

Association of protein intake with the outcomes of critically ill patients: a post hoc analysis of the PermiT trial

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ABSTRACT

Background: The optimal amount of protein intake in critically ill patients is uncertain.

Objective: In this post hoc analysis of the PermiT (Permissive Underfeeding vs. Target Enteral Feeding in Adult Critically Ill Patients) trial, we tested the hypothesis that higher total protein intake was associated with lower 90-d mortality and improved protein biomarkers in critically ill patients.

Design: In this post hoc analysis of the PermiT trial, we included patients who received enteral feeding for ≥ 3 consecutive days. Using the median protein intake of the cohort as a cutoff, patients were categorized into 2 groups: a higher-protein group ($>0.80 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) and a lower-protein group ($\leq 0.80 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$). We developed a propensity score for receiving higher protein. Primary outcome was 90-d mortality. We also compared serial values of prealbumin, transferrin, 24-h urinary nitrogen, and 24-h nitrogen balance on days 1, 7, and 14.

Results: Among the 729 patients included in this analysis, the average protein intake was $0.8 \pm 0.3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ [$1.0 \pm 0.2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in the higher-protein group ($n = 365$) and $0.6 \pm 0.2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in the lower-protein group ($n = 364$); $P < 0.0001$]. There was no difference in 90-d mortality between the 2 groups [88/364 (24.2%) compared with 94/363 (25.9%), propensity score-adjusted OR: 0.80; 95% CI: 0.56, 1.16; $P = 0.24$]. Higher protein intake was associated with an increase in 24-h urea nitrogen excretion compared with lower protein intake, but without a significant change in prealbumin, transferrin, or 24-h nitrogen balance.

Conclusions: In the PermiT trial, a moderate difference in protein intake was not associated with lower mortality. Higher protein intake was associated with increased nitrogen excretion in the urine without a corresponding change in prealbumin, transferrin, or nitrogen balance. Protein intake needs to be tested in adequately powered randomized controlled trials targeting larger differences in protein intake in high-risk populations. *Am J Clin Nutr* 2018;108:988–996.

Keywords: critical illness, calories, protein catabolism, NUTRIC score, enteral feeding

INTRODUCTION

Critical illness is associated with a catabolic state and proteolysis, primarily in the skeletal muscles (1, 2). The amino acids released into the circulation are used for tissue repair and synthesis of acute phase proteins and other inflammatory mediators. The resulting protein catabolic state may be associated with immunosuppression (3), poor wound healing (4), and intensive care unit (ICU)-acquired weakness, which are associated with increased mortality and delayed recovery (5). Higher protein intake has been thought to mitigate the negative protein catabolic state by increasing the availability of exogenous amino acids. Several observational studies suggested that outcomes are improved with higher protein intake (6). Consequently, current clinical practice guidelines suggest that critically ill patients should receive higher protein intake than healthy individuals, in

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Supplemental Figure 1 and Supplemental Table 1 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: aOR, propensity score-adjusted OR; ICU, intensive care unit; NUTRIC, Nutrition Risk in the Critically Ill; PermiT, Permissive Underfeeding vs. Target Enteral Feeding in Adult Critically Ill Patients; UUN, urinary urea nitrogen.

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the range of 1.2–2.0 g · kg⁻¹ · d⁻¹ (6, 7). However, data supporting the hypothesis that higher protein intake is associated with improved clinical outcomes are limited at present. In addition, a number of studies suggest that higher protein intake may actually cause harm through inhibition of autophagy and increased ureagenesis (8–11). A substudy of the Early Parenteral Nutrition to Supplement Insufficient Enteral Nutrition in Intensive Care (EPaNIC) trial suggested that higher protein delivery in the first week of critical illness might actually be associated with delayed recovery (12). Therefore, the optimal amount of protein intake in critically ill patients remains largely unclear and is considered a high priority for research (2). It is also unclear whether protein intake should vary according to nutritional status; specifically, it is unclear whether patients at greater nutritional risk would have improved outcomes with greater protein prescription.

The discrepancy between the results of reported studies calls for further studies on protein intake in ICU patients (13, 14). The Permissive Underfeeding vs. Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial was a randomized controlled trial of restricted caloric intake compared with standard feeding while targeting the full recommended amount of protein in both groups; there was no difference in the primary outcome of mortality in the 2 groups (15). In this post hoc analysis of the PermiT trial, we tested the hypothesis that higher total protein intake may be associated with lower 90-d mortality and improved protein biomarkers in critically ill patients.

METHODS

Study design

This is a post hoc analysis of data from the PermiT trial (registered at the ISRCTN Registry as ISRCTN68144998), which was conducted in 7 tertiary-care centers in Saudi Arabia and Canada between November 2009 and September 2014. The trial was approved by each local institutional board review. Briefly, 894 patients were randomly assigned to permissive underfeeding (goal 40–60% caloric requirement) or standard feeding (goal 70–100% caloric requirement), with similar targets of protein intake (1.2–1.5 g · kg⁻¹ · d⁻¹) in both groups. The treating team selected the enteral feeding formulae. When the protein from the enteral feeding formula was insufficient, supplemental protein (Beneprotein; Nestlé Health Sciences) was added. The intervention was continued for 14 d or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition as part of palliation.

In this analysis, we included only patients who received feeding for ≥3 consecutive days from enrollment to mitigate the confounding effect of short-stay patients, who typically receive less feeding and have better outcomes. We excluded patients who had end-stage kidney disease and cirrhosis, as these conditions confound the amount of protein prescribed. Using the median protein intake of this cohort as a cutoff, the patients were categorized into 2 groups: a higher-protein group (>0.80 g · kg⁻¹ · d⁻¹) and a lower-protein group (≤0.80 g · kg⁻¹ · d⁻¹).

Outcomes

The primary endpoint was 90-d mortality. The secondary endpoints included mortality while the subject was in the hospital, mortality while the subject was in the ICU, 28-d mortality (including postdischarge 28-d mortality), and 180-d mortality (including 180-d postdischarge mortality). Tertiary outcomes included mechanical ventilation duration, ICU and hospital lengths of stay, mechanical ventilation-free days (calculated based on 90 d), ICU-free days (calculated based on 90 d), and health care-associated infections during the ICU stay. Protein biomarker outcomes included serum prealbumin, serum transferrin, 24-h urinary urea nitrogen (UUN), and 24-h nitrogen balance collected on days 1, 7, and 14. The 24-h nitrogen balance was calculated as follows: total 24-h protein intake in g/6.25 – (24-h UUN in mmol/35.7) + 4 g. These protein biomarkers were performed as part of the study procedures and the results were not used to adjust nutritional support.

Baseline nutritional risk assessment

Similar to our previously published approach, we used several measures to categorize baseline patient nutritional risk, all assessed at the time of enrollment (except for UUN, which was collected in the first 24 h after enrollment onto the trial). Each of the measures described below were used separately to categorize the subject's nutritional status. Separate analyses based on each of the characterizations were performed. Using a modified Nutrition Risk in the Critically Ill (NUTRIC) score (16), patients were considered at high nutritional risk if the NUTRIC score was 5–9 and at low nutritional risk if the NUTRIC score was 0–4. Patients were categorized according to the WHO criteria for BMI [= weight in kilograms divided by the square of the height in meters (kg/m²)] as underweight (<18.5), normal weight (18.5–24.99), overweight (25.0–29.99), obese (30.0–40), or very obese (>40) (17). Patients were categorized as having refeeding hypophosphatemia if their blood phosphate concentration was >0.70 mmol/L on day 1 but ≤0.70 mmol/L on day 2 or 3 (18). Baseline prealbumin of ≤0.10 g/L was considered as an indicator of severe nutritional risk, >0.10 and ≤0.15 g/L as mild to moderate risk, and >0.15 g/L as no risk (19, 20). Baseline serum transferrin of ≤1.0 g/L was considered as an indicator of severe nutritional risk and >1 g/L as no to moderate nutritional risk (20). Patients were categorized based on baseline 24-h UUN using the median of the cohort as the cutoff value. Patients were categorized according to baseline 24-h nitrogen balance: a negative balance (≤0) was a marker of catabolism and a positive balance (>0) was an indicator of anabolism (21).

Statistical analysis

Continuous variables are reported as means ± SDs, and categorical data are reported as numbers and percentages. Because the patient assignment into higher- and lower-protein groups was not random, we developed a propensity score model for being in the higher-protein group using the following variables, which were selected as being clinically relevant and statistically different on univariate analysis: age, sex, BMI, Acute Physiology and Chronic Health Evaluation (APACHE) II score, admission diagnostic category, traumatic brain injury, history of

diabetes, sepsis, creatinine, and randomization (to permissive underfeeding or standard feeding).

We examined the association between protein intake and different outcomes using logistic regression and linear regression analyses, with adjustment of the propensity scores. The results of the associations are reported as propensity score-adjusted ORs (aORs) or as β coefficients with 95% CIs, as appropriate.

In order to determine if baseline nutritional status (determined by NUTRIC score, BMI, phosphate, prealbumin, transferrin, 24-h UUN, 24-h nitrogen balance, and APACHE II score) modified the association of outcome with nutrition group, we entered nutritional status as a categorical variable and a nutritional status by protein group interaction in a series of analyses (one for each marker of nutritional status) and examined the *P* value of the interaction.

To test the association of protein intake with serum and urine protein markers, we compared serial values of prealbumin, transferrin, 24-h UUN, and 24-h nitrogen balance on days 1, 7, and 14 between the higher- and the lower-protein groups and between these 2 groups over time using mixed linear models. For comparisons that showed significant time-by-group difference using a mixed linear model, the 2 groups on each day were

compared using the independent Student's *t* test. Tests were 2-sided, and significance was determined at *P* < 0.05. Analyses were conducted using SAS version 9.2 (SAS Institute).

RESULTS

Patient characteristics

Of the 894 patients enrolled in the PermiT trial, 729 patients met the inclusion criteria for this subanalysis (**Supplemental Figure 1**). The average protein intake in this substudy cohort was $0.8 \pm 0.3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. There were 365 patients in the higher-protein group ($>0.80 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) and 364 in the lower-protein group ($\leq 0.80 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (**Table 1**). When adjusted to propensity scores, baseline characteristics were generally balanced.

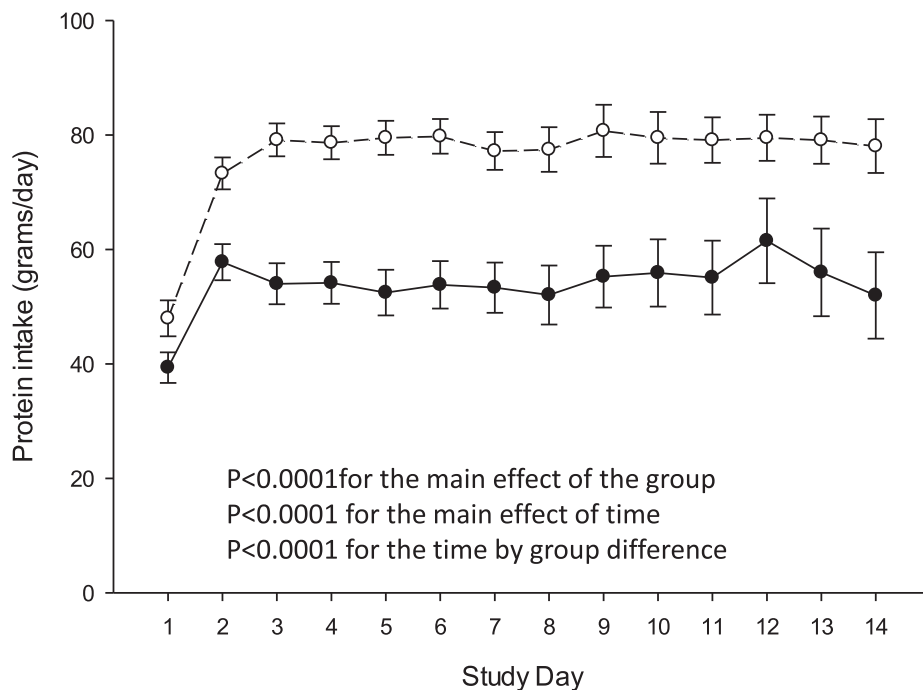
Nutritional data

The daily average protein intake in the higher-protein group was $1.0 \pm 0.2 \text{ g/kg}$ and in the lower-protein group was $0.6 \pm 0.2 \text{ g/kg}$ (*P* < 0.0001), and the difference was significant throughout

TABLE 1
Baseline characteristics of patients in the higher- and lower-protein groups¹

Variables	Higher-protein group ($>0.80 \text{ g/kg}$) (<i>n</i> = 365)	Lower-protein group ($\leq 0.80 \text{ g/kg}$) (<i>n</i> = 364)	<i>P</i> (PS-adjusted)
Age, y	47.5 ± 20.0	51.6 ± 19.3	0.98
Female sex, <i>n</i> (%)	111 (30.4)	130 (35.7)	0.99
Weight, kg	72.4 ± 17.3	88.4 ± 25.3	0.46
BMI, kg/m ²	26.1 ± 6.1	32.3 ± 9.7	0.89
Admission category, <i>n</i> (%)			0.96
Medical	207 (56.7)	232 (63.7)	
Surgical	21 (5.8)	25 (6.9)	
Nonoperative trauma	137 (37.5)	107 (29.4)	
Diabetes, <i>n</i> (%)	82 (22.5)	157 (43.1)	0.89
Sepsis, <i>n</i> (%)	97 (26.6)	116 (31.9)	0.99
Traumatic brain injury, <i>n</i> (%)	69 (18.9)	43 (11.8)	0.99
APACHE II score	20.1 ± 7.6	20.8 ± 8.5	0.99
SOFA score on day 1	9.3 ± 3.3	9.9 ± 3.3	0.02
Mechanical ventilation, <i>n</i> (%)	354 (97.0)	355 (97.5)	0.96
Vasopressor therapy, <i>n</i> (%)	208 (57.0)	200 (55.0)	0.93
Renal replacement therapy, <i>n</i> (%)	16 (4.4)	33 (9.1)	0.37
Inclusion blood glucose, mmol/L	10.1 ± 4.6	11.2 ± 5.3	0.49
Creatinine, μmol/L	108.1 ± 112.5	131.1 ± 118.4	0.99
Bilirubin, μmol/L	22.9 ± 34.0	22.0 ± 34.4	0.50
Platelets, 10 ⁹ /L	199.1 ± 126.0	222.4 ± 132.2	0.10
INR	1.3 ± 0.6	1.4 ± 0.8	0.22
PaO ₂ :FiO ₂ ratio	208.7 ± 114.1	179.1 ± 100.9	0.14
Glycated hemoglobin, %	6.9 ± 6.5	7.7 ± 8.7	0.63
C-reactive protein, mg/L	131.2 ± 81.0	128.8 ± 75.3	0.30
Albumin, g/L	27.5 ± 6.2	28.6 ± 6.8	0.03
Prealbumin, g/L	0.15 ± 0.16	0.13 ± 0.07	0.16
24-h urinary nitrogen, mmol/d	294 ± 171	322 ± 224	0.56
Transferrin, g/L	1.36 ± 0.45	1.42 ± 0.48	0.22
Hemoglobin, g/L	106 ± 22	107 ± 24	0.28

¹Values are means ± SDs except where indicated. The denominator for all percentages is the *n* for each column. APACHE II, Acute Physiology and Chronic Health Evaluation II; INR, international normalized ratio; PaO₂:FiO₂ ratio, the ratio of partial pressure of oxygen to the fraction of inspired oxygen; PS, propensity score; SOFA, Sequential Organ Failure Assessment.



Number of patients

Higher-protein	361	363	363	332	297	254	227	198	175	157	139	119	116	107
Lower-protein	363	363	365	354	340	324	310	293	270	252	234	217	205	189

FIGURE 1 The protein intake (in grams per day) in the higher-protein ($n = 365$) and lower-protein ($n = 364$) groups presented as means and 95% CIs. P values for the main effect of the group, the main effect of time, and for the time by group difference are shown.

the 14-d study period (**Figure 1**). Patients in the higher-protein group received more calories than the lower-protein group (1273 ± 452 compared with 969 ± 373 kcal/d; $P < 0.0001$) (**Table 2**).

Outcomes

There was no difference in 90-d mortality between the 2 groups [88/364 (24.2%) compared with 94/363 (25.9%); aOR: 0.80; 95% CI: 0.56, 1.16; $P = 0.24$] (**Table 3**). Similarly, there were no between-group differences in secondary or tertiary outcomes, including mechanical ventilation-free days, ICU-free days, incident renal replacement therapy, or health care-associated infections (**Supplemental Table 1**).

Nutritional protein biomarkers over time

Figure 2 depicts the serial measurements of prealbumin, transferrin, 24-h UUN, and 24-h nitrogen balance in the higher- and lower-protein groups. Prealbumin and transferrin concentrations did not differ between the 2 groups over time. The 24-h UUN increased significantly over time in the higher-protein group compared with the lower-protein group (P value for the time-by-group difference <0.0001). However, the 24-h nitrogen balance did not differ between the 2 groups over time.

Stratified analyses by nutritional risk

The 90-d mortality was not different in the patients with higher- and lower-protein intake in the subgroups with different nutritional risks (**Table 3**).

DISCUSSION

Our study shows that moderate differences in protein intake were not associated with lower mortality in critically ill patients enrolled in the PermiT trial. Higher protein intake was associated with increased nitrogen excretion in the urine without corresponding increases in nitrogen balance or serum prealbumin or transferrin concentrations, suggesting that higher protein intake might not be fully utilized to increase anabolism.

The protein requirement of a healthy adult is $\sim 0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. It has been suggested that protein intake of $1.1\text{--}1.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in critically ill patients reduces protein catabolism by 50% (**22, 23**). Hence, the commonest recommendation for protein provision in critical illness ranges between 1.2 and $2.0 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (**6, 24, 25**). In this study, the mean daily protein intake in the higher-protein group was $1.0 \pm 0.2 \text{ g/kg}$ (corresponding to $85.4\% \pm 15.4\%$ of calculated requirement) and in the lower-protein group was $0.6 \pm 0.2 \text{ g/kg}$ (corresponding to $57.2\% \pm 20.5\%$ of calculated requirement). Although the achieved protein intake was, on average, lower than the target, this is consistent with the protein intake in most nutritional studies in critically ill patients, especially when protein intake is mainly

TABLE 2Nutritional data in higher- and lower-protein groups¹

Variables	Higher-protein group (>0.80 g/kg) (n = 365)	Lower-protein group (≤0.80 g/kg) (n = 364)	P (PS-adjusted)
Calculated caloric requirement, kcal/d	1817 ± 377	1891 ± 375	0.06
Achieved daily caloric intake, kcal	1273 ± 452	969 ± 373	<0.0001
% of requirement	70 ± 19	52 ± 18	<0.0001
Caloric source, kcal			
Enteral	1187 ± 442	852 ± 374	<0.0001
Propofol	65 ± 78	72 ± 101	0.39
Dextrose	21 ± 39	42 ± 64	<0.0001
Parental nutrition	4 ± 50	6 ± 54	0.71
Average nonprotein calories, kcal/d	976 ± 427	772 ± 325	<0.0001
Calculated protein requirement, g/d	88.1 ± 22.0	87.5 ± 21.6	0.0002
Achieved protein intake, g/d	74.5 ± 19.3	49.4 ± 20.1	<0.0001
% of requirement achieved	85.4 ± 15.4	57.2 ± 20.5	<0.0001
Daily average protein intake, g · kg ⁻¹ · d ⁻¹	1.0 ± 0.2	0.6 ± 0.2	<0.0001
Protein source, g/d			
Main enteral formula	53.0 ± 21.8	35.7 ± 17.7	<0.0001
Supplemental enteral protein	21.8 ± 19.6	13.6 ± 15.0	<0.0001
Parenteral protein	0.1 ± 1.5	0.4 ± 3.8	0.19
Formulas, n (%)			
Disease-nonspecific ²	251 (68.8)	190 (52.2)	0.12
Disease-specific ³	114 (31.2)	173 (47.5)	
Duration of intervention, d	11.2 ± 3.6	8.8 ± 4.0	<0.0001
Received insulin, n (%)	154 (42.2)	198 (54.4)	0.66
Daily insulin dose, units	14.5 ± 32.7	22.5 ± 36.0	0.12
Average blood glucose during the study period, mmol/L	8.2 ± 3.2	9.1 ± 4.4	0.28

¹Values are means ± SDs except where indicated. The denominator for all percentages is the *n* for each column. PS, propensity score.

²Disease-nonspecific formulas: Osmolite, Jevity, Promote, Ensure plus, Ensure, and Jevity (1.2), Abbot Nutrition; Resource and Resource plus, Nestle Nutrition.

³Disease-specific formulas: Glucerna, Nepro, Pulmocare, Suplena, and Oxepa, Abbott Nutrition; Nutrihep, Novasource Renal, Peptamen (1.0), and Peptamen (1.2), Nestle Nutrition.

provided via the enteral route (24). An international prospective, observational cohort study in 158 adult ICUs found that the average nutritional adequacy for protein was 60.3% (site average range: 18.6–152.5%) (26).

In this study, we found that higher protein intake was associated with higher excretion of nitrogen in the urine but with no measurable increase in nitrogen balance compared with lower protein intake and no change in serum prealbumin. In one study, increased protein intake at 1.5 g · kg⁻¹ · d⁻¹ was associated with attenuation of the negative protein balance (22). In that study, when protein intake was increased from 1.1 to 1.5 g · kg⁻¹ · d⁻¹, protein loss decreased by ~50% (22). Further increase in protein intake up to 1.9 g · kg⁻¹ · d⁻¹ resulted in no further improvement in protein loss (22). Whether achieving energy balance decreases nitrogen loss or improves nitrogen balance in ICU patients is debatable (27, 28). Additionally, nitrogen balance has not been associated with mortality (29).

There are conflicting data regarding the association of protein intake and outcomes. Several studies have shown better outcomes with higher protein intake. A prospective observational cohort study found that ICU patients receiving higher protein (average of 1.5 ± 0.3 g · kg⁻¹ · d⁻¹) had a lower mortality than those who received lower protein (0.79 ± 0.29 or 1.1 ± 0.2 g · kg⁻¹ · d⁻¹), independent of energy intake (29). An observational study showed that increased protein intake was associated with reduced 60-d mortality (OR per 30 g protein received/d: 0.84; 95% CI:

0.74, 0.96) (30). Another observational study suggested that a protein intake between 1.2 and 1.5 g · kg⁻¹ · d⁻¹ was associated with better outcomes in mechanically ventilated, critically ill patients (31). In a recent large, multicenter, observational study, achieving ≥80% of prescribed protein intake was associated with increased survival and a shorter time to discharge alive from the ICU (32). In an observational cohort, there was a significant association between protein intake (as a percentage of requirement) and lower mortality (HR per percentage of requirement: 0.99; 95% CI: 0.98, 0.99; *P* = 0.018) (33). A systematic review of clinical trials that compared the metabolic or clinical effects of different protein intakes in adult critical illness concluded that a protein intake of 2.0–2.5 g · kg⁻¹ · d⁻¹ was safe and could be optimum for most critically ill patients, although the evidence was limited and of poor quality (24). Data from individual randomized controlled trials are limited. In the supplemental parenteral nutrition trial, which compared enteral nutrition with enteral nutrition plus supplemental parenteral nutrition, the latter group, which received higher protein (1.2 g · kg⁻¹ · d⁻¹), had fewer nosocomial infections (HR: 0.65; 95% CI: 0.43, 0.97; *P* = 0.03) (34). In a randomized controlled trial in 119 ICU patients requiring parenteral nutrition, patients received 0.9 and 1.1 g amino acid · kg⁻¹ · d⁻¹ over the first 7 d. The primary endpoint of grip strength at ICU discharge was not significantly different between groups, although patients who received higher amino acids had stronger grip strength, less

TABLE 3

Mortality at 90 d in higher- and lower-protein groups in the whole cohort and in subgroups of patients categorized by different nutritional assessment measures¹

	Higher-protein group (>0.80 g/kg) (n = 365)	Lower-protein group (≤0.80 g/kg) (n = 364)	aOR (95% CI)	P-interaction
All patients	88/364 (24.2)	94/363 (25.9)	0.80 (0.56, 1.16)	
NUTRIC score				0.53
Low	47/251 (18.7)	35/209 (16.8)	1.05 (0.63, 1.75)	
High	41/113 (36.3)	59/154 (38.3)	0.60 (0.33, 1.09)	
BMI, kg/m ²				0.92
<18.50	6/27 (22.2)	3/9 (33.3)	0.65 (0.12, 3.59)	
18.50–24.9	40/135 (29.6)	18/71 (25.4)	1.09 (0.56, 2.13)	
25.0–29.9	23/130 (17.7)	24/86 (27.9)	0.54 (0.27, 1.06)	
30–39.9	15/62 (24.2)	36/136 (26.5)	0.79 (0.38, 1.61)	
≥40	4/10 (40)	13/61 (20.0)	3.00 (0.68, 13.2)	
Phosphate				0.44
Hypophosphatemia on admission ²	18/113 (15.9)	21/94 (22.3)	0.64 (0.30, 1.35)	
Normal or elevated phosphate ³	44/137 (32.1)	54/180 (30.0)	0.87 (0.52, 1.48)	
Refeeding syndrome ⁴	19/98 (19.4)	13/71 (18.3)	1.12 (0.46, 2.74)	
Baseline prealbumin, g/L				0.49
<0.10	20/72 (27.8)	26/82 (31.7)	0.65 (0.29, 1.47)	
0.10–0.15	12/104 (11.5)	31/119 (26.1)	0.34 (0.16, 0.73)	
>0.15	19/85 (22.4)	18/93 (19.4)	1.10 (0.50, 2.39)	
Baseline transferrin, g/L				0.25
≤1.0	27/71 (38.0)	22/62 (35.5)	0.91 (0.39, 2.11)	
>1.0	34/218 (15.6)	52/242 (21.5)	0.59 (0.36, 0.98)	
Baseline 24-h urinary urea, mmol/d				0.76
≤266	33/132 (25.0)	36/120 (30.0)	0.83 (0.45, 1.51)	
>266	16/112 (14.3)	27/137 (19.7)	0.54 (0.26, 1.11)	
Baseline 24-h nitrogen balance				0.48
Negative	24/166 (14.5)	42/200 (21.0)	0.59 (0.33, 1.07)	
Positive	12/37 (32.4)	11/33 (33.3)	0.91 (0.30, 2.75)	
APACHE II score				0.51
≤19	23/163 (14.1)	20/157 (12.7)	0.90 (0.46, 1.78)	
>19	65/200 (32.5)	72/202 (35.6)	0.71 (0.45, 1.13)	

¹The results of multivariate analyses were adjusted to propensity scores and are reported as aORs (95% CIs). The denominator for all percentages is the *n* for each column. Results are also shown for stratified analyses based on the baseline nutritional risk categories (NUTRIC, BMI, phosphate, prealbumin, transferrin, 24-h urinary urea, and 24-h nitrogen balance) as well as APACHE I scores. NUTRIC scores range from 1 to 9; high NUTRIC score = 5–9; low NUTRIC score = 0–4. To further assess whether the associations were different among the strata, *P* values for interactions are reported. The 90-d mortality was not available for 2 patients in the studied cohort. aOR, propensity score-adjusted OR; APACHE II, Acute Physiology and Chronic Health Evaluation II; NUTRIC, Nutrition Risk in the Critically Ill.

²Hypophosphatemia on admission: ≤0.70 mmol/L.

³Normal or elevated phosphate: >0.70 mmol/L on days 1, 2, and 3.

⁴Refeeding syndrome is defined as serum phosphate concentration >0.70 mmol/L on day 1 but falling to ≤0.7 mmol/L on day 2 or 3 (refeeding hypophosphatemia).

fatigue, and greater forearm muscle thickness on ultrasound at study day 7. There was no difference between groups in mortality or length-of-stay measures (35). On the other hand, some studies have not shown better outcomes with lower protein intake. Puthuchery et al. (36) observed that muscle protein synthetic rate was depressed in the first week of ICU stay and correlated with multiorgan failure independent of nutritional load. In a post hoc analysis of the EPaNIC trial, the amount of proteins or amino acids rather than the amount of glucose appeared to explain delayed recovery with early feeding (12). These findings are consistent with observations that administering increased protein may suppress autophagy and lead to the accumulation of damaged mitochondria and toxic proteins, which may actually lead to increasing muscle weakness and impaired recovery in the early phase of critical illness (8, 9, 37). In critically ill rabbits, feed deprivation compared with early nutrition was associated with catabolism but also with functional autophagy,

better cell integrity, and protected organ function (8). In our study, higher compared with lower protein intake was associated with similar mortality, incident renal replacement, and infection rates. However, the lack of statistical significance for the observed association with 90-d mortality (aOR: 0.80; 95% CI: 0.56, 1.16) may reflect the lack of adequate power; we estimate that 2188 patients would be required to show a 20% risk reduction from a baseline mortality risk of 25–20% with a power of 80% and an α error of 0.05. In patients with a high NUTRIC score, 90-d mortality was not significantly different between patients in the higher-protein and lower-protein groups (aOR: 0.60; 95% CI: 0.33, 1.09), but again, whether significant differences would be observed with a larger sample size and with wider differences in protein intake will need to be examined in randomized controlled trials.

The results of this post hoc analysis should be interpreted taking into account its strengths and limitations. The strengths

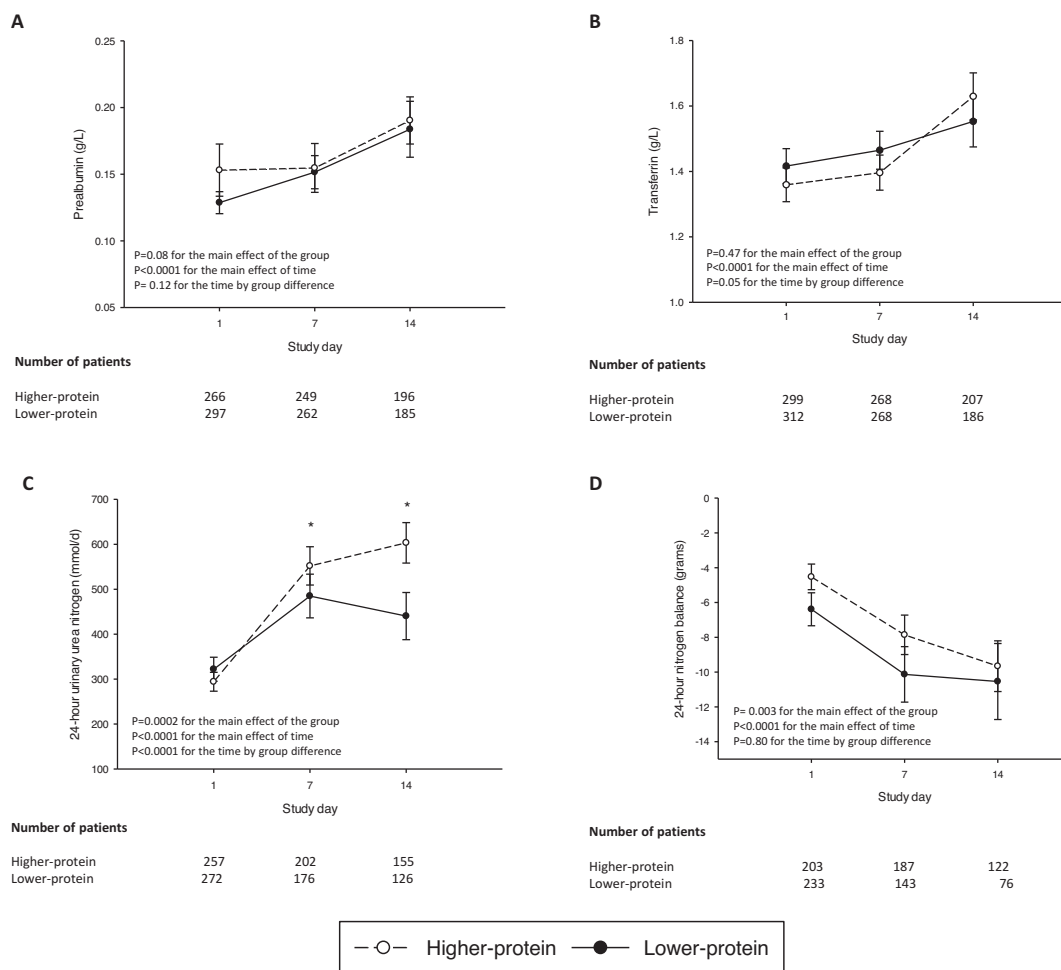


FIGURE 2 Serial measurements of prealbumin (A), transferrin (B), 24-h urinary urea nitrogen (C), and 24-h nitrogen balance (D) in the higher-protein and lower-protein groups. Values are means (95% CIs). *P* values for the main effect of the group, the main effect of time, and for the time-by-group difference using mixed linear model are shown. For comparisons that showed significant time-by-group differences using a mixed linear model, the 2 groups were compared each day using the independent Student's *t* test. **P* < 0.05.

include the multicenter design, detailed records of nutritional data, restriction to patients staying ≥ 3 d in the ICU, and the prospective data collection. The limitations include being a post hoc analysis, the observational nature, and the fact that the protein intake administered was generally lower than the recommended amount. Residual confounding cannot entirely be excluded, given the nonrandomized nature of the exposure. The difference in exposures between the 2 protein-intake groups was modest, and it remains unclear whether wider differences in protein intake would be associated with more significant differences in outcomes. Because of the power limitation of the study, which reduces the precision of treatment effect estimates, the study should be interpreted as suggestive, but not conclusive, of lack of benefit with moderate increase in protein intake. Additionally, the study may not have been powerful enough to detect differences in certain subgroups, and therefore significant associations of small treatment effects cannot be excluded. We used serum markers of protein metabolism, but we did not include assessment of muscle mass or functional status. Given the importance of the clinical question, the results of this analysis may be used to inform the design for future clinical trials that would need to be adequately

powered, should target larger differences in protein intake, and should probably focus on a high-risk population.

In conclusion, post hoc analysis of the PermiT trial showed that moderately higher protein intake was not associated with lower mortality in critically ill patients. Higher protein intake was associated with increased nitrogen excretion in the urine without a corresponding increase in nitrogen balance, suggesting that only a fraction of the protein intake may be used in protein anabolism.

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Hospital, Toronto: Sangeeta Mehta, Kristen MacEachern, Marnie Jakob, Sumesh Shah, Brittany Giacomino, and Alan Kraguljac; Health Sciences Center, Manitoba: Anand Kumar, Sevita Bector, Clinical Dietician, and Wendy Janz; University of Alberta Hospital, Edmonton: Sean M Bagshaw, Sonya Hoag, Nadia Baig, Miranda Wong, Adele Delgado, and Leanne Melusa.

The authors' responsibilities were as follows—YMA: conceived the design of the study, made an analytical plan, acquired data, drafted the manuscript, and critically revised the manuscript for important intellectual content; HMA-D, SM, SHH, GJ, LM, OS, MHS, MS, LA, AK, SMB, and ASA: acquired data and critically revised the manuscript for important intellectual content; HMT: performed statistical analyses and critically revised the manuscript for important intellectual content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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