Intensive Care Med (2009) 35:1728–1737
DOI 10.1007/s00134-009-1567-4

ORIGINAL

Cathy Alberda
Leah Gramlich
Naomi Jones
Khursheed Jeejeebhoy
Andrew G. Day
Rupinder Dhaliwal
Daren K. Heyland

The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study

Received: 5 March 2009
Accepted: 13 June 2009
Published online: 2 July 2009

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-009-1567-4) contains supplementary material, which is available to authorized users.

C. Alberda · L. Gramlich
Alberta Health Services Edmonton, Edmonton, AB, Canada
e-mail: cathy.alberda@capitalhealth.ca

L. Gramlich
University of Alberta, Edmonton, AB, Canada
e-mail: leah.gramlich@ualberta.ca

N. Jones · A. G. Day · R. Dhaliwal · D. K. Heyland (✉)
Clinical Evaluation Research Unit, Kingston General Hospital, Angada 4, 76 Stuart Street, K7L 2V7
Kingston, ON, Canada
e-mail: dkh2@queensu.ca
Tel.: +1-613-5496666
Fax: +1-613-5482428

N. Jones
e-mail: jonesn@kgh.kari.net

A. G. Day
e-mail: daya@kgh.kari.net

R. Dhaliwal
e-mail: dhaliwar@kgh.kari.net

N. Jones · A. G. Day · D. K. Heyland
Department of Community Health and Epidemiology, Queen's University, Kingston, ON, Canada

K. Jeejeebhoy
St. Michael's Hospital, Toronto, ON, Canada
e-mail: khushjeejeebhoy@compuserve.com

K. Jeejeebhoy
Department of Medicine, University of Toronto, Toronto, ON, Canada

D. K. Heyland
Department of Medicine, Queen's University, Kingston, ON, Canada

Abstract *Purpose:* The objective of this study was to examine the relationship between the amount of energy and protein administered and clinical outcomes, and the extent to which pre-morbid nutritional status influenced this relationship. *Methods:* We conducted an observational cohort study of nutrition practices in 167 intensive care units (ICUs) across 37 countries. Patient demographics were collected, and the type and amount of nutrition received were recorded daily for a maximum of 12 days. Patients were followed prospectively to determine 60-day mortality and ventilator-free days (VFDs). We used body mass index (BMI, kg/m^2) as a marker of nutritional status prior to ICU admission. Regression models were developed to evaluate the relationship between nutrition received and 60-day mortality and VFDs, and to examine how BMI modifies this relationship. *Results:* Data were collected on 2,772 mechanically ventilated patients who received an average of 1,034 kcal/day and 47 g protein/day. An increase of 1,000 cal per day was associated with reduced mortality [odds ratio for 60-day mortality 0.76; 95% confidence intervals (CI) 0.61–0.95, $p = 0.014$] and an increased number of VFDs (3.5 VFD, 95% CI 1.2–5.9, $p = 0.003$). The effect of increased calories associated with lower mortality was observed in patients with a BMI <25 and ≥ 35 with no benefit for patients with a BMI 25 to <35. Similar results were observed when comparing increasing protein intake and its effect on mortality. *Conclusions:* Increased intakes of energy and protein appear to be associated with improved clinical outcomes in critically ill patients, particularly when BMI is <25 or ≥ 35.

Keywords Critical care · Nutrition therapy · Nutritional status · Body mass index

Introduction

The optimal amount of energy and protein required by critically ill patients to reduce morbidity and mortality is controversial. On one hand, observational studies have shown that a cumulative energy deficit or caloric debt is associated with adverse clinical outcomes in critically ill patients [1–3]. In contrast, another observational study suggests that feeding fewer than goal calories, between 33% and 66% of estimated energy needs, resulted in improved clinical outcomes compared to patients who received closer to 100% of goal calories [4].

Previous work in non-critically ill patients clearly has demonstrated how the effect of the nutritional intervention varies with pre-morbid nutritional status [5–7]. The progression towards critical malnutrition will occur with greater rapidity in those who are admitted with limited nutritional reserves and in those who are markedly underfed. The objective of this observational study was to examine the relationship between the amount of energy and protein received and clinical outcomes [60-day mortality and ventilator-free days (VFD)], and to explore how nutritional status prior to ICU admission modifies this relationship in a large cohort of critically ill adults. Our a priori hypothesis was that the clinical outcomes may be associated with the amount of energy and protein received in relation to the nutritional status of the patient at admission to the ICU. Specifically, patients with a poor nutritional status (i.e., very low reserve as demonstrated by a low BMI) are more likely to experience adverse effects from underfeeding or benefit the most from receiving an increased amount of energy and protein.

Methods

Study design and participants

We conducted a prospective observational study of nutrition practices in intensive care units (ICUs) across the world. Participating ICU sites were recruited by disseminating study information on our website (http://www.criticalcarenutrition.com) to the membership registries of clinical nutrition societies and critical care societies across the world and by e-mailing individual health-care providers known to have an interest in critical care or nutrition therapy. To be eligible, ICUs had to have access to an individual with knowledge of clinical nutrition to complete data collection and have adequate resources to collect the required patient data within the study period.

On 25 January 2007, participants identified eligible study patients who were being cared for in their units on that day. Critically ill adult (i.e., $\geq$18 years of age) patients that were mechanically ventilated within the first 48 h of admission to the ICU and who remained in the ICU for more than 72 h were enrolled in this study. We excluded non-intubated patients.

Data collection

Using a secure web-based data collection tool (see http://www.criticalcarenutrition.com), we collected the following information related to the enrolled patients: admission category (surgery vs. medical), primary admission diagnosis, sex, age, weight, height, and APACHE II score [8, 9]. Height (actual or estimated) and weight at admission (estimated or actual weight) were used to calculate BMI [i.e., weight (kg)/height (m^2)]. The determination of the optimal nutrition prescription was left to the judgment of the individual provider. We recorded daily the type and amount of nutrition received, and morning blood glucose levels, for a maximum of 12 days or until death or discharge from the ICU. We followed patients while in hospital for a maximum of 60 days and reported on their ICU and hospital outcomes at 60 days.

Statistical analysis

Given the observational nature of this study, no formal sample size calculation was performed. Rather, we aimed to enroll 20 consecutive eligible patients at each site in order to give a representative sample of usual practice. Patients missing BMI, caloric intake, or 60-day mortality status were excluded. Categorical variables are reported as counts and percents. Continuous variables are described by means and standard deviations, except for the length of stay variables, which are summarized by medians and quartiles due to their positive skew. To assess nutritional adequacy, the total amount of energy or protein received from either enteral (EN) or parenteral nutrition (PN), inclusive of propofol, over the first 12 ICU days was divided by the amount prescribed as per the baseline assessment and expressed as a percentage. BMI levels were categorized a priori as $<$20, 20 to $<$25, 25 to $<$30, 30 to $<$35, 35 to $<$40, and $\geq$40 kg/m^2 based on a modification of an existing categorization [10]. Differences in these characteristics across BMI levels were calculated using the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables.

Logistic regression models, with random ICU intercepts [10] to account for potential within ICU correlation, were fit to estimate 60-day mortality as predicted by the daily average of total energy and protein received during the first 12 ICU days prior to death or permanent switch to exclusive oral feeding. This model was estimated separately for calories and protein using residual pseudo-likelihood as implemented by the GLIMMIX procedure in SAS [11]. Since most feeding protocols recommend gradually increasing nutrition over the first several days of ICU stay, the daily average amount of energy and protein

received is expected to be lower for patients with fewer days of enteral or parenteral feeding. Consequently, our analysis adjusted for the number of days of observation in the 12-day study period in calculating the daily averages of nutritional intake in addition to prior known risk factors for mortality including: primary admission diagnosis (see Table 1 for categories) with separate categories for medical and surgical admissions of the same diagnosis, age, and APACHE II score. We arbitrarily report the change in odds in mortality per 1,000 cal and per 30 g of protein as they reflect an amount that is achievable with an aggressive feeding strategy. This arbitrary selection of parameter scale does not affect p values.

Using the approach recommended and implemented by Harrell, restricted (natural) cubic spline with knots at the 5th, 27.5th, 50th, 75.5th, and 95th percentiles was used to examine the relationship between 60-day mortality as predicted by BMI, energy or protein, and the interaction between BMI and energy or protein [12]. This approach demonstrated that the amount of energy and protein received was linearly related to mortality, but BMI had a non-linear U-shaped relationship with mortality that interacted with nutritional intake. For this reason, the reported analysis models nutritional intake as linear, but models BMI as categorical with the six BMI groups defined a priori. Interaction terms were included in the final model to allow the relationship between calories and outcome to vary by BMI group. The same approach was taken using a linear mixed effects model to analyze ventilator-free days as a continuous outcome [13]. We modeled VFD rather than length of stay variables because mortality is a competing risk for length of stay, whereas it is incorporated into VFD. VFDs were defined as all days liberated from mechanical ventilation within the 60-day period of observation. If a patient died while undergoing mechanical ventilation, their VFD = 0.

Statistical analysis was completed using SAS v9.1.3 (SAS Institute Inc., Cary, NC). All tests were two sided with statistical significance considered as a p value <0.05. Institutional ethics approval was obtained from the Health Sciences Research Ethics Board at Queen's University, Kingston, Ontario, and additional centers if required for their participation. The need for informed patient consent was waived given the nature of this study.

Results

Data were collected on 2,884 patients from 167 ICUs from 37 countries across 5 continents. Table 1 shows characteristics of participating sites. Due to missing data or patients having less than 3 ICU days before death or permanent switch to exclusive oral feeding, 112 (3.9%) patients were excluded from the analysis, leaving 2,772 for evaluation. Sites contributed an average of 17 patients each, with 117 (70%) contributing 16–20 patients, 46 (28%) contributing ≤15 patients, and 4 (2%) contributing between 21 and 24 patients. Patient demographics are shown in Table 2. The mean BMI of enrolled patients was 27.5 kg/m^2, with a BMI range of 12.9–102.0 kg/m^2 with weights ranging from 30.0 to 310.5 kg.

Table 1 Characteristics of participating sites

	All sites (n = 167)
Hospital type	
Teaching	130 (77.8%)
Non-teaching	35 (21.0%)
Size of hospital (beds)	
Mean (range)	648.1 (138.0, 4,000.0)
Multiple ICUs in hospital	
Yes	87 (52.1%)
ICU structure	
Open	33 (19.8%)
Closed	131 (78.4%)
Other	3 (1.8%)
Case type	
Medical	141 (84.4%)
Surgical	147 (88.0%)
Trauma	103 (61.7%)
Pediatrics	26 (15.6%)
Neurological	105 (62.9%)
Neurosurgical	79 (47.3%)
Cardiac surgery	52 (31.1%)
Burns	28 (16.8%)
Other	20 (12.0%)
Presence of medical director	
Yes	157 (94.0%)
Size of ICU (beds)	
Mean (range)	17.4 (4.0, 75.0)
Presence of dietician(s)	
Yes	141 (84.4%)
Full time equivalent dietician (per 10 beds)	
Mean (range)	0.5 (0.1, 6.7)

Nutrition therapy

Of all patients surveyed, 69.0% received enteral nutrition (EN) only, 8.0% received parenteral nutrition (PN) only, 17.6% received EN plus PN, and 5.4% received no EN or PN. The energy and protein prescribed and received (total and per kg) are described in Table 3. The mean energy and protein prescribed per kg body weight were significantly lower in patients with a BMI ≥40 (15.0 kcal/kg/day and 0.8 g protein/kg/day) than in those with a BMI <20 (31 kcal/kg/day and 1.4 g/kg/day, $p < 0.0001$).

Overall, study patients received a mean intake of 1,034 kcal/day (range 0–2780) and 47.1 g protein/day (range 0–178.3). The energy and protein received on a per kg basis varied significantly across BMI groups (see Table 3). Overall, patients received 59.2% of the energy and 56% of protein prescribed, with those in the BMI <20 group receiving proportionately greater amounts than

Table 2 Characteristics of study patients

	Total	BMI <20	20 to <25	25 to <30	30 to <35	35< to 40	≥40	*p* value
N	2,772	289	937	818	395	162	171	
Age, years (SD)	59.6 (17.6)	58.7 (19.0)	58.3 (19.0)	60.0 (17.8)	62.2 (15.3)	62.3 (13.7)	56.9 (13.3)	0.0007
Sex, male (%)	1630 (58.8%)	147 (50.9%)	560 (59.8%)	537 (65.6%)	227 (57.5%)	82 (50.6%)	77 (45%)	<0.0001
Admission category medical	1,710 (61.7%)	183 (63.3%)	581 (62%)	497 (60.8%)	237 (60%)	98 (60.5%)	114 (66.7%)	0.32
Elective surgery	371 (13.4%)	41 (14.2%)	114 (12.2%)	106 (13%)	64 (16.2%)	29 (17.9%)	17 (9.94%)	
Emergent surgery	691 (24.9%)	65 (22.5%)	242 (25.8%)	215 (26.3%)	94 (23.8%)	35 (21.6%)	40 (23.4%)	
Admission diagnosis: cardiovascular	488 (17.6%)	32 (11.1%)	144 (15.4%)	165 (20.2%)	84 (21.3%)	41 (25.3%)	22 (12.9%)	<0.0001
Respiratory	734 (26.5%)	103 (35.6%)	239 (25.5%)	182 (22.2%)	104 (26.3%)	48 (29.6%)	58 (33.9%)	
Gastrointestinal	455 (16.4%)	58 (20.1%)	157 (16.8%)	129 (15.8%)	61 (15.4%)	22 (13.6%)	28 (16.4%)	
Neurologic	339 (12.2%)	37 (12.8%)	124 (13.2%)	114 (13.9%)	37 (9.37%)	16 (9.88%)	11 (6.43%)	
Sepsis	249 (8.98%)	24 (8.3%)	92 (9.82%)	61 (7.46%)	37 (9.37%)	17 (10.5%)	18 (10.5%)	
Trauma	280 (10.1%)	14 (4.84%)	107 (11.4%)	97 (11.9%)	38 (9.62%)	9 (5.56%)	15 (8.77%)	
Other	227 (8.19%)	21 (7.27%)	74 (7.9%)	70 (8.56%)	34 (8.61%)	9 (5.56%)	19 (11.1%)	
Height, m (SD)	1.69 (0.11)	1.68 (0.10)	1.70 (0.10)	1.70 (0.10)	1.68 (0.12)	1.67 (0.11)	1.64 (0.17)	<0.0001
Weight, kg (SD)	78.51(24.15)	50.86 (7.40)	65.84 (9.13)	79.59 (9.85)	90.99 (13.04)	104.68 (14.93)	135.94 (36.94)	<0.0001
BMI, mean (SD)	27.49 (8.19)	18.06 (1.67)	22.80 (1.40)	27.36 (1.41)	31.93 (1.40)	37.20 (1.51)	50.35 (11.28)	<0.0001
APACHE II score, mean (SD)	21.68 (7.99)	22.04 (7.71)	21.40 (8.15)	21.43 (7.96)	22.41 (7.40)	21.62 (8.36)	22.21 (8.53)	0.18

APACHE II acute physiology and chronic health evaluation, *m* meters; *kg* kilograms, *BMI* body mass index [weight (kg)/height (m^2)]

patients with higher BMIs. Average morning blood glucose levels ranged from 7.3 to 8.0 mmol/l and were significantly different across groups (see Table 3).

Clinical outcomes

The clinical outcomes for the overall cohort are shown in Table 4. Table 5a presents the results of the logistic regression modeling mortality as predicted by energy received with separate odds ratios for each BMI group to reflect the effect of BMI on the energy-mortality association ($p = 0.027$ for interaction). The results are consistent before and after adjusting covariates. The provision of higher calories was associated with a significant overall reduction in mortality; the adjusted odds ratio (OR) for 60-day mortality for every 1,000 cal/day provided was 0.76 [95% confidence intervals (CI) 0.61–0.95, $p = 0.014$]. This relationship varied across the BMI groups in which the odds ratio of mortality per 1,000 kcal received per day was consistent with a large mortality reduction at the extremes of BMI and no association with mortality in the groups with a BMI 25–35 (Table 5a, Fig. 1). Similar trends were seen with protein (Table 5b) with the benefits of an additional 30 g protein associated with an adjusted OR 0.84 (95% CI: 0.74–0.96, $p = 0.008$). Again, the benefit was largely observed in patients with a BMI $\leq$25 and $\geq$35. For the subgroup with a BMI $\geq$40 the findings were not statistically significant with an OR of 0.63 (95% CI 0.32–1.24, $p = 0.18$) for increasing calories and 0.72 (95% CI 0.51–1.03, $p = 0.07$) for increasing protein (see Table 5a, b).

With respect to VFDs, the unadjusted analysis demonstrated that each additional 1,000 kcal/day was associated with a decrease of 3.3 (95% CI −5.1–1.5, $p < 0.001$) VFDs, while after adjustment an increase of 1,000 kcals/day was associated with a increase of 3.5 (95% CI 1.2–5.9, $p = 0.003$) VFDs (see Table 6a). After adjusting for covariates, greater amounts of protein were not significantly associated with VFDs (see Table 6b).

Discussion

We hypothesized that the baseline nutritional status of the patient entering the ICU, as determined by BMI, would determine the effect of energy and protein intake on outcome, and that those patients who present to the ICU with pre-existing malnutrition or lack of nutritional reserve would benefit the most from aggressive provision of energy and protein intake. We conducted a prospective multicenter observational study of nutrition therapy to evaluate the impact of the amount of nutrition received by 2,772 critically ill patients in 167 ICUs across 5

Table 3 Nutrition therapy of study patients

	Total	BMI <20	20 to <25	25 to <30	30 to <35	35< to 40	≥40	*p* value
Nutritional prescription								
Mean energy, kcal/day (SD)	1,794 (364)	1,561 (314)	1,721 (350)	1,892 (334)	1,841 (368)	1,866 (363)	1,948 (389)	<0.0001
Mean energy, kcal/kg/day (SD)	24.0 (5.8)	30.9 (5.8)	26.2 (4.6)	23.8 (3.7)	20.2 (3.4)	17.9 (2.8)	15.0 (4.0)	<0.0001
Mean protein, grams/day (SD)	87.5 (25.1)	70.2 (17.9)	81.8 (22.0)	91.7 (23.9)	94.7(25.0)	95.5 (25.9)	103.6 (32.1)	<0.0001
Mean protein, [grams/kg/day] (SD)	1.2 (0.3)	1.4 (0.3)	1.2 (0.3)	1.2 (0.3)	1.0 (0.2)	0.9 (0.2)	0.8 (0.3)	<0.0001
Nutrition received								
Mean energy received, kcal/day (SD)	1,034 (514)	994 (469)	1,024 (490)	1,074 (536)	1,008 (534)	1,009 (532)	1,048 (531)	0.12
Mean energy, Kcal/kg/day (SD)	14.0 (7.6)	19.7 (9.3)	15.7 (7.5)	13.6 (6.7)	11.2 (5.9)	9.8 (5.1)	8.1 (4.4)	<0.0001
Adequacy of calories from nutrition therapy[a]	59.2% (0.0–236)	64.4% (0.0–140)	61.3% (0.0–236)	57.7% (0.0–208)	56.2% (0.0–117)	55.6% (0.0–122)	56.2% (0.0–115)	<0.0001
Mean protein, grams/day (SD)	47.1 (26.9)	44.727 (23.4)	46.653 (25.9)	47.469 (26.7)	47.928 (28.3)	45.825 (29.2)	50.349 (33.3)	0.66
Mean protein, grams/kg/day (SD)	0.6 (0.4)	0.9 (0.5)	0.7 (0.4)	0.6 (0.3)	0.5 (0.3)	0.4 (0.3)	0.4 (0.3)	<0.0001
Received EN protein supplements	173 (6.2%)	13 (4.5%)	43 (4.6%)	50 (6.1%)	28 (7.1%)	17 (10.5%)	22 (12.9%)	0.0002
Adequacy of protein from nutrition therapy[b]	56.1% (0.0–207)	65.4% (0.0–180)	59.4% (0.0–207)	53.5% (0.0–134)	51.8% (0.0–121)	49.8% (0.0–132)	50.4% (0.0–118)	<0.0001
Number of patients on nutrition therapy (%)								0.16
EN only	1,912 (69.0%)	192 (66.4%)	633 (67.6%)	566 (69.2%)	274 (69.4%)	116 (71.6%)	131 (76.6%)	
PN only	221 (8.0%)	29 (10.0%)	82 (8.8%)	53 (6.5%)	33 (8.4%)	10 (6.2%)	14 (8.2%)	
EN + PN	489 (17.6%)	58 (20.1%)	169 (18.0%)	154 (18.8%)	68 (17.2%)	25 (15.4%)	15 (8.8%)	
None	150 (5.4%)	10 (3.5%)	53 (5.7%)	45 (5.5%)	20 (5.1%)	11 (6.8%)	11 (6.4%)	
Hours to initiation of EN, mean (SD)	41.7 (45.1)	35.9 (38.1)	38.1 (43.4)	42.5 (45.0)	48.2 (52.5)	52.5 (50.2)	41.8 (39.2)	0.0003
Of patients on PN, % starting PN within 48 h of starting EN	47.1%	64.0%	46.7%	49.2%	42.9%	45.5%	0.0%	0.07
Mean a.m. blood glucose (mmol/l)	7.5 (1.8)	7.32 (1.5)	7.27 (1.6)	7.47 (1.6)	7.69 (2.5)	8.01 (1.8)	7.76 (1.6)	<0.0001

EN enteral nutrition, *PN* parenteral nutrition

[a] Calories received/calories prescribed (%)

[b] Protein received/protein prescribed (%)

Table 4 Clinical outcomes of study patients

BMI group	Median (IQR)							
	Total	BMI <20	20 to <25	25 to <30	30 to <35	35< to 40	≥40	*p* value
Length of ICU stay (days)	12.0 (6.9–23.4)	11.3 (7.0–24.7)	11.7 (6.7–22.5)	12.4 (7.0–23.3)	12.0 (7.0–23.9)	11.2 (7.5–22.6)	13.6 (6.8–26.2)	0.49
Length of hospital stay (days)	24.2 (12.9–46.9)	23.1 (11.1–47.1)	24.6 (12.6–46.3)	24.4 (13.1–49.0)	24.7 (13.9–42.3)	23.4 (12.5–43.5)	22.0 (13.2–50.8)	0.94
Length of mechanical ventilation (days)	9.0 (4.3–20.8)	8.8 (4.2–22.5)	8.6 (4.0–18.7)	9.1 (4.2–21.1)	9.2 (4.3–22.3)	8.9 (5.5–20.0)	10.8 (5.0–22.7)	0.40
Mortality % (60 days)	29.1	35.6	29.9	28.2	26.1	24.7	29.2	0.08
VFD	43.4 (0.5–54.4)	33.8 (0.2–54.3)	44.2 (0.4–54.5)	45.3 (0.9–54.7)	43.5 (0.7–54.6)	43.7 (0.3–53.6)	39.0 (0.2–53.9)	0.27

IQR interquartile range, *BMI* body mass index [weight (kg)/height (m^2)]

continents. We developed regression models adjusting for important known confounding variables and have shown a significant relationship between the amount of nutrition received in the first 12 days and subsequent 60-day mortality and VFDs. The effect of increasing provision of nutrition on these outcomes seemed to be largest in patients with low BMI (<25) and high BMI (≥35) with little evidence of a treatment effect in patients in the mid range (BMI 25–35).

Controversy continues to exist over what the optimal goals for provision of energy and protein are [14]. Hypocaloric feeding of all critically ill patients and "permissive underfeeding" of the obese critically ill have been recommended by some [4, 15, 16]. Despite the desire to provide different nutrition prescriptions across different BMI levels, current nutritional practices show that ICU patients are fed uniformly low levels of calories and protein across BMI groups, with an average intake of 1,034 kcal and 47 g of protein. Hence, all of these groups in our study may have received insufficient energy and protein. These observations are consistent with the published literature showing that the majority of critically ill patients do not meet nutritional requirements, and average intakes are 49–70% of calculated requirements when enteral nutrition is the major or only source of nutritional intake [17–19].

Since the 1950s, protein–energy malnutrition has been recognized as a cause of increased morbidity and mortality [20]. Our finding that increasing amounts of energy and protein are associated with improvements in clinical outcomes in lean critically ill patients is consistent with published data on community malnutrition. Studies by Scrishaw and his colleagues showed that there was a cycle of malnutrition resulting in increased propensity for infection that in turn reduced food intake and intensified malnutrition [21]. Similarly, Collins et al. demonstrated that refeeding Somalian adults with a BMI ~13 with a high-energy diet of mixed substrates lowered mortality [22]. This parallels the finding in our study where increased energy and protein intake was associated with reduced odds of dying in patients with a low BMI.

The other main finding was that increased feeding in patients with a BMI ≥35 was associated with a further reduction in mortality. Admittedly, some of the *p* values describing the relationship between increased calories and protein in the subgroup of patients with a BMI >40 lacked statistical significance. However, the magnitude of the treatment effect was similar to the other subgroups, and the lack of statistical significance was probably due to the small sample size of this subgroup. The mechanism for this treatment effect in this obese population may be different than in patients who become critically ill with a pre-existing low nutritional reserve and may relate more to iatrogenic malnutrition. Their supernormal lean body mass results in a higher than normal requirement for energy, and yet the actual mean delivery of energy was

Table 5 Relationship between increased nutrition and 60-day mortality

(a) Increased energy intake

BMI group	Unadjusted (n = 2,772)				Adjusted (n = 2,729[a])			
	Odds ratio	95% CI		p value	Odds ratio	95% CI		p value
		LCL	UCL			LCL	UCL	
Overall	0.73	0.62	0.87	0.001	0.76	0.61	0.95	0.014
<20	0.48	0.28	0.83	0.009	0.52	0.29	0.95	0.033
20 to <25	0.61	0.45	0.82	0.001	0.62	0.44	0.88	0.007
25 to <30	1.01	0.75	1.36	0.960	1.05	0.75	1.49	0.768
30 to <35	0.84	0.54	1.30	0.439	1.04	0.64	1.68	0.889
35 to <40	0.47	0.23	0.95	0.036	0.36	0.16	0.80	0.012
≥40	0.78	0.41	1.47	0.442	0.63	0.32	1.24	0.180

(b) Increased protein intake

BMI group	Unadjusted (n = 2,771[b])				Adjusted (n = 2,728[a])			
	Odds ratio	95% CI		p value	Odds ratio	95% CI		p value
		LCL	UCL			LCL	UCL	
Overall	0.83	0.75	0.92	<0.001	0.84	0.74	0.96	0.008
<20	0.60	0.43	0.84	0.003	0.60	0.41	0.87	0.007
20 to <25	0.79	0.66	0.94	0.008	0.81	0.66	0.99	0.036
25 to <30	0.95	0.80	1.14	0.609	0.97	0.79	1.19	0.758
30 to <35	0.92	0.72	1.19	0.533	1.04	0.79	1.37	0.774
35 to <40	0.70	0.47	1.04	0.075	0.62	0.39	0.98	0.039
≥40	0.82	0.59	1.14	0.237	0.72	0.51	1.03	0.072

Odds of 60-days mortality per increase of 1,000 kcal (a) and 30 g of protein (b) received per day both unadjusted and adjusting for nutrition days, BMI, age, admission category, admission diagnosis, and APACHE II score. Estimates are from the generalized linear (logistic) mixed effects model with a random ICU effect. Interaction terms were used to produce BMI-specific estimates. p values are Wald type t tests

CI confidence interval, *LCL* lower confidence limit, *UCL* upper confidence limit, *BMI* body mass index, *APACHE* acute physiology and chronic health evaluation, *ICU* intensive care unit

[a] Forty-three (1.6%) patients are excluded due to missing one or more covariates in the adjusted model

[b] One patient missing protein intake

the lowest in the entire survey cohort reported, being 8–9 kcal/kg with about 0.4 g/kg protein. Despite recommendations that obese patients receive high-protein diets, the actual intake was very low, and few patients received supplemental protein. Hence, these patients had the most severe discrepancy between needs and receipt of nutrition, a form of iatrogenic malnutrition—iatrogenic in the sense that they do not start their critical illness malnourished, but develop protein and energy deficits through the course of their ICU stay. Under these circumstances, any increase in nutritional intake would be of benefit. In this obese group, the inadequacy of protein intake in relation to lean body mass would lead to erosion of lean body mass and depletion of key amino acids and micronutrients, which are essential for immune function [23]. Thus, the benefits of increased nutrition in this group could be due to the increased protein intake, which reached a more acceptable intake of up to 1.2 g/kg/day, while the maximum energy delivered of 22 kcal/kg/day remained hypocaloric.

Our overall findings are consistent with the published literature describing an association between worse clinical outcomes and increasing caloric debt [1–3], but are discordant with the findings of Krishnan and colleagues that showed that 33–66% of goal calories were associated with

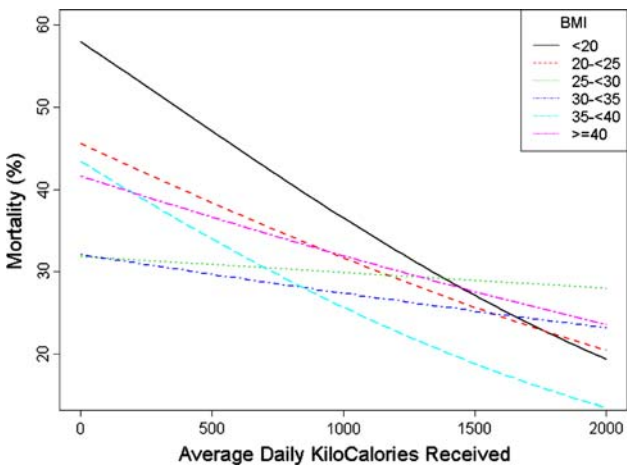

Fig. 1 The relationship between increasing calories/day and 60-day mortality by BMI. *BMI* body mass index

Table 6 Relationship between increased nutrition and ventilator-free days

(a) Increased energy intake

BMI group	Unadjusted ($n = 2,772$)				Adjusted ($n = 2,729$[a])			
	Beta	95% CI		p value	Beta	95% CI		p value
		LCL	UCL			LCL	UCL	
Overall	−3.3	−5.1	−1.5	<0.001	3.5	1.2	5.9	0.003
<20	−2.3	−8.2	3.7	0.452	2.8	−2.9	8.5	0.337
20 to <25	−1.1	−4.3	2.0	0.482	4.7	1.5	7.8	0.004
25 to <30	−5.8	−8.9	−2.7	<0.001	0.1	−3.0	3.2	0.958
30 to <35	−5.4	−9.8	−1.0	0.017	−1.5	−5.8	2.9	0.508
35 to <40	0.5	−6.5	7.4	0.891	8.7	2.0	15.3	0.011
≥40	−0.9	−7.7	5.9	0.797	6.4	−0.1	12.8	0.053

(b) Increased protein intake

BMI group	Unadjusted ($n = 2,771$[b])				Adjusted ($n = 2,728$[a])			
	Beta	95% CI		p value	Beta	95% CI		p value
		LCL	UCL			LCL	UCL	
Overall	−2.3	−3.4	−1.2	<0.0001	1.0	−0.3	2.3	0.121
<20	−2.2	−5.8	1.4	0.240	0.7	−2.8	4.1	0.710
20 to <25	−1.1	−2.9	0.7	0.230	1.5	−0.3	3.3	0.101
25 to <30	−3.8	−5.7	−1.9	<0.0001	−0.5	−2.4	1.4	0.601
30 to <35	−3.4	−6.0	−0.9	0.008	−1.3	−3.8	1.2	0.303
35 to <40	−0.4	−4.2	3.4	0.827	3.4	−0.2	7.1	0.063
≥40	−0.8	−4.1	2.4	0.612	2.4	−0.7	5.5	0.136

Beta estimates expected increase in ventilator-free days per 1,000 kcal (a) and 30 g of protein (b) per day both unadjusted and adjusting for nutrition days, BMI, age, admission category, admission diagnosis, and APACHE II score. Estimates are from the linear mixed effects model with a random ICU effect. Interaction terms were used to produce BMI-specific estimates. p values are Wald type t tests

CI confidence interval, *LCL* lower confidence limit, *UCL* upper confidence limit, *BMI* body mass index, *APACHE* acute physiology and chronic health evaluation, *ICU* intensive care unit

[a] Forty-three (1.6%) patients are excluded due to missing one or more covariates in the adjusted model

[b] One patient missing protein intake

a higher hospital survival and shorter duration of mechanical ventilation [4]. Our study differed from the Krishnan study in that our sample size was much larger, including patients from 167 ICUs with a larger range of BMI of included patients, and we adjusted for length of stay, an important confounding variable that is related both to the exposure (amount of feeds) and clinical outcomes. Adjusting for this confounding effect of the number of ICU days used to calculate average daily calories was extremely important since non-survivors with short ICU stays would not have time to reach goal calories. Survivors with long lengths of stays would have the greatest likelihood of receiving the most nutrition. The importance of this adjustment was evident in our statistical models demonstrating the relationship between VFDs and amount of nutrition in that the direction of the association was reversed when we adjusted for days of observation.

Our findings further suggest that in the design (and interpretation) of trials of macronutrients, we cannot expect the therapies studied to behave the same in all patients. We have shown that the treatment effect may vary depending on their baseline BMI. This is consistent with results of RCTs of parenteral nutrition in elective surgery patients, which show a benefit in malnourished patients only [6, 7]. Of the 24 randomized trials of critically ill patients comparing EN vs. PN or early EN vs. delayed EN, no studies were stratified on the basis of nutrition status at admission to ICU or adjusted for it post hoc, which is particularly important since these studies were small and subject to variability [24]. This must be taken into consideration in the design of future randomized controlled trials by either including only 'at risk' patients or stratifying on the basis of that risk.

The major strength of this study is the large number of subjects enrolled from multiple critical care units across five different continents, enhancing the generalizability of our findings. The most obvious limitation of the study is that this study design cannot definitively prove causality since unknown confounders may remain in any observational study, and not all variables can be adjusted for in our analysis. However, our analysis does account for the expected variability in timing, route, and composition of nutrition therapy that occurs across all sites, and key patient demographics that relate to outcome. We further acknowledge that it is also plausible that decreased ability to feed may be associated with increased mortality or that the recovery of the underlying disease allows for better tolerance of feeding. We are limited in making causal inferences because of the observational nature of our data; however, there are data from randomized trials that do support our observations that better fed patients have fewer complications and superior clinical outcomes [25, 26]. Another important limitation is the use of BMI as the only tool to define nutritional reserve. There is no consistently used nutritional risk stratification tool in the critically ill patient population; we used BMI because of its ease of measurement. We acknowledge that BMI is often derived from estimates of height and weight, and yet, despite these limitations, we were able to see differences across BMI subgroups.

In interpreting our findings, it is important to note that the maximum mean energy received in our observational dataset was 2,780 kcal/day; therefore, we are unable to infer that the linear relationship between additional calories and protein and decreasing mortality would continue beyond this threshold. We did not observe a threshold where increasing energy or protein caused an increase in mortality, but presuppose that such a threshold exists. Although we demonstrated a similar association with outcomes with both energy and protein, it was not

possible to separate the effects of increased energy from that of protein since they are strongly correlated due to the fixed ratio in most feeding regimens. Similarly, we cannot comment on whether the observed benefit effect of more energy and protein came from EN, PN, or both since we focused on nutrition from all sources. Other sources of evidence [15] from randomized controlled trials would offer more robust estimates of the relative merits of EN compared to PN.

Conclusions

We observed that greater intakes of energy and protein were associated with better clinical outcomes of critically ill patients, particularly if their BMI is <25 or ≥35. Given the observational nature of this study, we cannot make definitive causal inferences from our findings. We would hypothesize, however, that increasing nutrient provision in the early phase of critical illness, to minimize protein–energy deficit, may improve clinical outcomes, particularly in lean and obese patients. Randomized trials where delivery of goal calories is optimized in critically ill patients at the extremes of BMI are necessary to test this hypothesis. Future randomized trials of macronutrients need to consider the pre-ICU nutritional status in their design and interpretation and utilize effective nutrition screening tools to determine nutritional risk.

Acknowledgments We are grateful to the scores of participants across the world that collected data for this study, to Xuran Jiang who assisted with the data analysis, and to Drs. John Drover, Andrew Davies, and Renee Stapleton for their assistance in reviewing the manuscript.

References

1. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, Berger MM (2005) Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 24:502–509
2. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA (2004) Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 32:350–357
3. Petros S, Engelmann L (2006) Enteral nutrition delivery and energy expenditure in medical intensive care patients. Clin Nutr 25:51–59
4. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG (2003) Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest 124:297–305
5. Heyland DK, MacDonald S, Keefe L, Drover JW (1998) Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 280:2013–2019
6. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group (1991) Perioperative total parenteral nutrition in surgical patients. N Engl J Med 325:525–532
7. Braunschweig CL, Levy P, Sheean PM, Wang X (2001) Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr 74:534–542
8. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
9. World Health Organization. Available at: http://www.who.int/bmi/index.jsp?introPage=intro_3.htmp
10. Demidenko E (2004) Mixed models: theory and applications. Wiley, New Jersey
11. SAS Institute Inc. (2005) The GLIMMIX Procedure. SAS/STAT User's Guide, Version 9.1.3 Cary, NC
12. Harrell FE (2001) Regression modeling strategies: with application to linear models, logistic regression and survival analysis. Springer, New York
13. SAS Institute Inc (1999) The MIXED Procedure. SAS/STAT User's Guide, vol 8. SAS Institute Inc, Cary, pp 2083–2226
14. Stapleton RD, Jones N, Heyland DK (2007) Feeding critically ill patients: what is the optimal amount of energy? Crit Care Med 35:S535–S540
15. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P (2003) Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 27:355–373
16. Jeejeebhoy KN (2004) Permissive underfeeding of the critically ill patient. Nutr Clin Pract 19:477–480
17. Rice TW, Swope T, Bozeman S, Wheeler AP (2005) Variation in enteral nutrition delivery in mechanically ventilated patients. Nutrition 21:786–792
18. Heyland DK, Schroter-Noppe D, Drover JW, Jain M, Keefe L, Dhaliwal R, Day A (2003) Nutrition support in the critical care setting: current practice in Canadian ICUs—opportunities for improvement? JPEN J Parenter Enteral Nutr 27:74–83
19. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, Outin H (2001) A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 29:8–12
20. Heimburger DC (2006) Adulthood in modern nutrition. In: Shike M, Ross AC, Caballero B, Cousins RJ (eds) Health and disease, vol 53. Lippincott Williams &Wilkins, New York, pp 830–842
21. Katona P, Katona-Apte J (2008) The interaction between nutrition and infection. Clin Infect Dis 46:1582–1588
22. Collins S, Myatt M, Golden B (1998) Dietary treatment of severe malnutrition in adults. Am J Clin Nutr 68:193–199
23. Li P, Yin Y-L, Li D, Kim SW, Wu G (2007) Amino acids and immunity. Br J Nutr 98:237–252

24. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, for the Canadian Critical Care Clinical Practice Guidelines Committee (2003) The Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. J Parenter Enteral Nutr 5:355–373

25. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ (1999) 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 27:2525–2531

26. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ (2004) Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ 170:197–204