ORIGINAL ARTICLE

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

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ABSTRACT

BACKGROUND

The appropriate caloric goal for critically ill adults is unclear. We evaluated the effect of restriction of nonprotein calories (permissive underfeeding), as compared with standard enteral feeding, on 90-day mortality among critically ill adults, with maintenance of the full recommended amount of protein in both groups.

METHODS

At seven centers, we randomly assigned 894 critically ill adults with a medical, surgical, or trauma admission category to permissive underfeeding (40 to 60% of calculated caloric requirements) or standard enteral feeding (70 to 100%) for up to 14 days while maintaining a similar protein intake in the two groups. The primary outcome was 90-day mortality.

RESULTS

Baseline characteristics were similar in the two groups; 96.8% of the patients were receiving mechanical ventilation. During the intervention period, the permissive-underfeeding group received fewer mean (±SD) calories than did the standard-feeding group (835±297 kcal per day vs. 1299±467 kcal per day, P<0.001; 46±14% vs. 71±22% of caloric requirements, P<0.001). Protein intake was similar in the two groups (57±24 g per day and 59±25 g per day, respectively; P=0.29). The 90-day mortality was similar: 121 of 445 patients (27.2%) in the permissive-underfeeding group and 127 of 440 patients (28.9%) in the standard-feeding group died (relative risk with permissive underfeeding, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P=0.58). No serious adverse events were reported; there were no significant between-group differences with respect to feeding intolerance, diarrhea, infections acquired in the intensive care unit (ICU), or ICU or hospital length of stay.

CONCLUSIONS

Enteral feeding to deliver a moderate amount of nonprotein calories to critically ill adults was not associated with lower mortality than that associated with planned delivery of a full amount of nonprotein calories. (Funded by the King Abdullah International Medical Research Center; PermiT Current Controlled Trials number, ISRCTN68144998.)

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Nutritional support is an essential component of the care of critically ill adults.[1] Achieving caloric targets has been recommended with the premise that attenuating malnutrition and protein catabolism, which are associated with increased morbidity and mortality, will improve outcomes.[2] Observational studies examining various doses of enteral feeding have yielded conflicting results.[3-7] Two cluster-randomized, controlled trials comparing higher enteral nutritional delivery with usual care in critically ill patients showed no reduction in mortality with the higher enteral nutrition.[8,9] Augmenting energy intake with early parenteral nutrition has been shown to result in no change in mortality[10] and in an increased time to discharge from the intensive care unit (ICU).[11]

Conversely, caloric restriction may be beneficial; it has been shown to prolong life span in several species,[12-14] promote mammalian cell survival,[15] and improve longevity biomarkers in humans,[16] possibly through its effects on metabolic, hormonal, and inflammatory pathways.[12,14,16] Among critically ill patients receiving parenteral nutrition, lower morbidity was observed with hypocaloric nutrition than with standard nutritional support.[17,18] Two randomized, controlled trials involving patients with acute lung injury or acute respiratory failure evaluated minimal or trophic enteral feeding (15 to 25% of estimated caloric requirements) with no protein supplementation for up to 6 days and showed outcomes that were similar to those with standard enteral feeding.[19,20] Whether restricting nonprotein calories (permissive underfeeding) in conjunction with meeting full protein requirements improves outcomes is unclear, although reviews of the existing evidence recommend a level of protein intake during early critical illness that is sufficient to satisfy full protein requirements,[21] regardless of the simultaneous caloric intake.[22] A study in rats showed that protein refeeding, but not glucose refeeding, restores mitochondrial function that has been reduced by malnutrition.[23] Therefore, it has been suggested that caloric restriction may be beneficial only if adequate dietary protein is provided.[24]

Such findings prompt the question of whether moderate caloric restriction while protein intake is preserved would improve the outcomes in critically ill adults. In a single-center, randomized, controlled trial of moderate caloric intake (60 to 70% of the estimated caloric requirement) versus standard caloric intake (90 to 100%), with maintenance of the full targeted protein intake in both groups, we observed that the lower caloric intake was associated with a reduction in in-hospital mortality, which was a secondary end point.[25] We hypothesized that a permissive-underfeeding strategy that restricts nonprotein calories but preserves protein intake, as compared with a standard feeding strategy, would reduce 90-day mortality among critically ill adults.

Methods

Study Design

The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial was an unblinded, pragmatic, randomized, controlled trial conducted at seven tertiary care centers in Saudi Arabia and Canada between November 2009 and September 2014. The institutional review board at each participating center approved the study. Written informed consent was obtained from all the patients or their legal representatives. The study was sponsored by the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, and the investigators designed, managed, and analyzed the study independently. Patients were eligible for the trial if they were fed enterally within 48 hours after ICU admission. Inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study protocol is also available at NEJM.org.

Interventions

Enrolled patients were randomly assigned to the permissive-underfeeding group or the standard-feeding group with the use of opaque, sealed, sequentially numbered envelopes. The randomization list was computer-generated. Randomization was performed in random permuted blocks and was stratified according to center. The feeding strategy was unblinded because of the need for adjustment of the nutritional support according to feeding tolerance and gastric residual volumes. ICU dietitians estimated patients' standard caloric requirements using the equation developed by investigators at Pennsylvania State

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University (the Penn State equation) for mechanically ventilated patients who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 30 and using the 1992 Ireton-Jones equation for mechanically ventilated patients who had a BMI of 30 or higher and for spontaneously breathing patients (Table S2 in the Supplementary Appendix).[26-28]

The caloric goal was 40 to 60% of caloric requirements in the permissive-underfeeding group and 70 to 100% of caloric requirements in the standard-feeding group. We set the caloric goal in the permissive-underfeeding group at a lower level than we did in the earlier trial,[25] with the premise that a larger separation in caloric intake between the two groups would lead to a larger treatment effect. The assigned intervention was continued for up to 14 days or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition as part of palliation. Participating centers used their own protocols to guide delivery of enteral feeding. Daily caloric targets were established to achieve the prescribed nutritional delivery, and if caloric intake was below the target on a given day, intake was increased the following day to compensate. Calculation of actual intake included calories received from propofol, intravenous dextrose, and parenteral nutrition. Additional details of the interventions have been published previously[29] and are also provided in the Supplementary Appendix.

COINTERVENTIONS

Protein requirements were calculated at 1.2 to 1.5 g per kilogram of body weight per day, in accordance with clinical practice guidelines.[1] To ensure that enteral protein and volume delivery in the permissive-underfeeding group would be similar to those in the standard-feeding group, the permissive-underfeeding group received additional protein (Beneprotein, Nestlé Nutrition) and normal saline or water at a dose of 2 ml per kilogram every 4 hours unless otherwise specified by the clinical team.[25] The study protocol provided suggestions on the selection of enteral formulas on the basis of published guidelines[1]; however, the decision was left to the clinical team (Table S3 in the Supplementary Appendix). Study centers used their own insulin protocols, with a target blood glucose level of 4.4 to 10 mmol per liter (80 to 180 mg per deciliter) in both groups. The study protocol recommended daily enteral multivitamins for all patients (Table S4 in the Supplementary Appendix). All other cointerventions were left to the discretion of the treating team.

DATA COLLECTION

At baseline, we collected data on patient demographics, diabetes history, admission category (medical, surgical, or trauma), Acute Physiology and Chronic Health Evaluation (APACHE) II score,[30] Sequential Organ Failure Assessment (SOFA) score,[31] and use of mechanical ventilation, vasopressors, or renal-replacement therapy. We also measured levels of blood glucose, creatinine, bilirubin, hemoglobin, platelets, glycated hemoglobin, C-reactive protein, serum lipids (triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein), albumin, prealbumin, and transferrin. In addition, we assessed the international normalized ratio, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and 24-hour urinary nitrogen excretion.

Daily during the intervention period, we obtained nutritional data (total calories and calories from enteral feeding, propofol, intravenous dextrose, and parenteral nutrition), laboratory data (levels of blood glucose, hemoglobin, creatinine, potassium, magnesium, and phosphate), and information on insulin dose, fluid intake and output, use of prokinetic agents, stool frequency and consistency, and duration of interruption in feeding. On a weekly basis, we recorded body weight; levels of lipids, prealbumin, and transferrin; and 24-hour urinary nitrogen excretion. We also recorded the use of selected medications during the ICU stay. Information on the monitoring of serious adverse events is provided in Table S5 in the Supplementary Appendix.

OUTCOMES

The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality in the ICU, 28-day mortality, in-hospital mortality, 180-day mortality, and serial SOFA scores. Tertiary outcomes included days free from mechanical ventilation, ICU-free days, hospital length of stay, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusions of packed

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red cells, ICU-associated infections (documented by the research coordinator according to published definitions[32]), feeding intolerance (vomiting, abdominal distention, or a gastric residual volume of more than 200 ml), and diarrhea.

STATISTICAL ANALYSIS

On the basis of the findings of our previous randomized, controlled trial,[25] we estimated that permissive underfeeding would be associated with an absolute risk reduction in mortality of 8 percentage points. Assuming an estimated 90-day mortality of 25% with standard feeding, we calculated that enrollment of 432 patients in each group would give the study 80% power to detect the 8-percentage-point difference in mortality. With an estimated 3% loss to follow-up, the final calculated sample size was 892 patients. The primary outcome was compared between the two groups with use of the chi-square test; the results were reported as relative risks and 95% confidence intervals. We performed an unadjusted Cox proportional-hazards analysis as well as an analysis adjusted for BMI, APACHE II score, and baseline vasopressor use, with the results reported as hazard ratios and 95% confidence intervals.

For serial measurements, we tested the change over time and the difference between the two groups over time using a repeated-measures analysis of variance, with no imputation for missing values. The primary outcome was compared between the two study groups in the following prespecified subgroups: nonsurgical patients versus surgical patients, patients with diabetes versus patients without diabetes, patients with an APACHE II score of 18 or lower versus those with a score higher than 18, patients with a specific admission diagnosis (severe sepsis or traumatic brain injury) versus patients without either of those diagnoses, patients using vasopressors at baseline versus those not using them, and patients with a blood glucose level of no more than the median value at randomization versus those with a level higher than the median value. Tests were two-sided and at the 5% significance level. For serial measurements, we used a Bonferroni correction to account for multiple comparisons. To account for alpha spending by the interim analyses, we used the O'Brien–Fleming method. A final P value of less than 0.045 was considered to indicate statistical significance for the primary outcome. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

A total of 894 patients underwent randomization (Fig. S1 in the Supplementary Appendix). At baseline, the two groups were similar with respect to demographic, physiological, and nutritional characteristics (Table 1, and Table S6 in the Supplementary Appendix). A total of 96.8% of the patients were receiving mechanical ventilation.

INTERVENTIONS AND COINTERVENTIONS

Throughout the intervention period, patients in the permissive-underfeeding group had a lower caloric intake than did patients in the standard-feeding group (Table 2 and Fig. 1, and Fig. S2 in the Supplementary Appendix); the average caloric intake during the intervention period was 46±14% versus 71±22% of daily requirements (P<0.001). Protein intake and the enteral formulas used did not differ significantly between the two groups (Table 2, and Table S7 and Fig. S3 in the Supplementary Appendix). Patients in the permissive-underfeeding group had lower glucose levels, required less insulin, and had lower daily fluid balance on several study days (Table 2 and Fig. 1). Other cointerventions and nutrition-related data are shown in Table 2 and Figure 1, and Figure S4 in the Supplementary Appendix.

OUTCOMES

Mortality

The 90-day mortality (primary end point) was 27.2% (121 of 445 patients) in the permissive-underfeeding group and 28.9% (127 of 440 patients) in the standard-feeding group (relative risk, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P=0.58) (Table 3). Unadjusted and adjusted hazard ratios were also nonsignificant (unadjusted hazard ratio, 0.92; 95% CI, 0.72 to 1.18; P=0.51; adjusted hazard ratio, 0.91; 95% CI, 0.71 to 1.17; P=0.48). Similarly, there were no significant between-group differences with respect to mortality in the ICU, in-hospital mortality, 28-day mortality, or 180-day mortality. Kaplan–Meier survival estimates showed no significant differ-

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Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)
Age — yr	50.2±19.5	50.9±19.4
Female sex — no. (%)	156 (34.8)	164 (36.8)
Body-mass index†	29.0±8.2	29.7±8.8
Diabetes — no. (%)	159 (35.5)	153 (34.3)
Admission category — no. (%)		
Medical	336 (75.0)	335 (75.1)
Surgical	19 (4.2)	12 (2.7)
Nonoperative trauma	93 (20.8)	99 (22.2)
Severe sepsis at admission — no. (%)	159 (35.5)	133 (29.8)
Traumatic brain injury — no. (%)	55 (12.3)	63 (14.1)
APACHE II score‡	21.0±7.9	21.0±8.2
SOFA score§	9.9±3.5	9.8±3.5
Mechanical ventilation — no. (%)	436 (97.3)	429 (96.2)
Vasopressor therapy — no. (%)	255 (56.9)	243 (54.5)
Glycated hemoglobin — mmol/liter	0.07±0.06	0.07±0.08
C-reactive protein — mg/liter	131±80	125±82
Serum lipid levels — mmol/liter		
Triglycerides	1.56±1.07	1.58±1.17
Total cholesterol	2.66±1.07	2.77±0.98
Low-density lipoprotein	1.29±0.78	1.34±0.72
High-density lipoprotein	0.59±0.33	0.64±0.40
Albumin — g/liter	28±7	28±6
Prealbumin — g/liter	0.15±0.13	0.14±0.12
Transferrin — g/liter	1.36±0.49	1.38±0.50
24-hour urinary nitrogen excretion — mmol	284±176	303±219
Time from eligibility to randomization — hr	8.3±11.6	7.9±12.3

* Plus–minus values are means ±SD. There were no significant between-group differences. Data on laboratory values were not available for some patients; the numbers of patients with available data in the permissive-underfeeding group and the standard-feeding group, respectively, were as follows: glycated hemoglobin, 268 patients and 284 patients; C-reactive protein, 357 patients and 360 patients; triglycerides, 375 patients and 376 patients; total cholesterol, 373 patients and 372 patients; low-density lipoprotein, 366 patients and 363 patients; high-density lipoprotein, 374 patients and 375 patients; prealbumin, 334 patients and 341 patients; transferrin, 359 patients and 361 patients; and 24-hour urinary nitrogen excretion, 305 patients and 292 patients.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease.
§ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure.

ence in the probability of survival between the two groups (P=0.43 by the log-rank test) (Fig. 2).

Other End Points

Serial SOFA scores, nitrogen balance, body weight, and levels of C-reactive protein, prealbumin, creatinine, bilirubin, partial pressure of arterial carbon dioxide, hemoglobin, lipids, potassium, magnesium, phosphate, transferrin, and urinary nitrogen excretion did not differ significantly between the two groups (Fig. 1, and Fig. S5 through S10 in the Supplementary Appendix). The number of days free from mechanical ventilation and the number of ICU-free

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Table 2. Study Interventions and Cointerventions.*

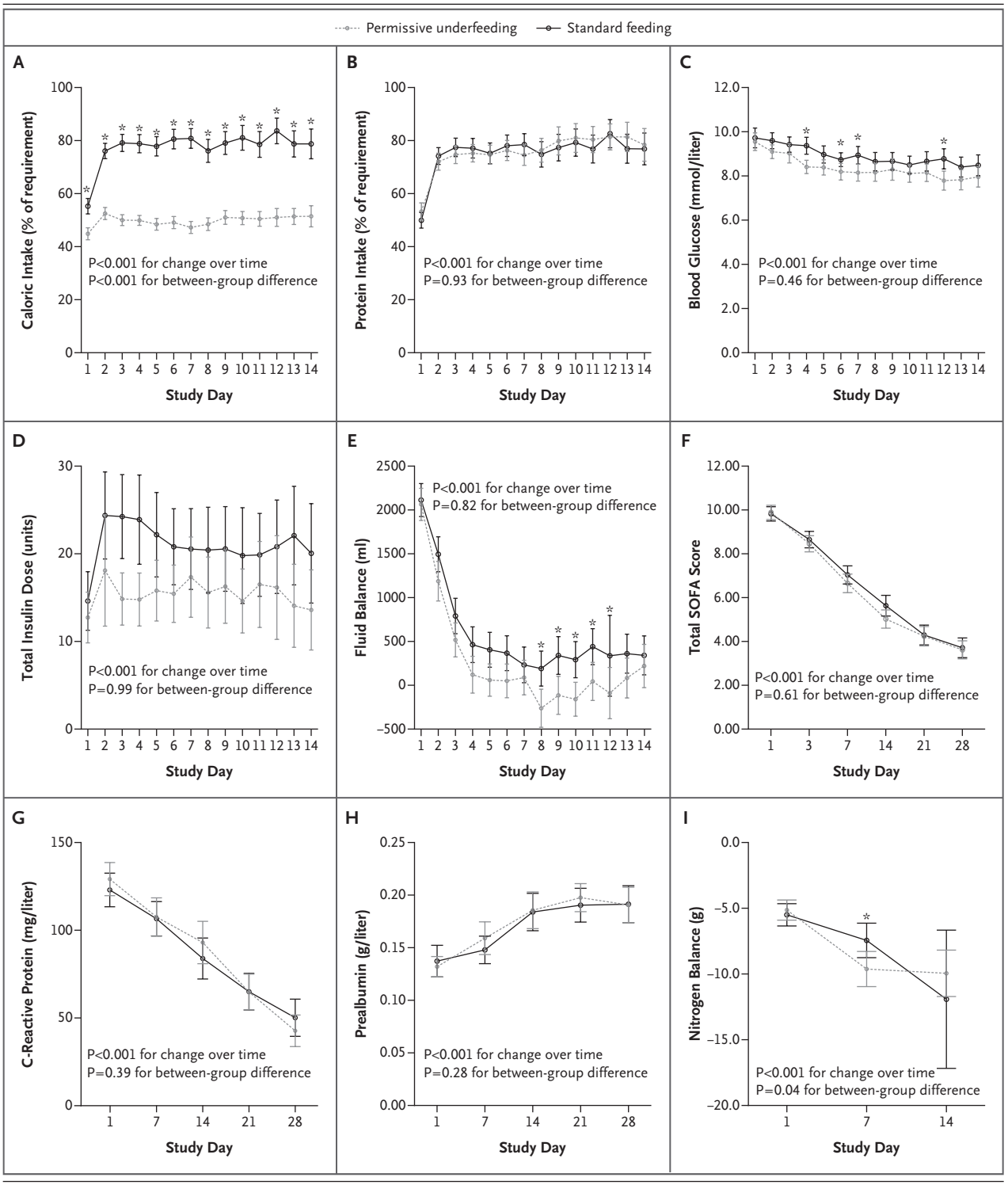
Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)	P Value
Calculated caloric requirement — kcal/day	1822±377	1842±370	0.51†
Caloric target for the trial — kcal/day	1036±262	1826±375	<0.001†
Daily caloric intake for duration of intervention			
No. of kilocalories	835±297	1299±467	<0.001‡
Percent of requirement	46±14	71±22	<0.001†
Caloric source for duration of intervention — kcal/day			
Enteral	740±294	1198±470	<0.001‡
Propofol	63±88	65±89	0.84†
Intravenous dextrose	32±59	35±60	0.23†
Parenteral nutrition	3±32	5±59	0.38†
Calculated protein requirement — g/day	85±21	88±23	0.18†
Daily protein intake for duration of intervention			
No. of grams	57±24	59±25	0.29†
Percent of requirement	68±24	69±25	0.56†
Protein source — g/day			
Main enteral formula	30±13	54±22	<0.001†
Supplemental enteral protein	27±16	6±10	<0.001†
Parenteral protein	0.2±2.6	0.2±2.7	0.79†
Duration of intervention — days	9.1±4.6	9.4±4.4	0.36†
Cointerventions during study period			
Insulin			
Use — no. (%)	205 (45.8)	235 (52.7)	0.04
Dose — units/day	15±27	22±40	0.02†
Enteral formulas on day 1 — no./total no. (%)§			
Without a specific disease indication	263/441 (59.6)	240/443 (54.2)	0.10
With a specific disease indication	178/441 (40.4)	203/443 (45.8)	
Prokinetics — no. (%)¶	120 (26.8)	127 (28.5)	0.57
Blood glucose — mmol/liter	9.1±5.3	9.4±5.0	0.04†
Fluid balance — ml/day	490±1408	688±1196	<0.001†

* Plus–minus values are means ±SD. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.
† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.
‡ P values were calculated with the use of the independent Student's t-test.
§ Information on formulas with a specific disease indication and those without a specific disease indication is provided in Tables S3 and S7 in the Supplementary Appendix.
¶ Prokinetics included metoclopramide, erythromycin, domperidone, and any combination of these.

Figure 1 (next page). Serial Measurements of the Intervention, Cointerventions, and Selected Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.

The values shown are means; I bars indicate 95% confidence intervals. Asterisks denote statistical significance, after Bonferroni correction, for the difference between the two groups on each day, with the use of the independent Student's t-test (for daily caloric intake) and Wilcoxon–Mann–Whitney test (for all other variables). P values for the change over time for both groups combined and for the difference between the two groups over time were calculated with the use of repeated-measures analysis of variance. Total scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Nitrogen balance was calculated as [total protein intake in grams÷6.25]−[(urinary nitrogen excretion in millimoles÷35.7)+4 g]. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.

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days did not differ significantly between the two groups (Table 3, and Table S8 in the Supplementary Appendix). In addition, there were no significant between-group differences with respect to hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusion of packed red cells, ICU-acquired infections, diarrhea, or feeding intolerance. Post hoc analysis showed

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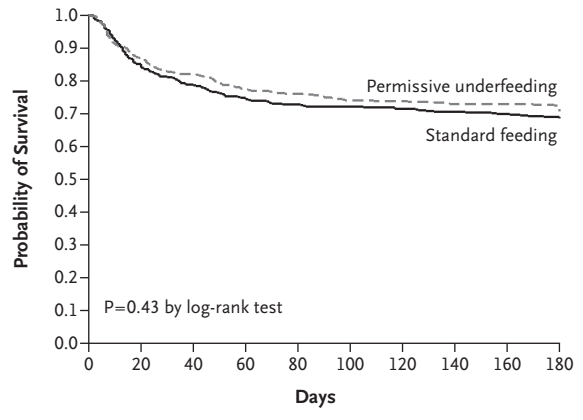
Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.*

Outcome	Permissive Underfeeding (N=448)	Standard Feeding (N=446)	Relative Risk (95% CI)	P Value
Death by 90 days — no./total no. (%)	121/445 (27.2)	127/440 (28.9)	0.94 (0.76–1.16)	0.58
Death in the ICU — no. (%)	72 (16.1)	85 (19.1)	0.84 (0.63–1.12)	0.24
Death by 28 days — no./total no. (%)	93/447 (20.8)	97/444 (21.8)	0.95 (0.74–1.23)	0.7
Death in the hospital — no./total no. (%)	108/447 (24.2)	123/445 (27.6)	0.87 (0.70–1.09)	0.24
Death by 180 days — no./total no. (%)	131/438 (29.9)	140/436 (32.1)	0.93 (0.76–1.14)	0.48
Duration of mechanical ventilation — days				
Median	9	10		0.49†
Interquartile range	5–15	5–16		
Days free from mechanical ventilation				
Median	77	75		0.48†
Interquartile range	0–84	0–84		
ICU length of stay — days				
Median	13	13		0.46†
Interquartile range	8–21	8–20		
ICU-free days				
Median	72	71		0.28†
Interquartile range	0–81	0–79		
Hospital length of stay — days				
Median	28	30		0.24†
Interquartile range	15–54	14–63		
Hypoglycemia — no. (%)	6 (1.3)	7 (1.6)	0.85 (0.29–2.52)	0.77
Hypokalemia — no. (%)	101 (22.5)	91 (20.4)	1.10 (0.86–1.42)	0.44
Hypomagnesemia — no. (%)	127 (28.3)	131 (29.4)	0.97 (0.79–1.19)	0.74
Hypophosphatemia — no. (%)	267 (59.6)	261 (58.5)	1.01 (0.91–1.14)	0.74
Transfusion of packed red cells — no. (%)	141 (31.5)	142 (31.8)	0.99 (0.82–1.20)	0.91
Incident renal-replacement therapy — no./total no. (%)	29/406 (7.1)	45/396 (11.4)	0.63 (0.40–0.98)	0.04
ICU-associated infection — no. (%)	161 (35.9)	169 (37.9)	0.95 (0.80–1.13)	0.54
Urinary tract infection — no. (%)	45 (10.0)	48 (10.8)	0.93 (0.64–1.37)	0.73
Catheter-related infection — no. (%)	11 (2.5)	19 (4.3)	0.58 (0.28–1.20)	0.13
Ventilator-associated pneumonia — no. (%)	81 (18.1)	90 (20.2)	0.90 (0.68–1.17)	0.43
ICU-associated severe sepsis or septic shock — no. (%)	61 (13.6)	58 (13.0)	1.05 (0.75–1.46)	0.79
Feeding intolerance — no. (%)	67 (15.0)	79 (17.7)	0.84 (0.63–1.14)	0.26
Diarrhea — no. (%)	97 (21.7)	117 (26.2)	0.83 (0.65–1.04)	0.11

* The number of days free from mechanical ventilation and the number of intensive care unit (ICU)–free days were calculated for the first 90 study days and were considered to be 0 for patients who died on or before day 90. Hypoglycemia was defined as a blood glucose level of less than 2.2 mmol per liter (40 mg per deciliter), hypokalemia as a potassium level of less than 2.8 mmol per liter, hypomagnesemia as a magnesium level of less than 0.60 mmol per liter, and hypophosphatemia as a phosphate level of less than 0.70 mmol per liter. Feeding intolerance was defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml. Diarrhea was defined as three or more loose or liquid stools per day for 2 consecutive days.

† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.

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No. at Risk

Standard feeding	446	380	352	334	325	322	319	315	312	308
Permissive underfeeding	448	390	368	346	340	331	330	326	326	324

Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.

that incident renal-replacement therapy was required less frequently in the permissive-underfeeding group than in the standard-feeding group (29 of 406 patients [7.1%] vs. 45 of 396 patients [11.4%]; relative risk, 0.63; 95% CI, 0.40 to 0.98; P=0.04). No serious adverse events were reported.

Prespecified Subgroup Analyses

There were no significant differences in 90-day mortality between the two study groups in any of the prespecified subgroups (Table S9 in the Supplementary Appendix). Tests of interactions were not significant for any of the subgroups.

DISCUSSION

In our study, a strategy of enteral feeding for critically ill adults in which patients received a moderate amount of nonprotein calories (40 to 60% of estimated caloric requirements), along with the full recommended amount of protein, had no significant effect on mortality, as compared with a strategy in which patients received 70 to 100% of estimated caloric requirements. These findings are similar to those of two previous randomized, controlled trials that evaluated minimal or trophic feeding (15 to 25% of caloric requirements for up to 6 days) in patients with acute lung injury or acute respiratory failure.[19,20]

Our trial has several important differences from the two earlier trials. First, the degree of caloric restriction in our trial was more moderate but the duration was more prolonged. Second, we administered supplemental protein in the permissive-underfeeding group, thus eliminating the confounding effect of differential and reduced protein intake. Third, we administered enteral normal saline or water to minimize the differences in delivered enteral volume, which may explain the lack of difference in the incidence of feeding intolerance between the study groups in our trial, a difference that was observed in the other two trials. Fourth, we estimated caloric requirements as total calories and not, as in the other two studies, as nonprotein calories. Although there is no evidence to support the superiority of our approach, we assumed that in the catabolic state of our severely ill patients, protein does contribute to energy requirements. Most commercial formulas list protein as a caloric component, accounting for 15 to 20% of calories (Table S3 in the Supplementary Appendix); therefore, not including calories from protein may lead to overfeeding.[33] Despite these differences, however, the collective results of our study and the two previous trials add to a growing body of research that suggests that standard feeding goals in critically ill patients do not improve clinical outcomes.

Permissive underfeeding was associated with lower blood glucose levels and reduced insulin requirements, findings that are consistent with those of other studies.[20,25] Our study does not support the premise that higher caloric intake attenuates protein catabolism in critically ill patients, because the two groups had similar clinical indexes of protein status, including nitrogen balance and levels of prealbumin, transferrin, and urinary nitrogen excretion. However, the limitations of these indexes in assessing protein status in ICU patients must be noted.[21] Prealbumin and transferrin levels are influenced by nonnutritional factors such as the level of inflammation, fluid status, and iron depletion. Nitrogen balance studies that are based on the measurement of urinary nitrogen excretion are subject to day-to-day variation and do not take into account nonurinary nitrogen losses such as those that occur as a result of diarrhea or fistulas.[21] We also found no significant between-group difference with respect to ICU-acquired infections, a finding that is consistent with the results of other studies.[19,20,25,34]

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Could caloric intake matter in certain subpopulations? One randomized, controlled trial involving 82 patients with traumatic brain injury showed better 3-month neurologic outcomes with a higher caloric intake but no significant differences in 6-month outcomes or mortality.[35] Similarly, we found no effect of feeding strategy on mortality among 118 patients with traumatic brain injury. The lack of significance in tests of interaction suggests that permissive underfeeding, as compared with standard feeding, has no differential effect in prespecified subgroups. However, some of these subgroup analyses may have been underpowered owing to the small size of the subgroup.

The lower requirement for incident renal-replacement therapy in the permissive-underfeeding group was a finding in a post hoc analysis and should therefore be interpreted cautiously. However, our finding supports the notion that higher caloric intake may be associated with kidney injury. Caloric restriction has been shown to be renoprotective in animal models of acute kidney injury,[36-38] through several mechanisms, including improved insulin sensitivity.[38] In contrast to our study, previous randomized, controlled trials did not show significant differences in the rates of renal-replacement therapy or in the number of days free from renal failure between patients assigned to caloric restriction and those assigned to full caloric intake.[19,20,25] However, those studies varied in the degree and duration of caloric restriction,[28,29] and some may have been underpowered.[25,39] Reductions in the rate of acute renal impairment and in the rate of the need for renal-replacement therapy were reported with intensive insulin therapy as compared with standard insulin therapy,[40] which suggests that hyperglycemia may contribute to kidney injury. A higher fluid balance in the standard-feeding group may correlate with the observed higher requirement for renal-replacement therapy. Clinical practice guidelines recommend standard caloric and protein intake in patients with acute kidney injury and increasing protein intake during renal-replacement therapy,[1] but further research is required.

Strengths of this study include the multicenter design and the pragmatic inclusion of critically ill adults with a medical, surgical, or trauma admission category; these features increase the generalizability of the results. The inclusion of patients in whom enteral feeding was initiated early during critical illness avoided the confounding effect of the timing of feeding.

The study also had limitations. First, only 14% of the patients who were admitted to the ICU and screened were included in the study; therefore, the results may not be generalizable to other patients, such as those in whom enteral feeding was initiated late. Second, the target caloric intake was not reached in some patients, particularly in the standard-feeding group. This is not unusual in critically ill patients, given that feeding intolerance and feeding interruptions are common. Nevertheless, there was significant separation in caloric intake between the two groups. Third, blinding of the intervention was not possible, but important nutritional cointerventions were standardized and the primary outcome was objective. Fourth, the duration of intervention in our study was fixed; therefore, the effect of permissive underfeeding for a duration that is individualized on the basis of the critical illness remains to be studied. Fifth, we did not monitor adherence to multivitamin supplementation and did not have a formal adjudication process for the secondary outcome of infections. Finally, our study was powered to detect an absolute risk reduction of 8 percentage points in 90-day mortality; thus, we cannot rule out a smaller treatment effect.

In conclusion, a strategy of enteral feeding to provide a moderate amount of calories to critically ill adults in the presence of full protein intake was not associated with lower mortality than a strategy aimed at providing a full amount of calories.

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REFERENCES

1. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. Crit Care Med 2009;37:1757-61.
2. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27:5-15.
3. Arabi YM, Haddad SH, Tamim HM, et al. Near-target caloric intake in critically ill medical-surgical patients is associated with adverse outcomes. JPEN J Parenter Enteral Nutr 2010;34:280-8.
4. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 2004;32:350-7.
5. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest 2003;124:297-305.
6. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition 2002;18:241-6.
7. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! Crit Care Med 2011;39:2619-26.
8. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ 2004;170:197-204.
9. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 2008;300:2731-41.
10. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130-8.
11. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.
12. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun 2014;5:3557.
13. Lin SJ, Kaeberlein M, Andalis AA, et al. Calorie restriction extends Saccharomyces cerevisiae lifespan by increasing respiration. Nature 2002;418:344-8.
14. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003;78:361-9.
15. Cohen HY, Miller C, Bitterman KJ, et al. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 2004;305:390-2.
16. Heilbronn LK, de Jonge L, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA 2006;295:1539-48.
17. Ahrens CL, Barletta JF, Kanji S, et al. Effect of low-calorie parenteral nutrition on the incidence and severity of hyperglycemia in surgical patients: a randomized, controlled trial. Crit Care Med 2005;33:2507-12.
18. McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications — a randomized clinical trial. Crit Care Med 2000;28:3606-11.
19. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 2011;39:967-74.
20. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307:795-803.
21. Weijs P, Cynober L, DeLegge M, Kreymann G, Wernerman J, Wolfe RR. Proteins and amino acids are fundamental to optimal nutrition support in critically ill patients. Crit Care 2014;18:591.
22. Singer P, Hiesmayr M, Biolo G, et al. Pragmatic approach to nutrition in the ICU: expert opinion regarding which calorie protein target. Clin Nutr 2014;33:246-51.
23. Briet F, Jeejeebhoy KN. Effect of hypoenergetic feeding and refeeding on muscle and mononuclear cell activities of mitochondrial complexes I–IV in enterally fed rats. Am J Clin Nutr 2001;73:975-83.
24. Boitano M. Hypocaloric feeding of the critically ill. Nutr Clin Pract 2006;21:617-22.
25. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr 2011;93:569-77.
26. Frankenfield D, Smith JS, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. JPEN J Parenter Enteral Nutr 2004;28:259-64.
27. Ireton-Jones CS, Turner WW Jr, Liepa GU, Baxter CR. Equations for the estimation of energy expenditures in patients with burns with special reference to ventilatory status. J Burn Care Rehabil 1992;13:330-3.
28. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. Respir Care 2009;54:509-21.
29. Arabi YM, Haddad SH, Aldawood AS, et al. Permissive underfeeding versus target enteral feeding in adult critically ill patients (PermiT Trial): a study protocol of a multicenter randomized controlled trial. Trials 2012;13:191.
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
31. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998;26:1793-800.
32. CDC/NHSN surveillance definition of healthcare-associated infections. Atlanta: Centers for Disease Control and Prevention, April 2015 (http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf).
33. Klein JA. Nonprotein vs total calories — what are most clinicians using? Nutr Clin Pract 1996;11:206.
34. Charles EJ, Petroze RT, Metzger R, et al. Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. Am J Clin Nutr 2014;100:1337-43.
35. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 1999;27:2525-31.
36. Lempiäinen J, Finckenberg P, Mervaala EE, Sankari S, Levijoki J, Mervaala EM. Caloric restriction ameliorates kidney ischaemia/reperfusion injury through PGC-1α-eNOS pathway and enhanced autophagy. Acta Physiol (Oxf) 2013;208:410-21.
37. Ning YC, Cai GY, Zhuo L, et al. Beneficial effects of short-term calorie restriction against cisplatin-induced acute renal injury in aged rats. Nephron Exp Nephrol 2013;124:19-27.
38. Mitchell JR, Verweij M, Brand K, et al. Short-term dietary restriction and fasting precondition against ischemia reperfusion injury in mice. Aging Cell 2010;9:40-53.
39. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med 2011;37:601-9.
40. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.

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