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Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

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Abstract

Purpose: We assessed the effects of early goal-directed nutrition (EGDN) vs. standard nutritional care in adult intensive care unit (ICU) patients.

Methods: We randomised acutely admitted, mechanically ventilated ICU patients expected to stay longer than 3 days in the ICU. In the EGDN group we estimated nutritional requirements by indirect calorimetry and 24-h urinary urea aiming at covering 100% of requirements from the first full trial day using enteral and parenteral nutrition. In the standard of care group we aimed at providing 25 kcal/kg/day by enteral nutrition. If this was not met by day 7, patients were supplemented with parenteral nutrition. The primary outcome was physical component summary (PCS) score of SF-36 at 6 months. We performed multiple imputation for data of the non-responders.

Results: We randomised 203 patients and included 199 in the intention-to-treat analyses; baseline variables were reasonably balanced between the two groups. The EGDN group had less negative energy ($p < 0.001$) and protein ($p < 0.001$) balances in the ICU as compared to the standard of care group. The PCS score at 6 months did not differ between the two groups (mean difference 0.0, 95% CI −5.9 to 5.8, $p = 0.99$); neither did mortality, rates of organ failures, serious adverse reactions or infections in the ICU, length of ICU or hospital stay, or days alive without life support at 90 days.

Conclusions: EGDN did not appear to affect physical quality of life at 6 months or other important outcomes as compared to standard nutrition care in acutely admitted, mechanically ventilated, adult ICU patients.

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Keywords: Critical care, Nutrition, Protein, Indirect calorimetry, Quality of life, Clinical outcome

Introduction

The importance of nutrition support during critical illness in the intensive care unit (ICU) has long been recognised [1] and various aspects of nutritional care have been investigated in randomised trials over the last few years [2–6]. The results of these trials appear, however, diverging [7], which may contribute to the variations seen in clinical practice and in national and international guidelines for nutrition therapy in the ICU setting [8–12].

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Individualised goal-directed nutrition therapy with measured requirements has been proposed as one of several potentially beneficial strategies, and in particular the focus on combined energy and protein nutrition has been hypothesised to improve short- and long-term outcomes in ICU patients [13–15]. However, no randomised trials have assessed individualised energy and protein supply to ICU patients based on measured requirements.

Measuring resting energy expenditure (REE) in ventilated patients in the ICU with indirect calorimetry (IC) as a goal for energy requirements is recommended in international guidelines [9, 12]. Protein requirements may be estimated on the basis of 24-h urinary urea excretion using Bistrian's equation [16].

The objective of the randomised EAT-ICU trial was to assess the effects of individualised energy and protein nutrition optimised by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance) on physical quality of life at 6 months in acutely admitted, adult ICU patients. We hypothesised that the early goal-directed nutrition (EGDN) would improve physical quality of life at 6 months compared to standard nutrition care in patients admitted to the ICU.

Methods

Trial design

EAT-ICU was a single-centre, randomised, stratified, parallel-group, clinical trial with blinded outcome assessment, conducted at the Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Denmark between June 2013 and October 2016 (last patient randomised in April 2016, followed by 6 months follow-up). The protocol was approved by The National Committee on Health Research Ethics (case no. 1300461), the Danish Medicines Agency (EudraCT no. 2011-002547-94) and the Danish Data Protection Agency (j. no. 30-0933), and registered at http://www.clinicaltrials.gov (identifier NCT01372176). The trial was monitored by the Good Clinical Practice (GCP) Unit, University of Copenhagen (GCP-monitor B. Sonne), according to EU Directive 2001/20, and adhered to the statutory order of GCP and the Declaration of Helsinki [17]. Full details on trial conduct, definitions and procedures, including the statistical analyses plan, have been published [18]. The current manuscript has been prepared in accordance with the CONSORT guidelines [19].

Participants

We consecutively screened patients 18 years of age or older within 24 h of any ICU admission for inclusion if they were (1) acutely admitted to the ICU; (2) had an expected length of stay in the ICU of more than 3 days; (3) were mechanically ventilated via a cuffed endotracheal or tracheotomy tube; (4) had a central venous catheter and (5) were expected to read and understand Danish. No formal nutrition risk screening was performed, but we excluded patients with a BMI equal to or below 17 and those who appeared malnourished. A full list of inclusion and exclusion criteria is presented in the Electronic Supplementary Material (ESM). We enrolled patients only if informed consent was obtained from two physicians, who were independent of the trial. As soon as possible, the next-of-kin and general practitioner of the patient were asked for consent. Lastly, written informed consent was obtained from the patient if possible.

Randomisation and blinding

A person independent of the trial prepared two computer-generated randomisation lists with random block size, varying from 2 to 6, using the SAS 9.1.3 software (SAS Institute, Cary, NC). Included patients were randomised 1:1 to the EGDN (intervention) or standard of care (control) groups stratified according to presence or absence of active haematologic malignancy, as these patients have high mortality [20]. Allocation was concealed by the use of consecutively numbered, sealed, opaque envelopes in accordance with the SNOSE principles [21]. After inclusion, investigators drew an envelope from either of two boxes, one per stratum, to allocate the patient.

The allocated nutrition strategy was not masked to research or clinical staff during the trial period. Investigators assessing quality of life at 6 months (the primary outcome) and rates of nosocomial infections (a secondary outcome) as well as the statistician performing the primary analysis of the primary outcome were all blinded to the intervention.

Interventions

Patients allocated to the EGDN group had energy expenditure measured by indirect calorimetry (Quark RMR Indirect Calorimeter, COSMED, Rome, Italy) as soon as possible after inclusion and thereafter every other day until tracheal extubation or ICU discharge. The 24-h urinary urea excretion was assessed daily and converted to metabolic protein consumption using Bistrian's equation [16]. We gave nutrition accordingly. Protein was provided as at least 1.5 g/kg/day at all times during admission, regardless of urea excretion. We aimed at covering 100% of measured requirements from the first full trial day and throughout the entire ICU stay to a maximum of 90 days. Calories from any propofol administration were included in the calculation of total calories. Enteral nutrition (Fresubin Original, Fresubin Energy

or Fresubin HP-energy, Fresenius Kabi) was initiated within 24 h of randomisation and supplemented parenterally (SmofKabiven, Mixamin Glucos or Glucose 50%, Vamin and SMOFlipid, Fresenius Kabi) if necessary to reach goal requirements. In case of sustained hyperglycaemia (defined as provision of insulin at least 5 IU/h for more than 12 consecutive hours), we reduced the provision of glucose, and at a plasma urea above 20 mmol/l, we reduced the provision of protein by 0.2 g/kg/day. More details are presented in the ESM, Fig. S1 and in the published protocol [18].

Patients allocated to the standard of care group had energy requirements calculated as 25 kcal/kg/day as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) [8]. Enteral nutrition (Fresubin Original, Fresenius Kabi) was initiated within 24 h of randomisation and gradually increased over the following days as tolerated by the patient. If the calculated goal was not met by day 7, we supplemented with parenteral nutrition (SmofKabiven, Mixamin Glucos or Glucose 50%, Vamin and SMOFlipid, Fresenius Kabi) as recommended [22].

For both groups, we aimed at blood glucose levels between 6 and 10 mmol/l using intravenous insulin if needed [23, 24]. We measured and substituted trace elements, including phosphate and magnesium, aiming at values within normal ranges, and gave multivitamins, and vitamin B if deemed relevant. We measured gastric residuals every 4–6 h; at 150–500 ml the rate of EN was reduced. Prokinetic agents were used at the clinicians' discretion. Both groups were mobilised to the edge of the bed or a chair as soon as possible, as per routine practice in our ICU.

Outcome measures

The primary outcome was physical quality of life 6 months after randomisation as assessed by the physical component summary (PCS) score of the Medical Outcomes Study 36-item short form health survey version 2 [25, 26]. The questionnaire survey was performed as a phone interview by research personnel who were blinded for the intervention. Patients who had died at 6 months were given the lowest possible PCS score (zero).

The secondary outcomes were 28-day, 90-day and 6-month mortality and survival time for all patients 6 months after randomisation of the last patient (4 October 2016). We also recorded the mental component summary (MCS) score of SF-36 at 6 months, length of stay in ICU and in hospital among 6 months survivors, percentage of days alive and without renal replacement therapy (RRT), mechanical ventilation, or inotropic/vasopressor support during the first 90 days after randomisation, acute use of RRT and new organ failure in the ICU [defined as Sequential Organ Failure Assessment (SOFA) score of 3 or above in any of the categories [27], excluding the Glasgow Coma Scale (GCS) score] in patients who did not have that particular organ failure at randomisation. Secondary outcomes also included rates of serious adverse reactions (defined as allergic reactions or elevated plasma levels of liver enzymes), and nosocomial infections [28] from 48 h after inclusion until ICU discharge as assessed by staff specialists in the ICU who were blinded to the intervention, accumulated energy and protein balances, doses of insulin, rates of severe hyper- and hypoglycaemia (defined as blood glucose greater than 15 mmol/l and at most 2.2 mmol/l, respectively). Data for the outcomes were obtained by the trial investigators or research nurses, from patient charts, national registries and telephone contact with patients.

Statistical analysis

We estimated that 200 patients were needed to show a 15% relative reduction in the primary outcome (PCS score at 6 months) corresponding to a difference of 5.5 points (minimal clinical important difference defined as half a standard deviation from our observed dataset) between the intervention and control group at a significance level of 0.05 and a power of 80%. The calculations were based on a PCS score of 37.5, SD 10.65 among survivors from our own data [29] and a 6-month mortality of 40% based on estimations from the clinical database of the Department of Intensive Care (CIS v. 3.7.1, Daintel, Copenhagen). We conducted all analyses according to the predefined statistical analysis plan published online before inclusion of the last patient [18] (and in ESM). Our primary analyses were done in the intention-to-treat-population comprising all randomised patients, except four patients, two in each group, who were excluded post-randomisation (one in each group withdrew consent for the use of data and one in each group died before receiving the intervention) [30] (Fig. 1). For the primary analysis of the primary outcome, the statistician did multiple imputation, based on chained equations as implemented in the R package 'mice', to account for the missing PCS scores of the 23 non-responders at 6-month follow-up [31]. As a sensitivity analysis we analysed the primary outcome in the complete case population (comprising all patients for whom we had a valid PCS score and those who had died) and in the two per-protocol populations: (PP#1) excluding patients who were stopped/withdrawn or monitoring revealed that one or more inclusion or exclusion criteria were violated; (PP#2) excluding patients who were stopped/withdrawn or monitoring revealed that one or more inclusion or exclusion criteria were violated, or one or more parental nutrition boluses (any combination of glucose and amino

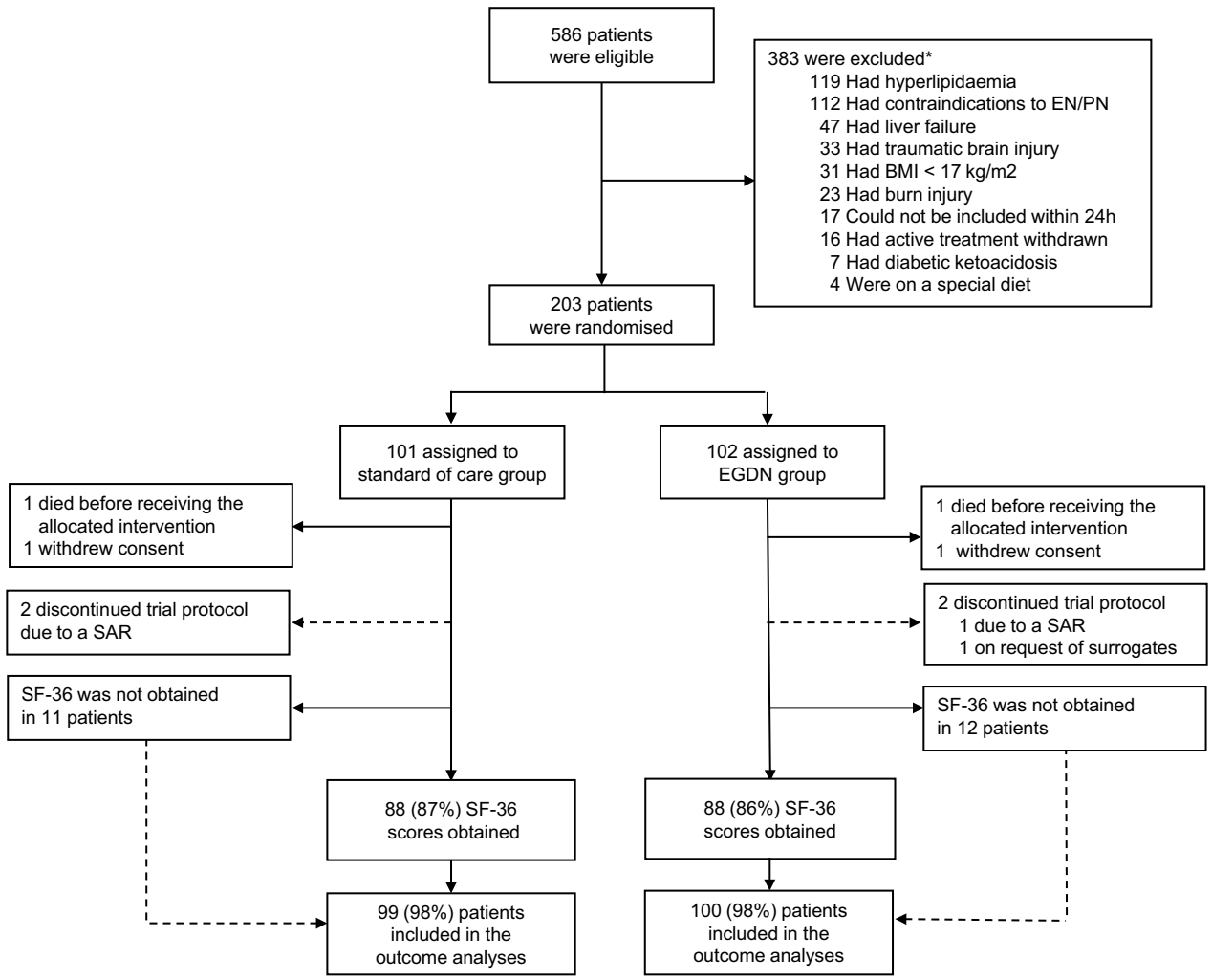

Fig. 1 Screening, assessment and follow-up in the EAT-ICU trial. Patients were not screened if more than 24 h had passed since ICU admission. *Some patients had more than one reason for exclusion. *BMI* body mass index, *EGDN* early goal-directed, *EN* enteral nutrition, *PN* parenteral nutrition, *SAR* serious adverse reaction, *SF-36* short form-36

acids and/or lipids) were given to patients randomised to the standard of care group before trial day 8.

The primary outcome was analysed by general linear regression analysis adjusted by the stratification variable (haematologic malignancy); as a sensitivity analysis we used Wilcoxon's test. We conducted two preplanned subgroup analyses, (1) in patients with and without plasma urea greater than 20 mmol/l or use of any form of RRT at baseline (assessing a possible better intervention effect in patients without renal impairment) and (2) in patients with baseline Simplified Acute Physiology Score (SAPS) II above the median of all included patients (assessing a possible better intervention effect in patients with SAPS II below the median).

For the secondary outcomes we used a Chi-squared test for dichotomous variables, regression analyses or Wilcoxon's test for rate and ordinal data and data expected to be non-normally distributed. Cox proportional hazards model was used for time-dependent variables. Data on accumulated energy and protein balances were analysed using a repeated measures mixed effect model including days in the ICU as a factor variable. Data are presented as means (SD), medians [interquartile ranges (IQR)], or number (%) as appropriate. We computed all analyses in the software SAS version 9.4, GraphPad Prism 4 or R version 3.2.2 and used two-tailed tests and p values below 5% to indicate statistical significance.

Results

Between June 2013 and April 2016, 2265 adult patients were acutely admitted to the ICU (mean 67 patients/month). We screened 586 patients who fulfilled the inclusion criteria and excluded 383 patients for the reasons given in Fig. 1. We randomised the remaining 203 (35%) (Fig. 1); 102 patients were allocated to the EGDN group and 101 to the standard of care group. One patient in each group died before receiving the intervention, and one in each group withdrew consent for the use of data; thus, we analysed data from 199 patients (99%). Baseline variables were reasonably balanced (Table 1; additional baseline data are presented in the ESM, Table S1).

Nutrition protocol

Ninety-five per cent of the patients received nutrition according to the protocol; six patients did not adhere to the EGDN protocol (they had reduced caloric and/or protein provision at clinicians' discretion) and five patients did not adhere to the standard of care protocol (they all received one or more boluses of parenteral nutrition before trial day 8).

Median calculated energy requirement (25 kcal/kg/day) did not differ between the two groups, but median measured REE and protein requirement calculated on the basis of urinary urea excretion were different between the groups (Table 2; Fig. 2 and Table S2

Table 1 Baseline characteristics

Variable	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)
Age, years	63 (51–72)	68 (52–75)
Male sex, no. (%)	65 (65%)	59 (60%)
Actual body weight, kg	78 (67–90)	80 (70–90)
BMI[a], kg/m^2	22 (20–26)	22 (20–25)
Source of ICU admission, no. (%)		
Emergency department	31 (31%)	30 (30%)
General ward	45 (45%)	38 (38%)
Operating or recovery room	6 (6%)	12 (12%)
Other ICU[b]	10 (10%)	11 (11%)
Other hospital	8 (8%)	8 (8%)
Admission type, no. (%)		
Medical	52 (52%)	43 (43%)
Emergency surgery	43 (43%)	53 (54%)
Elective surgery	5 (5%)	3 (3%)
Diagnoses and procedures, no. (%)		
Haematologic malignancy[c]	13 (13%)	12 (12%)
Multiple trauma	8 (8%)	10 (10%)
Severe sepsis	47 (47%)	47 (47%)
Dialysis on admission	6 (6%)	5 (5%)
Mechanical ventilation	100 (100%)	99 (100%)
Days in hospital before ICU admission, days	0.9 (0.2–4.1)	1.1 (0.2–4.8)
Time from ICU admission to randomisation, h	14 (10–20)	13 (7–20)
Nutrition given in ICU prior to randomisation		
Energy, kcal/day	140 (24–260)	122 (30–275)
Protein, g/day	0 (0–0)	0 (0–0)
SAPS II[d]	47 (37–54)	48 (39–59)
SOFA score[e]	8 (6–11)	8 (5–10)

Values are medians (interquartile ranges) or numbers (%). Additional baseline characteristics are presented in Table S1, ESM

BMI body mass index, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment

[a] BMI was calculated as estimated weight (kg) divided by height (cm) squared

[b] Patients were included within 24 h of admission to any ICU

[c] Stratification variable

[d] SAPS II was calculated from 17 variables. Scores range from 0 to 163 with higher scores indicating more severe disease

[e] SOFA score includes subscores ranging from 0 to 4 for each of 5 components (circulation, lungs, liver, kidneys and coagulation), aggregated scores ranging from 0 to 20 with higher scores indicating more severe organ failure. The scores were modified as cerebral failure was not assessed

in the ESM). Patients allocated to the EGDN group received more energy and protein compared to those allocated to the standard of care group: energy goals 97% (91–100) of indirect calorimetry in the EGDN group vs. 64% (40–84) of 25 kcal/kg/day in the standard of care group; protein goals 97% (75–115) of the minimum goal of 1.5/g/kg/day in the EGDN group vs. 45% (27–62) of the goal of 1.2 g/kg/day in the standard of care group.

Primary outcome measure

We obtained PCS scores from 176 (88%) patients, 88 (86%) patients in the EGDN group and 88 (87%) patients in the standard of care group. Of these, 37 (37%) patients in the EGDN and 35 (35%) patients in the standard of care group had died and were given a PCS score of zero. Values for the missing PCS scores of the 23 (12%) non-responding patients were imputed by multiple imputation (Table S3 in the ESM). We observed no difference between the two groups in the primary analysis of PCS scores at 6 months in the imputed dataset, adjusted for presence of haematologic malignancy; EGDN group (mean PCS score 22.9); standard of care group (mean PCS score 23.0), mean difference 0.0 (95% CI −5.9 to 5.8), $p = 0.99$ (Table 3). We had similar results in the predefined sensitivity analyses of the complete case population, the per-protocol populations, the two predefined subgroups and in the analyses adjusted for the stratification variable (haematologic malignancy) and the predefined baseline variables (age and SOFA score) (Tables S4 and S5, ESM).

Secondary outcome measures

The EGDN group had higher cumulative energy and protein balances at day 3 and 7 and over the course of the ICU stay as compared to the standard of care group (Table 3). More patients in the EGDN group experienced at least one episode of hyperglycaemia, and the cumulative dose of insulin administered was higher in the EGDN group as compared to the standard of care group (Table 3). None of the remaining secondary outcomes differed between the EGDN group and the standard of care group (Table 3; Fig. 3).

Discussion

In this single-centre, randomised trial with blinded outcome assessment of acutely admitted, mechanically ventilated, adult ICU patients, we succeeded in delivering a combined energy–protein nutrition based on individualised goals determined by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance). Patients allocated to the EGDN group received more energy and protein in the ICU, and consequently had higher energy and protein balances compared to patients allocated to the standard of care group. However, this difference in nutritional provision between the groups was not associated with an improved physical quality of life at 6 months as assessed by the PCS score, nor did it appear to affect mortality, rates of new organ failures, serious adverse reactions or nosocomial infections in the ICU, length of ICU or hospital stay, or days alive without life support at 90 days. However, more patients in the EGDN group had severe hyperglycaemia and received higher doses of insulin as compared to those in the standard of care group.

Table 2 Nutrition characteristics in ICU after randomisation

Variable	Early goal-directed nutrition ($N = 100$)	Standard of care ($N = 99$)
Measured[a] energy requirement, kcal/day	2069 (1816–2380)	1887 (1674–2244)
Calculated[b] energy requirement, kcal/day	1950 (1750–2125)	1875 (1650–2100)
Energy intake, kcal/day	1877 (1567–2254)	1061 (745–1470)
Energy balance[c], kcal/day	−66 (−157 to −6)	−787 (−1223 to −333)
Measured[d] protein requirement, g/kg/day	1.63 (1.36–2.05)	1.16 (0.89–1.62)
Protein intake, g/kg/day	1.47 (1.13–1.69)	0.50 (0.29–0.69)
Protein balance[c], g/kg/day	−0.28 (−0.76 to 0.11)	−0.69 (−1.02 to −0.38)
Plasma urea, mmol/l	13.5 (8.7–21.9)	9.0 (5.6–14.4)
24-h urinary urea, mmol/day	516 (368–760)	320 (175–482)

Values are medians (interquartile ranges). Trial day 1 to discharge for full patient cohort including patients receiving reduced protein provision because of a plasma urea value >20 mmol/l

[a] Measured by indirect calorimetry as soon as possible after randomisation and thereafter every other day throughout the ICU admission as long as the patient had a cuffed tube

[b] Calculated as 25 kcal/kg/day as recommended by ESPEN

[c] Energy and protein balances were calculated as measured requirements minus intake per day

[d] Calculated on the basis of 24-h urinary urea using Bistrian's Equation [metabolic protein requirement, g/day: 24-h urinary urea (mmol/day) × 0.028 × 100/16 + 25]

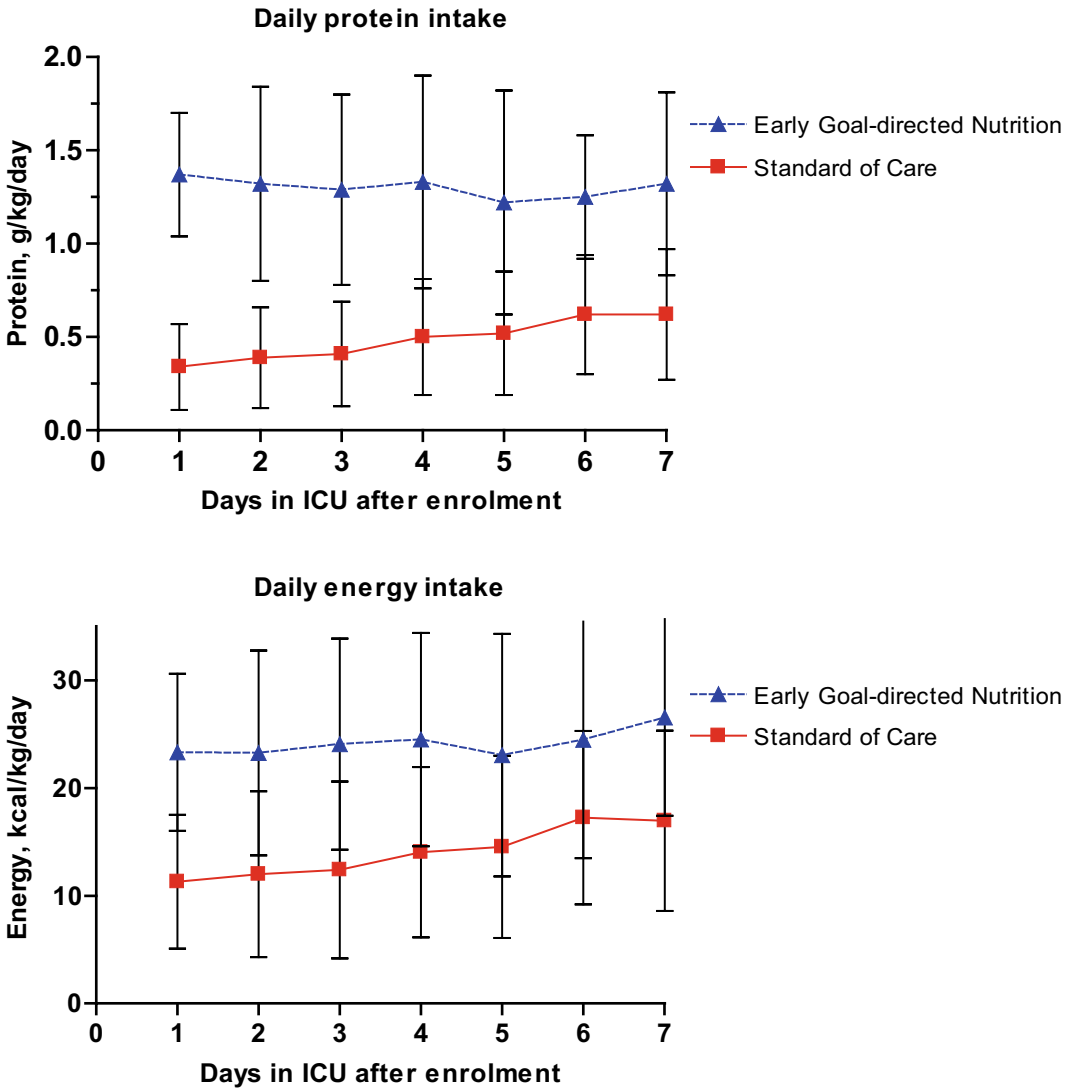

Fig. 2 Mean daily protein and energy intake per trial day 1–7 for the full patient cohort including those who had protein provision reduced because of a plasma urea value above 20 mmol/l. *Error bars* are SD for means in the two groups at each time point

Our observations are in line with the two previous randomised clinical trials on ICU nutrition using indirect calorimetry [4, 5]. However, we tested a nutrition therapy focussing *both* on provision of energy and protein guided by measurements of nutritional requirements. Our EGDN group reached a degree of coverage of energy targets similar to the intervention groups in the two previous trials [4, 5], but we delivered a higher amount of protein. We assessed energy requirements by indirect calorimetry and applied caloric load accordingly, as advised in international guidelines [9, 12]. Measurements were performed by trained personnel according to recommendations [32], and we used a device that had been validated for use in mechanically ventilated patients [33–35]. In the recent years some studies have indicated benefits of underfeeding in the acute phase of critical illness [36, 37]. We may have obtained different results if the intervention had been applied at a later phase of critical illness.

Regarding protein, we aimed for providing at least 1.5 g/kg/day from day 1 after inclusion in the EGDN group (as in the high protein group in our previously published cohort study [38]), in order to verify the possible association between a higher protein provision and improved outcome as previously observed [38]. We largely succeeded at reaching the defined protein goal.

Table 3 Primary and secondary outcome measures in the two intervention groups

Primary outcome measure	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Adjusted mean difference (95% CI)	*p* value
PCS score at 6 months adjusted for presence of haematologic malignancy, mean (SD)	22.9 (21.8)	23.0 (22.3)	−0.0[a] (−5.9 to 5.8)	0.99

Secondary outcome measures	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Relative risk or mean difference (95% CI)	*p* value
Vital status, no. (%)				
Dead at day 28	20 (20%)	21 (21%)	0.94 (0.55–1.63)	0.83
Dead at day 90	30 (30%)	32 (32%)	0.93 (0.61–1.40)	0.72
Dead at 6 months	37 (37%)	34 (34%)	1.08 (0.74–1.57)	0.70
Length of stay among 6-month survivors, median days (IQR)				
ICU	7 (5–22)	7 (4–11)	NA	0.21
Hospital	30 (12–53)	34 (14–53)	NA	1.00
Percentage of days alive without life support at day 90, median (IQR)				
RRT	100% (97–100)	100% (97–100)	NA	0.64
Mechanical ventilation	86% (39–96)	92% (56–96)	NA	0.27
Inotrope/vasopressor support	96% (82–98)	96% (84–98)	NA	0.67
Time to new organ failure, mean days (SD)	5.4 (0.4)	5.9 (0.5)	NA	0.33[b]
New organ failure in ICU, no. (%)	81 (81%)	77 (78%)	1.04 (0.90–1.20)	0.57
Time to death, mean days (SD)	60 (13)	91 (24)	NA	0.51[c]
New use of RRT in ICU, no. (%)	22 (22%)	17 (17%)	1.28 (0.73–2.26)	0.39
Time to any infection, mean days (SD)	20 (1)	51 (9)	NA	0.80[b]
Nosocomial infections, no. (%)				
Any	19 (19%)	12 (12%)	1.57 (0.80–3.05)	0.18[d]
Pneumonia	4 (4%)	4 (4%)		
Bloodstream infection	5 (5%)	4 (4%)		
CVC-related sepsis	3 (3%)	0 (0%)		
Intra-abdominal infection	3 (3%)	3 (3%)		
Urogenital sepsis	5 (5%)	1 (1%)		
Skin and soft-tissue infection	3 (3%)	0 (0%)		
Severe adverse reaction, no. (%)	1 (1%)	2 (2%)	NA	–[e]
Mental component summary score at 6 months, mean (SD)	23.6 (24.5)	26.8 (25.0)	−3.1 (−10.5 to 4.2)	0.40
Cumulative energy balance, mean kcal				<0.0001[f]
Trial day 1	−211	−1011	800 (594–1005)	
Trial day 3	−220	−924	704 (483–925)	
Trial day 7	−298	−702	404 (89–719)	
Last trial day	−249	−747	498 (282–715)	
Cumulative protein balance, mean g/kg				<0.0001[f]
Trial day 1	0.07	−0.70	0.77 (0.58–0.95)	
Trial day 3	−0.59	−0.83	0.24 (−0.02 to 0.50)	
Trial day 7	−0.65	−0.75	0.10 (−0.22 to 0.42)	
Last trial day	−0.56	−0.65	0.09 (−0.18 to 0.34)	

Table 3 continued

Secondary outcome measures	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Relative risk or mean difference (95% CI)	*p* value
Cumulative insulin dose in ICU, median IU (IQR)[g]	86 (2–530)	0 (0–39)	262 (71–453)	0.008
No. of patients (%) with at least one episode of				
Blood glucose ≤2.2 mmol/l	2 (2%)	1 (1%)	NA	–[e]
Blood glucose ≥15 mmol/l	52 (52%)	25 (25%)	2.06 (1.40–3.03)	0.0001

Values are medians [interquartile ranges (IQR)], means [standard deviations (SD)] or numbers (%)

CI confidence interval, *CVC* central venous catheter, *ICU* intensive care unit, *IU* insulin units, *PCS* physical component summary, *RRT* renal replacement therapy, *NA* no answer

[a] Mean difference adjusted for the stratification variable, resulting in minor difference between the absolute mean difference and the adjusted difference. The analysis was done on the imputed dataset

[b] Cox proportional hazards model; death treated as a competing event

[c] Cox proportional hazards model; survival status in the intention-to-treat population 6 months after randomisation of the last patient

[d] Analysed by Chi-squared test. Some patients had more than one infection

[e] Analysis planned but not executed because of the low number of events

[f] Analysed by repeated measures mixed effect model

[g] The mean difference is reported as mean (95% CI)

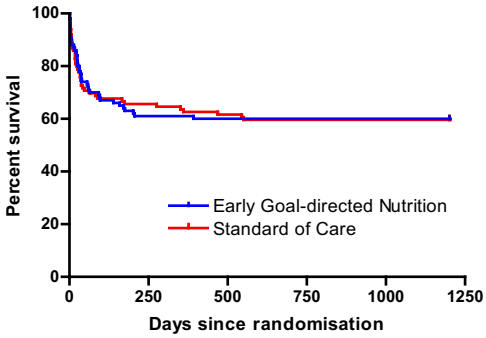

Fig. 3 Time to death analysis. The figure shows the survival curves for all included patients at 6 months after randomisation of the last patient. Kaplan–Meier analysis showed that survival time did not differ between the EGDN group and the standard of care group. Log rank $p = 0.51$

Our earlier observational study suggested an association between higher protein/AA intake and lower mortality. In addition to the obvious explanation that a higher intake is more easily obtained in patients who are less ill, it should also be noted that only sepsis and burn patients were included in the observational study and that ICU mortality was about 20%, which is higher than in the present study (data not shown).

Current recommendations on protein intake for the ICU patient are based mainly on observational data and on smaller clinical trials [39]. Even though the beneficial effect of a combined energy–protein nutrition has been proposed [15], none of the recently published nutrition trials have included protein provision explicitly in their feeding protocols. Whether this difference in provision of protein contributes to the diverging results obtained between our and the previous trials [4, 5] cannot be answered. The EGDN group had a much higher urinary urea excretion as compared to the standard of care group. Apparently, the protein balance improved from −0.69 in standard of care group to −0.28 in the EGDN group, i.e. by 0.41 g/kg/day. However, plasma urea also increased, and assuming a distribution volume of 60% of body weight, the increase in plasma urea nitrogen closely matches the apparent increase in protein balance. This indicates that no net protein gain was obtained with the extra supply of protein. Our reduction of protein load at a plasma urea above 20 mmol/l may explain why increased use of RRT was not observed in the EGDN group.

We performed blinded assessment of infections using definitions proposed for ICU patients [28] and used in previous nutrition trials [4, 6], but found no difference between the groups. The trial by Heidegger et al. reported a reduced rate of infections with optimised nutrition, but only from day 9 to 28 [5] and not in the intervention period from day 4 to 8, hampering the interpretation of these results. Whether the differences between our trial and previous trials arise from different methods of analysing nosocomial infections is not clear.

The strengths of our trial include low risk of bias owing to the randomised design, blinded outcome assessment and publication of the trial protocol and statistical analysis plan before inclusion of the last patient [18]. We tested an individualised, multimodal nutrition therapy in the EGDN group but remained pragmatic with regards to all concomitant interventions that were given according to

usual care for all included patients. We opted to use conventional enteral and parenteral products, which were administered by clinical staff according to prescription and routine practice. Actual delivery of the prescribed amount of nutrition is problematic, a fact that has been documented in the literature and is seen in everyday clinical practice [3, 14, 40]. In our trial we succeeded in providing patients with nutrition according to the goals defined in the protocol.

The EAT-ICU trial also has a number of limitations. The trial was performed in a single ICU and the nutrition prescriptions were done by trial investigators only; thus the results may not be generalisable to other settings. Masking of the allocated nutrition protocol to clinical staff was not feasible and full blinding, therefore, not possible; this may have introduced bias. We used indirect calorimetry and 24-h urinary urea to estimate requirements, and such methods are complex and may not be viable in all settings. Some baseline imbalance may have occurred, potentially confounding the results. Our patients had median two measurements of indirect calorimetry done, and for some patients this meant that energy prescriptions were stationary after extubation. We initially measured handgrip strength, but were not able to properly standardise these measurements and stopped using it. We did not register the level of physical activity, use of sedatives or depth of sedation in the two groups. We had missing values for our primary outcome for 23 (12%) patients, and these values were imputed. The patients who had died at 6-month follow-up were ascribed a PCS score of zero, and we did not account for this in our sample size estimation. Also the observed mortality was lower than expected. Consequently the power of our trial was reduced, and we cannot exclude a difference in PCS score between the two groups within the observed 95% CI of −6 to 6. More patients in the EGDN group had hyperglycaemia and they received a higher dosage of insulin than those in the standard of care group. We cannot know if this affected the overall results of the trial.

Conclusions

We conducted a single-centre, randomised, stratified, parallel-grouped, outcome assessor-blinded clinical trial including 203 acutely admitted, adult ICU patients who were mechanically ventilated, to test the effects of a combined and individualised energy–protein nutrition guided by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance), i.e. EGDN. The EGDN group received more energy and protein and had lower nutritional deficits in the ICU as compared to the standard of care group, but we observed no difference between the two groups in physical quality of life at 6 months or in mortality, rates of organ failures, serious adverse reactions or nosocomial infections in the ICU, length of ICU or hospital stay, or days alive without life support at 90 days.

Electronic supplementary material
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Author contributions
MJA, JW, JK and AP designed the study. MJA, JW, CC, UGP, RHR, MS, THJ, MRB and MHM collected the data. MJA and AP analysed the data and TL and MBM assisted with statistical analyses. MJA, AP and JK planned the article and MJA produced a detailed outline of the manuscript. All authors reviewed the article critically, contributed significantly and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest
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References

1. Van den Berghe G (2017) The 2016 ESPEN Sir David Cuthbertson lecture: interfering with neuroendocrine and metabolic responses to critical illness: From acute to long-term consequences. Clin Nutr 36:348–354
2. Casaer MP, Mesotten D, Hermans G et al (2011) Early versus late parenteral nutrition in critically ill adults. N Engl J Med 365:506–517
3. Harvey SE, Parrott F, Harrison DA et al (2014) Trial of the route of early nutritional support in critically ill adults. N Engl J Med 371(18):1673–1684
4. Singer P, Anbar R, Cohen J et al (2011) The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med 37:601–609
5. Heidegger CP, Berger MM, Graf S et al (2013) Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 381:385–393
6. Doig GS, Simpson F, Sweetman EA et al (2013) Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 309:2130–2138
7. Arabi YM, Casaer MP, Chapman M et al (2017) The intensive care medicine research agenda in nutrition and metabolism. Intensive Care Med. doi:10.1007/s00134-017-4711-6.

8. Kreymann KG, Berger MM, Deutz NEP et al (2006) ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 25:210–223
9. Singer P, Berger MM, van den Berghe G et al (2009) ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 28:387–400
10. Dhaliwal R, Cahill N, Lemieux M, Heyland DK (2014) The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. Nutr Clin Pract 29:29–43
11. Reintam Blaser A, Starkopf J, Alhazzani W et al (2017) Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 43:380–398
12. McClave SA, Taylor BE, Martindale RG et al (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enter Nutr 40:159–211
13. Weijs PJM, Stapel SN, de Groot SDW et al (2012) Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr 36:60–68
14. Elke G, Wang M, Weiler N et al (2014) Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care 18:R29
15. Oshima T, Deutz NE, Doig G et al (2015) Protein-energy nutrition in the ICU is the power couple: a hypothesis forming analysis. Clin Nutr 35:968–974
16. Blackburn GL, Bistrian BR, Maini BS et al (1977) Nutritional and metabolic assessment of the hospitalized putient. JPEN J Parenter Enter Nutr 1:11–22
17. Mellin-Olsen J, Staender S, Whitaker DK, Smith AF (2010) The Helsinki declaration on patient safety in anaesthesiology. Eur J Anaesthesiol 27:592–597
18. Allingstrup MJ, Kondrup J, Wiis J et al (2016) Early goal-directed nutrition in ICU patients (EAT-ICU): protocol for a randomised trial. Dan Med J 63:1–6
19. Moher D, Hopewell S, Schulz KF et al (2012) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 10:28–55
20. Perner A, Haase N, Guttormsen AB et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134
21. Doig GS, Simpson F (2005) Randomization and allocation concealment: a practical guide for researchers. J Crit Care 20:187–191
22. Martindale RG, McClave SA, Vanek VW et al (2009) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 37:1757–1761
23. Finfer S, Chittock DR, Su SY et al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283–1297
24. Wiener RS, Wiener DC, Larson RJ (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 300:933–944
25. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483
26. Chrispin PS, Scotton H, Rogers J et al (1997) Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia 52:15–23
27. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707–710
28. Calandra T, Cohen J (2005) The International Sepsis Forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 33:1538–1548
29. Schrøder MA, Poulsen JB, Perner A (2011) Acceptable long-term outcome in elderly intensive care unit patients. Dan Med Bull 58:A4297
30. Fergusson D, Aaron SD, Guyatt G, Hébert P (2002) Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 325:652–654
31. Schafer JL, Graham JW (2002) Missing data: our view of the state of the art. Psychol Methods 7:147–177
32. Compher C, Frankenfield D, Keim N, Roth-Yousey L (2006) Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc 106:881–903
33. Sundström M, Tjäder I, Rooyackers O, Wernerman J (2013) Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr 32:118–121
34. Graf S, Karsegard VL, Viatte V et al (2014) Evaluation of three indirect calorimetry devices in mechanically ventilated patients: which device compares best with the Deltatrac II(®)? A prospective observational study. Clin Nutr 34:60–65
35. Allingstrup MJ, Kondrup J, Perner A et al (2016) Indirect calorimetry in mechanically ventilated patients: a prospective, randomized, clinical validation of 2 devices against a gold standard. JPEN J Parenter Enteral Nutr. doi:10.1177/0148607116662000
36. Marik PE, Hooper MH (2015) Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. Intensive Care Med 42(3):316–323
37. Elke G, van Zanten ARH, Lemieux M et al (2016) Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 20:117
38. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A et al (2012) Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 31:462–468
39. Hoffer LJ, Bistrian BR (2012) Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr 96:591–600
40. Alberda C, Gramlich L, Jones N et al (2009) The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 35:1728–1737