15,17–20]. Low

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caloric and high-protein nutrition has proven better in critically ill obese patient [21], but there are no studies with this regimen in nonobese patients.

This randomized double-blind controlled trial compared 2 caloric schemes (15 or 25 kcal/kg per day) in a high-protein scheme (1.7 g/kg per day) in critically ill patients.

2. Methods

2.1. Study population

This randomized parallel arm clinical study was performed at the 30-bed ICU of our tertiary level university hospital. We enrolled newly admitted patients, which mostly came directly from the emergency unit. Patients were recruited during the 20-month period December 2013 to July 2015. Study population consisted of adult patients (18 years or older) admitted in the ICU and expected to require EN through nasoenteric tube for at least 96 hours. We excluded patients receiving previous nutritional support in the same hospitalization, with concomitant parenteral nutrition, pregnant women, in transplantation program, chronic renal failure, uremic encephalopathy, diabetes, morbid obesity, or do-not-resuscitate orders.

2.2. Randomization and blinding

Randomization was performed using dark sealed envelopes with computer-generated random allocations. Analysis only considered patients who completed 96 hours of follow-up and received more than 5 kcal/kg per day. When patients were excluded, their envelopes were returned to the sequence for patient replacement, until the calculated sample size was accomplished. All analyzed patients were assessed until death during the hospitalization or 28 days after their enrollment through telephone interview if discharged earlier. One investigator (LGV) knew patient allocation and prescribed and supervised the administration of nutritional regimens after randomization. Patients and ICU staff deciding on the rest of medical care were blinded to patient allocation; nutritional information and regimen formulation were not registered in clinical records, except for general information such as total liquids administered.

2.3. Intervention

Patients were allocated to 1 of 2 groups. Ideal body weight was used to calculate caloric and protein requirements. Nutritional goals in the intervention group were a hypocaloric EN of 15 kcal/kg per day of total calories and high protein intake (1.7 g of protein/kg per day). Control group goals were a normocaloric EN of 25 kcal/kg per day with high protein intake (1.7 g of protein/kg per day). Definitions of hyperproteic and normocaloric nutrition are taken from the American Society for Parenteral and Enteral Nutrition guidelines [5], and hypocaloric nutrition represented 60% of that. A commercial enteral formula was adjusted to achieve caloric goals (Online Table 1) and was enriched with additional modules of whey and soy protein diluted in water, given in 3 or 4 daily boluses (Online Table 2). All patients received allocated nutritional regimen until day 7. If further EN was necessary, all patients received normocaloric nutrition.

2.4. End points

Blinded ICU personnel reported clinical events and laboratory values in clinical records. One investigator (LGV) used these data to calculate SOFA score and report outcomes. Primary end point of the study was change in SOFA score from baseline (ΔSOFA) at 48 hours. Secondary end points were ΔSOFA at 96 hours, insulin requirements (mean daily units of insulin), frequency of hyperglycemia episodes (glycemic measurements >180 mg/dL) or hypoglycemia episodes (glycemic measurements <45 mg/dL), length of ICU stay, days on ventilator, days to start nutrition, and mortality within 28 days of randomization. An adverse event in our clinical trial was defined as an unfavorable and unexpected change in health or laboratory findings in trial participants. We had 3 categories: mild (tolerable transitory event), moderate (an uncomfortable event that disrupted normal activities), and severe (a life-threatening event). *Feeding intolerance* was defined as any of these 3 symptoms: vomiting defined as an ejection of stomach contents through the mouth (>2 episodes in 24 h), diarrhea defined as liquid stool that changes in amount (>3 episodes in 24 hours), and bowel distension defined by clinical examination and lasting at least 24 hours.

2.5. Statistical analysis

Sample size was calculated using TAMAMU software (Pontificia Universidad Javeriana, Bogota, Colombia). Sixty patients per arm were necessary to provide 80% power and α error of .05 to detect a 15% (1.7 points) difference in ΔSOFA at 48 hours between the 2 groups with an SD of 1.9 with a 2-tailed *t* test.

We used R version 3.2.2 (The R Foundation for Statistical Computing, 2015) for statistical analysis. Baseline characteristics and outcomes were analyzed depending on the nature of the variables. Normality of quantitative data was assessed by inspecting histograms and quantile-quantile plots. Normally distributed data were analyzed with a 2-tailed *t* test ($P = .05$). Otherwise, Wilcoxon rank sum test was used. We assessed categorical data using a normal *z* test. Contingency tables greater than 2×2 in size were analyzed with χ^2 or Fisher exact test when sparse data (<5 observations) were present. We performed a multivariate linear regression analysis for the primary outcome to check for possible confounding factors as antibiotic use, dialysis, blood cell or platelet transfusions, and cardiopulmonary resuscitation.

2.6. Ethical considerations

Written informed consent before enrollment in the study was provided by relatives. The study was approved by the Ethics Committee of the Pontificia Universidad Javeriana and complied with the provisions of the Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulations. This trial has been registered in ClinicalTrials.gov, identifier NCT02577211.

2.7. Role of the funding source

The study sponsor provided an unrestricted grant and was not involved in any of the stages of the study. All authors had full access to the data, and the corresponding author had final responsibility to submit the manuscript for publication.

3. Results

We assessed 443 patients and found 187 eligible patients who were then randomized. Exclusions after randomization happened in 36 hypocaloric and 31 normocaloric patients. Reasons for exclusion were balanced in both intervention groups. Calculated sample size was achieved (Fig. 1).

Baseline characteristics were similar between study groups (Table 1). Respiratory and neurologic etiologies were the main causes of ICU admission in both groups. Most patients had a B or C baseline subjective global assessment nutritional status. Intervention characteristics showed the expected differences. The delay between ICU admission and start of the EN was similar. The hypocaloric intake group received a minor amount of total calories, total formula, and metabolic flux and more protein modules compared to the normocaloric group. Protein intake was similar (Table 2). This tendency was stable during the 96 hours of observation in the ICU (Fig. 2).

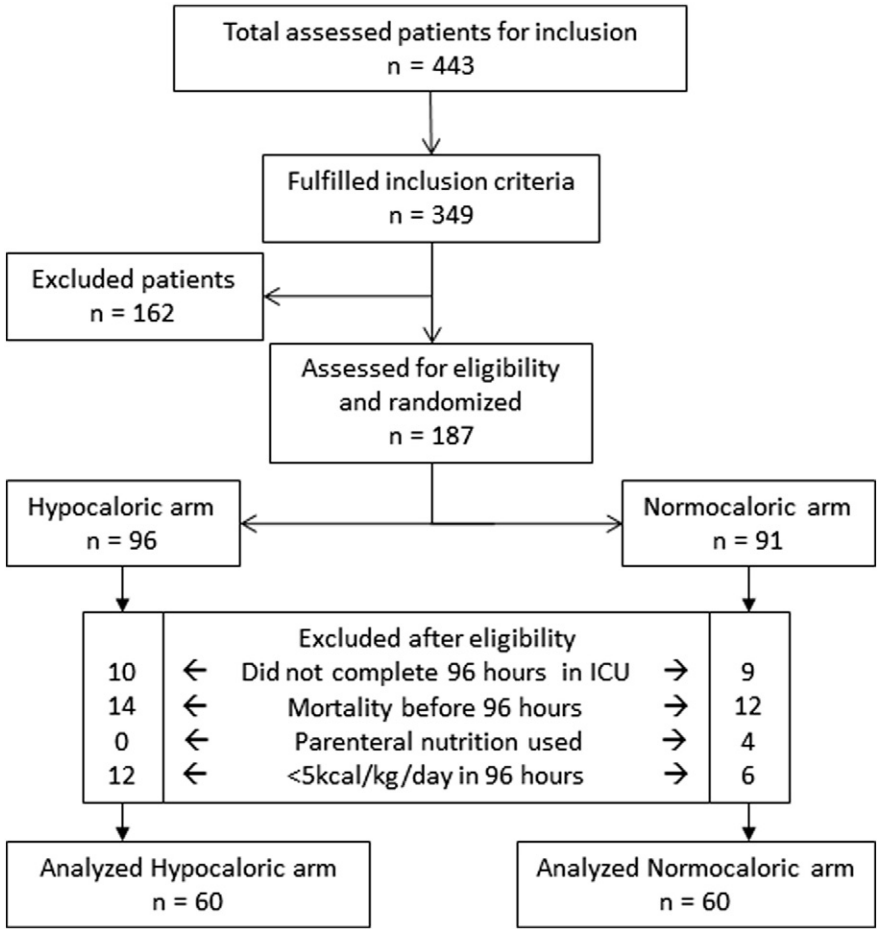

Fig. 1. Patients flow chart indicating assessment for eligibility, randomization, and exclusion.

Table 1
Baseline demographic and clinical and intervention variables in hypocaloric and normocaloric groups

Variable	Hypocaloric diet, n = 60	Normocaloric diet, n = 60
Baseline characteristics		
Age, mean (SD)	53.8 (19.0)	51.8 (20.3)
Males, n (%)	27 (45%)	33 (55%)
Body mass index, median, IQR[a]	25 (2.5)	25 (2.5)
TISS, mean (SD)	25.6 (3.4)	25.2 (3.5)
APACHE II, mean (SD)	13.5 (6.4)	13.7 (6.8)
Baseline SOFA, mean (SD)	6.8 (2.9)	6.8 (2.8)
Reasons for ICU admission, n (%)[b]		
Cardiovascular	7 (12%)	7 (12%)
Gastrointestinal	4 (7%)	6 (10%)
Hematology	4 (7%)	1 (2%)
Orthopedics	0 (0%)	1 (2%)
Respiratory	31 (52%)	22 (37%)
Central nervous system	8 (13%)	18 (30%)
Trauma	1 (2%)	1 (2%)
Urology	1 (2%)	0 (0%)
Other	4 (7%)	4 (7%)
Subjective global assessment nutritional status, n (%)[b]		
A	4 (7%)	4 (7%)
B	36 (60%)	43 (72%)
C	20 (33%)	13 (22%)

Percentages may not sum up to 100 due to rounding. *P* values for comparisons between groups are nonsignificant unless otherwise stated. IQR indicates interquartile range; TISS, Therapeutic Intervention Scoring System.
[a] Wilcoxon rank sum test performed.
[b] Fisher exact test performed.

Table 3 synthesizes study results. We did not find a statistically significant difference in ΔSOFA at 48 hours. The multiple linear regression model did not highlight any confounder of effect modification adjusting for variables that could potentially influence SOFA score. The 2 interventions did not differ significantly in ΔSOFA at 96 hours, hyperglycemic episodes, 28-day mortality, length of ICU stay, or mechanical ventilation. Patients in the hypocaloric group showed lower average daily insulin requirements as well as percentage of patients requiring insulin. No hypoglycemic episodes occurred. Only 1 patient in the hypocaloric arm developed intolerance, with 7 episodes of diarrhea on the third day of enrollment. Those episodes were described as liquid stool, approximately 250 mL each one.

Table 2
Intervention characteristics in hypocaloric and normocaloric groups

Variable	Hypocaloric diet, n = 60	Normocaloric diet, n = 60
Intervention characteristics		
Days in ICU until start of nutrition[a]	2.0 (2.2)	2.1 (1.9)
Total nutrition formula (mL), mean (SD)*	405.4 (94.4)	811.9 (199.5)
Protein modules per day, mean (SD)*	11.4 (2.8)	5.3 (1.2)
Caloric intake at 48 h (kcal/kg/d), mean (SD)*	12.6 (3.4)	20.5 (5.1)
Protein intake at 48 h (g/kg/d), mean (SD)	1.4 (0.4)	1.4 (0.3)
Caloric intake at 96 h (kcal/kg/d), mean (SD)*	12.1 (2.6)	19.2 (4.3)
Protein intake at 96 h (g/kg/d), mean (SD)	1.3 (0.3)	1.3 (0.3)
Metabolic flux at 96 h, mean (SD)*	0.8 (0.2)	1.7 (0.4)

P values for comparisons between groups are nonsignificant unless otherwise stated.
[a] Wilcoxon rank sum test performed.
* *P*< .0001.

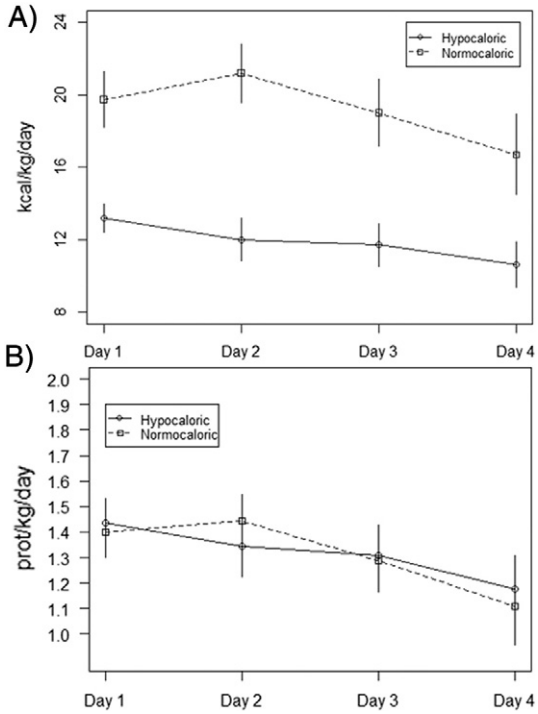

Fig. 2. Trends in caloric and protein intake from days 1 to 4. Brackets indicate 95% confidence interval. A, Caloric intake. B, Protein intake.

4. Discussion

Our study compares 1 hypocaloric (12.6 kcal/kg per day), hyperproteic (1.39 g/kg per day) group with a normocaloric (20.5 kcal/kg per day), hyperproteic (1.42 g/kg per day) group. Both groups were similar in severity and complexity without differences in Acute Physiology and Chronic Health Evaluation (APACHE), Therapeutic Intervention Scoring System, nutritional status, baseline SOFA, initial diagnosis, and delay in the onset of EN. Our results did not show difference in terms of SOFA score at 48 and 96 hours, mortality, days on ventilator, or ICU length of stay. However, insulin requirements and percentage of patients requiring insulin were lower in the hypocaloric group. We could then conclude that the regimen with fewer calories produces less metabolic impact and could reduce patient care requirements. Hypocaloric and hyperproteic regimen also requires low enteral infusion rate, resulting in better tolerance and easier achievement of caloric and protein goals.

A substantial proportion of screened patients (42%) in our tertiary level university hospital were eligible to this protocol of EN. Patients had a low baseline APACHE score (low severity), and most were nonsurgical. We realize the difficulties of the generalizability of this study in clinical practice in an ICU with different characteristics. However, the findings could result in changes in patient care with lower resource utilization and metabolic impact.

Several studies suggest that nutritional therapy in critically ill patients has an influence on mortality, length of hospital stay, duration of mechanical ventilation, and infectious complications [15,22].

The European Society for Clinical Nutrition and Metabolism guidelines warn that during the acute phase, an excess of 20 to 25 kcal/kg per day may be associated with less favorable outcomes [23]. The American Society for Parenteral and Enteral Nutrition guidelines recommend that energy requirements should be calculated by predictive equations (25-30 kcal/kg per day) or measured by indirect calorimetry to provide more than 50% to 65% of calorie goal over the first week. Protein requirements in patients with body mass index less than 30 should be in the range of 1.2 to 2 g/kg of actual body weight per day [5].

Recommendations regarding protein requirements in critically ill patients have changed over the past decades leading to a consensus. In 1983, Apelgren and Wilmore [24] suggested that high-protein parenteral nutrition (1.5-2 g/kg per day) reduced mortality in severe trauma patients. After that, most nutritional support teams used high-protein supply for the critically ill. However, when there was a shift from parenteral to EN (1990-2000), protein delivery to patients decreased because enteral formulas had lower protein content, and tolerance was not perfect. No studies had studied the impact of different protein deliveries in EN on outcomes. In a recent trial using EN, our group compared 2 hypocaloric regimes with different protein delivery in critically ill patients, finding that the hyperproteic group (1.4 g/kg per day) was associated with a reduction in SOFA score and less hyperglycemic events, regardless of caloric debt [15].

There is a consensus about providing high-protein nutrition to critically ill patients [5]. However, caloric requirements remain unclear, and recommendations are not well supported. The TICACOS [22] and Heidegger et al trials [25] suggested that EN should be supplemented with parenteral nutrition in critically ill patients. They proposed that avoiding caloric debt should result in mortality and nosocomial infection reduction. However, in both studies, the control group (not supplemented) had a low-protein delivery (53-56 g/d) compared with the intervention group (76-79 g/d), which was supplemented with parenteral nutrition. Protein delivery differences could have influenced final results.

Three studies similar to ours have been recently published. Charles et al [26] randomized 83 critically ill patients to eucaloric and hypocaloric enteral nutrition, with a high protein intake target. They found no differences in infections, mortality, blood glucose at 6 AM, and length of ICU and hospital stay. They achieved lower protein intake compared to our study (1.1 g/kg per day in both groups). Arabi et al [27] studied 894 patients with either enteral standard caloric intake or permissive underfeeding. They found no differences in mortality,

Table 3
Primary and secondary outcomes of the study

Outcome	Hypocaloric diet, n = 60	Normocaloric diet, n = 60	Mean difference	95% CI	*P*
ΔSOFA at 48 h, mean (SD)	−0.7 (2.4)	−0.9 (2.3)	0.17	(−0.7 to 1.0)	.695
ΔSOFA at 96 h, mean (SD)	−0.8 (3.1)	−1.0 (2.4)	0.22	(−0.78 to 1.22)	.669
Days of ICU stay, median (IQR)[a]	12 (7.3)	10.5 (8.0)	–	–	.4132
Days of ventilation, median (IQR)[a]	9 (8.3)	9 (8.3)	–	–	.632
Insulin requirements					
IU/day at 96 h, median (IQR)[a]	0 (0.25)	0 (14.3)	–	–	.027
Patients requiring insulin, n (%)	15 (25%)	27 (45%)	−20%	(−37% to −3%)	.022
Hyperglycemic episodes					
Total episodes, median (IQR)[a]	0 (0.56)	0.25 (1.06)	–	–	.131
Patients having at least 1 episode, n (%)	27 (45%)	33 (55%)	−10%	(−28% to 8%)	.273
28-d mortality, n (%)	18 (30%)	16 (27%)	3%	(−13% to 19%)	.685

Percentages may not sum up to 100 due to rounding. CI indicates confidence interval.
[a] Wilcoxon rank sum test performed.

infections, ICU stay, or feeding intolerance. Again, protein intake achieved was relatively low (around 70% of calculated). Finally, Petros et al [28] randomized 100 patients to receive normocaloric or hypocaloric nutrition for at least 72 hours in the ICU. They found no differences in mortality. Normocaloric patients showed higher insulin demand and gastrointestinal intolerance, whereas hypocaloric patients had more nosocomial infections. However, the latter received a lower protein intake.

A recent systematic review and meta-analysis [29] analyzed 6 studies that compared normocaloric and hypocaloric nutrition in ICU patients and found out no differences in the risk of acquired infections, hospital mortality, ICU length of stay, or ventilator-free days. However, in the 4 studies that reported protein intake, it was low in both groups.

Our trial has several differences in methodology and nutritional regimen when compared to similar trial [26–28]. First, none of our patients received parenteral nutrition. Second, our patients' protein daily intake was not only higher but also similar in both groups (1.39 and 1.42 g/kg per day), compared to the Charles et al [26] trial (1.1 g/kg per day in both groups) and the Petros et al [28] trial (<1.2 g/kg per day in the normocaloric group and <0.6 g/kg per day in the hypocaloric group). Our study focused on the acute phase (up to 7 days), followed the guidelines' recommendation of a high protein intake in critically ill patients [5], and centered exclusively on enteral nutrition.

Caloric debt has been the focus of modern clinical nutrition. These results, combined with those from our previous trial [15], suggest that high protein intake may be a fundamental target independently of caloric delivery in critically ill patients. Intensive care unit staff should then focus on preventing protein debt over caloric debt.

Limitations of our study include doubts on proper blinding of ICU staff. However, they were not informed of caloric and protein targets of enrolled patients or of the weight used for these calculations. They could potentially estimate caloric and protein delivery because infusion of EN and the number of modular protein supplements were disclosed. These data could not be withheld because they were necessary for appropriate patient care. Another important limitation regards power calculation, which was specifically calculated for ΔSOFA. Lack of statistically significant differences in other clinical end points could then be regarded as lack of statistical power, rather than absolute lack of difference. Similarities in results with comparable studies may indicate a general tendency toward similar results in many clinical end points between hypocaloric and normocaloric strategies shown here. It is worth noting that the reduction in insulin requirements in hypocaloric patients could underlie improvements in other clinical outcomes not noted because of underpowering. Lastly, the use of soy protein may be debatable due to possible low biologic value and poor tolerance. We used combined whey and isolated soy protein modules which enhance biological value. The fact that only 1 patient presented intolerance in this study reaffirms our previous positive experience in terms of tolerance of this diet in ICU patients [15].

Future research should perhaps focus on subgroups of critically ill patients. Diabetic patients were not included in this trial, and they are a challenge in clinical nutrition. No information regarding the effect of low caloric regimen is available in this population. Our finding of reduced insulin requirement could prove especially beneficial in diabetic patients, but more studies are needed to prove this point.

5. Conclusion

This study did not show differences in clinical results when a hypocaloric, hyperproteic regimen was compared with normocaloric, hyperproteic nutrition. Underpowering may be an issue for nonprimary outcomes. Hypocaloric nutrition was associated with lower insulin requirements. Current data suggest that providing high protein intake and avoiding protein debt should be a priority in ICU care. More studies are needed to support this conclusion in other subgroups of patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.05.004.

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