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Original article

Macronutrient intake and outcomes of ICU patients with refeeding hypophosphatemia

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SUMMARY

Background: Normocaloric vs. calorie-restricted feeding in Intensive Care Unit (ICU) patients with refeeding hypophosphatemia (RH) is associated with increased mortality rates. Until now, only total energy provision has been studied. Data on individual macronutrients (proteins, lipids, and carbohydrates) and clinical outcomes are lacking. This study evaluates associations between macronutrient intake among RH patients during the first week of ICU admission and clinical outcomes.

Methods: A single-centre retrospective observational cohort study was conducted among prolonged mechanically ventilated RH ICU patients. The primary outcome was the association of separate macronutrient intakes during the first week of ICU admission with 6-month mortality, adjusted for relevant variables. Other parameters included ICU-, hospital- and 3-month mortality, mechanical ventilation duration and length of ICU and hospital stay. Macronutrient intakes were subsequently analyzed during day 1–3 and day 4–7 of ICU admission.

Results: In total, 178 RH patients were included. Six-month all-cause mortality was 29.8%. Higher protein intake during days 1–3 of ICU admission (>0.71 g/kg*day; HR 2.224, 95%CI 1.261–3.923, p = 0.006), higher age (HR 1.040, 95%CI 1.015–1.066, p = 0.002) and higher APACHE II scores on ICU admission (HR 1.086, 95%CI 1.034–1.140, p = 0.001) were associated with increased 6-month mortality. No differences in other outcomes were observed.

Conclusion: High protein - not carbohydrate or lipid - intake during the first three days of ICU admission in patients with RH is associated with increased 6-month mortality, but not short-term outcomes. We hypothesize a time-dependent and dose–response relationship between protein intake and mortality in refeeding hypophosphatemia ICU patients, although additional (randomized controlled) studies are needed to confirm this hypothesis.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; 95%CI, 95% Confidence Interval; EN, Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; G, Grams; HR, Hazard Ratio; ICU, Intensive Care Unit; IQR, Interquartile Range; Kcal, Kilocalories; Kg, Kilograms; LOS, Length of Stay; NICE, National Institute for Health and Care Excellence; NUTRIC, Nutrition Risk in Critically ill; PDMS, Patient Data Management System; PN, Parenteral Nutrition; RFS, Refeeding Syndrome; RH, Refeeding Hypophosphatemia; SD, Standard Deviation; SOFA, Sequential Organ Failure Assessment; VIF, Variance Inflation Factor; FAO/WHO, Food and Agricultural Organization and World Health Organization; ZGV, Gelderse Vallei Hospital.

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1. Introduction

The reintroduction of macronutrients (proteins, lipids, carbohydrates) after a period of fasting or starvation might induce refeeding syndrome (RFS) in patients at risk [1–7]. RFS describes a spectrum of clinical symptoms resulting from biochemical abnormalities, typically consisting of fluid and electrolyte imbalances with refeeding hypophosphatemia (RH) playing a central role. Additionally, abnormalities in glucose metabolism and vitamin (thiamine) deficiencies are frequently seen [3–6,8–11]. Clinical symptoms are diverse, and multiple organ systems may be involved. Neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications lead to multisystem organ failure and, ultimately, death if not adequately treated [1,3,8–10,12–14].

Standard treatment of RH consists of strict monitoring of the patient, correction of electrolyte disorders, suppletion of vitamins (particularly thiamine), and, if necessary, fluid correction and insulin therapy [1,5,6,10–13]. There has been considerable debate about energy intake during this period; recommendations vary between a full energy strategy, restricted intake and immediate discontinuation of nutritional therapy [1,2,4,5,7,8,10,11,13,15,16]. The European Society for Clinical Nutrition and Metabolism (ESPEN) and National Institute for Health and Care Excellence (NICE) guidelines recommend “start low and go slow”, i.e., to gradually increase energy intake after a restricted-energy supply during the first 48 h of feeding [17,18]. Based on the recent observations by Doig et al., a restriction of energy intake at 480 kcal/24 h for at least 48 h is recommended [15]. In a randomized, multicentre, single-blind controlled trial, Doig and co-workers found that normocaloric feeding in RH patients admitted to an Intensive Care Unit (ICU) was associated with higher 60- and 90-day mortality rates ($p = 0.002$ and $p = 0.041$ respectively) [15]. Olthof et al. demonstrated a 6-month mortality reduction in RH patients who received hypocaloric feeding (<50% of calculated energy targets) in the first 72 h after ICU admission compared with RH patients who received more than 50% of calculated targets (adjusted hazard ratio (HR) 0.39, 95% confidence interval (95%CI) 0.16–0.95, $p = 0.037$) [1].

All current literature addresses the total energy provision but not specific macronutrients which are associated with higher mortality [19–22]. Nevertheless, there is increasing evidence that macronutrient intake, especially adequate and time-dependent protein provision, is more important than cumulative energy intake in critical illness [21–28]. Sufficient protein delivery is associated with improved survival [19,22,23,29–34]. Critically ill patients are hypercatabolic and may require up to 2.2–3.5 g of proteins per kilogram body weight per day to approach nitrogen balance [19]. On the other hand, increased protein delivery in the first week of critical illness has been associated with enhanced muscle wasting [29,35]. Recently, Koekkoek and colleagues conducted a retrospective study to identify the optimum timing and dose of proteins in critically ill patients who are mechanically ventilated for at least seven days. Their results show that low protein intake (≤0.8 g/kg/day) in the first two days after ICU admission, intermediate (0.8–1.2 g/kg/day) during days 3–5 and subsequently high intake (≥1.2 g/kg/day) was associated with reduced 6-month mortality rates [24]. It has been proposed that early feeding (and thus protein administration) may inhibit autophagy and harm the critically ill patient in the acute phase of illness [24,28,32,36–39]. Whether this is true for patients with RH as well is not known. Moreover, until now, no studies have been published on the associations of the individual macronutrients with outcomes of critically ill patients with RH.

The current study aimed to evaluate a possible association between 6-month mortality and individual macronutrients (proteins, lipids, carbohydrates) administered in the first week of ICU admission in mechanically ventilated ICU patients diagnosed with RH, irrespective of energy intake. Secondary outcomes were ICU-, hospital- and 3-month mortality, duration of mechanical ventilation and ICU and hospital length of stay (LOS). We hypothesize that RH patients with lower protein intake during the early acute phase of ICU admission (days 1–3) have a survival benefit compared to RH patients with higher protein intake.

2. Materials and methods

2.1. Study design

A single-centre retrospective observational cohort study was conducted in critically ill mechanically ventilated patients admitted to the mixed medical-surgical ICU of hospital Gelderse Vallei (ZGV, The Netherlands). This current study is a follow-up to the initial case–control study by Olthof et al., which studied the impact of energy intake during the first week of ICU admission in 124 critically ill mechanically ventilated patients with RH in the period 1-1-2011 until 31-12-2015 (hereafter called “cohort 1”) [1]. A new cohort of RH patients (hereafter called “cohort 2”) who had been admitted to the ICU between 1-1–2016 and 31-12-2018 was added to this existing cohort. Before this, baseline characteristics and nutritional data of both cohorts were compared to identify statistically significant differences that would hamper pooling. If this were the case, both cohorts would not be pooled.

2.2. Study participants

Adult patients (aged ≥18 years) being invasively mechanically ventilated for ≥7 days and receiving enteral or parenteral nutritional (EN/PN) support were identified. Only patients who developed RH were eligible, defined as new hypophosphatemia developed within 72 h after initiation of (par)enteral nutrition. Patients without RH and/or receiving EN/PN prior to ICU admission were excluded. Hypophosphatemia was determined by a phosphate drop of >0.16 mmol/L from a previous normal reading to below 0.65 mmol/L [1,12,15,16]. Patients were excluded when baseline phosphate levels on admission were low (<0.65 mmol/L) or if other causes of low serum phosphate were likely, such as renal replacement therapy, recent parathyroidectomy or treatment for hyperphosphatemia. Furthermore, patients were excluded when nutritional provision data or phosphate values were incomplete. Only the first admission was evaluated in case of ICU readmission within six months after ICU discharge. Based on our local ICU protocol, all patients received daily thiamine and electrolyte (potassium, magnesium, and phosphate) supplementation.

2.3. Data collection

Data collection from the patient data management system (PDMS) included patient characteristics (age, gender, anthropometry, comorbidities), admission type (medical, surgical or trauma), several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Nutrition Risk In Critically ill (NUTRIC), Charlson Comorbidity Index (CCI)), laboratory phosphate values, and lastly, duration of mechanical ventilation, ICU and hospital stay. Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands).

Regarding nutritional intake, macronutrient data from the first seven days of ICU admission (including daily protein, carbohydrate, and lipid intake from (par)enteral nutrition and propofol, trisodium citrate and glucose infusions) were collected manually. Nutritional

and non-nutritional macronutrient intakes were combined to calculate total energy, protein, carbohydrate and lipid loads in kilocalories (kcal) and grams (g) per kilogram (kg) actual bodyweight per day.

All parameters of interest were routinely collected during standard clinical care and therefore imposed no burden or risk to patients. The National Population Register was consulted for death records. Data verification was conducted manually.

2.4. Calculation of targets

To guide nutritional support, energy and protein targets were calculated using the Food and Agricultural Organization and World Health Organization (FAO/WHO/UNU) formulas, adapted for specific patient groups according to the local ICU protocol (see Supplement 1). Intake targets on the day of ICU admission (day 1) were adjusted for the actual time spent in the ICU this day. Days were defined as calendar days. Day 1–3 was called the acute early phase of critical illness, and day 4–7 was the acute late phase (adapted according to the terminology of the ESPEN critical care guidelines) [17].

2.5. Nutrition in RH patients

All patients in our ICU received nutritional support and glucose control according to our local ICU protocol. During the first 3 days, energy and protein intake are gradually increased in steps of 25% to full target on day 4. However, when RH is detected nutritional support is reduced to 25% of calculated energy and protein requirements and gradually increased from day three onwards with 25% per day (to a full strategy on day 5). Of note, an electronic energy restriction protocol for RH was implemented in our ICU in September 2017. This resulted in an immediate adaptation of energy- and protein targets, activated when refeeding hypophosphatemia occurred.

2.6. Study endpoints

The primary outcome of this study was 6-month mortality and its association with individual macronutrients (proteins, lipids, carbohydrates) administered in the first week of ICU admission, adjusted for other variables relevant for this endpoint. Secondary outcomes included ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation and ICU and hospital LOS. Early (day 1–3 of ICU admission) and late (day 4–7) acute phase intake of the macronutrients were subsequently analyzed.

Subgroup analyses were performed based on achieving less or more than 50% of prescribed cumulative energy targets during days 1–3 of ICU admission. The outcomes of the low (<50% of calculated targets) versus the high (>50%) intake groups were compared.

2.7. Statistical analysis

Discrete variables were reported as proportions. Continuous data were expressed as means, including standard deviations (SD) or, in the case of non-parametric data, as medians with interquartile ranges (IQR).

In the case of non-linearity with the outcome parameter, macronutrient intakes in g/kg per day were dichotomized. Cut-off values were chosen based on the assessment of Kaplan Meier curves of individual macronutrient intakes concerning 6-month mortality. Curves were compared using the Log-rank test. The dichotomized individual macronutrients (in g/kg*day) and all relevant variables for 6-month mortality based on current literature were included successively in the univariable Cox regression analysis to assess the primary study endpoint. Secondary outcome parameters were assessed using Cox or linear regression models where appropriate. Variables with a p-value <0.10 or deemed clinically relevant were included in multivariable regression analyses. These were: age, gender, BMI, APACHE II score on ICU admission and the intake of the separate macronutrients (proteins, carbohydrates and lipids). Multivariable Cox regression was conducted using the Forward Stepwise Wald and the Enter method. Morbidity outcomes were corrected for mortality as competing risk. The variance inflation factor (VIF) was used to detect multicollinearity. A VIF <2 was considered acceptable. All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Normality was assessed numerically and graphically (visual inspection of histograms and Q–Q plots). P-values <0.05 were considered statistically significant. P-values <0.10 were considered trends.

2.8. Ethical approval

The ethical approval committee of ZGV approved the study (study protocol number 1907–050). The retrospective study design and data anonymization provided a waiver concerning informed consent.

3. Results

During the study period, a total number of 3091 patients were admitted to the ICU. Of these, 54 patients were eligible for inclusion (hereafter called “cohort 2”) (see Fig. 1). Data of this cohort was pooled with the existing Olthof cohort from our group (n = 124, hereafter called “cohort 1″) after a comparison of baseline characteristics, nutritional data and outcomes of both cohorts (see Supplement 2-4).

3.1. Pooling cohorts

Cohort 2 had higher mean SOFA scores on ICU admission (8.1 (SD 2.6) versus 6.6 (2.7), p = 0.001), and lower serum phosphate levels (median 0.94 [IQR 0.84–1.19] versus 1.14 [0.95–1.37] mmol/L, p = 0.002) compared to cohort 1. Moreover, higher serum glucose levels were seen in the first 24 h after ICU admission in cohort 2 (median 10.2 [8.6–12.9] versus 7.5 [6.5–8.7] mmol/L, p < 0.001), although a trend towards lower cumulative insulin doses at day 7 (p = 0.085) was seen. Regarding nutritional intake, cohort 2 had significant lower protein (0.45 (SD 0.29) versus 0.64 (0.31) g/kg/day ideal body weight, p < 0.001) and carbohydrate (4.8 (SD 2.5) versus 6.1 (2.9) kcal/kg/day, p = 0.006) intake in the first three days of nutritional support after ICU admission. During days 4–7, this cohort 2 also had a significantly lower intake of all macronutrients (p < 0.001), as shown in Supplement 3. In addition to this, a higher percentage of patients from cohort 2 received energy (and protein) restriction, defined as an intake of <50% of prescribed targets, during day 1–3 (energy restriction 48.1% versus 25.8% (p = 0.003); protein restriction 72.2% versus 45.2% (p = 0.001)). Of note, 15 (27.8%) patients from cohort 2 were included from September 2017 onwards, benefiting from an immediate adaptation of their energy- and protein targets by the electronic energy restriction protocol when RH occurred.

Moreover, the percentage of non-nutritional calories to total caloric load were significant higher in cohort 2 (3-day propofol infusions: median 12.2% [3.7–25.8] versus 2.5% [0.0–10.0], p < 0.001; 3-day glucose infusions: 15.0% [6.2–27.5] versus 9.7% [1.0–17.4], p = 0.004). Finally, a statistically significant difference in 3-month mortality was seen in the benefit of cohort 2 (16.7 versus 33.1%, p = 0.025) (see Supplement 4). The baseline and

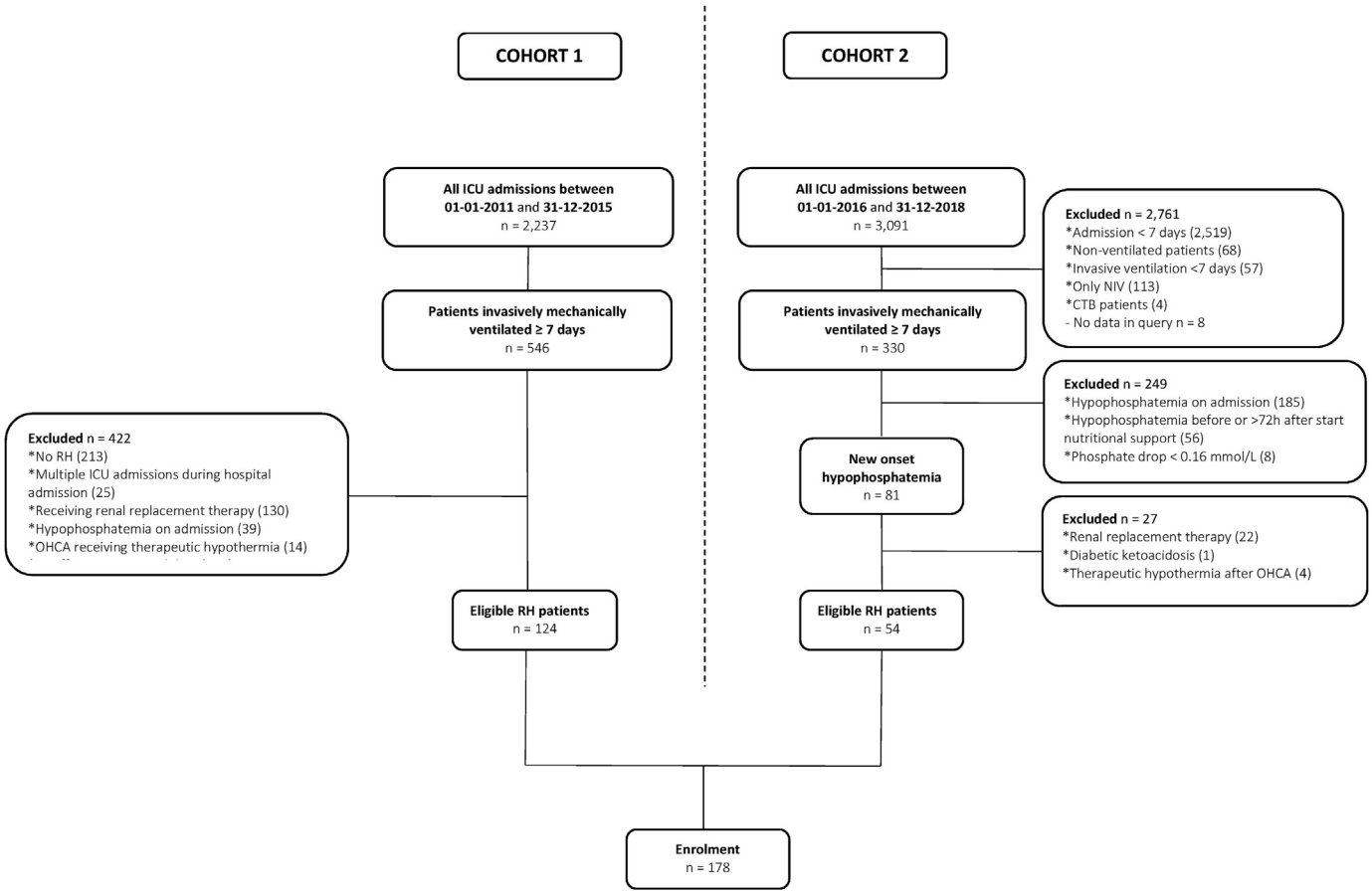

Fig. 1. Study flowchart. CTB = chronic non-invasive mechanical ventilation at home; ICU = Intensive Care Unit; NIV = noninvasive ventilation; OHCA = out of hospital cardiac arrest; RH = refeeding hypophosphatemia.

nutritional characteristics of the pooled cohort are shown in Tables 1 and 2.

3.2. Study population and nutritional intake

Of all included RH patients (n = 178), most patients were male (59.6%), overweight (median body mass index (BMI) 26.1 kg/m^2), non-surgical (61.8%), and had sepsis on ICU admission (51.1%). Nutritional support was initiated after a median time of 7.0 h after ICU admission [IQR 3.3–16.6]. RH was diagnosed at a mean of 2.9 (SD 1.0) days.

Mean energy intake was 11.8 (SD 5.2) and 22.9 (5.7) kcal/kg*day during the acute early (day 1–3) and acute late (day 4–7) phases, respectively. Regarding protein intake, this was 2.3 (SD 1.3; 0.58 g/kg*day) and 5.1 (SD 1.2; 1.29 g/kg*day) kcal/kg*day, respectively. In the first 72 h after the commencement of nutritional support, 58 patients (32.6%) received energy restriction, defined as an intake of less than 50% of the energy target. About seven patients (3.9%) had a restricted energy intake during days 4–7. An overview of the mean intake of (non-) nutritional macronutrients is depicted in Table 2.

At baseline, significant differences between the low (intake <50% of calculated energy targets of day 1–3) and high (>50%) intake groups were found for BMI (median 27.2 versus 25.3, p = 0.027) and SOFA score on ICU admission (mean 7.7 (SD 2.9) versus 6.7 (2.6); p = 0.023). Moreover, higher serum glucose values in the first 24 h were seen in the low energy intake group (median 9.3 versus 7.8 mmol/L, p = 0.003), whereas in the high intake group, more insulin was administered during the first 72 h of ICU admission (median 155 versus 121 units, p = 0.034). Regarding nutritional intake, a significant difference in time until the commencement of nutritional therapy was found: median 15.7 [IQR 6.5–27.6] hours in the low energy intake group versus 5.4 [2.9–11.7] hours in the high energy intake group (p < 0.001). These groups' energy and protein targets were similar (p = 0.154 and p = 0.288, respectively).

3.3. Primary outcome: 6-month mortality

Overall, 6-month mortality was 29.8% (n = 53). In univariable analyses, there was no statistically significant difference in 6-month mortality between subgroups with <50% and >50% of reached energy targets during the first three days of ICU admission (energy intake mean 6.6 (SD 2.2) versus 14.3 (SD 4.4) kcal/kg*day; energy adequacy 20.7 versus 34.2%), although a trend may be seen in benefit of the low intake group (p = 0.065, see Table 3). Regarding subgroups with <50% and >50% of reached energy targets during days 4–7 after commencement of nutritional support, there was no significant difference (energy intake mean 20.3 (SD 6.2) versus 24.2 (SD 5.1) kcal/kg*day; energy adequacy 28.6 versus 29.8%, p = 0.943).

The variables age, gender, BMI, APACHE II score and total energy intake during the first three days of ICU admission were considered relevant for univariable Cox regression for the association with 6-month mortality and individual macronutrient intake. However, total energy intake during days 1–3 and 4–7 was left out because matrix plots strongly correlated with the individual macronutrients. Because of non-linearity, all macronutrient variables were

Table 1
Baseline characteristics.

Gender (male)	*N (%)*	106 (59.6)
Age (years)	*median [IQR]*	68.0 [57–76]
Weight on admission (kg)	*median [IQR]*	78 [67–90]
Length on admission (cm)	*median [IQR]*	172 [166–178]
BMI on ICU admission (kg/m2)	*median [IQR]*	26.1 [23.1–29.3]
BMI <18.5	*N (%)*	8 (4.5)
Sepsis on ICU admission	*N (%)*	91 (51.1)
APACHE II score on ICU admission [n = 172]	*mean (SD)*	20.9 (5.7)
SOFA score on ICU admission	*mean (SD)*	7.1 (2.8)
Charlson Comorbidity Index	*mean (SD)*	3.6 (2.2)
NUTRIC score	*mean (SD)*	4.5 (1.6)
Baseline laboratory values	*median [IQR]*	
Leukocytes (x109/L)		13.8 [9.5–18.6]
Creatinine (μmol/L)		88 [67–110.3]
CRP (mg/L) [n = 174]		114.5 [31–219.8]
Bilirubin (mmol/L) [n = 173]		9 [6–14]
Albumin (g/L) [n = 175]		27 [21–33]
Highest glucose first 24 h (mmol/L) [n = 166]		8.1 [6.7–10.3]
Baseline electrolytes (mmol/L)	*median [IQR]*	
Sodium		139 [135–142]
Potassium		3.7 [3.3–4.1]
Magnesium [n = 172]		0.69 [0.59–0.80]
Phosphate		1.10 [0.89–1.33]
Admission type	*N (%)*	
Medical		110 (61.8)
Elective surgery		32 (18.0)
Emergency surgery		36 (20.2)

APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = Body Mass Index; CRP = C-reactive protein; ICU = Intensive Care Unit; IQR = interquartile range; N = number of patients; NUTRIC = Nutrition Risk In the Critically Ill; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.

dichotomized based on the Kaplan Meier survival curves (see Supplement 5). Early (day 1–3 of ICU admission) and late (day 4–7) acute phase intake of the macronutrients were subsequently analyzed.

3.3.1. Early acute phase (day 1–3)

Univariable Cox regression analysis showed a significant survival benefit of lower age (HR 1.043, 95%CI 1.018–1.069, p = 0.001), lower APACHE II score (HR 1.069, 95%CI 1.023–1.117, p = 0.003), lower protein intake (≤0.71 gr/kg*day during days 1–3; HR 2.201, 95%CI 1.178–3.466, p = 0.011, Fig. 2) and lower carbohydrate intake (≤1.02 g/kg*day during days 1–3; HR 2.498; 95%CI 1.255–4.973, p = 0.009). Lipid intake was not statistically significant (p = 0.340). In the multivariable model, age (HR 1.040, 95%CI 1.015–1.066, p = 0.002), APACHE II score on ICU admission (HR 1.086, 95%CI 1.034–1.140, p = 0.001) and protein intake during days 1–3 (HR 2.224, 95%CI 1.261–3.923, p = 0.006) were associated with the primary endpoint of 6-month mortality, as shown in Table 4. The VIF was <2 for the variables in this final model.

3.3.2. Late acute phase (day 4–7)

Univariable and multivariable COX regression analyses showed a significant survival benefit of lower age and APACHE II scores (see Table 4). No statistically significant association between macronutrient intake during the first week of ICU admission and 6-month mortality was demonstrated in univariable and multivariable analyses.

3.6. Secondary outcomes

An overview of ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation, and ICU and hospital LOS for both low and high energy intake groups is summarised in Table 3.

Table 2
Nutritional data.

Days until RH diagnosis	*mean (SD)*	2.9 (1.0)
Time until start nutrition (hours)	*median [IQR]*	7.0 [3.3–16.6]
Macronutrients (non-)nutritional (kcal/kg*day)	*mean (SD)*	18.2 (4.8)
day 1–3 energy intake (kcal/kg*day)		11.8 (5.2)
proteins		2.3 (1.3)
lipids		3.8 (2.3)
carbohydrates		5.7 (2.8)
day 4–7 energy intake		22.9 (5.7)
proteins		5.1 (1.2)
lipids		7.1 (3.5)
carbohydrates		10.6 (3.8)
Macronutrients (non-)nutritional (g/kg*day)	*mean (SD)*	
day 1–3		
proteins		0.58 (0.31)
lipids		0.42 (0.26)
carbohydrates		1.42 (0.71)
day 4–7		
proteins		1.29 (0.30)
lipids		0.79 (0.39)
carbohydrates		2.66 (0.96)
Energy targets (kcal/kg*day)	*mean (SD)*	
PS ventilation		25.7 (4.2)
PC ventilation		23.7 (3.9)
Protein targets	*mean (SD)*	
in kcal/kg*day		6.1 (0.4)
in g/kg*day		1.5 (0.1)
Energy and protein adequacy (%)	*mean (SD)*	
day 1–3 energy adequacy (PS)		57.8 (23.0)
day 1–3 energy adequacy (PC)		62.6 (25.0)
day 4–7 energy adequacy (PS)		90.0 (20.5)
day 4–7 energy adequacy (PC)		97.5 (22.2)
day 1–3 protein adequacy		47.4 (24.6)
day 4–7 protein adequacy		84.3 (19.3)
Non-nutritional to total caloric load (%)	*median [IQR]*	
day 1–3 glucose		10.2 [2.5–20.2]
day 4–7 glucose		1.6 [0.4–5.0]
day 1–3 citrate		0 [0]
day 4–7 citrate		0 [0]
day 1–3 propofol		4.3 [0.4–13.9]
day 4–7 propofol		1.4 [0.0–6.0]
Insulin administration (IU/day)	*median [IQR]*	
day 1–3 insulin dose		47.5 [28.0–79.0]
day 4–7 insulin dose		63.9 [38.8–105.2]
Energy intake <50% of target day 1–3 (PS)	*N (%)*	71 (39.9)
Energy intake <50% of target day 1–3 (PC)	*N (%)*	58 (32.6)
Energy intake <50% of target day 4–7 (PS)	*N (%)*	8 (4.5)
Energy intake <50% of target day 4–7 (PC)	*N (%)*	7 (3.9)
Protein intake <50% of target day 1–3	*N (%)*	95 (53.4)
Protein intake <50% of target day 4–7	*N (%)*	10 (5.6)

IQR = interquartile range; IU = international units; N = number of patients; PC = pressure control mechanical ventilation; PS = pressure support mechanical ventilation; RH = refeeding hypophosphatemia; SD = standard deviation.

There were no statistically significant differences between both subgroups in these secondary outcomes, although a trend in 3-month mortality was seen (p < 0.10), favouring the group which received energy restriction during days 1–3.

Regarding macronutrient intake and secondary outcomes, no statistically significant associations were observed (Supplement 6).

4. Discussion

4.1. Primary study endpoint: 6-month mortality

In this study, we found a significant association between 6-month mortality and protein intake of RH patients during days 1–3 of ICU admission in multivariable models, favouring the low intake group (≤0.71 g/kg*day; HR 2.224, 95%CI 1.261–3.923, p = 0.006). To date, no studies have been published investigating

Table 3
Outcomes energy intake subgroups.

		RH patients (n = 178)	Energy target reached		p-value[a]
			<50% (n = 58)	>50% (n = 120)	
Days 1–3					
Mortality	*N (%)*				
ICU		26 (14.6)	7 (12.1)	19 (15.8)	0.505
Hospital		38 (21.3)	10 (17.2)	28 (23.3)	0.353
3 months		50 (28.1)	11 (19.0)	39 (32.5)	0.060
6 months		53 (29.8)	12 (20.7)	41 (34.2)	0.065
Length of stay (days), TDA	*median [IQR]*				
ICU [n = 152]		14 [11–23]	13 [11–20]	15 [10–24]	0.928
Hospital [n = 140]		26 [18–39]	25 [17–36]	27 [19–41]	0.821
Mechanical ventilation (days) [n = 152]	*median [IQR]*	10 [8–14]	9 [8–13]	10 [8–16]	0.969
Days 4–7					
Mortality	*N (%)*				
ICU		26 (14.6)	2 (28.6)	24 (14.0)	0.286
Hospital		38 (21.3)	2 (28.6)	36 (21.1)	0.634
3 months		50 (28.1)	2 (28.6)	48 (27.0)	0.977
6 months		53 (29.8)	2 (28.6)	51 (29.8)	0.943
Length of stay (days), TDA	*median [IQR]*				
ICU [n = 152]		14 [11–23]	11 [10–41]	14 [11–23]	0.440
Hospital [n = 140]		26 [18–39]	21 [17–50]	26 [19–39]	0.255
Mechanical ventilation (days) [n = 152]	*median [IQR]*	10 [8–14]	9 [7–31]	10 [8–14]	0.600

ICU = Intensive Care Unit; IQR = interquartile range; N = number of patients; RH = refeeding hypophosphatemia; TDA = time to discharge alive.
< 50% energy target = less than 50 percent of energy targets reached during day 1–3 and 4–7 of ICU admission, respectively.
> 50% energy target = more than 50 percent of energy targets reached during day 1–3 and 4–7 of ICU admission, respectively.
[a] p-values were calculated using the chi-square or Mann–Whitney U test where appropriate.

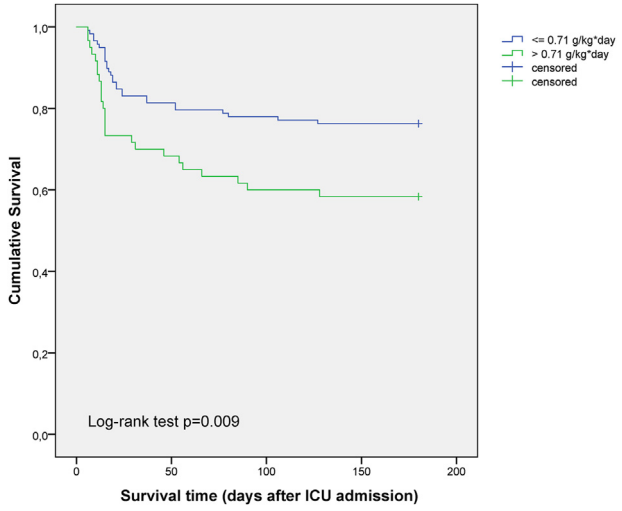

Fig. 2. Kaplan Meier curve for 6-month survival comparing a protein intake of ≤0.71 and > 0.71 g/kg*day during day 1–3 of ICU admission. ICU = Intensive Care Unit.

the association between macronutrient (more specific proteins) intake of RH patients and clinical outcomes (amongst others, 6-month mortality). Moreover, literature about protein intake and clinical outcomes in critically ill in general (RH and non-RH patients) is scarce and shows heterogenous methodology (study populations, measurement of nutritional intake, endpoints) and conflicting results, making a thorough comparison difficult. Our findings are consistent with Koekkoek et al. who demonstrated a time-dependent effect of protein intake in a non-RH mechanical ventilated ICU population (n = 455), with the lowest 6-month mortality in the patient group with low protein provision (i.e. <0.8 g/kg*day; HR for >0.8 g/kg*day: 1.231, 95%CI, 1.040–1.457, p = 0.016) during the early acute (day 1–3), and intermediate protein administration (i.e. 0.8–1.2 g/kg*day; HR 0.716, 95%CI 0.558–0.917, p = 0.008) during the late acute phase (day 4–7) [24]. Of note, this study did not distinguish between RH and non-RH patients, limiting the comparison with our results. No other studies evaluating macronutrient intake and 6-month mortality in general ICU populations were found.

4.2. Secondary outcomes

Regarding our secondary study aims (ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation, and ICU and hospital LOS), no statistically significant associations between macronutrient intake in the first week of ICU admission and clinical outcomes were demonstrated in multivariable analyses. No studies were found in current literature investigating these outcomes and macronutrient intake in RH patients.

Until now, explanatory mechanisms are lacking for the time-dependent and dose–response association of protein intake and clinical outcomes in critically ill patients. Patients are highly catabolic during the acute phase of critical illness, resulting in a high protein turnover to provide energy and enhanced synthesis of acute-phase response proteins, whereas skeletal muscle protein synthesis may be decreased [20,24,34]. However, in later phases of critical illness, amino acids are essential for protein synthesis and are involved in immune function to supporting recovery [21,24]. Additional protein supplementation in the early acute phase may inhibit or result in dysfunctional autophagy, leading to increased cell damage and loss of organ function [28,37]. Another explanation may be that more protein provision during the early phase may increase the oxidative burden [28]. Finally, early mitochondrial dysfunction leads to energy deficits, inducing proteostatic effects. In this phase, protein administration may lead to enhanced muscle wasting and hepatic protein breakdown in the context of elevated glucagon levels [34,40].

Strikingly, we found no association with protein intake and short-term outcomes, such as ICU or 3-month mortality. These findings are in contrast with Koekkoek and colleagues, who demonstrated an association between time-dependent protein intake and ICU and hospital mortality, favouring the group with restricted protein intake during the first 3 days [24]. It remains unclear why higher protein intake in the early acute phase results is

Table 4
Univariable and multivariable COX regressions for the association of primary endpoint 6-month mortality and macronutrient intake.

	Univariable	p-value	Multivariable	p-value
	HR (95% CI)		HR (95% CI)	
Days 1–3				
Age (years)	1.043 (1.018–1.069)	0.001*	1.040 (1.015–1.066)	0.002*
Gender (male)	1.386 (0.785–2.448)	0.260	1.557 (0.858–2.827)	0.145
BMI (kg/m^2)	0.946 (0.893–1.001)	0.055	0.963 (0.903–1.027)	0.254
APACHE II score on ICU admission	1.069 (1.023–1.117)	0.003*	1.086 (1.034–1.140)	0.001*
Protein intake (≤0.71 g/kg*day)	2.201 (1.178–3.466)	0.011*	2.224 (1.261–3.923)	0.006*
Lipid intake (≤0.51 g/kg*day)	1.311 (0.752–2.284)	0.340	0.998 (0.487–2.046)	0.996
Carbohydrate intake (≤1.02 g/kg*day)	2.498 (1.255–4.973)	0.009*	1.911 (0.838–4.359)	0.124
Days 4–7				
Age (years)	1.043 (1.018–1.069)	0.001*	1.042 (1.016–1.068)	0.001*
Gender (male)	1.386 (0.785–2.448)	0.260	1.445 (0.792–2.637)	0.230
BMI (kg/m^2)	0.946 (0.893–1.001)	0.055	0.962 (0.898–1.029)	0.257
APACHE II score on ICU admission	1.069 (1.023–1.117)	0.003*	1.074 (1.024–1.126)	0.003*
Protein intake (≤1.36 g/kg*day)	0.886 (0.517–1.520)	0.661	0.814 (0.429–1.541)	0.527
Lipid intake (≤0.77 g/kg*day)	0.970 (0.566–1.663)	0.912	1.155 (0.633–2.111)	0.638
Carbohydrate intake (≤2.58 g/kg*day)	1.485 (0.860–2.565)	0.156	1.460 (0.717–2.975)	0.297

APACHE II = Acute Physiology And Chronic Health Evaluation II; BMI = Body Mass Index.
95%CI = 95% confidence interval; HR = hazard ratio; ICU = Intensive Care Unit.
*p-value <0.05.

associated with an increased long-term mortality (i.e. 6-months), but not with short-term outcomes in our study. We speculate that this might be partly due to the higher hospital and ICU readmission rates observed in the higher protein group compared to the patients who receive less proteins during the first 72 h of ICU admission (41.7 versus 42.4% and 6.7 versus 5.1%), suggesting that these patients may survive their ICU and hospital admission, but have worse recovery and are prone to be readmitted with poor outcomes. Another possible and more plausible explanation is that there were additional confounding factors which were not accounted for (residual confounding).

4.3. Restricted energy intake

In univariable analysis, we did not find a statistically significant difference in 6-month mortality between RH subgroups with <50% and >50% of reached energy targets during days 1–3 and 4–7 of ICU admission ($p = 0.065$ and $p = 0.943$, respectively); only a trend was seen in the benefit of the low energy intake group at days 1–3 ($p < 0.10$). This observation is in contrast with the findings of Doig et al., who found a significant increased overall survival time and reduced mortality at day 60 follow-up (35 (21%) versus 15 (9%) for the group receiving energy restriction during treatment for RH [15]. Of note, in earlier analyses of the first part of our cohort (cohort 1, $n = 124$) by Olthof et al., a significant increase in overall survival time for the hypocaloric group in univariable and multivariable COX regressions (HR 0.39, 95%CI 0.16–0.95, $p = 0.037$) was demonstrated as well [1]. This striking difference may be explained by the fact that the additional cohort (cohort 2, $n = 54$), of whom more patients received energy restriction (48.1% versus 25.8%, $p = 0.003$), had higher SOFA scores on ICU admission (8.1 (SD 2.6) versus 6.6 (SD 2.7), $p = 0.001$), higher glucose values in the first 24 h (median 10.2 [8.6–12.9] versus 7.5 [6.5–8.7], $p < 0.001$) and lower phosphate laboratory values (0.94 [0.84–1.19] versus 1.14 [0.95–1.37], $p = 0.002$), suggesting that this second cohort was more severely ill. Moreover, as already noticed, the entire cohort 2 had significantly lower protein intake in the first three days of nutritional support after ICU admission compared to cohort 1 (0.45 versus 0.64 g/kg*day ideal body weight, $p < 0.001$), whether receiving energy restriction or not. These observations might have blunted the survival benefit in hypocaloric-fed patients. Similar findings were reported in a randomized controlled trial by Arabi et al. [41]. They studied permissive underfeeding (defined as 40–60% of energy targets) versus standard feeding (defined as 70–100% of energy targets) in 894 critically ill patients. No significant association with mortality up to 6 months was demonstrated [41]. However, additional protein supplements were administered in the permissive underfeeding group, which might have influenced their results. Although speculative, this may suggest that the protein supplementation in the permissive underfeeding group has impacted the effect of energy restriction on the outcome.

The significant difference in energy restriction observed between both cohorts in our study may be explained by the fact that in September 2017, an electronic energy restriction protocol for RH was implemented in our ICU. As mentioned in the methods section, this resulted in an immediate adaptation of energy- and protein targets which was activated when RH occurred.

4.4. Strengths

The extensive data set of (non-) nutritional intake during the (at least) first seven days of ICU admission of 178 critically ill patients with RH and a long follow-up period of 6 months are considered strengths of this study. Nutritional support was started early after ICU admission (median 7.0 h) compared to current literature (e.g., Doig et al. reported a mean of 1.4 days; Koekkoek et al. median 5.6 h [15,24].

4.5. Limitations

First of all, the retrospective, observational design of our study may have introduced bias and residual confounding. Moreover, there is a significant risk of selection bias due to the exclusion of patients with early mortality and early alive ICU discharge (exclusion criterium: mechanical ventilation <7 days). Thirdly, the long study period (2011–2018), including a defined change in nutrition delivery through adoption of the electronic energy restriction protocol, may have contributed to the heterogeneous study population and additional bias. Fourthly, we might have introduced bias by defining the cut-off values; the outcome may depend on how well the cut-off values have been chosen [22]. Fifthly, the strong association between caloric and macronutrient intake carries the risk of confounding in multivariable analyses (especially protein and carbohydrate intake), although we tried to correct for this. Furthermore, it is a single-centre study, and we only included critically ill patients with RH who were mechanically ventilated for

at least seven days limiting the external validity. Also, we did not correct data for pre-ICU nutrition status and adherence to micronutrient supplementation in the ICU (34,43). Finally, energy targets were based on a static formula (FAO/WHO/UNU), not accounting for individual needs (as measured with indirect calorimetry).

4.6. Further research

Additional (randomized controlled) studies are needed to confirm the hypothesis of a potential survival benefit in patients with low protein intake during days 1–3 of ICU admission, especially in patients with RH. The underlying mechanisms are still unclear. Future studies could include pre-ICU nutrition status, body composition and biomarkers of optimal protein intake, such as nitrogen balance, physical function tests, and clinical outcomes, as was previously suggested [20].

Moreover, indirect calorimetry should guide targeting the individual energy needs of patients after the initial ICU phase (around day four after ICU admission) as progressive energy increase during the first days of ICU stay is recommended [17,42].

5. Conclusion

Associations between 6-month mortality and protein intake during the first three days of ICU admission in critically ill patients with refeeding hypophosphatemia were found. All-cause six-month mortality was significantly lower in the low protein intake group ($\leq$0.71 g/kg*day), but ICU, hospital, 3-month mortality and other secondary outcomes were not. No association with carbohydrate intake was demonstrated. We suggest a time-dependent association between early protein intake and 6-months mortality among refeeding hypophosphatemia patients, although additional studies are warranted to confirm this hypothesis. Our findings may implicate that when refeeding hypophosphatemia in critical illness is encountered, and thus total caloric restriction is warranted for some days, during this phase, no protein supplementation should be provided.

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Author contributions

Study design and concept: HSB, EFR, WACK, ARHvZ
Data collection: HSB, EFR.
Statistical analysis and interpretation of data: HSB, EFR, WACK, MSA, ARHvZ
Manuscript draft: HSB.
Critical revision of the manuscript: HSB, EFR, WACK, MSA, ARHvZ
Administrative and data support: DvB.

Declaration of competing interest

Prof. Dr A.R.H. van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AOP Pharma, Baxter, Cardinal Health, Danone-Nutricia, Dim-3, Fresenius Kabi, Mermaid, Lyric, and Nestle-Novartis. The other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.03.003.

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