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Original article

Achieving protein targets without energy overfeeding in critically ill patients: A prospective feasibility study

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SUMMARY

Background & aims: High protein delivery during early critical illness is associated with lower mortality, while energy overfeeding is associated with higher mortality. Protein-to-energy ratios of traditional enteral formulae are sometimes too low to reach protein targets without energy overfeeding. This prospective feasibility study aimed to evaluate the ability of a new enteral formula with a high protein-to-energy ratio to achieve the desired protein target while avoiding energy overfeeding.

Methods: Mechanically ventilated non-septic patients received the high protein-to-energy ratio nutrition during the first 4 days of ICU stay (n = 20). Nutritional prescription was 90% of measured energy expenditure. Primary endpoint was the percentage of patients reaching a protein target of ≥1.2 g/kg ideal body weight on day 4. Other endpoints included a comparison of nutritional intake to matched historic controls and the response of plasma amino acid concentrations. Safety endpoints were gastro-intestinal tolerance and plasma urea concentrations.

Results: Nineteen (95%) patients reached the protein intake target of ≥1.2 g/kg ideal body weight on day 4, compared to 65% in historic controls (p = 0.024). Mean plasma concentrations of all essential amino acids increased significantly from baseline to day 4. Predefined gastro-intestinal tolerance was good, but unexplained foul smelling diarrhoea occurred in two patients. In one patient plasma urea increased unrelated to acute kidney injury.

Conclusions: In selected non-septic patients tolerating enteral nutrition, recommended protein targets can be achieved without energy overfeeding using a new high protein-to-energy ratio enteral nutrition.

1. Introduction

Enteral nutrition (EN) is the preferred way of feeding critically ill patients. However, reaching nutritional targets by the enteral route is challenging because early EN is often hindered by delayed gastric emptying or gastrointestinal dysfunction. Much controversy exists concerning the optimal energy and protein intake during the early phase of intensive care unit (ICU) admission. To support protein synthesis and overcome anabolic resistance a high protein delivery may be important [1]. On the other hand, energy overfeeding should be avoided [2]. We as well as others found that early high protein delivery (≥1.2 g/kg/day) was independently associated with lower mortality, while early energy overfeeding was associated with increased mortality [3,4]. Therefore, providing early high

Abbreviations: ABW, actual pre-admission body weight; APACHE, acute physiologic and chronic health evaluation; BCAA, branched-chain amino acid; BIA, bioelectrical impedance analysis; EAA, essential amino acid; EE, energy expenditure; EN, enteral nutrition; GRV, gastric residual volume; HP/E, high protein-to-energy ratio; IBW, ideal body weight; ICU, intensive care unit; PDMS, patient data management system; PN, parenteral nutrition; SOFA, sequential organ failure assessment.

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protein while avoiding early energy overfeeding might be a beneficial nutritional strategy. To attain this goal a nutritional formula with a high protein-to-energy ratio (HP/E) is required [5].

In addition to the amount of protein, the type may also matter. Whey protein has the highest leucine content, and leucine plays a crucial role in stimulating muscle protein synthesis [6]. Furthermore, hydrolysed protein seems to improve gastric emptying and absorption [7,8].

We conducted a prospective feasibility study in critically ill patients to determine the ability to achieve individualized protein targets early during ICU admission, without energy overfeeding, using an enteral HP/E formula containing 100% of protein in the form of hydrolysed whey protein. Nutritional prescription was based on energy expenditure. The attained protein intake was the endpoint with the achievement of an individualized protein target of $\geq$1.2 g/kg ideal body weight (IBW)/day on day 4 as primary aim. Secondary aims included a comparison of nutritional intake to historic controls, determining gastro-intestinal tolerance, and efficacy in terms of changes in plasma amino acid concentrations.

2. Materials and methods

2.1. Patients and data

This is an unblinded, pilot prospective, single-centre observational feasibility study evaluating the achievement of protein targets without energy overfeeding using an enteral HP/E formula containing hydrolysed whey protein in critically ill patients admitted to a mixed medical-surgical university hospital ICU. Patients were included between March 2016 to March 2017. The study was approved by the VU University Medical Center institutional review board (OHRP registration number IRB00002991, decision number 2015.560). All participants or their legal representatives provided written informed consent. Because early initiation of the nutrition is essential, the institutional review board allowed deferred consent within 24 h. The trial protocol was registered at ClinicalTrials.gov (NCT02815527). We included non-septic mechanically ventilated patients if they were 18 years or older, had an expected ICU stay of- and needed EN for at least 4 days, and when an investigator was available. Patients were excluded if contraindications for EN were present (gut ischemia, -obstruction, or -perforation; or active gastro-intestinal bleeding); intolerance to EN was expected (e.g. paralytic ileus); start of EN was not possible within 24 h of ICU admission (e.g. surgery or other interventions); energy expenditure (EE) could not be measured (e.g. air leakage); short bowel syndrome, Child Pugh class C liver cirrhosis, acute liver failure, or dialysis dependency was present at time of screening; specific nutrition was required for medical reasons; or if written informed (proxy) consent could not be obtained. Septic patients were not included because we previously did not find an association between higher protein intake and lower mortality in this group of patients [3]. Furthermore, patients with (expected) intolerance to EN were excluded to limit influence of this confounding factor on the achievement of protein goals.

2.2. Feeding protocol

Study nutrition was started enterally via nasogastric tube within 24 h after ICU admission and after hemodynamic stabilisation; the need of vasopressors at a stable dose was no contraindication for the start of nutrition. The study nutrition, an EN formula (Fresubin Intensive®, Fresenius-Kabi, Bad Homburg, Germany; Supplemental Table 1) containing 1220 kcal and 100 g of hydrolysed whey protein per 1000 ml (protein-to-energy ratio 82 g/1000 kcal), was administered for a total of 4 days, or less in case of oral intake, discharge or death. The nutritional target was set at 90% of measured EE, using ventilator derived VCO_2 (24-h average VCO_2 * 8.19 [9]). VCO_2 is routinely collected in the patient data management system (PDMS; EpicCare, Epic Systems Corporation, Verona, WI, U.S.A.) and 24-h mean VCO_2 is continuously calculated using hourly validated values. The nutritional target was based on an energy target rather than a protein target to reflect daily practise, the practise in the control group, and to prevent overfeeding. Feeding rates were adjusted accordingly each day. Study nutrition was initiated at a rate of 20 ml/h and increased up to target if gastric residual volume (GRV; measured every six hours) was 250 ml or less. If GRV was more than 250 ml the feeding rate was not increased. When GRV was more than 250 ml in two subsequent measurements intravenous erythromycin was started as a prokinetic. In cases where GRV remained more than 250 ml a duodenal tube was placed to facilitate feeding. No (supplemental) parenteral nutrition (PN) was used during the study period.

Macrogol was routinely administered to prevent obstipation and to facilitate the use of a faecal collection system. All patients received selective decontamination of the digestive tract [10].

2.3. Study measurements

Blood for plasma amino acid analysis was sampled in an EDTA-treated tube at inclusion, before start of study nutrition, and after 2 and 4 days during continuous administration of study nutrition. After direct centrifugation at 1920g for 10 min, two samples of 500 μL of plasma were pipetted into two cryogenic storage vials containing 20 mg of sulfosalicylic acid and stored at −80 °C until analysis. Plasma amino acid concentrations were determined on a Biochrom 30 Amino Acid Analyser (Biochrom Ltd., Cambridge, U.K.). Inter-assay variation ranged from 0.9% to 3.1%. Deficiency was defined as a plasma concentration more than 2 SD below the mean of healthy volunteers [11].

We performed bioelectrical impedance analysis (BIA), to measure phase angle, a biomarker of cellular health [12]. Measurements were performed at inclusion, and after 2 and 4 days, using the 50 kHz single-frequency, phase sensitive BIA 101 Anniversary edition (AKERN Bioresearch srl, Florence, Italy), which applies an alternating current of 400 μA.

Daily visits were made to determine gastro-intestinal tolerance by abdominal examination (distension, peristalsis), GRVs, need for prokinetics or duodenal tube, and faecal volume and consistency.

2.4. Other measurements

Patient data including age; sex; weight; height; BMI; admission diagnosis; Acute Physiologic And Chronic Health Evaluation (APACHE) II and IV scores [13,14]; daily Sequential Organ Failure Assessment (SOFA) scores [15]; daily amounts of nutrition, propofol, insulin, and glucose provided; need for- and duration of renal replacement therapy, sedation, and opioids; daily biochemistry on plasma and urine; length of stay; and length of ventilation were collected from the PDMS. Manual double data entry was used to ensure data quality. IBW was calculated using the Hamwi equation [16,17].

Males: *Ideal body weight* (*IBW*) (*lb*) = 106 + 6*(height−60)

Females: *Ideal body weight* (*IBW*) (*lb*) = 106 + 5*(height−60)

2.5. Historic controls

To determine efficacy of achieving protein targets, a matched historical control population with an ICU stay of 4 days or more was selected from patients admitted during the year before the study

period. The primary inclusion criterion of an *expected* ICU stay of more than 4 days could not be reproduced retrospectively. Control patients receiving EN were subsequently matched to study patients who received the study nutrition for at least 2 days by APACHE IV score (+/− 10), admission diagnosis, age (+/− 10 years), and sex. If no patients meeting these criteria were available, the age range was extended and/or the sex unmatched until a matching control was found.

Control patients' energy target was initially calculated using the Harris and Benedict formula +30% for activity and stress and adjusted when measured energy expenditure was available. Protein target was 1.2–1.5 g/kg actual pre-admission body weight (ABW). Nutrition was guided by our algorithm which selects the nutritional formula best suited to meet both the individual patient's energy and protein needs [18]. The protocol regarding route and timing of initiation of enteral feeding and GRV's was similar to the study period. The enteral formulae with protein-to-energy ratios of 40–63 g/1000 kcal used in control patients were Nutrison Standard® and Protein Plus ® (Nutricia, Zoetermeer, Netherlands), and Osmolite HP® (Abbott Nutrition, Lake Forest, IL, U.S.A.).

2.6. Outcome measures

Primary endpoint was the percentage of patients reaching a protein target of ≥1.2 g/kg IBW on day 4 while patients were fed based on energy targets set at 90% of measured EE.

Secondary endpoints were the percentage of patients reaching the protein target of ≥1.2 g/kg IBW by day 2 and of ≥1.2 g/kg ABW by day 2 and 4; protein intakes in g/kg IBW and in g/kg ABW on day 2 and 4; response of plasma amino acids concentrations on day 2 and 4, especially of leucine concentration, and change in BIA-derived phase-angle as a measure of cellular health [12].

Safety endpoints were signs of gastro-intestinal intolerance: abdominal distension, vomiting, need for prokinetics or a duodenal tube, diarrhoea (defined as Bristol Stool Scale 7 [19]), and plasma urea concentrations (above 10 mmoL/L).

2.7. Statistics

A sample size calculation was performed based on the nutritional database in our ICU, in which 42% of patients had a protein intake of >1.2 g/kg ABW on day 4. To detect an increase to 90% with an alpha of 0.05 and beta of 0.10, inclusion of 18 patients was needed. To compensate for unexpected disease-related intolerance for enteral nutrition, we included an additional 10% of patients and used strict inclusion criteria. Therefore, we decided to include 20 patients.

To evaluate within-patient changes over time, paired samples T-tests were used for normally distributed variables, Wilcoxon matched-pair signed rank tests for non-normally distributed continuous variables, and related samples McNemar test for dichotomous variables. For comparisons between groups, independent samples T-tests, Mann–Whitney U-tests, Fisher Exact tests, and Chi^2-tests were used as appropriate. To determine correlations between protein intake and the change in plasma leucine concentration and change in phase angle, markers of severity of disease, and medical interventions Spearman's rank correlation coefficient was used. Pearson's r was used to determine the correlation between phase angle and fluid balance. To determine whether reaching the protein target was associated with severity of disease and medical interventions, logistic regression was used with APACHE IV score, duration of vasopressor support, opioids, and sedatives as independent variables.

IBM SPSS Statistics 22 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Values are reported as number (%), mean (±SD), or median (25–75% IQR) as appropriate. All statistical tests were conducted two-sided. A $p < 0.05$ was considered statistically significant.

3. Results

During the study period, 1259 patients were admitted to the ICU and screened for inclusion. Retrospectively, 173 of these patients were ventilated, admitted for more than 4 days, and received enteral nutrition. Thirty-one patients met inclusion criteria and were included. The most important reasons for non-inclusion were an expected oral intake within 4 days or the presence of sepsis. Twenty-six patients received the study nutrition for at least 2 days and 20 patients for 4 days (Fig. 1). Among the historical controls, 26 patients received enteral nutrition for 2 days and 23 for 4 days.

Baseline characteristics were not significantly different between study patients receiving study nutrition for 4 days and historic controls, except for study patients having higher SOFA scores at admission (Table 1). Admission diagnoses and severity of illness at time of admission, as reflected by the APACHE II and -IV scores, were similar between both groups. Characteristics of the patients who received more than 2 days of study nutrition are shown in Supplemental Table 2.

3.1. Protein intake

The percentage of study patients reaching the protein target of ≥1.2 g/kg IBW on day 4 was 95% compared to 65% in the historic controls ($p = 0.024$), and on day 2 75% vs. 39% ($p = 0.031$; Table 2). Also when expressing the protein target as ≥1.2 g/kg ABW, a significantly higher percentage of study patients reached the protein target on day 4 (90% vs. 52%, $p = 0.009$) and on day 2 (80% vs. 26%, $p = 0.001$). Furthermore, mean protein intake was significantly higher in study patients when compared to historic controls, both on day 2 and 4 (Fig. 2). The delivered nutritional volume was not significantly different between study patients and historic controls on day 4 (Table 2).

Protein intake on day 4 in study patients was not related to any risk factors for feeding intolerance (age, APACHE II, -IV, and SOFA scores; duration of mechanical ventilation, vasopressor support, opioids, or sedatives) and in logistic regression no association was found between achievement of the protein target and risk factors (APACHE IV score, duration of vasopressors, opioids, and sedatives, data not shown).

3.2. Energy intake

Median energy intake from both nutritional and non-nutritional sources, expressed as percentage of measured EE, was not significantly different between study patients and historic controls on day 2 (85% (72–93) vs. 83% (62–105), $p = 0.884$), nor on day 4 (89% (85–94) vs. 90% (78–110), $p = 0.922$; Table 2 and Fig. 2).

3.3. Amino acids

Mean plasma leucine concentration was available at baseline, day 2, and 4 for 20 patients and was 49% ($p < 0.001$) and 43% ($p < 0.001$) higher compared to baseline on day 2 and day 4, respectively (Fig. 3 and Supplemental Table 3). Furthermore, 6 out of 26 patients were deficient for leucine at baseline, while none were deficient on day 2 and 4.

Similarly, mean plasma concentrations of all other essential amino acids (EAAs), including the other branched chain amino acids (BCAAs) isoleucine and valine, were significantly higher on day 2 and 4 compared to baseline. Of the non-essential amino acids only taurine significantly decreased, by 23% on day 4 ($p = 0.002$).

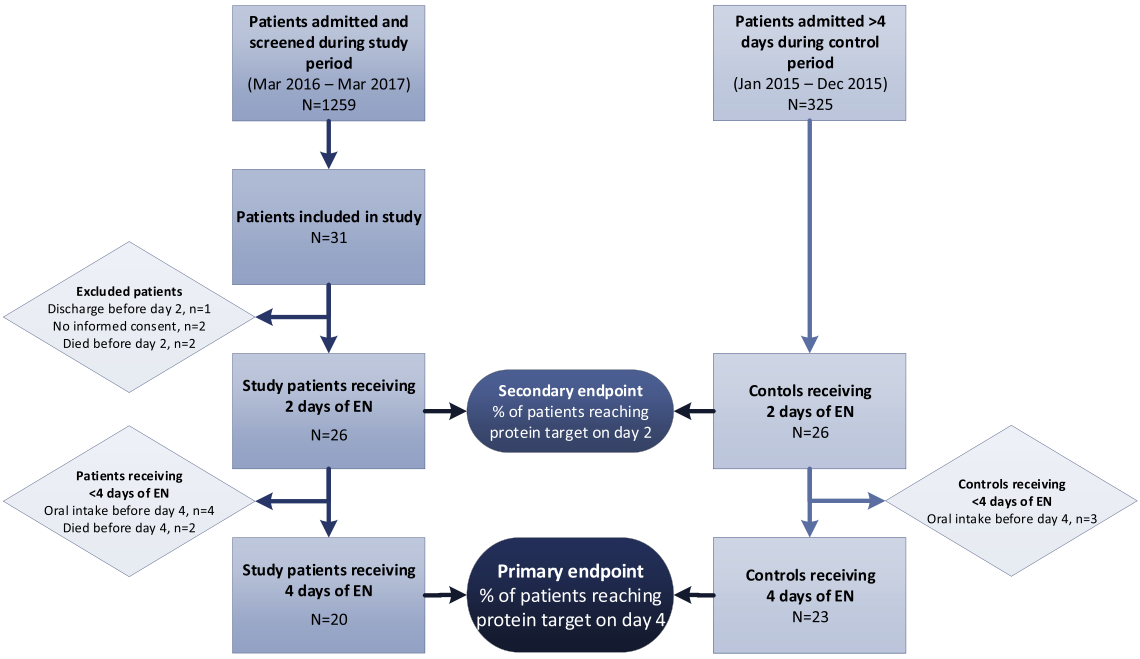

Fig. 1. Flow chart showing the inclusion process and matching of historic control patients.

Table 1
Baseline characteristics for study patients receiving study nutrition for 4 days and matched historic controls.

	Study patients (n = 20)		Matched historic controls[a] (n = 23)		*P*-value study patients vs. matched historic controls
	Mean/median/n	SD/IQR/%	Mean/median/n	SD/IQR/%	
Age, y	60	42–64	62	46–73	0.355
Sex male	13	65%	19	83%	0.295
Height, cm	176	±11	172	±9	0.249
Weight, kg	82.4	72.5–90.0	80.0	70.0–87.0	0.427
BMI, kg/m^2	24.5	23.3–28.5	26.2	23.2–29.4	0.609
Admission diagnosis					
Traumatic brain injury	12	60%	11	48%	0.840
Cardiac failure	2	10%	4	17%	
Respiratory failure	5	25%	7	30%	
Neurological	1	5%	1	4%	
Surgical patients	15	75%	14	61%	0.353
Trauma patients	12	60%	11	48%	0.544
APACHE II score	23	±6	22	±6	0.643
APACHE IV score	76	±20	81	±19	0.315
APACHE IV estimated hospital mortality, %	46.6	24.7–62.0	39.5	21.2–49.7	0.284
SOFA score					
Admission	13	±3	8	±2	**0.002**
Day 2	10	±4	8	±3	0.060
Day 4	9	±3	7	±3	0.106
Time from ICU admission to start of nutrition, hours	16.0	9.3–20.0	17.0	6.0–21.0	0.807

APACHE: Acute Physiological And Chronic Health Evaluation, ICU: Intensive Care Unit, SOFA: Sequential Organ Failure. P-values in bold indicate a significant test result (p<0.005).
[a] Patients admitted in the year before the study period, matched on APACHE IV score (+/− 10), admission diagnosis, age (+/− 10 years), and sex. If no matching patients were found, the age range was extended and/or the sex was unmatched.

Moreover, at baseline deficiencies were present among all EAAs except for phenylalanine, while by day 4 nearly all EAA plasma concentrations had returned to normal values in all patients. The only EAA not returning to normal values was tryptophan, however, the proportion of tryptophan deficient patients decreased from 18/26 patients at baseline to 4/20 patients on day 4 (p = 0.003).

3.4. Phase angle

BIA measurements for baseline, day 2, and 4 were available for 15 patients. Although the difference was not significant, phase angle decreased from 5.3° (±1.3) at baseline to 4.9° (±1.0) on day 2 (p = 0.073), to remain 4.9° (±1.4) on day 4 (p = 0.104 vs. baseline).

The change in phase angle from baseline to day 2 was related to protein intake on day 2 (Spearman's rho 0.612, p = 0.015), phase angle decreased in patients with low protein intake and increased in those with high protein intake. Although a trend was visible, this relation was not significant on day 4 (Spearman's rho 0.481, p = 0.070). Cumulative fluid balance was +2967 (±574) ml on day 2 and + 3187 (±1031) ml on day 4. The change in phase angle from baseline to day 2 and 4 was inversely related to cumulative day 2 and 4 fluid balance (Pearson's r −0.728, p = 0.002 and −0.599, p = 0.018, respectively).

Table 2
Nutritional intake on day 2 and 4 of ICU admission for study patients and matched historic controls.

		Study patients (n = 20)		Matched historic controls[a] (n = 23)		*P*-value study patients vs. matched historic controls
		Mean/median/n	SD/IQR/%	Mean/median/n	SD/IQR/%	
		Day 4		Day 4		
Protein intake	≥1.2 g/kg IBW	19	95%	15	65%	**0.024**
	≥1.2 g/kg ABW	18	90%	12	52%	**0.009**
	g/kg IBW	1.98	±0.58	1.33	±0.44	<**0.001**
	g/kg ABW	1.69	±0.46	1.11	±0.26	<**0.001**
Energy intake	% of energy expenditure	89	85–94	90	78–110	0.922
	Kcal	1892	±419	2019	±624	0.446
	Kcal/kg ABW	23.2	±5.5	25	±6.0	0.324
Nutrition volume ml		1375	±337	1602	±579	0.130
		Day 2		Day 2		
Protein intake	≥1.2 g/kg IBW	15	75%	9	39%	**0.031**
	≥1.2 g/kg ABW	16	80%	6	26%	**0.001**
	g/kg IBW	1.68	±0.67	1.01	±0.53	**0.001**
	g/kg ABW	1.44	±0.47	0.84	±0.40	<**0.001**
Energy intake	% of energy expenditure	85	72–93	83	62–105	0.884
	Kcal	1679	±508	1637	±704	0.826
	Kcal/kg ABW	20.4	±5.8	20.6	±8.6	0.925
Nutrition volume ml		1171	±373	1218	±684	0.785

ABW: actual pre-admission body weight, IBW: ideal body weight calculated by the Hamwi equation [14]. P-values in bold indicate a significant test result (p<0.005).
[a] Patients admitted in the year before the study period, matched on APACHE IV score (+/− 10), admission diagnosis, age (+/− 10 years), and sex. If no matching patients were found, the age range was extended and/or the sex was unmatched.

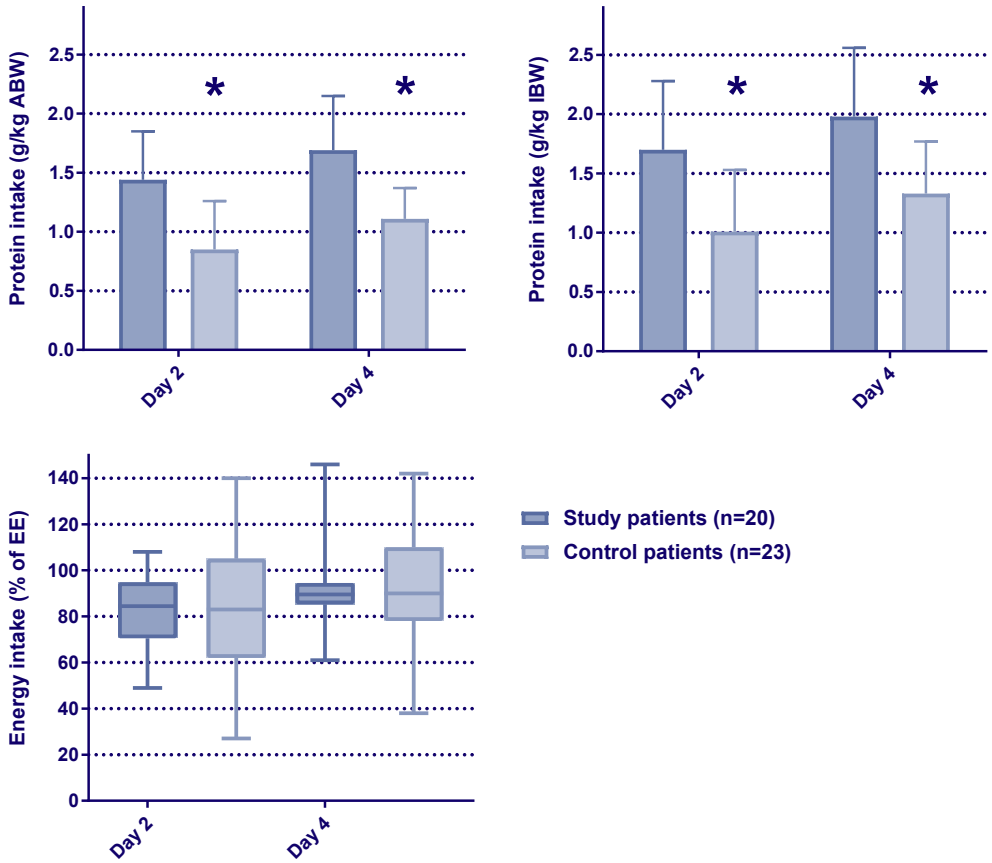

Fig. 2. Top: mean (with SD) protein intake in g/kg ABW (left) and in g/kg IBW (right) on day 2 and 4. Bottom: median energy intake as % of EE on day 2 and 4. Due to a large decrease of EE after increased sedation, one study patient received 146% of EE on day 4. *p < 0.05 study patients vs. matched historic controls. ABW: actual pre-admission body weight, EE: measured energy expenditure, IBW: ideal body weight calculated by the Hamwi equation [14].

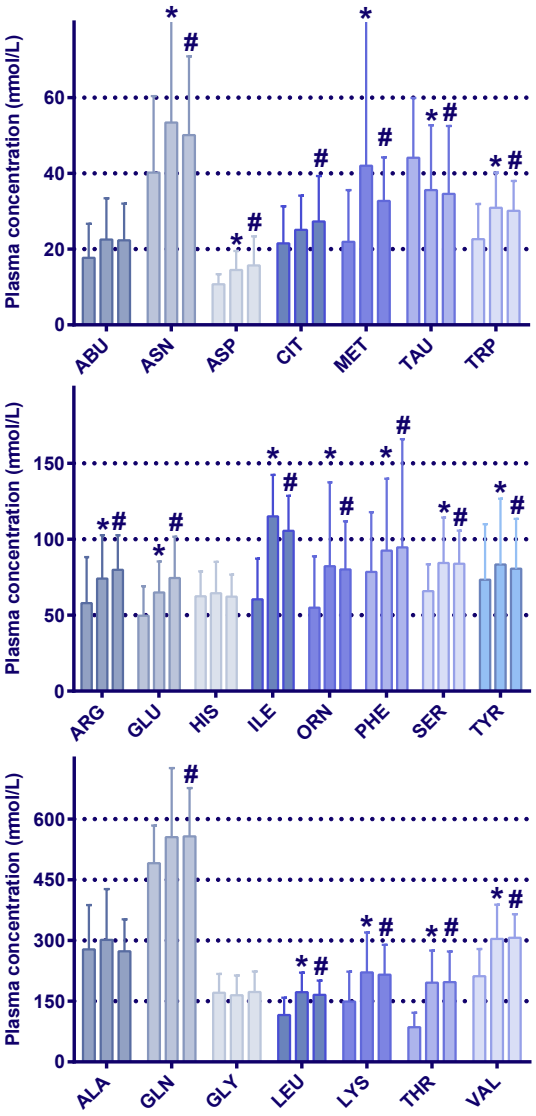

Fig. 3. Mean (with SD) plasma amino acids concentrations on baseline (n = 26), day 2 (n = 25), and day 4 (n = 20). *p < 0.5 day 2 vs. baseline. #p < 0.05 day 4 vs. baseline. ABU: aminobutyric acid, ALA: alanine, ARG: arginine, ASN: asparagine, ASP: aspartic acid, CIT: citrulline, GLN: glutamine, GLU: glutamic acid, GLY: glycine, HIS: histidine, ILE: isoleucine, LEU: leucine, LYS: lysine, MET: methionine, ORN: ornithine, PHE: phenylalanine, SER: serine, TAU: taurine, THR: threonine, TRP: tryptophan, TYR: tyrosine, VAL: valine.

3.5. Safety endpoints

During the study period, abdominal distension and vomiting occurred once in one patient. Nine patients had high GRVs and required prokinetics; placement of duodenal tubes was not necessary. Diarrhoea occurred in 10 patients. Plasma urea concentrations above normal values were seen in 5 patients (Fig. 4; patient 1, 6, 7, 10, and 14). In 4 patients this was related to acute kidney injury, as reflected by a simultaneous increase in plasma creatinine concentration, while in 1 patient (patient 7) no concomitant increase in creatinine concentration was observed. This patient received >2.0 g/kg (both in IBW and ABW) of protein on day 4.

3.6. Unexpected finding

Two patients developed remarkably foul smelling diarrhoea.

4. Discussion

This prospective feasibility study in ventilated non-septic ICU patients expected to tolerate enteral nutrition demonstrates that high protein targets can be achieved without energy overfeeding by using an enteral formula with a high protein-to-energy ratio (82g protein/1000 kcal). The protein target of ≥1.2 g/kg IBW/day on day 4 was achieved in 95% of patients, a higher percentage than in matched historic controls, while the nutritional volume delivered was comparable. We also found that plasma concentrations of all branched-chain amino acids and other essential amino acids increased from day 2. Therefore, when aiming for high protein targets without energy overfeeding, this new HP/E formula seems appropriate.

4.1. Protein/energy delivery

Adequate protein delivery seems important to support protein synthesis and overcome anabolic resistance [1]. Current guidelines recommend a protein delivery of ≥1.2 g/kg/day [20,21]. Nevertheless, protein intakes of 50–60% of this target are common [22,23]. On the other hand, protein may suppress autophagy, a cellular housekeeping system clearing cellular debris [24]. Furthermore, high protein delivery may be accompanied by high energy delivery which seems detrimental [3,4,25,26], possibly due to refeeding or disease-related endogenous energy production [2,27].

Multiple large observational studies in heterogeneous critically ill populations show an association between high protein intake and lower mortality [3,4,22,23,28–31], less infections [32], and more ventilator-free days [30]. However, these positive signals are not consistent and may depend on type of disease and energy intake. In two of the aforementioned observational studies, no positive signal of protein was found in septic or energy-overfed patients [3], or during the first three days of ICU admission [31]. In RCTs specifically investigating a high protein intervention, a sustained benefit on clinical outcomes has not been shown [33–35]. However, a post hoc analysis of one of these trials showed a mortality benefit in patients with normal kidney function receiving an intravenous amino acid supplement, and no harm in those with baseline or developing kidney dysfunction [36]. In a recent RCT on early goal directed nutrition achieving significantly higher protein and energy deliveries from day one, neither 6-month quality of life nor mortality was different between groups [37]. Unexpectedly, an observational landmark study found an association between muscle wasting and protein delivery [38]. Furthermore, post hoc analyses of the EPaNIC and PePanNIC studies suggest that intravenous amino acids may explain the harm caused by early supplemental PN [39,40]. However, in these studies energy intake in the first week was above 25 kcaL/kg. Contrary, in two other RCTs, supplementing PN without energy overfeeding caused less muscle wasting and ventilation time [41], and infections [42]. Altogether, the benefit of early high protein delivery remains inconsistent, and especially the conjunction with high energy delivery might have negative effects.

In the present study we targeted an energy delivery of 90% of EE. We presently do not know whether lower caloric goals might be preferable. Two RCTs have shown that permissive underfeeding is not harmful [43,44]. Using this HP/E nutrition, protein delivery targets can be reached in a hypocaloric nutritional strategy.

4.2. Hydrolysed whey protein

Not only the amount of protein, but also the type may matter. The study nutrition contains hydrolysed whey protein. Whey protein contains the highest concentration of leucine which plays a

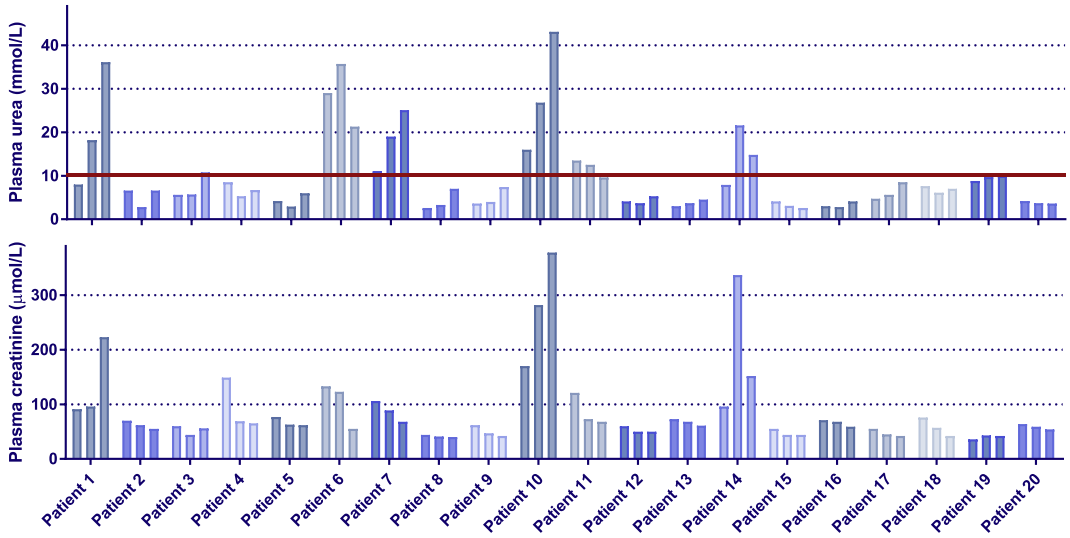

Fig. 4. Plasma urea and creatinine concentrations for all 20 patients on baseline, day 2, and day 4. Patient 7 had an increase of plasma urea above normal levels without concomitant increase in creatinine.

central role in muscle synthesis [6,45]. However, other protein sources contain leucine as well and whether whey protein-based nutrition can reduce muscle loss in critically ill patients remains to be determined. Additionally, absorption of protein is an important area of concern. Hydrolysation may improve protein absorption [7,8]. In the past, high protein EN formulae based on casein caused coagulation of proteins, delaying gastric emptying and hampering absorption [46]. Compared to whole casein, whey protein may promote gastric emptying [8].

We found that concentrations of all EAAs, especially of leucine and other BCAAs already increased after 2 days. Unfortunately, amino acid concentrations were not available in the historical control group. However, in a study in shock patients receiving enteral formulae containing 38–55 g/1000 kcal of predominantly casein protein, no significant increase in leucine concentrations was found [47]. Although we cannot determine whether the increase of amino acids in our patients was nutrition-related, increased circulating concentrations may favour whole body protein metabolism.

4.3. Bioelectrical impedance analysis

Phase angle represents the arc tangent of the resistance of a current passing through body fluids and the opposition against this current by membranes, reflecting cellular mass, membrane integrity, and hydration [12,48,49]. Phase angle has appeared as a simple biomarker of cellular health. Low phase angle at ICU admission was independently associated with increased mortality in two observational studies [48,49]. We found a positive correlation between the change in phase angle and protein intake, phase angle decreased with low protein intake and increased with high protein intake. However, these results must be interpreted with caution as phase angle was inversely related to fluid balance, a confounder of phase angle.

4.4. Safety endpoints

Because nutritional prescription was based on energy expenditure, several patients in the present study had a protein intake of over 2.0 g/kg/day. We do not know whether such a high protein intake is beneficial or might in fact be harmful, especially in patients with sepsis, renal-, or liver failure [3,36,50]. We therefore recommend to reduce the feeding rate or to change to a formula with a lower protein-to-energy ratio if protein intake is above 1.5 g/kg/day until RCTs show that higher protein intake is safe. Incorporating the present formula in a nutritional algorithm selecting the optimal formula to meet both protein and energy targets seems the best solution [18].

Another safety endpoint was plasma urea. One patient had a mild rise in plasma urea to 25 mmoL/L without concomitant rise in creatinine. This patient received diuretics and the relative dehydration may have contributed to this rise. Regardless, there is no evidence that elevated urea concentrations due to high protein delivery are associated with worse outcome [51]. Indeed, no signal of harm of a high intravenous amino acid dose was found in patients with kidney dysfunction [36].

4.5. Unexpected finding

Diarrhoea was not an issue, because all patients received macrogol. However, two patients had large amounts of foul smelling diarrhoea. The cause of the foul smell has not been elucidated. Mucosal dysfunction or osmotic forces might induce malabsorption, causing bacterial proteolysis or bacterial fermentation in the colon [52]. The relatively high dose of hydrolysed protein or of isomaltulose, a slowly digested carbohydrate (76 g/L), or both, or interactions with other enterally substances might play a role.

4.6. Limitations

Our study has several limitations. First, it was not randomized and the sample size was small, precluding the evaluation of clinical outcomes. Second, the nutrition was only used during the first four days, tolerability during longer use can therefore not be appraised. Third, due to strict inclusion criteria (expected tolerance of EN, duration of EN > 4 days, and no sepsis) only a small proportion of all admitted patients was included. We retrospectively assessed that about one fifth of the potentially eligible patients was included. Furthermore, almost half of patients had traumatic brain injury. This limits the generalizability of our findings. Fourth, a single investigator performed patient screening and study measurements. As a result eligible patients were missed which might be a source of

selection bias. Fifth, controls were less severely ill as illustrate by lower SOFA scores. This might be related to the inclusion criterion expected ICU stay >4 days, which cannot be applied retrospectively. Finally, although the increase in amino acid concentrations suggests an effect from nutrition, without amino acid concentrations from controls we do not know whether this increase is nutrition- or recovery-related and we cannot make any inference regarding protein absorption.

5. Conclusion

In this prospective feasibility study in selected ventilated non-septic ICU patients expected to tolerate enteral nutrition, we achieved the preset protein intake target of ≥1.2 g/kg/day early during ICU stay and avoid energy overfeeding by using an enteral formula with a high protein-to-energy ratio. Plasma concentrations of all essential amino acids increased after two days which may favour protein synthesis. Randomized controlled trials in different patient groups are needed to evaluate the effects of the early use of a high protein-to-energy nutrition on protein metabolism and clinical outcomes.

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Statement of authorship

WGPML participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafted the manuscript. ND and BB participated in acquisition of data and revised the manuscript. ARJG participated in interpretation of data and revised the manuscript. PJMW participated in the conception and design of the study and interpretation of data, and revised the manuscript. HMO participated in the conception and design of the study and analysis and interpretation of data, and revised the manuscript.

All authors read and approved the final version of the manuscript.

Conflict of interest

WGPML has received congress support and speaker's honorary from Baxter and Fresenius-Kabi.

ARJG holds stock options as commissioner of a start-up company for development of new antibiotics.

PJMW has received funds from Baxter, Fresenius-Kabi, Nestlé, and Nutricia.

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ND and BB have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.11.012.

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