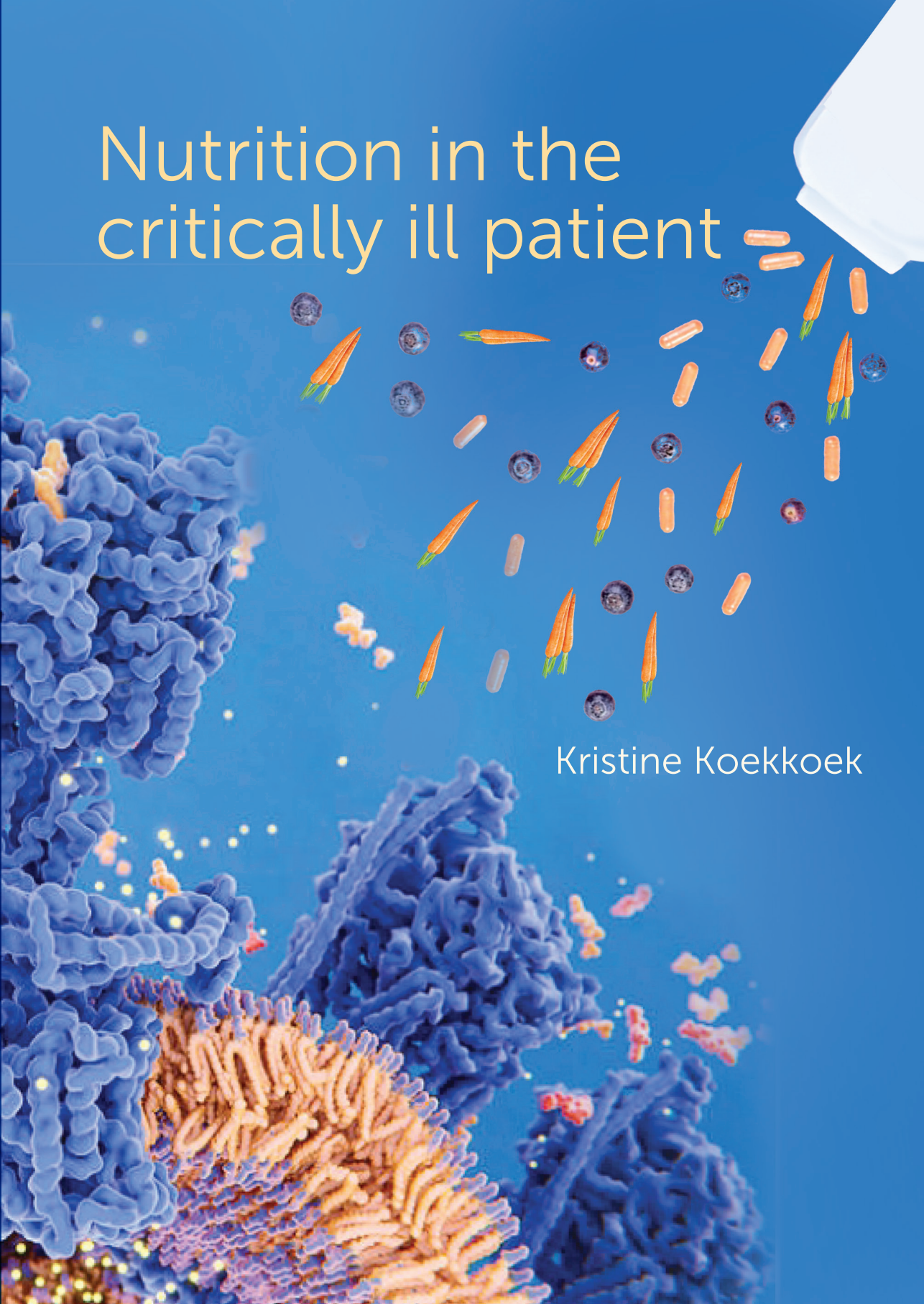
Nutrition in the critically ill patient



Kristine Koekkoek

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Colophon

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Nutrition in the critically ill patient

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CHAPTER

Introduction

Based on
Nutrition in the critically ill patient

W.A.C. Koekkoek
A.R.H. van Zanten

Curr Opin Anaesthesiol. 2017; 30(2):178-185

INTRODUCTION

The nutritional status of intensive care unit (ICU) patients deteriorates rapidly after admission due to severe catabolism caused by stress related and proinflammatory cytokines and hormones, even when patients are well nourished. Within 10 days patients may lose 10–25% of their body protein content (i.e. 1kg muscle mass per day), most pronounced encountered among patients with multiorgan dysfunction syndrome [1]. This profound loss of muscle mass is likely to contribute to the long term impairment in physical function observed in many ICU survivors [2,3]. In addition, persistence of muscle weakness until and after ICU discharge may reduce long term survival [3].

Although ICU and hospital mortality from critical illness have significantly improved in the past decades [4], the number of patients with long term functional disabilities has increased. This leads to increased instrumental activities of daily living (IADL) dependency in up to 70% of ICU survivors [5]. In addition, only half of previously employed survivors returns to work within the first year post-ICU discharge [6].

Optimal nutritional support during and after ICU admission is important as it has been associated with improving clinical outcomes [7]. Ideally, nutritional support reduces the loss of muscle mass in the early phases of ICU admission and later on encourages muscle anabolism and recovery leading to better functional outcomes. However, many questions remain in achieving optimal nutritional support in critically ill patients. This introduction will review several important aspects of nutritional support, followed by the aim and outline of this thesis.

The optimal caloric target

The caloric feeding target has been defined as the amount of energy required for basal metabolism to preserve lean body mass (LBM) and to limit deleterious effects of catabolism [8]. Guidelines advise 80–100% of energy expenditure (normocaloric goals) within 24–48 hours of ICU admission [9-13]. A retrospective cohort study evaluated outcomes and percentages of administered calories divided by resting energy expenditure (REE) obtained by indirect calorimetry and with protein intake. A significant decrease in mortality was observed when caloric intake was increased from 0 to 70% of REE. However, an increase in mortality and ICU length of stay (LOS) and duration of mechanical ventilation when caloric intake was more than 70% was found. Increasing protein intake was associated with lower mortality [7].

Energy expenditure can be best assessed through indirect calorimetry. If not available, equations are used but show poor accuracy. A review of 160 variations

of 13 predictive equations showed 38% underestimated and 12% overestimated energy expenditure by more than 10% at group level. On individual patient level underestimation and overestimation was found in 13–90 and 0–88%, respectively. Therefore, indirect calorimetry is recommended if available [14,15]. Recently, an alternative has been provided to estimate energy expenditure. The VCO_2 * 8,19 measured by the mechanical ventilator is reported to reflect energy expenditure and shows better accuracy than equations [16].

Nutritional dose and timing of initiation

The optimum caloric and protein goals remain unclear as well as the timing of initiation of feeding. Observational studies suggest underfeeding is associated with worse patient outcomes [17]. However, a randomized controlled trial (RCT) comparing permissive underfeeding (40–60% of caloric target) with standard enteral (70–100% of caloric target) while ensuring similar protein intake by supplements found no differences in 90-day mortality, ICU and hospital LOS, feeding intolerance, diarrhea or rates of ICU acquired infection [18]. Another RCT comparing hypocaloric (15 kcal/kg/day) with normocaloric (25 kcal/kg/day) feeding with similar protein intake (1.7 g/kg/day) showed no significant differences in 28-day mortality, ICU LOS, duration of mechanical ventilation or sequential organ failure assessment (SOFA) scores after 48 and 96 hours[19]. A third RCT comparing hypocaloric and normocaloric feeding observed more nosocomial infections during hypocaloric feeding (26.1 vs 11.1%) [20]. In this trial, protein intake was also significantly lower in the hypocaloric group. These findings may suggest no harm of hypocaloric feeding as long as adequate protein intake is guaranteed.

Two meta-analyses, comparing normocaloric with hypocaloric feeding, show no differences in overall mortality, hospital and ICU LOS, rate of infectious complications, gastrointestinal intolerance or duration of mechanical ventilation. Neither of the meta-analyses did correct for protein intake [21,22].

Most studied patients were well nourished (high body mass index (BMI), low mNUTRIC score) and extrapolating results to patients with high nutritional risk may be unacceptable [23].

Protein requirements

Currently, there is no specific method to clinically measure protein requirements [24]. Guidelines recommendations are available (Table 1). Adjustment for LBM rather than BMI may be superior, however, has not been studied yet.

Table 1| Recommended protein intake for adult critically ill patients

BMI<30 kg/m2	1.2–2.0 g protein per kg body weight
BMI 30–40 kg/m2	2 g/kg ideal body weight
BMI>40 kg/m2	2.5 g/kg ideal body weight

Adapted with permission from McClave et al. and Critical Care Nutrition Guidelines [9,10].

There is growing evidence that protein intake may be more important than caloric intake. Observational studies show higher protein intake is associated with better survival and more ventilator free days [25-29]. The most recent observational study found protein intake to be linearly associated with decreased mortality (1% mortality reduction per gram of daily protein more ingested) [29].

Recent prospective trials show conflicting results. In a prospective study higher provision of protein and amino acids was associated with lower mortality, not observed for the provision of energy [30]. In addition, early high protein intake (>1.2 g/kg protein on day 4) showed lower mortality [12]. An RCT comparing 0.8 g/kg of protein provision with 1.2 g/kg/day in patients requiring parenteral nutrition demonstrated that patients in the high protein group had less fatigue and greater forearm muscle thickness on ultrasound; however, no differences in mortality or LOS were found [31].

In another study, higher protein delivery during the first week was associated with greater muscle wasting [1]. Moreover, based on a post-hoc analysis of the EPANIC trial, a time-dependent association of protein intake and clinical outcome, with possible harmful effects of protein intake during the first 3 days of ICU admission, was suggested [32].

Refeeding syndrome

Refeeding syndrome (RFS) refers to biochemical and clinical symptoms, and metabolic disturbances including hypophosphatemia, hypokalemia, fluid overload and thiamine deficiency in malnourished patients undergoing refeeding [33]. Many ICU patients are at risk [34]. Until recently, recommendations that caloric intake should be restricted in ICU patients were based solely on expert opinion. In a randomized multicenter trial, Doig et al. compared standard nutritional support and protocolized caloric restriction (500 kcal/day) in adult ICU patients developing RFS within 72 hours of feeding initiation. Although the primary endpoint was negative, full caloric feeding induced higher mortality rates at hospital discharge and at day 90, and more infections were reported [35]. Only supplementation of vitamins and trace elements seems insufficient, and caloric restriction for several days and gradual increase of caloric intake is recommendable [34].

Pharmaconutrition

Many trials have been performed with specific micronutrients and macronutrients enhanced enteral or parenteral nutrition.

Micronutrients

Vitamin A, C, E, selenium and zinc have been frequently studied because of antioxidant properties and possible beneficial effects on oxidative stress. However, large trials and meta-analyses do not show benefits of supplementation of antioxidant cocktails [36-39]. Therefore, supplementation of antioxidant vitamins and trace-elements in dosages above nutritional goals is currently not recommended [40].

The association between vitamin D levels at ICU admission and mortality in sepsis patients was investigated, and no differences in 90-day mortality were reported [41]. In addition, high-dose vitamin D supplementation (540 000 IU) conferred no mortality benefits. However, in severe vitamin D deficiency (<30nmol/l), lower mortality was observed [42]. Routine vitamin D supplementation cannot be recommended.

Macronutrients

Low plasma glutamine levels are frequently encountered and were associated with increased mortality. Supplementation was considered. It was hypothesized that glutamine becomes a conditionally essential amino acid [43]. However, this hypothesis has been challenged and seems to be false [44,45]. Early observational studies and RCTs with low-dose glutamine supplementation showed significant reductions in ICU mortality and infection rates [46–48]; however, the REDOXS and MetaPlus trials suggested harm [36,37]. In these trials, glutamine was administered without knowledge of baseline glutamine levels. As glutamine levels do not correlate with the severity of illness hyperglutaminemia may have existed before supplementation and may have led to negative outcomes. Moreover, Rodas et al. showed that also high baseline glutamine levels are negatively associated with survival [49]. A recent meta-analysis on enteral glutamine no longer showed any benefits except for a subset of patients with burns [50]. In a meta-analysis on parenteral glutamine, positive findings were only shown in single-center trials, with no effect in multicenter studies [48]. Whether glutamine supplementation is beneficial may be dependent on dose, patient category, timing and route of administration [51].

Fish-oil baseline levels have rarely been studied, and it is unknown whether deficiency exists, and supplementation improves outcome [52,53]. In a systematic review of 10 RCTs, no effect of fish-oil supplementation on mortality was found. Significant reductions of infections were reported and in subgroup analysis of high

quality trials reduction of in-hospital LOS was found [53]. However, in a posthoc analysis of the MetaPlus trial – in which both glutamine, antioxidant vitamins and trace elements and fish-oil were supplemented to enteral nutrition in combination – increase in eicosapentaenoic acid and docosahexaenoic acid plasma levels seemed to be associated with the increased 6-month mortality among medical patients [54]. Therefore, regular supplementation of fish-oil cannot be recommended.

AIMS OF THIS THESIS

The central question in critical care nutrition is: what is optimal nutritional support and how can this help improve patient outcomes?

This thesis aims to contribute to this main question by focusing on the following questions:

- What methods are reliable to estimate the optimal caloric target in critically ill patients?
- What is the optimal protein dose in critically ill patients?
- Does the optimal protein dose change during ICU admission?
- Is refeeding syndrome relevant in critically ill patients?
- What is the incidence of refeeding syndrome in critically ill patients?
- Is caloric restriction safe in patients with refeeding syndrome and does it improve clinical outcomes?
- What is known about antioxidant micronutrients mechanisms in critically ill patients?
- Are micronutrients deficient in critical illness?
- Does supplementation of micronutrients improve clinical outcomes?
- Does enteral fish oil supplementation affect clinical outcomes in critically ill patients?

OUTLINE OF THIS THESIS

This thesis is divided in four parts, focusing on different aspects of nutritional support in critically ill patients.

PART I – Estimating the optimal caloric target

Ideally, energy expenditure is assessed by indirect calorimetry. However, this is often unfeasible. This thesis starts with testing the hypothesis that energy expenditure estimated by ventilator-derived carbon dioxide consumption is an accurate, precise and reliable alternative to indirect calorimetry in chapter 2.

In the absence of indirect calorimetry, predictive equations are often used to estimate energy expenditure. Increasing accuracy of these equations may help to avoid both over- and underfeeding of critically ill patients. Several factors that influence energy expenditure have been studied previously (i.e. sepsis, trauma, burns, body temperature). The effect of neuromuscular blocking agents on energy expenditure, which conceptually would lower energy expenditure, has not been extensively investigated nor included in predictive equations. In chapter 3 the effect of continuous cisatracurium infusion on energy expenditure is studied.

PART II – Nutritional dose and timing of initiation

Protein intake may be more important than caloric intake for clinical outcomes. Earlier studies suggest a time-dependent association between protein dose and mortality. Chapter 4 reports on the results of a retrospective study evaluating a possible time-dependent association between protein dose and long term mortality.

Although protein intake may be more important overall, the amount of caloric intake is of specific interest in patients with refeeding syndrome. Chapter 5 reports on the results of a retrospective cohort study comparing long term mortality in patients with refeeding syndrome to patients without refeeding syndrome and investigating the association between mortality and caloric intake in both groups. In addition, chapter 6 reviews the relevance of refeeding syndrome in critically ill patients for clinical practice.

PART III – Pharmaconutrition

Pharmaconutrition involves research on specific micro- and macronutrients, in which nutrients are viewed and tested as pharmacological agents. Of particular interest in critical illness are micronutrients with antioxidant properties due to their theoretical potential to reduce oxidative stress. In chapter 7 a review of literature on antioxidant mechanisms, antioxidant status and effects of supplementation of antioxidant vitamins and trace-elements in critically ill patients is presented.

Low micronutrient levels, or micronutrient deficiencies, have been reported in critical illness. However, it was unclear whether these micronutrient concentrations were different from healthy controls and what the course of micronutrient concentrations was during ICU admission without micronutrient supplementation. Chapter 8 reports on the results of a prospective comparative cohort study on micronutrient concentrations in critically ill patients versus healthy age-matched controls.

Macronutrient supplementation has mainly focused on glutamine and fish oil. Although a meta-analysis of intravenous fish oil supplementation shows no harm and a reduction in infections and hospital LOS, a large study on enteral fish oil supplementation revealed an association with increased mortality. In chapter 9 the results of a systematic review and meta-analysis on enteral fish oil supplementation are presented.

PART IV – Future perspectives for nutrition in the ICU

Chapter 10 reviews new developments in critical care nutrition. Finally, the answers on the questions proposed in the "aims of this thesis" are discussed in chapter 11 and translated into clinical implications. A summary of the main findings is provided in the appendices.

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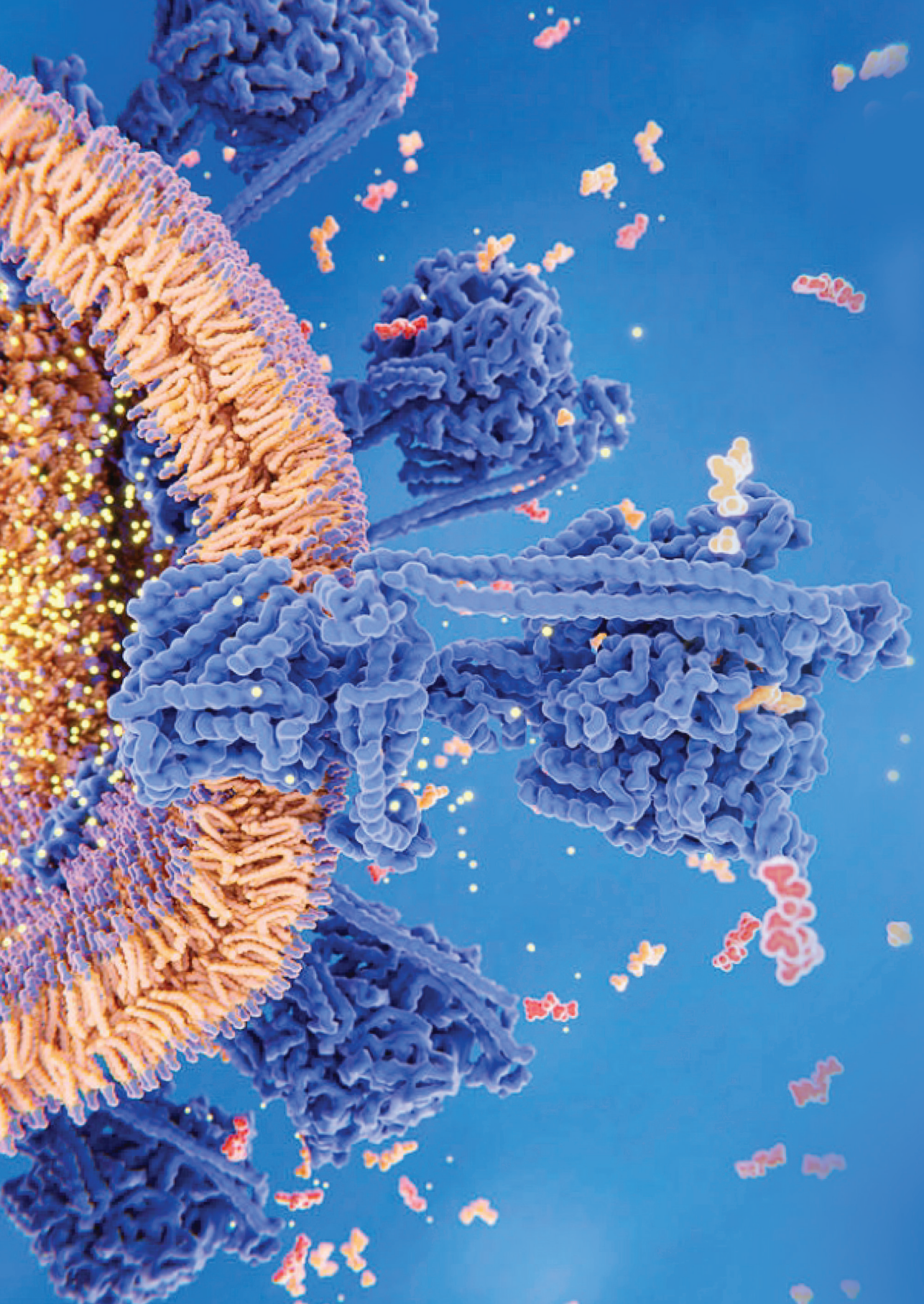

PART I

Estimating the optimal caloric target

2

CHAPTER

Resting energy expenditure by indirect calorimetry versus the ventilator-VCO2 derived method in critically ill patients: The DREAM-VCO2 prospective comparative study

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ABSTRACT

Background & aims

Both overfeeding and underfeeding of intensive care unit (ICU) patients are associated with worse outcomes. Predictive equations of nutritional requirements, though easily implemented, are highly inaccurate. Ideally, the individual caloric target is based on the frequent assessment of energy expenditure (EE). Indirect calorimetry is considered the gold standard but is not always available. EE estimated by ventilator-derived carbon dioxide consumption ($EEVCO_2$) has been proposed as an alternative to indirect calorimetry, but there is limited evidence to support the use of this method.

Methods

We prospectively studied a cohort of adult critically ill patients requiring mechanical ventilation and artificial nutrition. We aimed to compare the performance of the $EEVCO_2$ with the EE measured by indirect calorimetry through the calculation of bias and precision (accuracy), agreement, reliability and 10% accuracy rates. The effect of including the food quotient (nutrition intake derived respiratory quotient) in contrast to a fixed respiratory quotient (0.86), into the $EEVCO_2$ formula was also evaluated.

Results

In 31 mechanically ventilated patients, a total of 414 paired measurements were obtained. The mean estimated $EEVCO_2$ was 2134 kcal/24 h, and the mean estimated EE by indirect calorimetry was 1623 kcal/24 h, depicting a significant bias of 511 kcal (95% CI 467–560, $p < 0.001$). The precision of $EEVCO_2$ was low (lower and upper limit of agreement −63.1 kcal and 1087. o kcal), the reliability was good (intraclass correlation coefficient 0.613; 95% CI 0.550–0.669, $p < 0.001$) and the 10% accuracy rate was 7.0%. The food quotient was not significantly different from the respiratory quotient (0.870 vs. 0.878), with a small bias of 0.007 (95% CI 0.000–0.015, $p = 0.54$), low precision (lower and upper limit of agreement −0.16 and 0.13), poor reliability (intraclass correlation coefficient 0.148; 95% CI 0.053–0.240, $p = 0.001$) and a 10% accuracy rate of 77.5%. Estimated mean $EEVCO_2$, including the food quotient, was 2120 kcal/24 h, with a significant bias of 496 kcal (95% CI 451–542; $p < 0.001$) and low precision (lower and upper limit of agreement −157.6 kcal and 1170.3 kcal). The reliability with EE estimated by indirect calorimetry was good (intraclass correlation coefficient 0.610, 95% CI 0.550–0.661, $p < 0.001$), and the 10% accuracy rate was 9.2%.

Conclusions

$EEVCO_2$, compared with indirect calorimetry, overestimates actual energy expenditure. Although the reliability is acceptable, bias is significant, and the precision and accuracy rates are unacceptably low when the VCO_2 method is used. Including the food quotient into the $EEVCO_2$ equation does not improve its performance. Predictive equations, although inaccurate, may even predict energy expenditure better compared with the VCO_2-method. Indirect calorimetry remains the gold standard method.

INTRODUCTION

Targeting optimal nutrition using energy goals is essential in critically ill patients, as both underfeeding and overfeeding have been associated with increased morbidity and mortality [1]. International guidelines recommend to prescribe calories based on energy expenditure (EE) measured by indirect calorimetry [2]. Due to the pathophysiological response to critical illness, iatrogenic interventions, and differences in body composition, EE is highly variable in and between critically ill patients [3]. Indirect calorimetry is considered the gold standard and can be used to assess EE reliably. However, indirect calorimetry is not available in many hospitals and not feasible in all patients. Even under the conditions of a prospective clinical study indirect calorimetry was effectively performed in only 40% of patients [4].

In the absence of indirect calorimetry, predictive equations have been used to assess EE. However, most have been developed in specific, non-intensive care unit (ICU), patient populations and are not generalizable to ICU patients [5]. Moreover, multiple validation cohort studies among ICU patients report poor performance when compared with indirect calorimetry [6, 7, 8], with the best predictive equations reaching an accuracy of 35–45% [6,7].

Alternative methods in estimating EE have been suggested, including the use of carbon dioxide consumption (VCO_2) measurements made by volumetric capnography, derived from mechanical ventilators ($EEVCO_2$) based on an adjusted version of Weir's equation. Weir's equation defines EE (kcal/day) as (3.941 * VO_2 + 1.1106 * VCO_2) * 1440. However, mechanical ventilators can only measure VCO_2, and not the oxygen consumption (VO_2). Weir's equation is adjusted in order to calculate EE (3.941 * VCO_2/RQ + 1.106 * VCO_2) * 1440. This approach assumes the respiratory quotient (RQ) to be either equal to the food quotient or a fixed value derived from population-based means (0.86) [9, 10, 11]. Thus far, only one study of sufficient sample size has compared the EEVCO2 with the EE from indirect calorimetry. This study found $EEVCO_2$ acceptably accurate and more precise than predictive equations of [10].

This study aimed to prospectively compare the performance of the $EEVCO_2$ in adult mechanically ventilated critically ill patients with indirect calorimetry. Also, we analyzed whether the use of the food quotient leads to further improvement of the performance of the $EEVCO_2$ compared with using a fixed RQ of 0.86.

MATERIALS & METHODS

We performed a prospective observational study in critically ill patients receiving artificial nutrition at the mixed medical-surgical adult ICU of Gelderse Vallei Hospital,

Ede, The Netherlands between October 29th, 2015, and December 2nd, 2015, and between May 27th, 2016, and August 27th, 2016. Patients were included when they met the following inclusion criteria: adult critically ill patients (age ≥ 18 years) requiring endotracheal intubation and mechanical ventilation and artificial nutrition (either enteral nutrition, parenteral nutrition, or a combination of both).

Exclusion criteria were: expected to be in the ICU for less than 48 h after inclusion, expected to die shortly after ICU admission, continuous renal replacement therapy or intermittent haemodialysis, indirect calorimetry and/or ventilatory assessment of VCO_2 was technically not possible or expected to be inaccurate (i.e. in case of FiO_2 >0.6, PEEP≥12 cmH2O, body temperature <32 °C or >42 °C, major air leaks through cuffs or around the endotracheal tube, subcutaneous emphysema, tracheal-oesophageal fistula, chest tubes draining air or air leaks around the chest tube, ventilatory modes using bias flow or leak compensation). In addition, patients were not enrolled when informed consent was not provided by the patient or his/her representative or when indirect calorimetry was unfeasible due to logistic reasons.

Methods of assessing EE

Ventilator derived energy expenditure

For each patient, the mean VCO_2 measured by the mechanical ventilator (Hamilton-S1, Hamilton Medical AG, Bonaduz, Switzerland) during the 10-min measurement of the metabolic monitor was recorded. Because VO_2 is not measured by the mechanical ventilator, an adjusted version of Weir's equation was used to estimate ventilator derived energy expenditure:

$$\text{Energy expenditure} = 3.941 * VCO_2(\text{L/min})/RQ + 1.106 * VCO_2(\text{L/min}) * 1440$$

We assumed the RQ to be either a fixed value of 0.86 [9,10] or equal to the food quotient. The food quotient is the RQ estimated from the oxidation of the administered nutrients or total caloric intake. The calculation of the food quotient was based on the actual intake of all (non)nutritional macronutrients of the patients during the 2 h before the measurements. We assumed RQs of 1.0 for carbohydrates, 0.8 for proteins, 0.7 for fat, and 1.33 for citrate [10, 11, 12]. The weighted average RQ was used as the food quotient. An example is provided in supplement 1.

Energy expenditure from indirect calorimetry

Indirect calorimetry was performed with the Quark RMR Metabolic Monitor (Cosmed, Rome, Italy) [13, 14, 15, 16]. Before each (series of) measurement(s) the gas- and flowmeter were calibrated, and the heat and moisture exchanging filter was

changed according to the manufacturer's instructions. A 10-min measurement was deemed valid when the variability of VCO_2 and VO_2 within the measurement period was less than 10%. The metabolic monitor continuously recorded VCO_2, VO_2, RQ and EE from indirect calorimetry during the measurements.

Data collection

Several patient characteristics were recorded upon ICU admission including age, gender, weight, height, admission category (medical/surgical), admission diagnosis, Acute Physiology And Chronic Health Evaluation (APACHE)-II score, APACHE-IV score, modified Nutrition Risk in Critically Ill (NUTRIC) score, and sequential organ failure assessment (SOFA) score. Indirect calorimetry was performed in sessions of 10 min six times daily on six consecutive days or until withdrawal from endotracheal mechanical ventilation or death. Ventilator-derived VCO_2 was recorded simultaneously. Ventilator settings, respiratory parameters, and all macronutrient intake during the measurements, including both nutritional and non-nutritional calories, were routinely stored in our patient data management system (PDMS; iMDsoft MetaVision®, Tel Aviv, Israel). Also, patients were followed until hospital discharge. Length of mechanical ventilation, ICU, and hospital stay were recorded as well as ICU and hospital mortality.

Data analysis and statistical considerations

We performed a primary analysis evaluating the performance of the $EEVCO_2$ compared with the EE measured by indirect calorimetry through the determination of accuracy, agreement, reliability and 10% accuracy rates. In addition, a secondary analysis was performed evaluating the performance of the food quotient compared with the RQ measured by indirect calorimetry, and the performance of the $EEVCO_2$ including the food quotient compared with the EE measured by indirect calorimetry.

Accuracy was assessed through the calculation of bias and precision. Bias was defined as the mean difference between the measurements obtained from the mechanical ventilator and indirect calorimetry (the gold standard). A bias of <10% of the gold standard was deemed acceptable. Precision was defined as the random error of the measurements, visualized by the limits of agreement in Bland–Altman plots. Agreement is visualized by the complete Bland–Altman plots. Because of repeated measures and clustering of data, a multilevel random-effects model was used to estimate the mean values and the mean difference. Bland–Altman plots, including standard deviations and limits of agreement, were also corrected for repeated measurements.

In addition, reliability was assessed through the calculation of the absolute intraclass correlation coefficient. Reliability was considered poor with an intraclass correlation coefficient <0.40, fair between 0.40 and 0.59, good between 0.60 and 0.74 and excellent between 0.75 and 1.00.

Furthermore, accuracy rates were calculated, defined by the proportion of estimates for which the $EEVCO_2$ and food quotient predicted paired measurements by indirect calorimetry within 10%.

Additionally, a post-hoc analysis was performed assessing the predictive performance of four commonly used predictive equations. Accuracy, agreement, reliability and accuracy rates were calculated as described above.

Descriptive data are reported as means and standard deviation (SD) or median and interquartile range (IQR) in case of skewed distributions, or as frequencies and percentages when appropriate.

A p-value <0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 25.0 (IBM Corporation, released 2017, Armonk, New York, USA) was used to perform analyses. MedCalc version 19 (MedCalc bv, Ostend, Belgium) was used to create Bland–Altman plots.

RESULTS

During the study period, 274 patients were admitted to the ICU, of which 45 were eligible for inclusion. However, 13 patients were not enrolled due to logistic reasons (n = 7) or no informed consent (n = 6). One patient was excluded from data analysis due to the variability of >10% of all measurements (Fig. 1). Baseline characteristics, nutritional, and ventilatory parameters are shown in Table 1, Table 2.

Primary analysis

The estimated mean $EEVCO_2$ was 2134 kcal/24 h compared with an estimated mean EE from indirect calorimetry of 1623 kcal/24 h (the uncorrected mean and median values are depicted in Table 3). This resulted in a significant bias of 511 kcal (95% CI 467–560 kcal; p < 0.001). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 2. Reliability was good, with an absolute intraclass correlation coefficient of 0.613 (95% CI 0.550–0.669, p < 0.001). The 10% accuracy rate was 7.0%, with $EEVCO_2$ overestimating and underestimating the EE in respectively 92.8% and 0.2% of cases.

Secondary analysis

Performance of the food quotient

The estimated mean food quotient was 0.870 compared with an estimated RQ by indirect calorimetry of 0.878. This resulted in an acceptable bias of 0.007 (95% CI 0.000–0.015, p = 0.54). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 3A. Because of proportional bias regression-based limits of agreement were also calculated as shown in Fig. 3B [17]. Reliability was poor with an absolute intraclass correlation coefficient of 0.148 (95% CI 0.053–0.240, p = 0.001). The 10% accuracy rate was 77.5%, with the food quotient overestimating and underestimating RQ in 13.8% and 8.7% of cases, respectively.

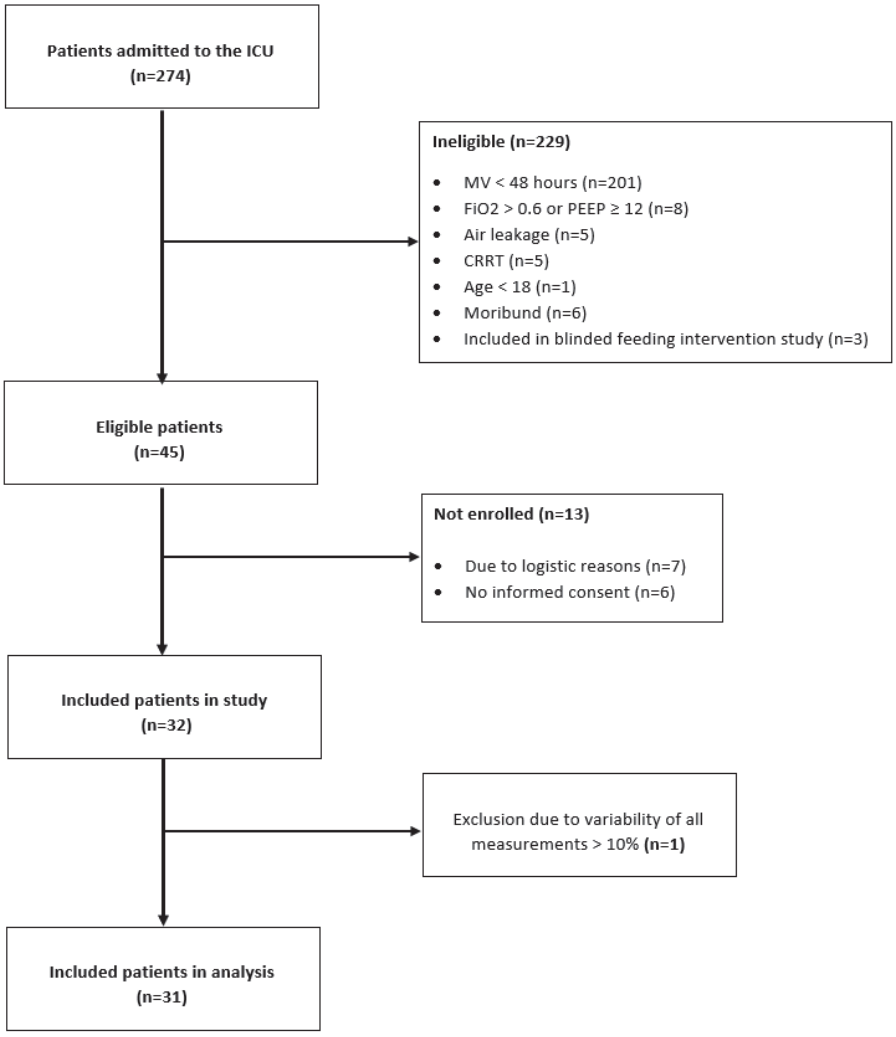
Estimating EE with ventilator derived VCO_2 including the food quotient

The estimated mean $EEVCO_2$, including the food quotient, was 2120 kcal/24 h compared with an estimated mean EE from indirect calorimetry of 1624 kcal/24 h, resulting in a significant bias of 496 kcal (95% 451–542; p < 0.001). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 3C. Reliability was good, with an absolute intraclass correlation coefficient of 0.610 (95% CI 0.550–0.661, p < 0.001). The 10% accuracy rate was 9.2%, with $EEVCO_2$ including the food quotient overestimating and underestimating the EE in respectively 90.6% and 0.2% of cases.

Performance of predictive equations

In a post-hoc analysis we evaluated the performance of four commonly used predictive equations for EE: The World Health Organization and Food and Agriculture Organization (WHO/FAO) [18], Penn State [19], Harris-Benedict [20] and the American College of Chest Physisians (ACCP) [21]. The results are shown in supplement 2.

Figure 1| Flowchart



Abbreviations: ICU: intensive care unit, MV: mechanical ventilation, FiO_2: the fraction of inspired oxygen, PEEP: positive end-expiratory pressure, CRRT: continuous renal replacement therapy.

Table 1| Baseline characteristics

Characteristics	Data
Number of patients	31
Male, n (%)	18 (58.1)
Female, n (%)	13 (41.9)
Age, year, median (IQR)	69 (55-79)
Height, cm, (mean ± SD)	172.8 (10.9)
Weight, kg, median (IQR)	84 (75-100)
BMI, kg/m^2, median (IQR)	27.9 (25.9-32.4)
APACHE II score, mean (± SD)	19.2 (7.8)
SOFA score, mean (± SD)	5.3 (2.0)
ICU admission diagnosis, n (%)	
Sepsis	11 (35.5)
Respiratory insufficiency	10 (32.3)
Cardiovascular	4 (12.9)
Post-surgery	3 (9.7)
Endocrine/Metabolic	1 (3.2)
Neurologic	1 (3.2)
Post-cardiac arrest	1 (3.2)
Length of ICU stay, days, median (IQR)	13 (8-22)
Length of mechanical ventilation, days, median (IQR)	7.8 (3.9-16.3)
Length of stay hospital, days, median (IQR)	22 (14-41)
ICU mortality, n (%)	3 (9.7)
Hospital mortality, n (%)	4 (13.0)
NUTRIC score on admission (mean ± SD)	6.1 ± 2.1

Abbreviations: IQR = interquartile range; SD = standard deviation; BMI = body mass index; APACHE = Acute Physiology And Chronic Health Evaluation; SOFA = Sequential Organ Failure Assesment; ICU = intensive care unit; NUTRIC score = Nutrition Risk in Critically ill score;

Table 2| Clinical, nutritional and ventilatory characteristics during measurements

Measurements, n	414
Clinical characteristics	
ICU day of evaluation, days, median (IQR)	4.3 (2.2-9.2)
Body temperature, ºC, median (IQR)	37.5 (37.0-37.9)
Heart rate, beats/min, median (IQR)	88 (78-103)
Vasopressor use, n (%)	28 (35.4)
Nutritional characteristics	
Type of nutrition, n (%)	
Enteral, n (%)	75 (94.9)
Parenteral, n (%)	2 (2.5)
Combination enteral and parenteral, n (%)	2 (2.5)
Non-nutritional energy intake, kcal/24h, median (IQR)	108 (0-264)
Glucose intake, kcal/24h, median (IQR)	48 (0-204)
Propofol intake, kcal/24h, median (IQR)	0 (0-0)
Citrate intake, kcal/24h, median (IQR)	0 (0-0)
Nutritional energy intake, kcal/24h, median (IQR)	1524 (876-1818)
Carbohydrate intake, kcal/24h, median (IQR)	600 (348-780)
Protein intake, kcal/24h, median (IQR)	336 (204-480)
Fat intake, kcal/24h, median (IQR)	396 (228-516)
Total nutritional intake, kcal/24h, median (IQR)	1572 (1020-2016)
Ventilator Settings	
PEEP, cmH_2O, median (IQR)	8 (6-8)
FiO_2, %, median (IQR)	34 (30-39)
Minute volume, L/min, median (IQR)	10.2 (8.2-12.0)
Respiratory rate, breaths/min, median (IQR)	21 (16-26)
Tidal volume, ml, median (IQR)	494 (427-602)
$ETCO_2$, kPa ,mean (± SD)	5.7 (± 0.72)

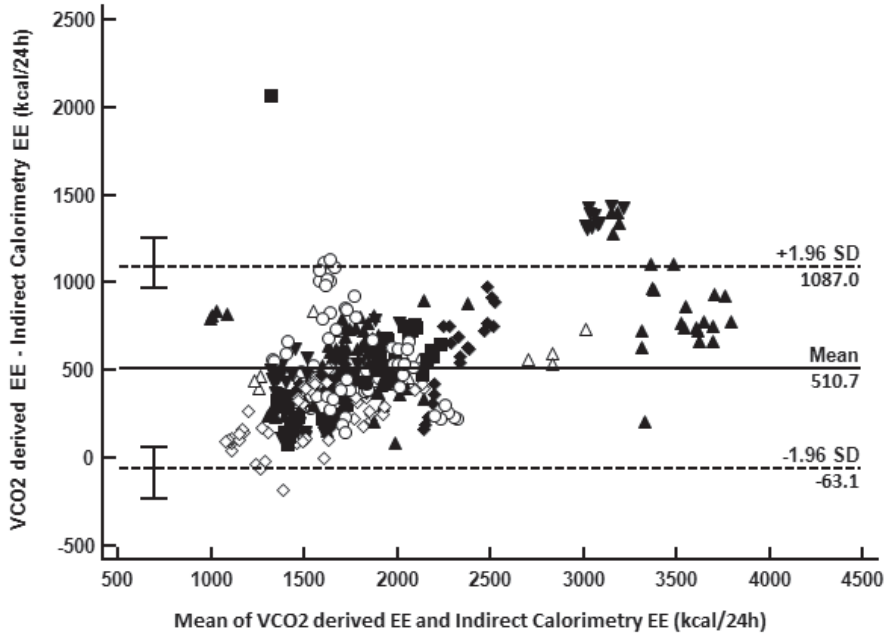
Abbreviations: ICU = intensive care unit; IQR = interquartile range; PEEP = positive end-expiratory pressure; FiO2 = fraction of inspired oxygen; ETCO2 = end-tidal carbon dioxide; SD = standard deviation

Table 3| Energy expenditure, VCO_2, VO_2 and respiratory quotient

	mean ± SD	median (IQR)
VCO_2 (ml/min)		
Calorimetry		193 (166-218)
Ventilator		249 (210-273)
VO_2 (ml/min)		
Calorimetry		220 (195-255)
Respiratory quotient		
Calorimetry	0.8676 ± 0.0657	
Food quotient		0.8691 (0.8546-0.8871)
Energy expenditure (kcal/24hours)		
Calorimetry		1544 (1359-1778)
VCO2- and food quotient-derived		1967 (1705-2268)
VCO2 and respiratory quotient 0.86		2035 (1724-2239)

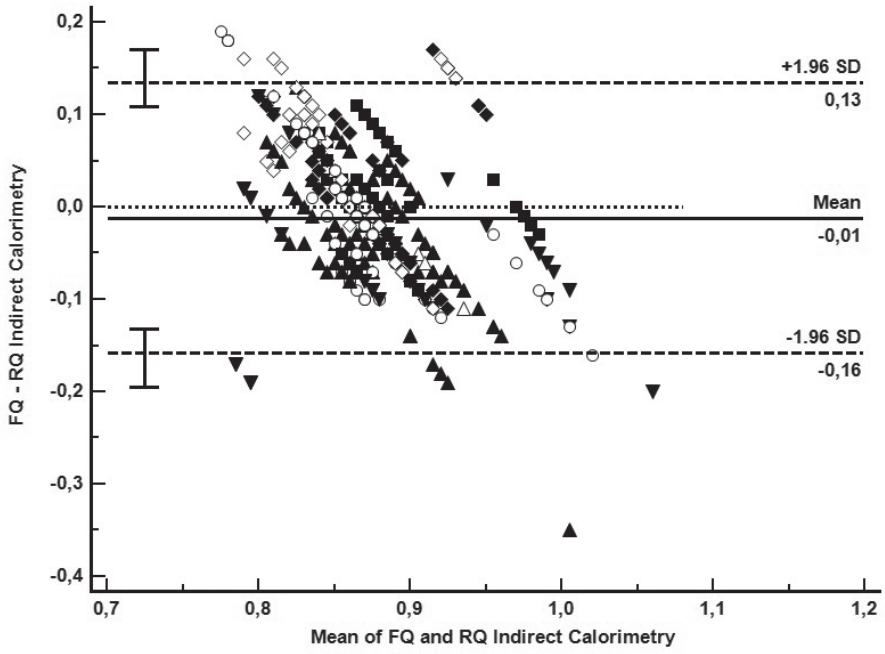
The median energy expenditure and median food quotient, without correction for repeated measures, are reported in this table in addition to the estimated mean energy expenditure and estimated mean food quotient in the results section.
Abbreviations: VCO_2 = carbon dioxide consumption; VO_2 = oxygen consumption; SD = standard deviation; IQR = interquartile range.

Figure 2| Bland-Altman plot of EEVCO2 and EE by IC

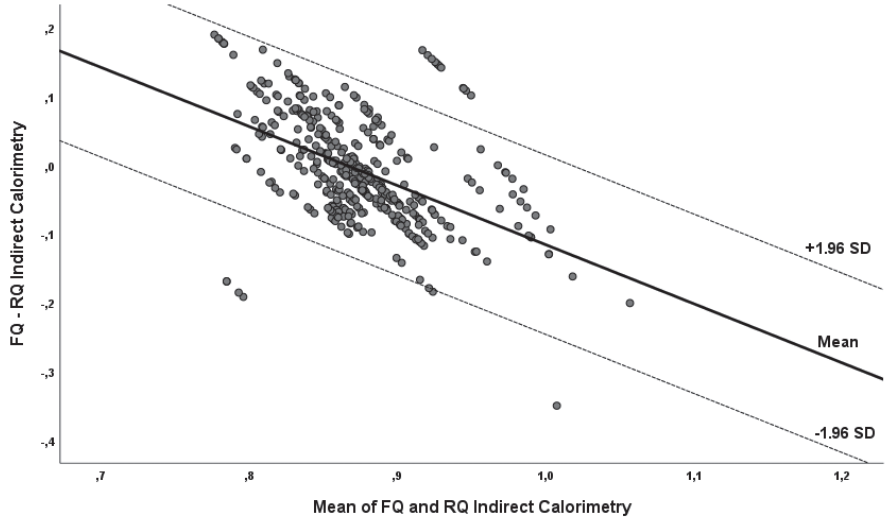


Similar symbols indicate separate measurements in the same patient.
Abbreviations: EEVCO2: energy expenditure calculated with ventilator-derived carbon dioxide production, EE: energy expenditure, IC: indirect calorimetry, SD: standard deviation, kcal: kilocalories.

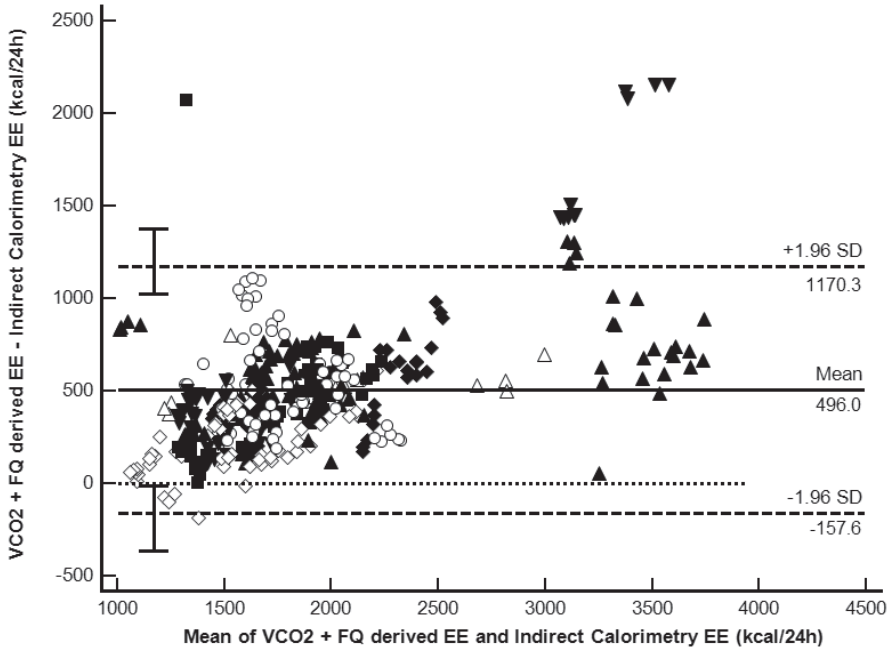
Figure 3| Performance of the food quotient
A: Bland-Altman plot of FQ and RQ by IC



B: Bland-Altman plot of FQ and RQ by IC with regression based limits of agreement.



C: Bland-Altman plot of EEVCO2 adjusted for FQ and EE by IC.



Similar symbols indicate separate measurements in the same patient.
Abbreviations: RQ: respiratory quotient, IC: indirect calorimetry, EEVCO2: energy expenditure calculated with ventilator-derived carbon dioxide production, EE: energy expenditure, IC: indirect calorimetry, SD: standard deviation, FQ: food quotient.

DISCUSSION

We prospectively compared the performance of the $EEVCO_2$ with the EE measured by indirect calorimetry, using 414 paired measurements among 31 adult critically ill patients. The performance of the $EEVCO_2$ in this study was poor, shown by a large bias of 511 kcal and a low 10% accuracy rate of 7.0%. Reliability between $EEVCO_2$ and EE by indirect calorimetry was good, suggesting that there may be a systematic error causing the $EEVCO_2$ to be significantly higher. However, precision was low, reducing the accuracy of the $EEVCO_2$ regardless of whether a systematic error could be corrected for or not.

Two previous prospective studies have compared the $EEVCO_2$ with the EE measured by indirect calorimetry and found significantly higher 10% accuracy rates of 61% and 89% and smaller biases, but one of these studies [9] had a small sample size of only 18 measurements. $EEVCO_2$ was also found to be more precise in one study compared with our results [10], but not reported in the other study [9]. Reliability was not reported in either study [9,10].

The significant bias and low 10% accuracy rates in our study are either due to the inaccuracy of the VCO_2 measurements by the ventilator, the RQ estimation or inaccuracy of the Quark RMR metabolic monitor. The inaccuracy of the VCO_2 derived from the ventilator can be due to calibration errors, rapid or irregular breathing, and patient-ventilator dyssynchrony. Inaccuracy of the Quark RMR metabolic monitor may also be due to calibration errors or a large variability (>10%) in VCO_2 and VO_2 during the measurement. The differences in accuracy rates and biases between the studies may be explained by the use and calibration of different mechanical ventilators and metabolic monitors. The higher precision may be explained by the differences in duration of the measurements, which was 24 h in the study by Stapel and coworkers and 10 min in our study [10].

In addition, one retrospective study compared $EEVCO_2$ derived from the mechanical ventilator with the EE from indirect calorimetry and found a 5% accuracy of 11–18% and 15% accuracy of 37–43% depending on the value of the fixed RQ that was used (between 0.80 and 0.89) [22].

Use of the food quotient as a substitute of RQ

We found a very poor correlation between the food quotient and the RQ, as shown by the intraclass correlation coefficient of 0.148 (95% CI 0.053–0.240, p = 0.001). Food quotient is the RQ estimated from the oxidation of the administered nutrients or total caloric intake; therefore, only the exogenous energy sources are taken

into account. A possible explanation for our results is that endogenous substrate utilization accounts for a large part of energy expenditure in the early phase of critical illness and cannot be estimated by nutritional intake [23]. Our findings are in line with previous studies reporting no correlation between the food quotient and RQ, nor improvement of the performance of the $EEVCO_2$ when the food quotient is used instead of a fixed RQ value [10,24].

Strengths & weaknesses

Although the study population was small, a large amount of paired repeated measurements could be analyzed in this study, improving the overall statistical power. Multiple aspects of $EEVCO_2$ were analyzed, including bias, precision, 10% accuracy rates, and reliability, providing a complete picture of its performance.

Our study has several limitations. A steady-state, whereby there is less than 10% variation in oxygen consumption and CO_2 production over a 5-min interval, was not possible in a certain amount of measurements, leading to the exclusion of multiple measurements from the analysis. A second limitation is the generalizability of the study as only one type of mechanical ventilator and one type of indirect calorimeter were used.

Clinical implications

Based on our results, we cannot recommend $EEVCO_2$ as a substitute for EE measured by indirect calorimetry. $EEVCO_2$ may over- or underestimate EE in a large proportion of patients, and when nutritional goals are based on this, it may inflict harm. In addition, the food quotient should not be used as a substitute for the RQ as they are not correlated in critically ill patients.

When indirect calorimetry is not feasible or available, alternatives should be used to estimate EE. In patients with pulmonary artery catheters, VCO_2 and VO_2 can be measured and used to calculate EE, and this is, however, a select population. The performance of the $EEVCO_2$ may be increased with higher accuracy of $(V)CO_2$ detection and analysis in mechanical ventilators as well as a standard calibration of the mechanical ventilators with indirect calorimeters. Predictive equations are available but not accurate. New techniques, including isotopic CO_2 breath measurement and wearable bracelets and waistbelts are being developed, but are not available yet [25].

CONCLUSIONS

$EEVCO_2$, compared with indirect calorimetry, overestimates actual energy expenditure. Although reliability is acceptable, bias is significant, and precision and the accuracy rates are unacceptably low when the VCO_2 method is used. Including food quotient into the $EEVCO_2$ equation does not improve the accuracy nor the agreement of the $EEVCO_2$. Predictive equations, although inaccurate, may even predict energy expenditure better compared with the VCO_2-method. Indirect calorimetry remains the gold standard method.

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SUPPLEMENTARY DATA

Supplementary Table 1| Calculation of the food quotient, an example

	kcal in 2 hours before measurement	***Respiratory quotient (RQ)***
Nutritonal intake		
Carbohydrates	48	1.0
Proteins	28	0.8
Fat	57	0.7
Non-nutritional intake		
Glucose	9	1.0
Propofol	28	0.7
Citrate	0	1.33
Total intake	170	0.87 **(= food quotient)**

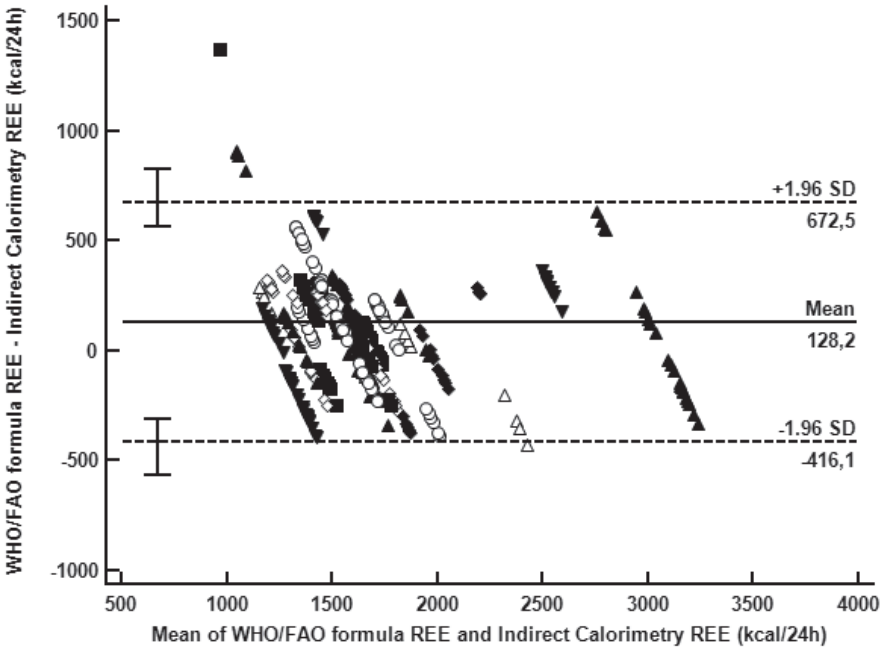
*Food quotient = (carbohydrates * 1 + proteins * 0.8 + fat * 0.7 + glucose * 1 + propofol * 0.7 + citrate * 1.33) / total caloric intake*

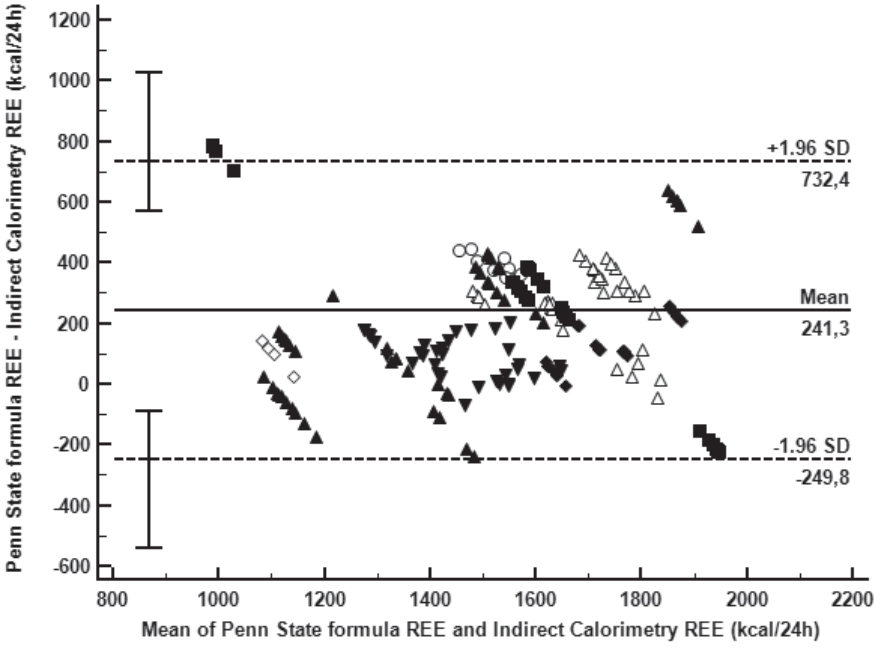
Supplement 2: Performance of predictive equations

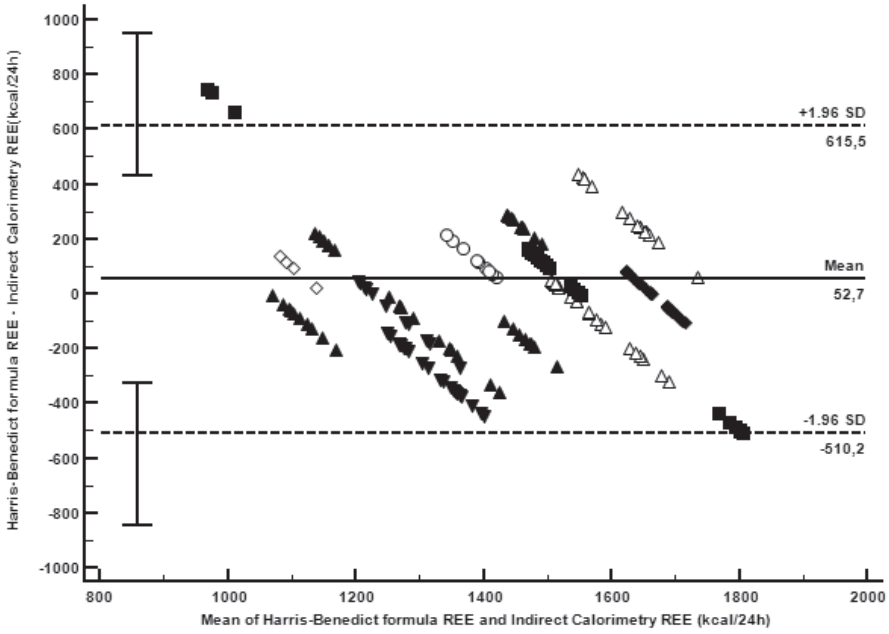
We compared the performance of four commonly used predictive equations estimating energy expenditure (EE) with the EE measured by indirect calorimetry. The performance of the following equations was evaluated:

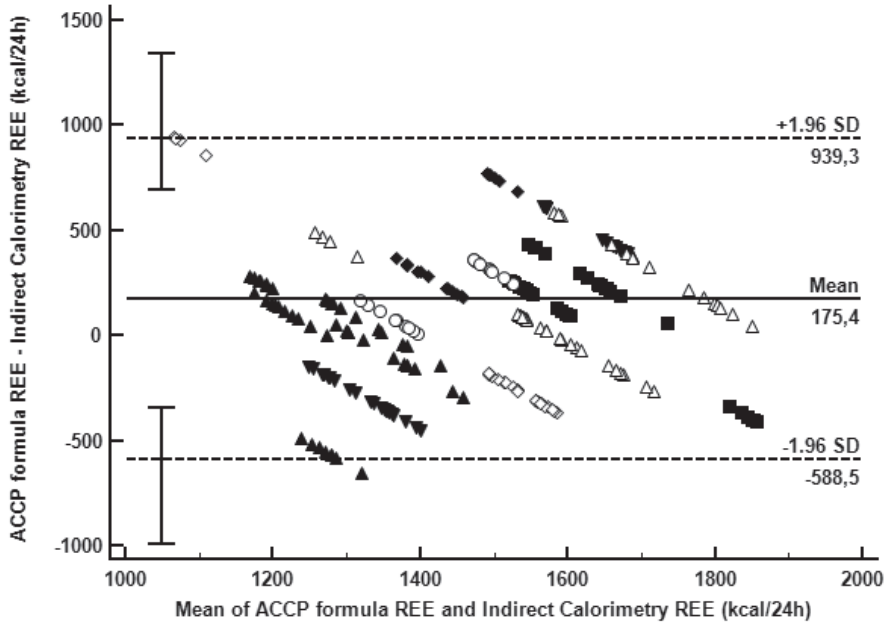
1. World Health Organization & Food and Agriculture Organization (WHO/FAO) [1]:
   - Men:
     i. 18 – 30 years: 15.4 * weight (kg) – 27 * height (cm) + 717
     ii. 31 – 60 years: 11.3 * weight (kg) + 16 * height (cm) + 901
     iii. > 60 years: 8.8 * weight (kg) + 1128 * height (cm) - 1071
   - Women:
     i. 18 – 30 years: 13.3 * weight (kg) + 334 * height (cm) + 35
     - ii. 31 – 60 years: 8.7 * weight (kg) – 25 * height (cm) + 865
     - iii. > 60 years: 9.2 * weight (kg) – 637 * height (cm) - 302
2. Penn State University (PSU) [2]:
   - Men: 0.96 (10 * actual body weight (kg) + 6.25 * height (cm) – 5 * age + 5) + 167 * maximum body temperature in previous 24 hours (°C) + 31 * minute ventilation (L) - 6212
   - Women: 0.96 (10 * actual body weight (kg) + 6.25 * height (cm) – 5 * age - 161) + 167 * maximum body temperature in previous 24 hours (°C) + 31 * minute ventilation (L) - 6212
3. Harris Benedict [3]:
   - Men: (66.5 + (13.8 * actual body weight (kg)) + (5 * height (cm)) – (6.8 * age)) * 1.5
   - Women: (655 + (9.6 * actual body weight (kg)) + (1.8 * height (cm)) – (4.7 * age)) * 1.5
4. American College of Chest Physicians (ACCP) [4]:
   - BMI < 25: actual body weight (kg) * 25
   - BMI ≥ 25: ideal body weight (kg) * 25

Bland-Altman plots






Harris-Benedict formula REE - Indirect Calorimetry REE(kcal/24h)
1000
800
600
400
200
0
-200
-400
-600
-800
-1000
+1.96 SD
615,5
Mean
52,7
-1.96 SD
-510,2
800
1000
1200
1400
1600
1800
2000
Mean of Harris-Benedict formula REE and Indirect Calorimetry REE (kcal/24h)


ACCP formula REE - Indirect Calorimetry REE (kcal/24h)
1500
1000
500
0
-500
-1000
+1.96 SD
939,3
Mean
175,4
-1.96 SD
-588,5
1000
1200
1400
1600
1800
2000
Mean of ACCP formula REE and Indirect Calorimetry REE (kcal/24h)

Reliability

	ICC	95% CI	p value
EE WHO/FAO	0.839	0.808 – 0.865	< 0.001
EE PSU	0.534	0.423 – 0.629	<0.001
EE Harris Benedict	0.481	0.363 – 0.584	<0.001
EE ACCP	0.053	-0.074 – 0.179	0.191

10%-accuracy rates

	10% accuracy	underestimation	overestimation
EE WHO/FAO	46.9%	12.8%	40.3%
EE PSU	71.5%	1.7%	26.8%
EE Harris-Benedict	75.6%	12.8%	11.6%
EE ACCP	57.2%	15.9%	26.8%

Abbreviations: ACCP = American College of Chest Physicians; CI = confidence interval; EE = energy expenditure; FAO = Food and Agriculture Organization; ICC = intraclass correlation coefficient; PSU = Penn State University; REE = resting energy expenditure; SD = standard deviation; WHO = World Health Organization.

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3

CHAPTER

The effect of cisatracurium infusion on the energy expenditure of critically ill patients: an observational cohort study

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ABSTRACT

Background

Both overfeeding and underfeeding of intensive care unit (ICU) patients are associated with worse outcomes. A reliable estimation of the energy expenditure (EE) of ICU patients may help to avoid these phenomena. Several factors that influence EE have been studied previously. However, the effect of neuromuscular blocking agents on EE, which conceptually would lower EE, has not been extensively investigated.

Methods

We studied a cohort of adult critically ill patients requiring invasive mechanical ventilation and treatment with continuous infusion of cisatracurium for at least 12 h. The study aimed to quantify the effect of cisatracurium infusion on EE (primary endpoint). EE was estimated based on ventilator-derived VCO2 (EE in kcal/day = VCO2 × 8.19). A subgroup analysis of septic and non-septic patients was performed. Furthermore, the effects of body temperature and sepsis on EE were evaluated. A secondary endpoint was hypercaloric feeding (> 110% of EE) after cisatracurium infusion.

Results

In total, 122 patients were included. Mean EE before cisatracurium infusion was 1974 kcal/day and 1888 kcal/day after cisatracurium infusion. Multivariable analysis showed a significantly lower EE after cisatracurium infusion (MD − 132.0 kcal (95% CI − 212.0 to − 52.0; p = 0.001) in all patients. This difference was statistically significant in both sepsis and non-sepsis patients (p = 0.036 and p = 0.011). Non-sepsis patients had lower EE than sepsis patients (MD − 120.6 kcal; 95% CI − 200.5 to − 40.8, p = 0.003). Body temperature and EE were positively correlated (Spearman's rho = 0.486, p < 0.001). Hypercaloric feeding was observed in 7 patients.

Conclusions

Our data suggest that continuous infusion of cisatracurium in mechanically ventilated ICU patients is associated with a significant reduction in EE, although the magnitude of the effect is small. Sepsis and higher body temperature are associated with increased EE. Cisatracurium infusion is associated with overfeeding in only a minority of patients and therefore, in most patients, no reductions in caloric prescription are necessary.

BACKGROUND

Targeting optimal nutrition concerning energy goals is essential in critically ill patients, as both underfeeding and overfeeding have been associated with increased morbidity and mortality [1]. Ideally, the target is based on energy expenditure (EE). However, due to the pathophysiological response to critical illness, iatrogenic interventions, and differences in body composition, EE is highly variable in and between critically ill patients [2]. Frequent monitoring of EE may circumvent this problem and help to adjust the optimal amount of calories on an individual basis. At present, indirect calorimetry is considered the gold standard. However, frequently, this technique is not available and often unfeasible [3].

To optimize nutritional targets without frequent monitoring of EE, it is essential to know which factors are associated with either an increase or decrease in EE.

Specific conditions expected to influence EE have been studied such as sepsis [4–6], burns [4, 7], trauma [4, 8], cerebrovascular accidents [4, 9], pregnancy [10], body temperature [4], administration of sedatives [11], and therapeutic hypothermia [4, 12]. An increased EE has been reported in patients with sepsis, trauma, burns, fever, and pregnancy. Therapeutic hypothermia and the administration of sedatives are associated with a decrease in EE [4]. However, limited information is available on the effects of neuromuscular blocking agents (NMBAs) on EE. Furthermore, it is not known whether NMBA administration affects the EE in sepsis patients similarly compared with non-sepsis patients and in relation to the baseline temperature.

This study aimed to quantify the effect of cisatracurium infusion on EE of adult critically ill patients. Also, we analyzed the effects of body temperature and sepsis on EE. Secondary endpoint was hypercaloric feeding as a consequence of muscle relaxation.

MATERIALS AND METHODS

We performed a retrospective observational study in patients treated with cisatracurium at the mixed medicalsurgical adult intensive care unit of the Gelderse Vallei Hospital, Ede, The Netherlands, between January 1, 2011, and October 31, 2016. Patients were included when they met with the following inclusion criteria: adult critically ill patients (≥ 18 years) requiring invasive mechanical ventilation and treatment with cisatracurium for at least 12 h.

Exclusion criteria were pregnancy, hypothermia induced by therapeutic temperature management, burns, and malignant hyperthermia because these conditions have a substantial effect on EE. Patients were also excluded when data on VCO2 were

incomplete. In patients with multiple ICU admissions during the study period, data from readmissions were excluded. An ICU admission was considered readmission when the patient was admitted within 6 months from the primary ICU admission.

Administration of cisatracurium

Cisatracurium is the NMBA of choice for sustained neuromuscular blockade during critical illness in Gelderse Vallei Hospital. Cisatracurium was administered when indicated according to the international clinical practice guidelines for the sustained neuromuscular blockade in the adult critically ill patient [13]. An infusion was started at doses of 3 μg/kg per minute and then adjusted by assessment of the train-of-four (TOF) using a peripheral nerve stimulator (TOF-watch® S, Dublin, Ireland). According to the hospital protocol, TOF measurements were performed every hour, and dosage adjustments were made to achieve a TOF level of 1 or lower. The electrodes of the TOF-watch® were placed on the other wrist daily to prevent skin lesions.

Outcome measures

The primary endpoint was the total EE, expressed as kcal/day, which was measured before and during cisatracurium infusion. Indirect calorimetry was not routinely available during the study period. EE was, therefore, estimated by an adjusted version of Weir's equation using the ventilator-derived VCO2 (EEVCO2). EEVCO2 = 3.941 × VCO2(L/min) / respiratory quotient + 1.11 × VCO2(L/min) × 1440. The respiratory quotient was considered to be a fixed value of 0.86 [14-16]. The mechanical ventilator measured the VCO2 (Hamilton-S1, Hamilton Medical AG, Bonaduz, Switzerland), and every minute, data are automatically sent to our electronic patient data management system (MetaVision; iMDsoft MetaVision®, Tel Aviv, Israel). For each patient, the VCO2 was collected during the 12 h before and during the 12 h after the start of cisatracurium infusion. When patients were not admitted to the ICU 12 h before the start of cisatracurium infusion, the parameters of the available hours were used. The EEVCO2 was calculated every 2 h using the mean VCO2 measurements from the previous 2 h.

Secondary endpoint was hypercaloric feeding (> 110% of EE) after cisatracurium infusion. We also evaluated ICU length of stay (LOS) and in-hospital mortality in patients receiving hypercaloric versus regular or hypocaloric feeding.

Calculation of nutritional goals

The World Health Organization/Food and Agricultural Organization of the United Nations (WHO/FAO) formulas were used to calculate caloric and protein targets by our computerized feeding protocol [17]. According to BMI, the actual (BMI < 27),

corrected (BMI 27–30; regression to BMI of 27), or ideal body weight (BMI > 30; regression to BMI 21 in women and BMI 22.5 in men) was used. An addition to the resting EE (REE) of 20% was used to correct for disease activity [18].

Data collection

Most parameters were routinely collected into an extensive ICU database during standard clinical care. Data extraction was performed using SAS Enterprise Guide queries (version 7.12HF1) searching our Patient Data Management System (MetaVision; iMDsoft MetaVision®, Tel Aviv, Israel, and neoZIS®, Electronic Medical Record, MI Consultancy, Katwijk, The Netherlands). Data to calculate the Charlson Comorbidity Index (CCI) [19] were obtained from the quality management system for hospital mortality registration. Data verification was performed manually. Collected data were de-identified and stored on a secure hospital computer. There were no identifiable paper documents.

Data analysis and statistical considerations

Descriptive data are reported as means and standard deviation (SD) or median and interquartile range in case of skewed distributions, or as frequencies and percentages when appropriate. For the primary analysis, comparing the EE before and after cisatracurium infusion, a general linear mixed model analysis for repeated measures was performed with an autoregressive covariance structure. In this analysis, we corrected for body temperature, sedative and noradrenaline dosages, pH, PEEP, and FiO2 and repeated measurements.

We performed a subgroup analysis of septic and nonseptic patients. We also evaluated the effects of body temperature on EE with the Pearson or Spearman rank correlation tests. The effects of sepsis on EE were analyzed through general linear mixed models, correcting for the following confounders: cisatracurium, temperature, NUTRIC score, gender, BMI, admission type, and repeated effects. Finally, we evaluated the effect of hypercaloric feeding vs. normocaloric and hypocaloric feeding on in-hospital mortality and ICU length of stay (LOS) by chi-square test and one-way ANOVA, respectively. A p value of < 0.05 was considered statistically significant.

The data analyses were performed using IBM corp. SPSS statistics for Windows (version 24.0, released 2015 New York, USA).

RESULTS

Patients

During the study period, 4247 patients were admitted to the ICU, of which 179 received cisatracurium for at least 12 h and therefore were eligible for inclusion. We excluded 57 patients according to the exclusion criteria. In total, 122 patients were enrolled in this study (Fig. 1).

Baseline characteristics and nutritional parameters are shown in Tables 1, 2, and 3. The median age was 65.5 years, and 36.1% were female. The median SOFA and APACHE II scores on admission were 8 and 22, respectively. Most patients were septic (58.2%) and admitted to the ICU because of medical reasons (73%). A median ICU and hospital LOS of 15 and 23 days were found. The in-hospital mortality was 28.7%.

Figure 1| Flowchart

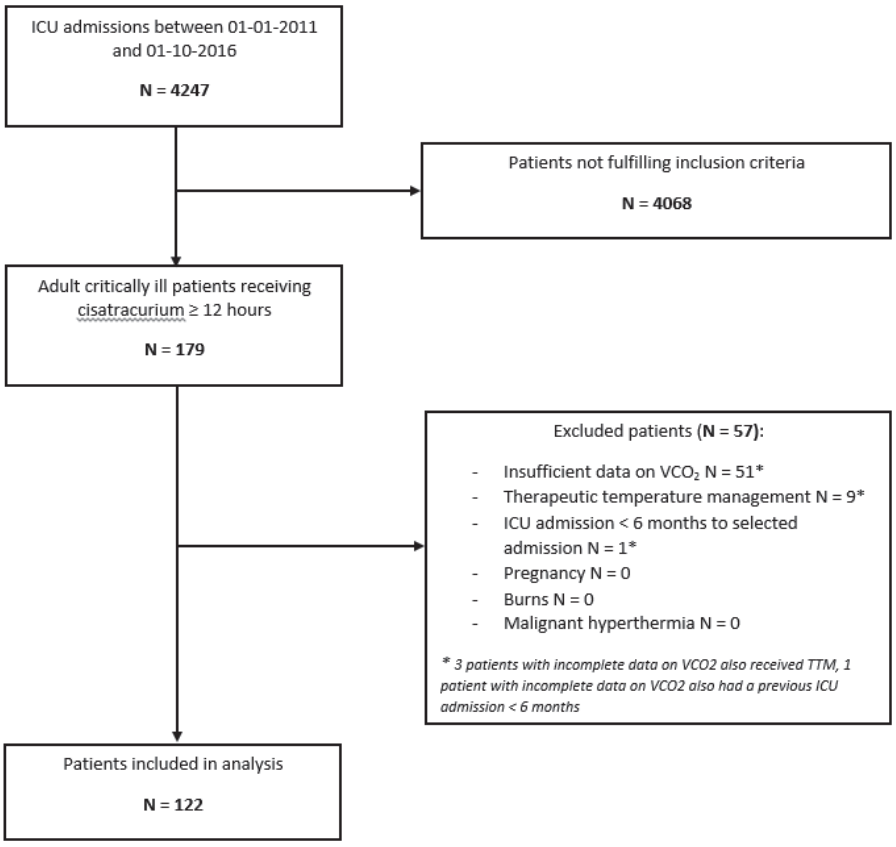


Table 1| Baseline Characteristics

		Total (n = 122)
Gender (female)	N (%)	44 (36.1)
Age (years)	Median [IQR]	66 [55 – 73]
BMI on admission (kg/m2)	Median [IQR]	27.6 [24.0 – 31.0]
• Malnourished (<18.5)	N (%)	3 (2.5)
• Normal (18.5 – 24.9)		33 (27.0)
• Overweight (25 – 29.9)		44 (36.1)
• Obese (30 – 34.9)		26 (21.3)
• Morbidly obese (>35)		16 (13.1)
Admission type	N (%)	
• Medical		89 (73.0)
• Emergency surgery		16 (13.1)
• Elective surgery		17 (13.9)
Sepsis	N (%)	72 (59.0)
Charlson comorbidity index	Median [IQR]	4 [2-5]
SOFA score on admission	Median [IQR]	8 [5 – 9.5]
APACHE II score on admission	Median [IQR]	21.5 [19 – 26.25]
ICU length of stay (days)	Median [IQR]	15 [8 – 26.5]
Hospital length of stay (days)	Median [IQR]	23 [12 – 42]
In-hospital mortality	N (%)	36 (29.5)

Abbreviations: BMI = body mass index; IQR = interquartile range; SOFA = sequential organ failure assessment ; APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit.

Table 2| Baseline Characteristics before and after cisatracurium administration

		Before cisatracurium (n=122)	After cisatracurium (n=122)	p-value
PEEP (cmH2O)	Mean ± SD	9.8 ± 3.0	10.6 ± 3.9	0.012
FiO2 (%)	Median [IQR]	49 [40 - 59]	44.5 [36 – 55]	0.008
Noradrenalin (µg/kg/min)	Mean ± SD	0.16 ± 0.64	0.33 ± 1.25	0.178
Propofol (mg/h)	Mean ± SD	44.9 ± 73.1	42.2 ± 70.8	0.570
Midazolam (mg/h)	Mean ± SD	7.5 ± 5.3	9.0 ± 5.8	<0.001
Morphin (mg/h)	Mean ± SD	1.2 ± 1.3	1.5 ± 1.4	<0.001
pH	Mean ± SD	7.31 ± 0.11	7.32 ± 0.10	0.600
TOF	Median [IQR]	NA	0 [0 – 1]	NA

Abbreviations: PEEP = positive end-expiratory pressure; FiO_2 = fraction of inspired oxygen; TOF = train of four ; NA = not applicable.

Table 3| Nutritional parameters

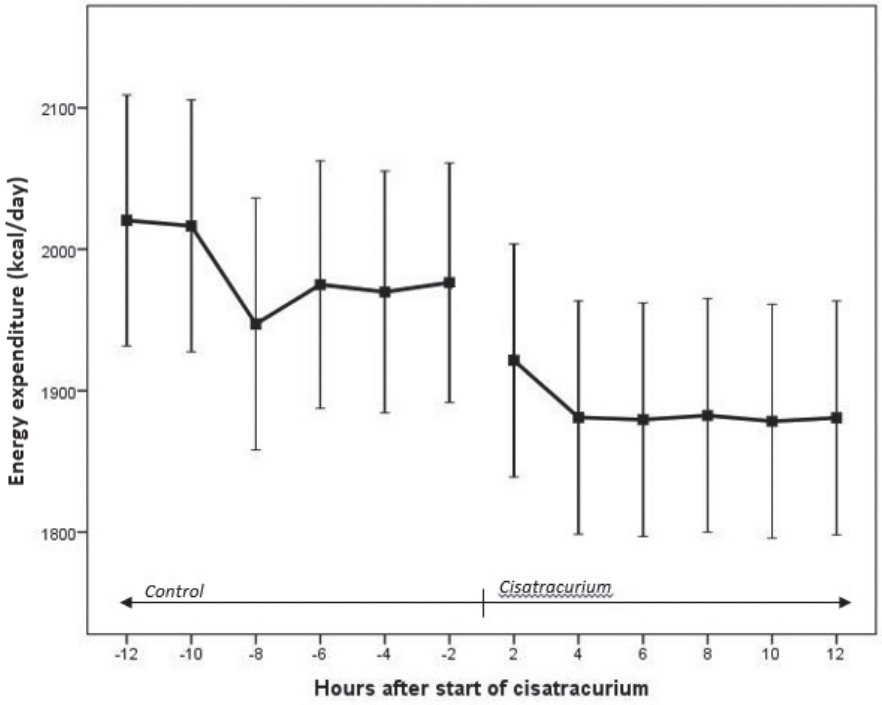
		Total (n = 122)
NUTRIC-score at admission	Median [IQR]	6 [4 – 7]
Low risk (0-4 points)	N (%)	35 (29.9)
High risk (5-9 points)	N (%)	82 (71.1)
Nutritional route	N (%)	
Enteral		91 (91.9)
Parenteral		6 (6.1)
Both		2 (2.0)
Average caloric intake (kcal/day)b	Mean (±SD)	831 (612)

Abbreviations: NUTRIC = Nutrition risk in critically ill [25]; IQR = interquartile range; SD = standard deviation.
a) Nutritional route during the first 24 hours of ICU admission.
b) Average caloric and protein intake during the first day of cisatracurium administration (kcal/day).

Primary outcome

The mean EE was 1974 kcal/day before cisatracurium infusion (= control period) and 1888 kcal/day during cisatracurium infusion resulting in a mean difference of − 85.9 kcal (95% CI − 151.8 to − 20.0; p = 0.011). After correction for body temperature, sedative and noradrenalin dosages, pH, PEEP, and FiO2 in mixed model multivariable analysis, the significant treatment effect of cisatracurium on EE persisted, with a mean difference of − 132.0 kcal (95% CI − 212.0 to − 52.0; p = 0.001). Cisatracurium significantly lowered EE by 6.6% (95% CI 2.6– 10.6%). The results are depicted in Fig. 2.

Figure 2| Energy expenditure before and during continuous cisatracurium infusion



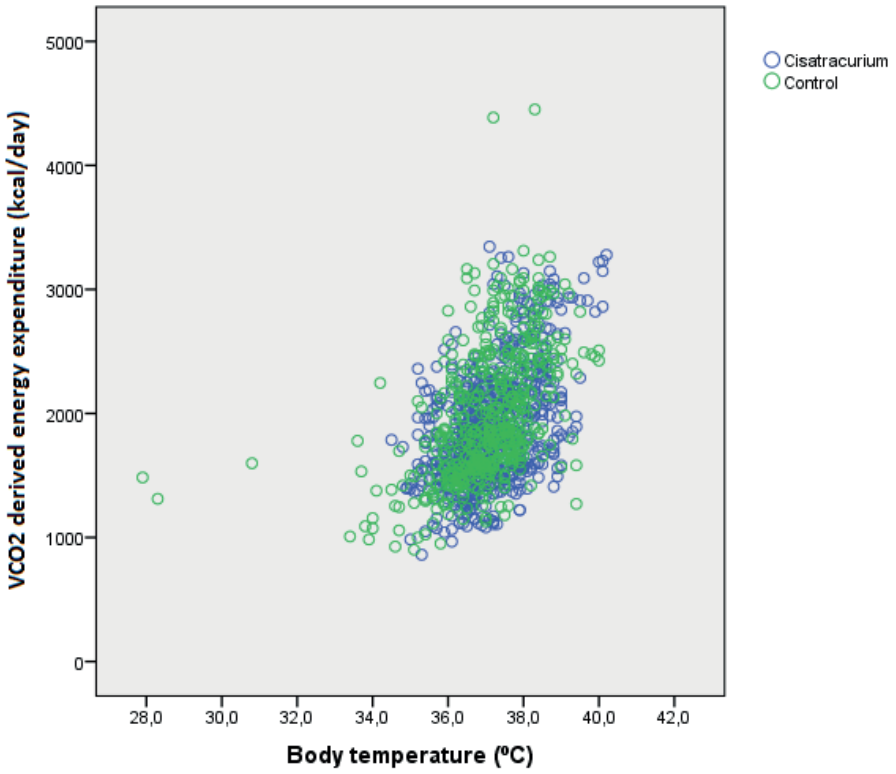
Subgroup analysis of sepsis patients

In the subgroup of sepsis patients, cisatracurium reduced EE from 2058 kcal/day to 1932 kcal/day (mean difference of − 125.7 kcal; 95% CI − 243.0 to − 8.4; p = 0.036). In the subgroup of non-sepsis patients, cisatracurium reduced EE from 1932 kcal/day to 1795 kcal/day (mean difference − 137.2 kcal; 95% CI − 243.0 to − 31.4; p = 0.011). In both analyses, adjustment for body temperature, sedative and noradrenaline dosages, pH, PEEP, and FiO2 were performed.

Effect of body temperature on EE

A significant non-linear positive association between body temperature and EE was found (Spearman's rho = 0.486, p < 0.001; Fig. 3).

Figure 3| Association between body temperature and energy expenditure



Effect of sepsis on EE

Mean EE was 1805 kcal (95% CI 1721–1888) in nonseptic patients and 1909 kcal (95% CI 1838–1978) in septic patients (p = 0.062). In mixed-model multivariable analysis, a significantly lower EE was observed in nonseptic patients than in septic patients (mean difference − 120.6 kcal, 95% CI − 200.5 to − 40.8; p = 0.003).

Hypercaloric feeding

Only seven patients (5.7%) received > 110% of their caloric target (estimated by EEVCO2) on the first day of cisatracurium infusion. Twenty patients (16.4%) received between 80 and 110% of their caloric target, while 95 patients (77.9%) were fed hypocalorically (< 80% of caloric target). Because of the small number of patients with hypercaloric intake, no associations between hypercaloric intake and ICU LOS or mortality were calculated.

DISCUSSION

We studied the effect of cisatracurium infusion on EE in a cohort of 122 adult critically ill patients. Cisatracurium infusion lowered EE as estimated by the VCO2 method by 6.6%.

NMBAs act by interfering with the binding of acetylcholine to the motor endplate in the synaptic cleft of the neuromuscular junction, thereby ultimately preventing muscle contraction. Indications for the continuous infusion of NMBAs during critical illness comprise severe acute respiratory distress syndrome (ARDS) (PaO2/FiO2 < 150), overt shivering during therapeutic hypothermia, and other life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise in case of failure of other measures such as deep sedation [13]. Cisatracurium is one of the most widely used NMBAs for continuous infusion as it can also be used in patients with hepatic or renal insufficiency [21].

Due to the blocking of muscle contractions and as a consequence of the subsequent lower muscular heat production, NMBAs should conceptually reduce EE. However, this hypothesis has not been studied in ICU patients with the previously described indications for the use of continuous NMBA infusion. Overall, only one earlier study has evaluated the effects of NMBAs on EE in adults, reporting a significant increase in EE of 18.6% after discontinuation of pancuronium in patients with severe head injury [22]. Additionally, one study investigated the effects of NMBA infusion (vecuronium, pancuronium, and atracurium) in 20 critically ill children reporting a significant reduction of 10.3% of EE 1 h after infusion of NMBAs [23].

Effect of body temperature on EE

We observed a non-linear positive association between body temperature and EE. Four small previous studies reported an association between body temperature and EE in critically ill patients [4, 24, 25]. A reduction of 6.6% of EE per 1 °C decrease at temperatures below 36 °C and an increase of 8.2% per 1 °C at temperatures above 37 °C have been reported [24, 25].

Effect of sepsis on EE

We observed a higher EE in septic patients than in nonseptic patients. This was in line with our expectations based on previous studies in which EE in septic patients was 102–198% of EE in non-septic patients [4]. However, a recent observational study in 205 patients found no differences in EE between septic and nonseptic patients (1434 vs. 1430 kcal/day) [20].

Strengths and weaknesses

This is the largest cohort of critically ill patients in which the effects of NMBAs on EE have been studied. The effects of NMBAs, especially cisatracurium, in this specific patient population have not been studied before. A large number of patient variables were available with few missing data, providing enough data to perform rigorous multivariable and repeated measure analyses.

However, our study has several limitations. Indirect calorimetry was not routinely available during the study period. Therefore, EE was calculated using VCO2 obtained from the mechanical ventilator. Calculation of EE from VCO2 has been demonstrated to be more accurate than predictive equations, but less than indirect calorimetry. Finally, limitations related to the retrospective design may potentially have introduced bias and residual confounding.

Clinical implications

As cisatracurium reduces EE, reduction of caloric intake after the start of NMBAs should be considered, especially in those patients that are on full feeding or considered to reach this target soon, because they are at risk of hypercaloric feeding and associated harm. Before we designed the study, we expected, due to the drop in EE induced by the NMBA, that some of the patients would be overfed. Based on the results, we noticed that a reduction of EE by NMBA could induce an almost 10% overfeeding risk in individual patients. In daily practice, this did not occur as the patients were not on nutrition target. Thus, for most patients, adjustment may not be necessary as in our analysis the reduction of EE found was only 6.6% and hypercaloric feeding was only present in 5.7%, while most other patients were fed (77.9%) hypocalorically after initiation of cisatracurium infusion.

Although not the focus of our present study, it should be noted that the recent ROSE trial, studying the effect of early neuromuscular blockade (48-h continuous infusion of cisatracurium) with concomitant heavy sedation, compared with usual care, did not result in a significant mortality difference at 90 days in patients with moderate to severe acute respiratory distress syndrome in contrast to an earlier RCT [26, 27]. This trial was stopped early at the second interim analysis for futility. This study may lead to reevaluation of the use of NMBAs in severe respiratory failure.

CONCLUSIONS

Our data suggest that continuous infusion of cisatracurium in mechanically ventilated ICU patients is associated with a significant reduction in EE as estimated by the VCO2 method, although the magnitude of the effect is small. Sepsis and higher body temperature are associated with increased EE. Cisatracurium infusion is associated with overfeeding in only a minority of patients, and therefore, in most patients no reductions in caloric prescription are necessary.

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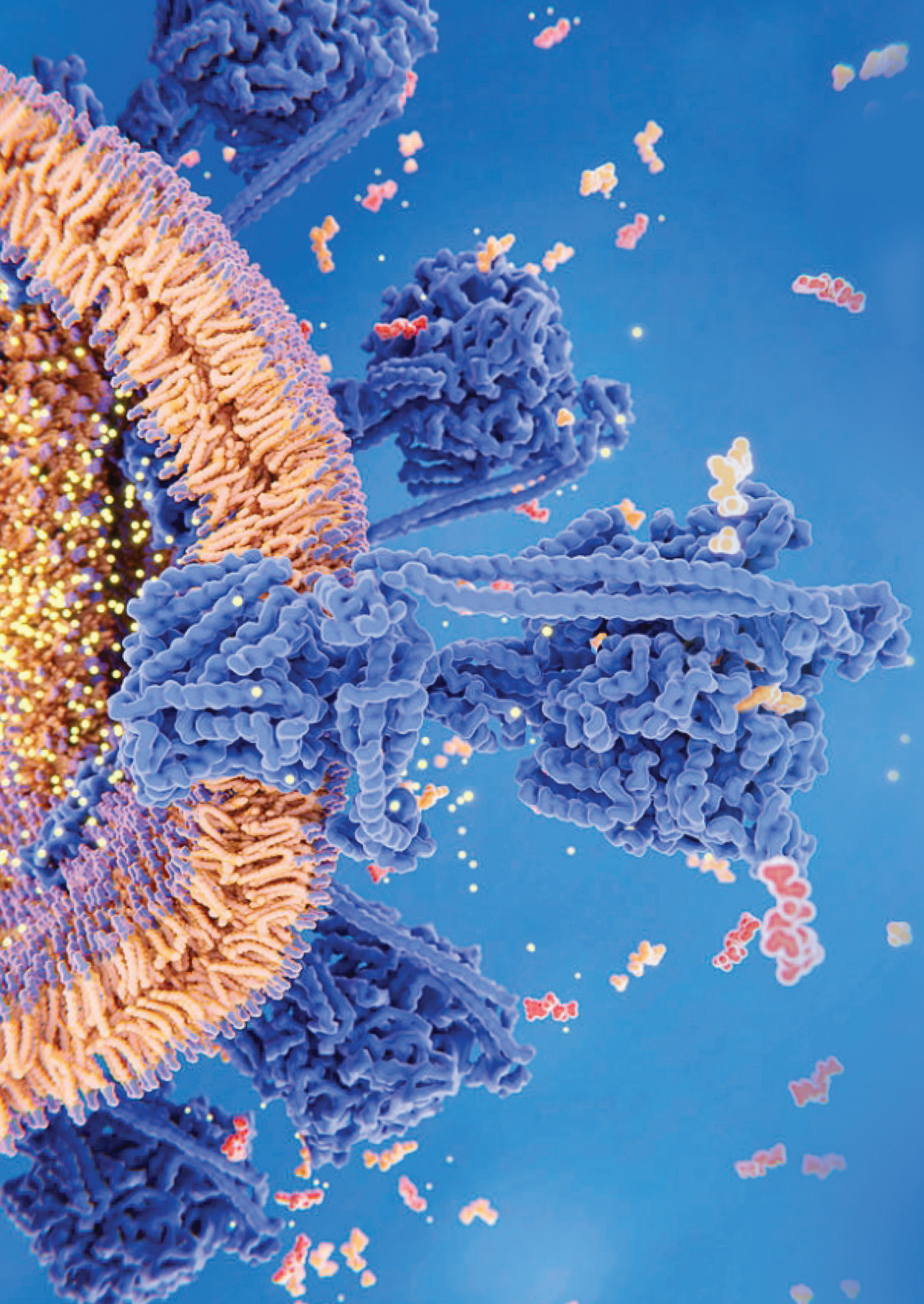

II PART

Nutritional dose and timing of initiation

4

CHAPTER

Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study

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ABSTRACT

Background & aims

Optimal protein intake during critical illness is unknown. Conflicting results on nutritional support during the first week of ICU stay have been published. We addressed timing of protein intake and outcomes in ICU patients requiring prolonged mechanical ventilation.

Methods

We retrospectively collected nutritional and clinical data on the first 7 days of ICU admission of adult critically ill patients, who were mechanically ventilated in our ICU for at least 7 days and admitted between January 1st 2011 and December 31th 2015. Based on recent literature, patients were divided into 3 protein intake categories, <0.8g/kg/day, 0.8-1.2g/kg/day and >1.2g/kg/day. Our primary endpoint was 6-month survival. Secondary endpoints were ventilation duration, need for renal replacement therapy (RRT), ICU length of stay (LOS) and mortality and hospital LOS and mortality.

Results

In total 455 patients met the inclusion criteria. We found a time-dependent association of protein intake and mortality; low protein intake (<0.8g/kg/day) before day 3 and high protein intake (>0.8g/kg/day) after day 3 was associated with lower 6-month mortality, adjusted Hazard Ratio 0.609; 95%CI 0.480-0.772, p<0.001) compared to patients with overall high protein intake. Lowest 6-month mortality was found when increasing protein intake from <0.8g/kg/day on day 1-2 to 0.8-1.2g/kg/day on day 3-5 and >1.2g/kg/day after day 5.

Moreover, overall low protein intake was associated with the highest ICU, in-hospital and 6-month mortality. No differences in ICU LOS, need for RRT or ventilation duration were found.

Conclusions

Our data suggest that although overall low protein intake is associated with the highest mortality risk, high protein intake during the first 3 days of ICU stay is also associated with increased long-term mortality. Therefore, timing of high protein intake may be relevant for optimizing ICU, in-hospital and long-term mortality outcomes.

INTRODUCTION

Nutritional support during critical illness is heavily debated [1]. Many studies have evaluated effects of nutritional support on clinical outcomes in ICU. Most studies have focused on energy provision [2-4], however there is growing evidence that protein intake may be more important than caloric intake [5-7]. As fixed protein to energy ratios in most feeding regimens are used, it is complex to separate effects of protein intake from those of energy intake. Furthermore, in several studies both energy and protein intake were similarly associated with clinical outcomes in univariate analyses [8]. Other studies showed that high protein intake was associated with reduced mortality risk [9], whereas energy overfeeding was associated with increased mortality risk [10].Lower mortality and more ventilator free days were reported in patients with sepsis or severe pneumonia reaching higher protein and caloric intake in the early phase of ICU stay [11]. This might even be more relevant for patients with Body Mass Index (BMI)<25 or >35 $kg*m^{-2}$ [12]. Recently, a retrospective analysis of energy provision during the first week of ICU stay in 475 patients with prolonged mechanical ventilation showed beneficial effects from early full energy feeding on mortality and quality of life 3 months post ICU discharge [13]. In this study protein intake was not studied separately. From the non-nutritional calories (e.g. dextrose, citrate and propofol infusions) only propofol infusions were taken into account, although non-nutritional calories may contribute for up to 20% of total caloric intake in individual patients [14]. Moreover, in that study cumulative caloric intake over one week was studied and daily effects of intake were not assessed.

Casaer and co-workers, based on a post hoc analysis of the EPANIC randomized trial, suggested a time-dependent association of protein intake and clinical outcome, with possible harmful effects of protein intake during the first 3 days of ICU admission [15].

In order to achieve a personalized nutritional approach several questions need to be answered [16,17]. Therefore, we addressed how protein intake during the first week of ICU admission influences clinical outcomes among prolonged mechanically ventilated critically ill patients.

Our primary aim was to determine the best timing and dose of protein intake to support the lowest 6-month mortality. Secondary outcome measures were the effect of timing and dose of protein intake on ICU and hospital length of stay (LOS), ICU and hospital mortality, ventilation duration and need for renal replacement therapy (RRT).

MATERIALS AND METHODS

For this single center cohort study we retrospectively collected data from patients fulfilling inclusion criteria, who were admitted to our ICU between January 1st 2011 and December 31st 2015. Inclusion criteria were: adult critically ill patients (≥18 years), requiring invasive mechanical ventilation for a minimum duration of 7 days. Patients were excluded if the time from admission to start of mechanical ventilation exceeded 48 h, if data on nutritional needs were incomplete, in case of contraindications to full nutrition, if their condition influenced their nutritional needs in a way that we were unable to estimate or compare results with other patients, such as pregnancy, preexistent neuromuscular diseases, known protein malabsorption or metabolic abnormalities. In patients with multiple ICU admissions during the study period, to avert bias we excluded data from ICU readmissions. An ICU admission was considered a readmission when the patient was admitted within 6 months of the primary ICU admission.

Ethical approval

The institutional review board of Gelderse Vallei Hospital approved the study andwaived informed consent for reasons of the retrospective design and anonymization of patient identifiers before analysis.

Data collection

Data extraction was performed using SAS Enterprise Guide queries (version 7.12HF1), from our MetaVision (Patient Data Management System, iMDsoft, Tel Aviv, Israel) database and other hospital electronic patient records. Baseline characteristics were listed; age, gender, primary admission diagnosis, baseline APACHEII and SOFA-scores, several baseline blood tests, admission type (medical, elective and non-elective surgery), comorbidities, modified Nutrition Risk in Critically ill (mNUTRIC) score [18] and administered non-nutritional calories (dextrose infusion, propofol and trisodium citrate) [14]. Data to calculate the Charlson Comorbidity Index (CCI) [19] were obtained from the quality management system for hospital mortality registration. All deaths in the Netherlands are registered in the municipal personal records database of the Dutch government. As our electronic patient management system is directly connected to this database date of death could be extracted. When date of death was not registered the patient was presumed alive. Days were defined as calendar days.

Nutritional parameters

We collected data on nutritional intake for the first 7 days of ICU admission, including protein and energy targets, actual given doses of proteins (g) and calories (kcal) from enteral (EN) and parenteral

nutrition (PN). Additionally non-nutritional calories from trisodium citrate, glucose and propofol infusions were calculated and added to calculate total caloric intake [14]. We divided total caloric intake into adequacy categories based on recent literature [6,10] (3 groups: hypocaloric: <80% of energy target, normocaloric: 80-110% of energy target and hypercaloric: more than 110% of energy target).

Calculation of nutritional goals

In all patients body weight and height were measured on ICU admission. The World Health Organization/Food and Agricultural Organization of the United Nations (WHO/FAO) formulas were used to calculate caloric and protein targets by our computerized feeding protocol [14]. According to BMI, the actual, corrected (weight on BMI 27) or ideal body weight (women weight on BMI 21, men weight on BMI 22.5) was used. An addition to resting energy expenditure (REE) of 20% was used to correct for disease activity. Our target protein intake was 1.5 g per kilogram bodyweight per day ($g*kg^{-1}*day^{-1}$) for patients with BMIs up to 27 $kg*m^{-2}$. In case of BMI 27-30 $kg*m^{-2}$, weight was corrected to BMI 27 $kg*m^{-2}$. In case of BMI >30 $kg*m^{-2}$we used ideal body weight and protein administration was set to 2.0 $g*kg^{-1}*day^{-1}$, whereas patients with a BMI >40 $kg*m^{-2}$ prescription was 2.5 g per kg ideal weight per day according to international guidelines [20].

Protein categories

We used protein targets in grams per kilogram uncorrected body weight on ICU admission to divide patients into categories according to their mean protein intake during the first week of ICU admission. The chosen cut-off values are based on recent literature [10]; protein intake less than 0.8 $g*kg^{-1}*day^{-1}$, 0.8 $g*kg^{-1}*day^{-1}$ to 1.2 $g*kg^{-1}*day^{-1}$ and more than 1.2 $g*kg^{-1}*day^{-1}$.

Study end points

Our primary endpoint was the association of 7-days protein intake and 6-months survival. We considered this to be the most appropriate time window, because the effects of protein provision may not be expected within a short timeframe and previous studies on critical care nutrition feeding interventions show effects on long-term but not early mortality endpoints [21]. Moreover, long-term outcomes are clinically very important for patient prognosis and recovery. Secondary endpoints included ICU and in hospital mortality, ICU and hospital LOS, ventilation duration, need for and duration of RRT and all cause hospital readmission within 6 months from ICU admission.

Data analysis

Descriptive data are reported as means and standard deviation (SD) or median and interquartile range (IQR) in case of skewed distributions, or as frequencies and percentages or ranges (minimum-maximum).

Statistical analysis

Baseline characteristic differences and secondary endpoints were assessed with Chi square tests or Fisher's exact tests and ANOVA or Kruskal-Wallis tests where appropriate. Six-month survival was assessed by Kaplan Meier survival estimate curves and Cox Proportional Hazards Models. A P-value <0.05 was considered statistically significant. For univariate analysis all variables considered to be relevant based on literature were included. For the primary outcome measure, when univariate analysis revealed $p < 0.10$ multivariate analysis was performed. Multicollinearity of variables included into multivariate analyses was assessed by calculation of the variance inflation factor (VIF), we considered a VIF above 2 as an indicator of relevant collinearity. IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, released 2014, Armonk, New York, USA) was used to perform analyses.

RESULTS

Patients

During the study period 2237 patients were admitted to our ICU, of which 546 were considered eligible for inclusion. We excluded 91 patients; reasons were delayed intubation (N = 59), ICU admission within the six months previous to the selected admission (N = 25) and insufficient data on nutritional intake due to participation in a blinded tube feeds study (N = 7, Fig. 1). In total, 455 individual patients were enrolled in our study, of which four were enrolled twice.

Baseline characteristics and feeding parameters are shown in Tables 1 and 2. Significant differences were observed between the 3 protein intake subgroups for BMI, SOFA-score, admission type, hours to start feeding, route of feeding, daily protein target, total protein and caloric intake, adequacy of protein and caloric intake and percentage of non-nutritional calories.

Figure 1| Flowchart of the study population

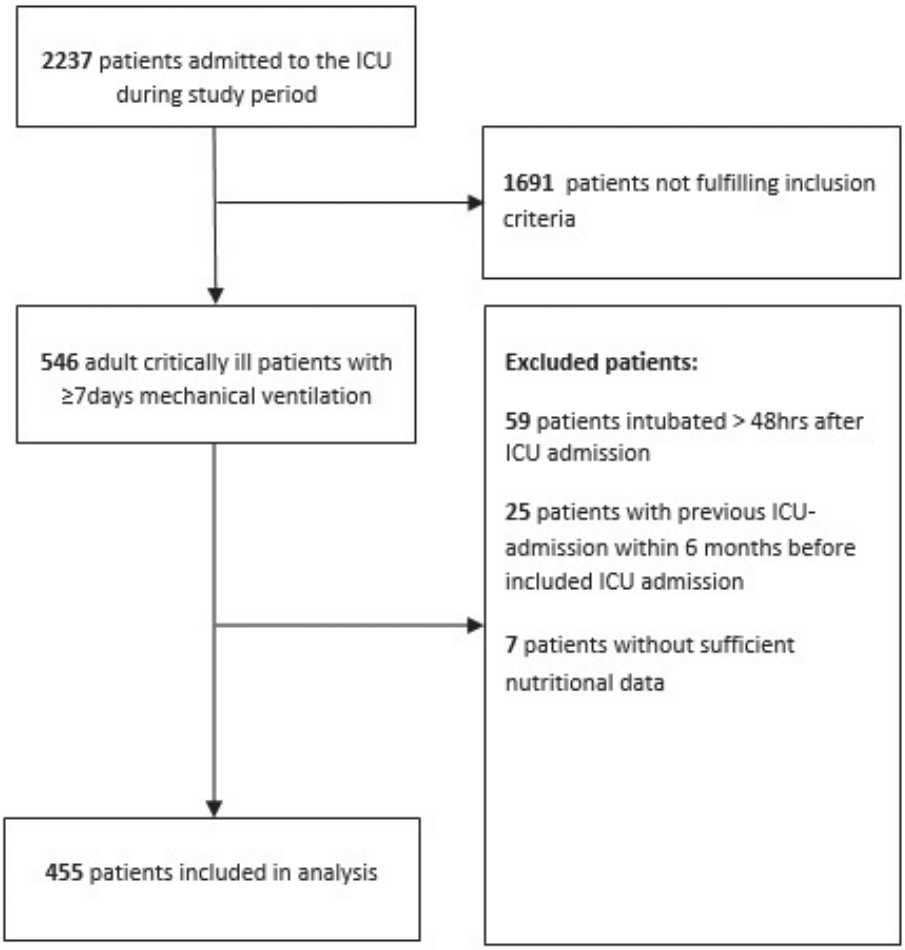


Table 1| Baseline characteristics

	Total population	Protein intake categories			p-value ^
Protein intake in g*kg^{-1}*day^{-1}		LOW <0.8	INTERMEDIATE 0.8-1.2	HIGH >1.2	
N (%)	455 (100)	128 (28.1)	264 (58.0)	63 (13.8)	
Females N (%)	170 (37.4)	47 (36.7)	98 (37.1)	25 (39.7)	0.933
Age, median [IQR]	70 [61-77]	68 [60-77]	70 [61 -76]	70 [61-79]	0.633
BMI,kg*m^{-2}, median[IQR]	26.4 [23.5-30.0]	28.4 [24.7-32.9]	26.2 [23.6-29.4]	24.6 [21.4-26.6]	<0.001
BMI categories					<0.001
< 18.5	16 (3.5)	4 (3.1)	10 (3.8)	2 (3.2)	
18.5 - 25	157 (34.5)	31 (24.2)	93 (35.2)	33 (52.4)	
25 - 35	234 (51.4)	68 (53.1)	140 (53.0)	26 (41.3)	
> 35	48 (10.5)	25 (19.5)	21 (8.0)	2 (3.2)	
ICU admission year					0.818
2011	105 (23.1)	35 (27.3)	59 (22.3)	11 (17.5)	
2012	84 (18.5)	20 (15.6)	51 (19.3)	13 (20.6)	
2013	81 (17.8)	21 (16.4)	48 (18.2)	12 (19.0)	
2014	91 (20.0)	25 (19.5)	50 (18.9)	16 (25.4)	
2015	94 (20.7)	27 (21.1)	56 (21.2)	11 (17.5)	
APACHE II score, median [IQR] n=433	22 [18-28]	24 [19-29]	22 [18-27.5]	23 [18-28.5]	0.167
SOFA score, median[IQR] N=435	8.0 [6-10]	8.0 [6-11]	8.0 [6-9]	7.0 [5-9.75]	0.050
CCI, median[IQR]	4.0 [2-5]	4.0 [2-6]	4.0 [3-5]	4.0 [2-6]	0.985
mNUTRIC score, median[IQR]	5 [4-6]	5 [4-6]	5 [4-6]	5 [3-6]	0.648
mNUTRIC risk group					0.524
low (<5), N(%)	183 (40.2)	46 (35.9)	111 (42.0)	26 (41.3)	
high (5-9), N(%)	272 (59.8)	82 (64.1)	153 (58)	37 (58.7)	

	Total population	Protein intake categories			p-value ^
Admission categories, N(%)					0.032
Surgical emergency					
Surgical	90 (19.8)	35 (27.3)	47 (17.8)	8 (12.7)	
Medical	63 (13.8)	17 (13.3)	41 (15.5)	5 (7.9)	
	302 (66.4)	76 (59.4)	176 (66.7)	50 (79.4)	

Abbreviations: N = number of patients; $g*kg^{-1}*day^{-1}$ = gram per kilogram uncorrected bodyweight per day; BMI= body mass index; APACHE II score = Acute Physiologic and Chronic Health Evaluation II score; SOFA score = sequential organ failure assessment score; CCI = Charlson Comorbidity Index; mNUTRIC score = modified Nutrition Risk in Critically Ill score; IQR = interquartile range (1st - 3th quartile), percentiles by Tukey's Hinges distributions; ^ Calculated by Pearson's Chi square or Fishers exact test, Anova or Kruskal Wallis test as appropriate.

Table 2| Feeding parameters

	Total population	Protein intake categories			p-value^
Protein intake in g*kg^{-1}*day^{-1}		LOW <0.8	INTERMEDIATE 0.8-1.2	HIGH >1.2	
Time to start feeding, hours, median [IQR]	5.55 [2.8-14.4]	11.7 [4.4-25.8]	5.1 [2.6-11.8]	3.4 [2.1-6.5]	<0.001
Route of feeding (EN vs PN)					0.035
EN, N (%)	362 (79.7)	92 (71.9)	213 (81.0)	57 (90.5)	
PN , N (%)	59 (13.0)	22 (17.2)	32 (12.2)	5 (7.9)	
EN + PN, N (%)	33 (7.3)	14 (10.9)	18 (6.8)	1 (1.6)	
Protein target in g*day^{-1}, median [IQR]	115 [102-128]	121 [111-135]	114 [102-125]	109 [95-117]	<0.001
7-day protein intake, g, median [IQR]	535 [423-624]	391 [317-471]	554 [471-641]	639 [577-737]	<0.001
Protein adequacy days 1-3, %, median [IQR]	51 [31-69]	27 [9-39]	55 [40-69]	83 [69-90]	< 0.001
Protein intake (g*kg^{-1}*day^{-1}) days 1-3					< 0.001
< 0.5, N (%)	182 (40.0)	105 (82.0)	77 (29.2)	0 (0)	
0.5 - 0.8, N (%)	156 (34.3)	19 (14.8)	127 (48.1)	10 (15.9)	
0.8 - 1.0, N (%)	82 (18.0)	3 (2.3)	52 (19.7)	27 (42.9)	
1.0 - 1.2, N (%)	28 (6.2)	1 (0.8)	7 (2.7)	20 (31.7)	
> 1.2, N (%)	7 (1.5)	0 (0)	1 (0.4)	6 (9.5)	
Protein adequacy days 4-7, %, median [IQR]	88 [72-99]	66 [53-75]	92 [82-99]	103 [98-111]	< 0.001
Protein intake (g*kg^{-1}*day^{-1}) days 4-7					< 0.001
< 0.5, N (%)	12 (2.6)	12 (9.4)	0 (0)	0 (0)	
0.5 - 0.8, N (%)	28 (6.2)	27 (21.1)	1 (0.4)	0 (0)	
0.8 - 1.0, N (%)	62 (13.6)	44 (34.4)	18 (6.8)	0 (0)	
1.0 - 1.2, N (%)	102 (22.4)	39 (30.5)	62 (23.5)	1 (1.6)	
> 1.2. N (%)	251 (55.2)	6 (4.7)	183 (69.3)	62 (98.4)	
Caloric target, kcal*day^{-1}, median [IQR]	1750 [1492-1957]	1687 [1357-1978]	1768 [1523-1955]	1763 [1618-1886]	0.263

	Total population	Protein intake categories			p-value^
7-day caloric intake, kcal, median [IQR]	10068 [8179-11485]	7907 [6229-9903]	10321 [8723-11522]	11617 [10566-12532]	<0.001
Caloric adequacy days 1-3, %, median [IQR]	91.4 [78.3-102.5]	46.4 [25.8-70.1]	70.1 [52.6-88.7]	86.3 [76.4-95.9]	<0.001
<80%, N (%)	297 (65.3)	106 (82.8)	168 (63.6)	23 (36.5)	<0.001
80 - 110%, N (%)	132 (29.0)	19 (14.8)	76 (28.8)	37 (58.7)	
> 110%, N (%)	26 (5.7)	3 (2.3)	20 (7.6)	3 (4.8)	
Caloric adequacy days 4-7, %, median [IQR]	103.9 [93.3-116.2]	94.3 [75.7-116.5]	105.2 [96.6-115.4]	108.8 [101.8-116.7]	<0.001
<80%, N (%)	55 (12.1)	40 (31.3)	14 (5.3)	1 (1.6)	<0.001
80 - 110%, N (%)	241 (53.0)	49 (38.3)	159 (60.2)	33 (52.4)	
> 110 %, N (%)	159 (34.9)	39 (30.5)	91 (34.5)	29 (46.0)	
Non nutritional to total caloric intake, %, median [IQR]	5.6 [2.1-11]	9.3 [5.6-22.8]	4.6 [1.8-8.8]	3.3 [1.0-8.0]	<0.001

Abbreviations: N = number of patients; g*kg-1*day-1 = gram per kilogram uncorrected bodyweight per day; IQR = interquartile range (1st - 3th quartile), percentiles by Tukey's Hinges distributions; ^ Calculated by Pearson's Chi square or Fishers exact test, Anova or Kruskal Wallis test as appropriate; EN = Enteral nutrition; PN = Parenteral nutrition

Primary outcome

The 6-months survival was 65.6%, 68.9% and 55.6% in the low (0.8 g*kg^{-1}*day^{-1}), intermediate (0.8-1.2 g*kg^{-1}*day^{-1}) and high (>1.2 g*kg^{-1}*day^{-1}) protein intake groups, respectively. Univariate analysis showed a significant survival benefit of the intermediate protein intake category compared with the high protein intake category (p = 0.043). However, this significance was lost in Cox regression multivariate analysis (p = 0.209).

Time dependent effect of protein intake

We subsequently analyzed the early (days 1-3) and late phase (days 4-7) of ICU admission separately (Table 3). Protein intake was classified for mean daily protein intake during early and late phase. Low protein intake during days 1e3 was associated with a statistically significant reduction in 6-month mortality, whereas higher protein intake during days 4-7 was associated with better outcome by unadjusted Cox proportional hazard regression (Table 3). For days 1-3 a Hazard Ratio (HR) of 1.231 (95% CI: 1.040-1.457; p = 0.016) in the >0.8 g*kg^{-1}*day^{-1} group compared to the <0.8 g*kg^{-1}*day^{-1} group was found. Low protein intake <0.8 g*kg^{-1}*day^{-1} during days 4-7 has a HR of 1.605 (95% CI 1.118-2.186; p = 0.003) compared to the high protein intake group. The lowest HR was found in the group with intermediate protein intake during days 4-7 (HR 0.716 95% CI 0.558-0.917; p = 0.008). Further validation of these results was done by assessing days 1-2, showing similar association of low protein intake and 6-month survival. When considering days 1-4, no difference between the low and high intake group was observed (data not shown).

Table 3| Cox Proportional Hazard Model Analysis: Average protein intake during day 1-3 and day 4-7 and 6-month mortality comparing protein intake categories

Average protein intake	N	B	Hazard Ratio	95% CI	p-value
Days 1 to 3					0.019
< 0.8 g*kg^{-1}*day^{-1}	338			reference	
> 0.8 g*kg^{-1}*day^{-1}	117	0.208	1.231	1.040 - 1.457	0.016
Days 4 to 7					0.008
<0.8 g*kg^{-1}*day^{-1}	40	0.473	1.605	1.178 - 2.186	0.003
0.8 - 1.2 g*kg^{-1}*day^{-1}	164	-0.335	0.716	0.558 - 0.917	0.008
>1.2 g*kg^{-1}*day^{-1}	251			reference	

Time-dependent protein intake subgroups

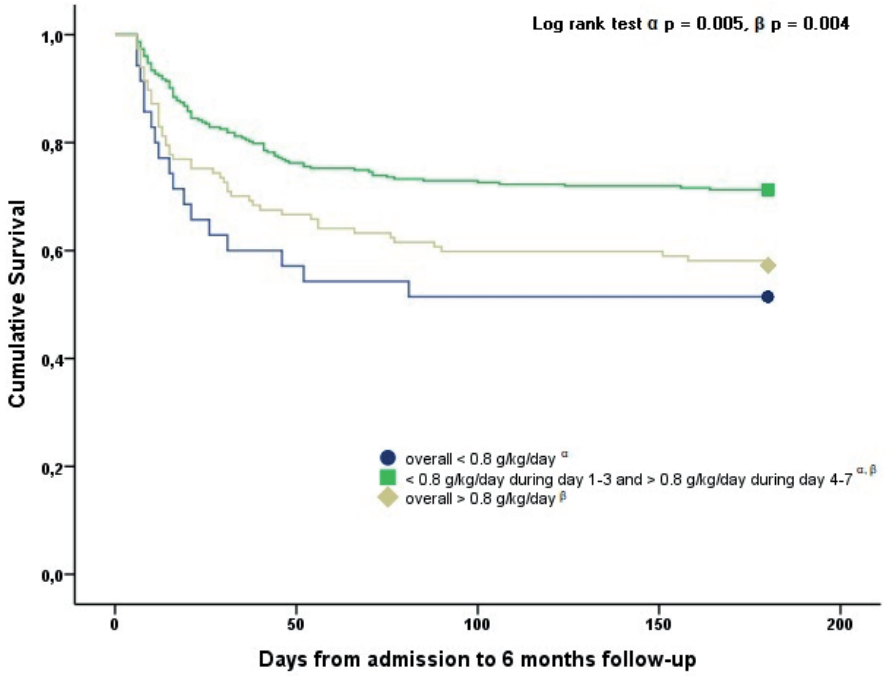
We subsequently compared patients with protein intakes less than 0.8 g*kg^{-1}*day^{-1} during the whole week (group 1 (g1)), with patients who initially received less than 0.8

$g*kg^{-1}*day^{-1}$during day 1-3 but advanced to more than 0.8 $g*kg^{-1}*day^{-1}$ (group 2 (g2)) on day 4 and later and patients who had protein intake of more than 0.8 $g*kg^{-1}*day^{-1}$ during the whole week (group 3 (g3)). A significant difference in 6-month survival was observed between g1 and g2 ($p = 0.005$) and g2 and g3 ($p = 0.004$) in univariate analysis (Fig. 2). In multivariate analysis the significance between g1 and g2 was lost. However, the survival benefit was confirmed between g2 and g3, HR 0.609 (95% 0.480-0.772; $p < 0.001$). Moreover, a significant difference was observed between and g1 and g3 in multivariate analysis, HR 1.495 (95% CI 1.020-2.190; $p = 0.039$).

Time-dependent optimal protein intake

Furthermore, we analyzed the 6-month mortality risk of low, intermediate and high protein intake of each ICU admission day separately for the first week of admission in order to find daily optimum protein intake. On day 1-2 the lowest mortality was found with low protein intake, day 3 and 5 for intermediate protein intake and day 6 and 7 for high protein intake. When comparing this model to the previous mentioned protein intake categories and groups a survival benefit was shown with a 6-month survival of 76.6% for the group advancing from low, to intermediate to high intake.

Figure 2| Six-months survival by Kaplan-Meier estimates for time-dependent protein intake groups.



Secondary outcomes

Secondary outcome measures were assessed based on time-dependent subgroups. Statistical significant differences between groups were found in 6-month mortality (g1 48.6%, g2 28.7%, g3 42.7%, p = 0.004) ICU mortality (g1 40.0%, g2 13.5%, g3 22.2%, p = 0.001) and hospital mortality (g1 48.6%, g2 20.8%, g3 33.3%, p < 0.001). In addition, 6-months a significant difference was found in 6-months all cause hospital readmission (g1 14.3%, g2 33.3%, g3 24.8%, p = 0.025). No significant differences were observed in ventilation duration, need for RRT, ICU readmission within six months, ICU and hospital LOS and discharge destination (Table 4).

Table 4| Secondary outcomes for average protein intake during first week comparing time-dependent protein intake groups.

	< 0.8 g*kg^{-1}*day^{-1}during first week	<0.8 g*kg^{-1}*day^{-1}during day 1-3 and >0.8 g*kg^{-1}*day^{-1}during day 4-7	>0.8 g*kg^{-1}*day^{-1}during first week	p-value^
Patients at risk, N	35	303	117	
6-month mortality, N (%)	17 (48.6)	87 (28.7)	50 (42.7)	0.004
ICU-mortality, N (%)	14 (40.0)	41 (13.5)	26 (22.2)	< 0.001
In-hospital mortality, N (%)	17 (48.6)	63 (20.8)	39 (33.3)	< 0.001
ICU LOS, days, median [IQR]	16 [11-29]	16 [11-25]	15 [11-24.5]	0.798
Hospital LOS, days, median [IQR]	22 [15-43]	30 [20-44]	26 [17.5-41.5]	0.076
ICU TDA, days, median [IQR] (N=374)	18 [12.5-30.5]	16 [12-25.25]	16 [12-26]	0.693
Hospital TDA, days, median [IQR] (N=336)	24.5 [20-45]	32 [22-45]	30.5 [20.75-45.25]	0.741
Ventilation duration, days, median [IQR]	10 [8-21]	11 [8-17]	11 [8-15]	0.583
Need for CVVH, N (%)	11 (31.4)	86 (28.4)	20 (17.1)	0.037
CVVH, days, median [IQR]	9 [6-16]	8 [4-11.25]	6.5 [3.25-10.75]	0.402
6-months all cause hospital readmission, N (%)	5 (14.3)	101 (33.3)	29 (24.8)	0.025

Abbreviations: g*kg^{-1}*day^{-1} = gram per kilogram uncorrected bodyweight per day; IQR = interquartile range (1st - 3th quartile), percentiles by Tukey's Hinges distributions; N = number of patients; LOS = length of stay; TDA= time to discharge alive= length of stay measure which is not biased by the shorter LOS of in-hospital dead patients; CVVH = continuous venovenous hemofiltration

^ Assessed by Fishers' exact test or Kruskal-Wallis test where appropriate

DISCUSSION

We found a time-dependent association of protein intake and 6-month mortality, suggesting that increasing protein intake from low on day 1-2 (<0.8 g/kg/day) to intermediate on day 3-5 (0.8-1.2 g/kg/day) to high after day 5 (>1.2 g/kg/day) confers the best long-term outcome. The worst long-term outcome was observed with overall low protein intake (<0.8 g/kg/day).

Previous studies on efficacy of protein intake in adult critically ill patients show divergent results. Weijs reported improved outcomes in adult ICU patients with early high protein intake [10]. High intake was defined as >1.2 $g*kg^{-1}$ protein on day 4 of ICU admission. In our study day 4 is part of the late phase in which high protein intake indeed confers benefits for long-term mortality. Therefore we suggest that our findings are not in contrast with these observations.

Our results are in line with the findings of Casaer, who demonstrated comparing early and late PN to supplement EN, that providing higher amounts of protein might lead to inhibition of autophagy, which in turn leads to persisting cell damage and cell dysfunction [15] and worse clinical outcomes. This group suggested that proteins may lead to an autophagy deficient phenotype associated with lower survival rates. Strikingly, this deleterious effect of higher protein intake reached statistical significance only on day 3, not on day 5 and 7. Although this study was performed largely in short-stay surgical critically ill patients, we now show similar findings in prolonged mechanically ventilated ICU patients suggesting an early negative effect in the first three days after ICU admission.

Arabi [2] reported no significant differences in 180 days mortality between early caloric underfeeding and standard caloric feeding when maintaining a similar protein intake in both study arms. These results are not in contrast as the average weight in the studied patients was 80 kg with an average protein intake of 58 g per day suggesting an average intake of 0.725 $g*kg^{-1}$, below our cutoff value of 0.8 $g*kg^{-1}$ per day.

Although protein turnover and net balance between muscle protein synthesis and break down was subject of investigation for decades, mechanisms are still poorly understood in critically ill patients. During the initial phase of critical illness, catabolic pathways are activated, causing high protein turnover in order to enhance production of proinflammatory mediators and provide endogenous energy [22,23]. We speculate that in this phase autophagocytic capacity is blunted due to the inflammatory response and this mechanism may be further compromised by external protein administration. In later phases of ICU stay however, proteins and amino acids are strongly needed to provide substrate to synthesize proteins. Moreover during

critical illness anabolic thresholds seem to be elevated suggesting that more protein is needed to achieve similar protein synthesis rates.

Secondary endpoints

We also found an association between time-dependent protein intake and ICU and hospital mortality. Overall low protein intake was associated with the highest ICU and hospital mortality (40.0% and 48.6% respectively). In contrast, no effects on ICU and hospital mortality were found by Casaer [24] who studied early versus late initiation of parenteral nutrition conferring an early difference in protein and energy intake. It could well be that the benefits of larger late protein intake have been counteracted by the negative effects of early high intake. We found no significant differences related to protein intake and timing with respect to ICU and hospital length of stay. Casaer [24] did find a small beneficial effect of late initiation of PN on ICU and hospital LOS and observed a reduction in ventilation duration and need for RRT, which we could not confirm.

Strengths and weaknesses

A large number of critically ill patients were included in this study of which an extensive amount of (non)-nutritional variables were available. Only 7 patients were excluded for incomplete data. Due to strict adherence to our feeding protocol, early EN was started shortly after ICU admission (median 5.6 h) and high nutritional adequacy was found, as reported earlier [12]. Therefore evaluation of protein intake in a very early phase was possible (days 1-3). Furthermore, since our patient groups were heterogeneous from the start, we were able to correct for many nutritional (i.e. caloric intake from feeding and non-nutritional calories [14]) and other (i.e. SOFA-score, age, BMI) covariates. The prolonged duration of mechanical ventilation circumvented effects of nutritional intake on outcome in patients with short ICU stay. In patients with early ICU discharge it has been shown that lower intake is associated with better outcome as patients with lower mortality risk are discharged earlier [25,26]. In this study limited protein intake in the first days after ICU is not confounded by early discharge, as all patients were in the ICU for at least 1 week. Another strength is the long follow-up period (6 months).

Limitations of our study are mainly related to its retrospective design potentially introducing bias and residual confounding. Not all information could be collected in retrospect, for instance we lack data on muscle mass and on feeding after day 7 of ICU admission. Also, because of a gradual increase in intake over the first 72 h is specified in our feeding protocol the sample of patients receiving >1.2 g/kg/day of protein was too small for statistical power and could therefore not be analyzed

separately. Additionally, data are from a single center and inclusion criteria have selected patients with a high severity of illness and prolonged ICU LOS, potentially reducing external validity. Therefore, generalization of study results should be done with caution.

Implications of the study

Our findings suggest that although overall low protein intake is associated with the worst short- and long-term outcomes it may be beneficial in the first 3 days of ICU admission in adult ICU patients. After day 3 higher protein intake is associated with better outcome. This should change our ideas on aggressive early build-up schedules particularly for protein intake. As early high caloric intake may induce overfeeding, as endogenous production of energy may be marked, we suggest to gradually build-up nutritional support over 5 days to reach 0.8-1.2 g/kg/day of protein on day 3-5 and >1.2 g/kg/day on day 6 and later. Our findings are not contradictory to recent practice guidelines, however suggest that another approach in the early phase would be needed.

Unanswered questions and future research

Our study shows a time-dependent association of protein intake on outcome. However, prospective research is needed to confirm this. Furthermore, analysis of this effect in specific subgroups may be valuable as differences were shown in earlier studies regarding protein intake (i.e. septic vs non-septic patients) [10,27]. As time dependence of protein intake may be caused by autophagy interacting with critical illness and the immune response, outcomes may be different when studying less severely ill patients. New research should focus on underlying (patho)physiological mechanisms causing time-dependent effects of protein intake.

CONCLUSIONS

A time-dependent effect of protein intake in critically ill patients is observed. A gradual increase from low protein intake during the first 2 days of ICU stay to intermediate on day 3-5 and high protein intake from day 6 is associated with lower 6-month mortality. In addition, overall low protein intake is associated with the highest 6-month, ICU and hospital mortality and should be avoided.

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5 CHAPTER

Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study

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ABSTRACT

Background & aims

Refeeding syndrome comprises metabolic disturbances that occur after the reintroduction of feeding after prolonged fasting. Standard care consists of correcting fluid and electrolytes imbalances. Energy intake during refeeding syndrome is heavily debated. This study addresses the effect of caloric intake on outcome during the management of refeeding syndrome.

Methods

A retrospective study among critically ill invasive mechanically ventilated patients admitted for >7 days to a medical-surgical ICU. Refeeding syndrome was diagnosed by the occurrence of new onset hypophosphatemia (<0.65 mmol/l) within 72 h of the start of nutritional support. Primary outcome was 6-month mortality. Secondary outcomes were 3-month mortality, ICU and hospital length of stay and duration of mechanical ventilation. Outcomes of patients with and without refeeding syndrome were compared and subgroup analysis on energy intake within the refeeding population was performed for the duration of survival.

Results

Of 337 enrolled patients, 124 (36.8%) developed refeeding syndrome and 213 patients (63.2%) maintained normal serum phosphate levels. Between the two groups, no statistical significant differences in clinical outcomes were observed. Within the refeeding syndrome group, a reduced 6-month mortality risk for low caloric intake (<50% of target) was seen compared with normal intake, adjusted Hazard Ratio 0.39, (95% CI 0.16–0.95, p = 0.037). In this group, low caloric intake was associated with an increased overall survival time at day 180 (153.0 (SE 10.1) vs 119.1 (SE 8.0) days, log-rank p = 0.018).

Conclusions

Refeeding syndrome is common among prolonged mechanically ventilated critically ill patients, however not predictable by baseline characteristics. Among patients that develop refeeding syndrome low caloric intake was associated with a reduction in 6-month mortality risk. This effect was not seen in patients without refeeding syndrome. Findings support caloric restriction in refeeding syndrome during critical illness.

INTRODUCTION

Refeeding syndrome comprises metabolic disturbances that occur during reintroduction of feeding after a period of starvation or fasting, and was first described after the Second World War, when liberated prisoners resumed eating [1]. Three decades ago, the first deaths due to the initiation of aggressive parenteral nutrition (PN) and refeeding syndrome (RFS) were described [2]. RFS frequently occurs as result of the institution of nutritional support in severely malnourished patients [3]. Clinical symptoms are due to biochemical abnormalities, typically consisting of fluid and electrolyte imbalances, such as hypokalemia, hypomagnesaemia and hypophosphatemia. Additionally, insulin-induced glycolysis implies increased requirements of phosphate and thiamine, potentially leading to deficiencies. The spectrum of clinical symptoms is diverse. Metabolic abnormalities can affect the cardiac, respiratory, hepatic, haematological and neuromuscular system and can ultimately lead to multisystem organ failure and death [4]. RFS has been encountered in many patient groups, including critically ill patients admitted to the intensive care unit (ICU) [5]. Although all patients with poor nutritional status are at risk of developing refeeding associated complications, several risk factors have been identified such as chronic malnutrition, alcohol abuse, older age, malabsorption syndromes and oncological disease [6].

The incidence of RFS varies among reported studies, due to a lack of a universally accepted definition and objective diagnostic criteria [5, 7, 8, 9, 10, 11]. Commonly, it is pragmatically diagnosed based on the occurrence of refeeding induced hypophosphatemia, the predominant feature. Marik et al. performed a prospective observational cohort study among a heterogeneous group of ICU patients and reported an incidence of 34% of RFS, defined as new onset hypophosphatemia with a fall of phosphate levels >0.16 mmol/L to below 0.65 mmol/L [5].

Standard treatment for RFS comprises close monitoring and correction of fluid imbalances, phosphate and other electrolytes and thiamine supplementation. Energy intake during the treatment phase is heavily debated and experts vary in their preference for either full feeding or restricted caloric intake [12, 13]. The Institute for Health and Care Excellence (NICE) guidelines recommend to commence nutritional support for patients at risk of developing RFS at a maximum of 50% of requirements for the first days, increasing levels slowly to meet the full target by day 4–7 [14]. However, little evidence is available to support this statement. Also, no recommendations for caloric intake after RFS is diagnosed are provided.

Recently, Doig and colleagues conducted the first randomized controlled trial (RCT) on RFS to assess whether energy restriction affects outcome of critical illness compared with standard care [16]. They compared normal caloric intake versus restricted

intake after diagnosis of RFS among 339 adult mechanically ventilated ICU patients and found that the full caloric strategy was associated with higher mortality rates at 60 and 90 days. Moreover, caloric restriction significantly reduced the incidence of major infections, in particular respiratory infections.

Standard care for RFS in our ICU consists of correcting fluid and electrolytes imbalances. Restricting caloric intake during RFS management has not been implemented, as the results of the Doig RCT are only recently available. However, energy intake in individual patients will vary markedly due to feeding practicalities such as enteral feeding intolerance and use of non-nutritional calories.

Because little evidence is available on the incidence of RFS in the ICU, its relation with clinical outcomes and the effect of energy intake on patients at risk for RFS and during management of RFS, we designed a retrospective study among prolonged mechanically ventilated patients addressing these aspects. Based on previously performed studies we expected to find an incidence of RFS in ICU patients of around 34%, this is however highly dependent on the definition used [5, 10]. We hypothesized RFS may be associated with higher mortality caused by metabolic disturbances aggravating multi organ failure [4]. Although serum electrolyte imbalances usually are corrected in critically ill patients, this may not be enough to encounter the diverse metabolic consequences caused by refeeding syndrome. The NICE guidelines recommend starting nutritional support at <50% of caloric target in patients at risk of refeeding syndrome [14]. This recommendation is largely based on expert opinion. However, taking into account the recent results of the Doig RCT in which hypocaloric intake during treatment of RFS is associated with lower mortality rates [16], we hypothesized hypocaloric intake may be beneficial for both patients at risk of refeeding and after diagnosis of refeeding syndrome.

MATERIALS AND METHODS

Study description

We performed a retrospective study among critically ill patients, mechanically ventilated for >7 days in a mixed medical-surgical ICU in a tertiary University-affiliated teaching hospital between 01-01-2011 and 31-12-2015. In our computerized system, data on energy intake, calculated daily targets, laboratory results (including potassium, phosphate, magnesium and glucose) and electrolyte, insulin and glucose supplementation are accurately recorded for all admitted patients during the ICU admission period. RFS was defined as the occurrence of new onset hypophosphatemia within 72 h of the start of nutritional support. Outcomes of patients who developed RFS were compared with patients that did not.

Patient population

Adult critically ill patients (>18 years) who were mechanically ventilated for at least 7 days were included in this study. If patients were readmitted to the ICU during the same hospital admission period, only the first admission was evaluated. Only patients on enteral and/or parenteral feeding during ICU admission were eligible. RFS was defined as new onset hypophosphatemia developed <72 h of the commencement of nutritional support. Hypophosphatemia was defined, based on recent literature [10, 15], as a drop of >0.16 mmol/L from any previous measurement, to below 0.65 mmol/L. Baseline phosphate measurements prior to, and <72 h from the start of nutritional support had to be available. Patients were ineligible when baseline phosphate levels on admission were low (<0.65 mmol/l) or if other causes of low serum phosphate were present such as renal replacement therapy, recent parathyroidectomy, or use of phosphate binders. Patients admitted with diabetic ketoacidosis or undergoing therapeutic hypothermia were ineligible due to associated electrolyte abnormalities. Patients were excluded when data on nutritional provision were incomplete. The study population comprised two groups: patients that developed hypophosphatemia (<72 h after start nutritional support) and patients that remained normal serum phosphate. Groups were compared for the following baseline characteristics: age, gender, Body Mass Index (BMI), admission type (surgical/medical), Acute Physiology and Chronic Health Evaluation-II (APACHE-II)-score [16] and Sequential Organ Failure Assessment-score (SOFA-score) [17], baseline blood tests, sepsis (yes/no), comorbidities (according to Charlson comorbidity index (CCI)) [18], Nutrition Risk in Critically ill patients (NUTRIC) score [19] and time before commencement of feeding.

Subgroup analyses

Predefined subgroup analyses were performed addressing caloric intake within the total and the RFS population. Caloric intake, including calories from propofol or glucose infusion, was monitored during the complete ICU stay. During the first 7 days of admission the patients included in our study were invasively mechanically ventilated and did not receive oral intake. Patients who developed hypophosphatemia were analysed in two groups, having received less and more than 50% of their total caloric target of the first 3 days of admission, based on NICE recommendations on energy restriction for patients at risk for RFS [14]. This target was defined as the sum of caloric targets of day 1, 2 and 3. The caloric target of day 1 was adjusted for the actual time the patient had spent in the ICU during the first day.

Data on energy intake was documented in our patient data management system (PDMS) and targets were calculated by our computerized feeding protocol using the Food and Agricultural Organization and World Health Organization (FAO/WHO)

formula [20]. In line with international guidelines the body weight used in calculations was adjusted for BMI. For patients with BMIs up to 27 actual body weight was used. In case of BMI 27–30 body weight was corrected to BMI 27. In case of BMI > 30 ideal body weight was used for calculations. Ideal body weight was defined as BMI 21 in women and 22.5 in men [15]. The glucose strategy implemented recommended to commence insulin administration when plasma glucose levels were >8.3 mmol/L and to prevent hypoglycaemia in a nurse driven protocol. We aimed to commence EN early and advance EN aggressively if tolerated, guided by gastric residual volume with a 6 h threshold of 500 mL. PN was started when enteral feeding was contraindicated, if patients did not tolerate EN or when patients did not meet their nutritional targets with EN after 7 days. In this study an addition to resting energy expenditure (REE) of 20% was used to correct for disease activity. The impact of caloric intake on outcome measures was assessed.

Outcome

Primary outcome was 6-month mortality. Dates of death were collected from our electronic patient record system that connects to the population register. We additionally assessed 3-month, ICU and in-hospital mortality. Other secondary endpoints included ICU and hospital length of stay (LOS), duration of survival and the duration of mechanical ventilation (MV) in days. Phosphate levels, potassium and phosphate supplementation and required daily insulin dose in both patient groups were studied.

Data collection and protection

All parameters were routinely collected into a large ICU database during standard clinical care and were automatically extracted by queries searching our PDMS (MetaVision; iMDsoft MetaVision®, Tel Aviv, Israel and neoZIS®, Electronic Medical Record, MI Consultancy, Katwijk, The Netherlands). Verification was performed manually. Collected data were de-identified and stored on a secure hospital computer. There were no identifiable paper documents.

Ethics approval

The Gelderse Vallei Hospital institutional review board granted permission for the study. It did not require informed consent as a result of the retrospective design and anonymization of patient identifiers.

Data analyses and statistical considerations

Descriptive data for patient characteristics were calculated for all variables. Data normality was assessed by visual inspection of the distribution. Continuous data are reported as mean (±standard deviation (SD)) or as median (and interquartile range [IQR]) depending on data distribution. When necessary, continuous variables were dichotomized or categorized.

Categorical variables are presented as frequency or percentage. Differences in continuous variables were analysed using Independent T-test or Mann–Whitney U-test when appropriate. Levene's test was performed to assess equality of variances. Categorical variables and frequencies were analysed using chi-square-tests. Univariate and multivariate regression analyses were performed to assess the effect on outcome variables and for differences in baseline characteristics.

For the primary outcome, Kaplan–Meier estimates of survival functions were made and compared using log-rank tests. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were estimated using univariate COX regression analysis. Variables associated with an univariate effect on 6-month mortality (p-Value < 0.1) were included in the multivariate COX regression model using the enter method. Variables considered were: age, Charlson Comorbidity Index, NUTRIC score, SOFA score and APACHE-II score. Collinearity among confounding variables was investigated using correlation analysis and the assumption of proportional hazards over time in the COX regression model was estimated by visual inspection. Data analysis was performed using SPSS statistics for Windows (version 23.0, released 2015 New York, USA). For all analyses, $p < 0.05$ was considered statistically significant.

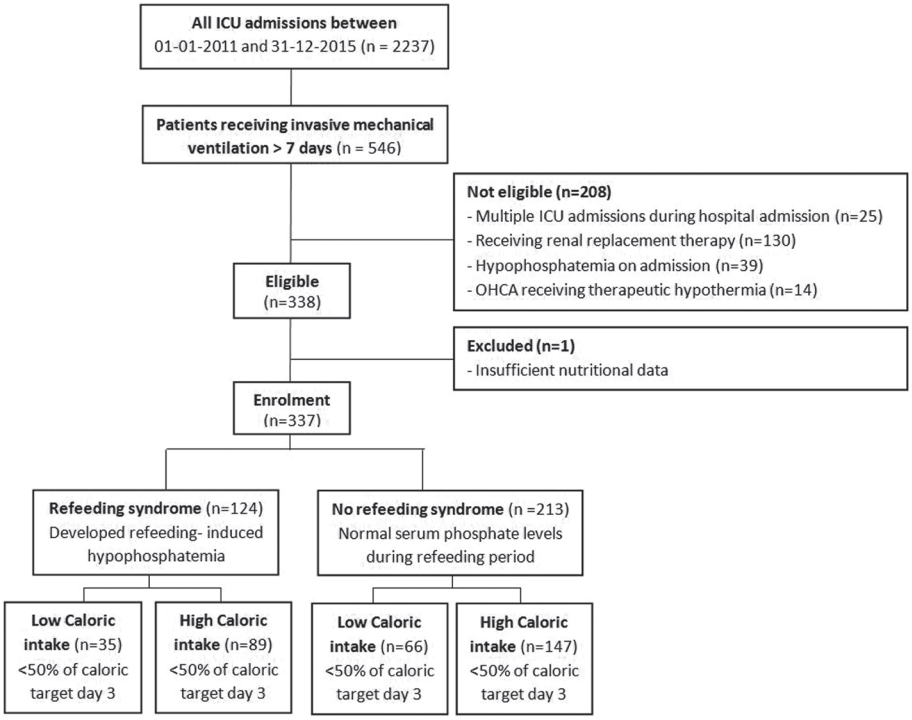
RESULTS

Patients

During the study period 2237 patients were admitted, of which 546 were intubated and mechanically ventilated for at least 7 days, of these patients 338 were eligible for enrolment. One patient was excluded because of insufficient nutritional data. Of enrolled 337 patients, 124 (36.8%) developed refeeding syndrome (Fig. 1).

Baseline characteristics of enrolled patients are depicted in Table 1. Baseline characteristics were comparable between groups except for baseline potassium (no RFS group 3.9 [3.2–4.1] vs RFS 3.7 [3.5–4.3] mmol/L, p = 0.004) and magnesium (0.74 [0.63–0.85] vs 0.69 [0.58–0.8] mmol/L, p = 0.004). There were no differences in nutritional parameters such as BMI, NUTRIC-score, total caloric intake (kcal) and time to start feeding.

Figure 1| Flowchart of enrolled patients



Abbreviations: ICU = intensive care unit, OHCA = out of hospital cardiac arrest

Table 1| Patient characteristics

		Total	RFS (n=124)	No RFS (n=213)	P value
Age (years)	mean (SD)	66.5 (13.4)	66.4 (13.2)	66.6 (13.6)	0.94
Gender, female	N (%)	126 (37.4%)	50 (40.3%)	76 (35.7%)	0.39
BMI on admission kg/m					
Mean		27.0 (5.6)	26.6 (5.7)	27.2 (5.5)	0.31
<18.5		14 (4.2%)	8 (6.5%)	6 (2.8%)	0.11
APACHE II-score	mean (SD)	21.6(6.5)	21.3 (5.8)	21.7 (6.9)	0.56
SOFA score	mean (SD)	6.9 (2.8)	6.6 (2.7)	7.1 (2.9)	0.17
Baseline blood test	median [IQR]				
Leukocytes (x10^9)		14.6 [9.2-17.6]	14.1 [9.8-19]	12.6 [8.7-17.4]	0.12
Creatinine (µmol/L)		88.5 [63.3-122]	86.0 [66.3-110.5]	90.5 [61-127.8]	0.50
CRP (mg/L)		131 [32.3-249.8]	117 [20.5-229.5]	145 [37-264.3]	0.10
Bilirubin (mmol/L)		8.5 [6-13]	9 [6-14]	8 [6-13]	0.48
Albumin (g/L)		27 [21-33]	28 [22-34.3]	26 [21-32]	0.10
Highest glucose in first 24 hours (mmol/L)		7.5 [6.4-8.7]	7.5 [6.5-8.7]	7.5 [6.3-8.7]	0.62
Baseline electrolytes					
Sodium (mmol/L)	median [IQR]	138 [135-141]	139 [136-142]	138 [134-141]	0.095
Potassium (mmol/L)	median [IQR]	3.8 [3.4-4.2]	3.9 [3.2-4.1]	3.7 [3.5-4.3]	0.004*
Magnesium (mmol/L)	median [IQR]	0.73 [0.62-0.83]	0.69 [0.58-0.8]	0.74 [0.63-0.85]	0.004*
Phosphate (mmol/L)	median [IQR]	1.17 [0.9-1.5]	1.14 [0.9-1.4]	1.20 [0.9-1.5]	0.320
Admission type	N (%)				0.85
Medical		210 (62.3%)	75 (60.5%)	135 (61.2%)	
Elective surgery		61 (18.1%)	23 (18.5%)	38 (17.8%)	
Emergency surgery		66 (19.6%)	26 (21.0%)	40 (18.8%)	
Charlson comorbidity index	Mean (SD)	3.8 (2.4)	3.7 (2.1)	3.9 (2.5)	0.54
NUTRIC- score	Mean (SD)	4.5 (1.8)	4.4 (1.6)	4.5 (1.9)	0.72
Nutritional parameters					
3- day caloric intake	Mean (SD)	2718 (1226)	2562 (1052)	2811 (1313)	0.067
7- day caloric intake (kcal)	Mean (SD)	9597 (2506)	9463 (2102)	9676 (2716)	0.42
Caloric target, (kcal*day)	Mean (SD)]	1581 (289)	1562 (299)	1593 (272)	0.33
7- day caloric adequacy	Mean (SD)	87.9% (22.9)	87.5% (25.8)	88.1% (17.2)	0.79
Non nutritional to total caloric intake	Median [IQR]	4.0% [1.5-7.5]	4.6% [1.9-8.1]	3.6% [1.3-7.4]	0.11
Time to start nutrition (hours)	Median [IQR]	5.9 [2.6-14.4]	6.4 [2.9-15]	5.3 [2.4-13.3]	0.32

Abbreviations: RFS = Refeeding Syndrome defined as hypophosphatemia <72 hours after start nutrition, BMI= Body Mass Index, CCI = Charlson Comorbidity Index, APACHE-II: acute physiology and chronic health evaluation, SOFA = sequential organ failure assessment, NUTRIC = Nutrition risk in critically ill.

Primary outcome

The primary outcome of 6-month mortality did not differ between RFS patients and those without RFS (42 (33.9%) versus 67 (31.5%), respectively, p = 0.65; Table 2). There was no association between the decline in serum phosphate levels and 6-month mortality (p = 0.87; Fig. 4). Also, no differences in other mortality endpoints were observed.

Table 2| Primary and secondary endpoints

	All patients	Patients without RFS	Patients with RFS	P value
Number of patients	337	213	124	
Mortality	N (%)	N (%)	N (%)	
ICU	55 (16.3%)	34 (16,0%)	21 (16.9%)	0.82
Hospital	79 (23.4%)	49 (23,0%)	30 (24.4%)	0.80
3 months	103 (30.6%)	62 (29.1%)	41 (33.1%)	0.45
6 months	109 (32.3%)	67 (31.5%)	42 (33.9%)	0.65
Length of Stay in Days	Median [IQR]	Median [IQR]	Median [IQR]	
ICU	15 [11-22]	15 [11-21]	15 [11-23]	0.56
Hospital	26 [14-18]	28 [17-34]	24 [19-42.5]	0.066
Duration of Mechanical Ventilation in Days	10 [8-15]	10 [8-14.8]	10 [8-15]	0.69

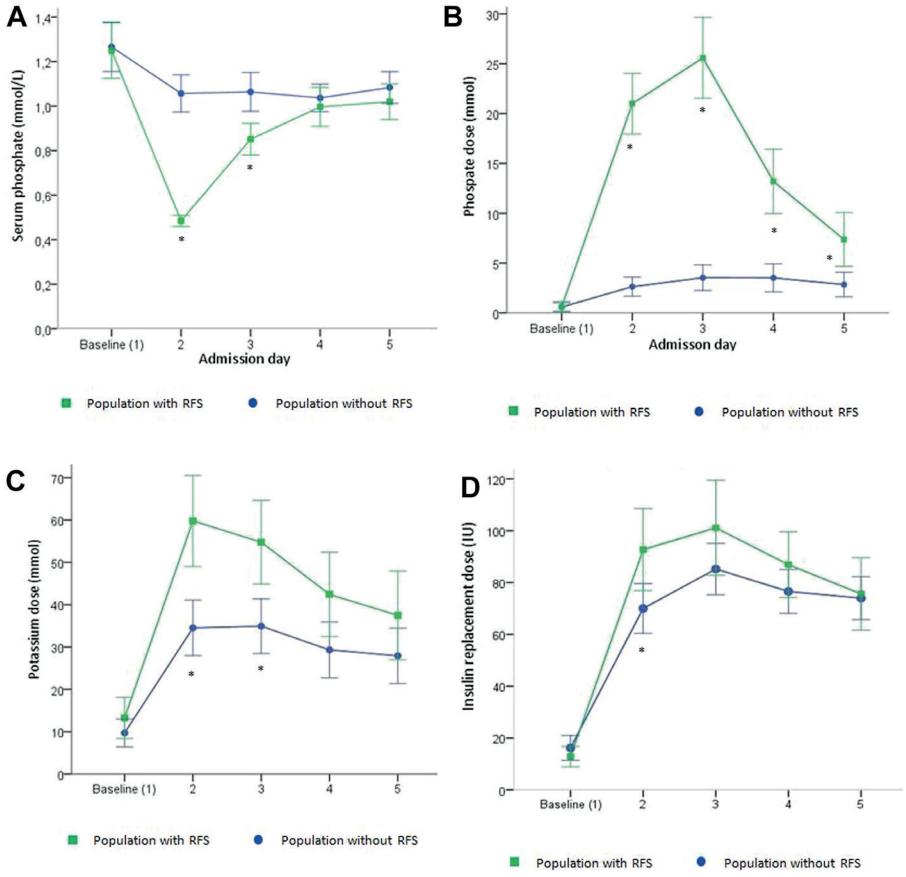
Abbreviations: RFS = Refeeding syndrome, defined as new-onset hypophosphatemia <72 hours after start nutrition; ICU = intensive care unit.

Secondary outcomes

Electrolyte levels and replacement doses are shown in Fig. 2. Lowest daily phosphate levels were significantly lower in the RFS group (Fig. 2a, p < 0.001 on day 2 and 3) compared with the non-RFS group. There was a greater need of IV phosphate supplementation (Fig. 2b, p < 0.001 on day 2, 3, 4, and 5) in the RFS group. Furthermore, daily potassium replacement dose was higher in the RFS group (Fig. 2c, p < 0.001 on day 2 and 3) and this group also required significantly more insulin administration on the second admission day (Fig. 2d, p = 0.001).

Median ICU length of stay was 15 days in both groups (p = 0.56; Table 2). We observed a trend towards reduction of hospital length of stay that did not reach statistical significance (28 versus 24 days, p = 0.066). Median duration of mechanical ventilation was 10 days in both groups.

Figure 2| Course of electrolytes and replacement doses



A. Lowest daily serum phosphate
B. Daily total intravenous phosphate replacement dose
C. Daily total intravenous potassium replacement
D. Daily total insulin replacement

Abbreviations: RFS = refeeding syndrome
Error bars indicate 95% CI for mean differences between the groups.
In the RFS group, measurements are depicted from the first day of RFS diagnosis.
*p ≤ 0.001.
Baseline measurements: for RFS group, first day of RFS diagnosis; for non RFS group, first day of ICU stay.

Subgroup analysis: hypocaloric intake

Overall 101 patients (30.0%) received less than 50% of their caloric target within 72 h after ICU admission. The mean caloric intake was significantly lower in this group than in the group of patients that received more than 50% of their caloric target (mean 1294 ± 669 vs 3281 ± 932 kcal, p = 0.001). No difference was observed between mean caloric intake of patients in the RFS compared with the no RFS group.

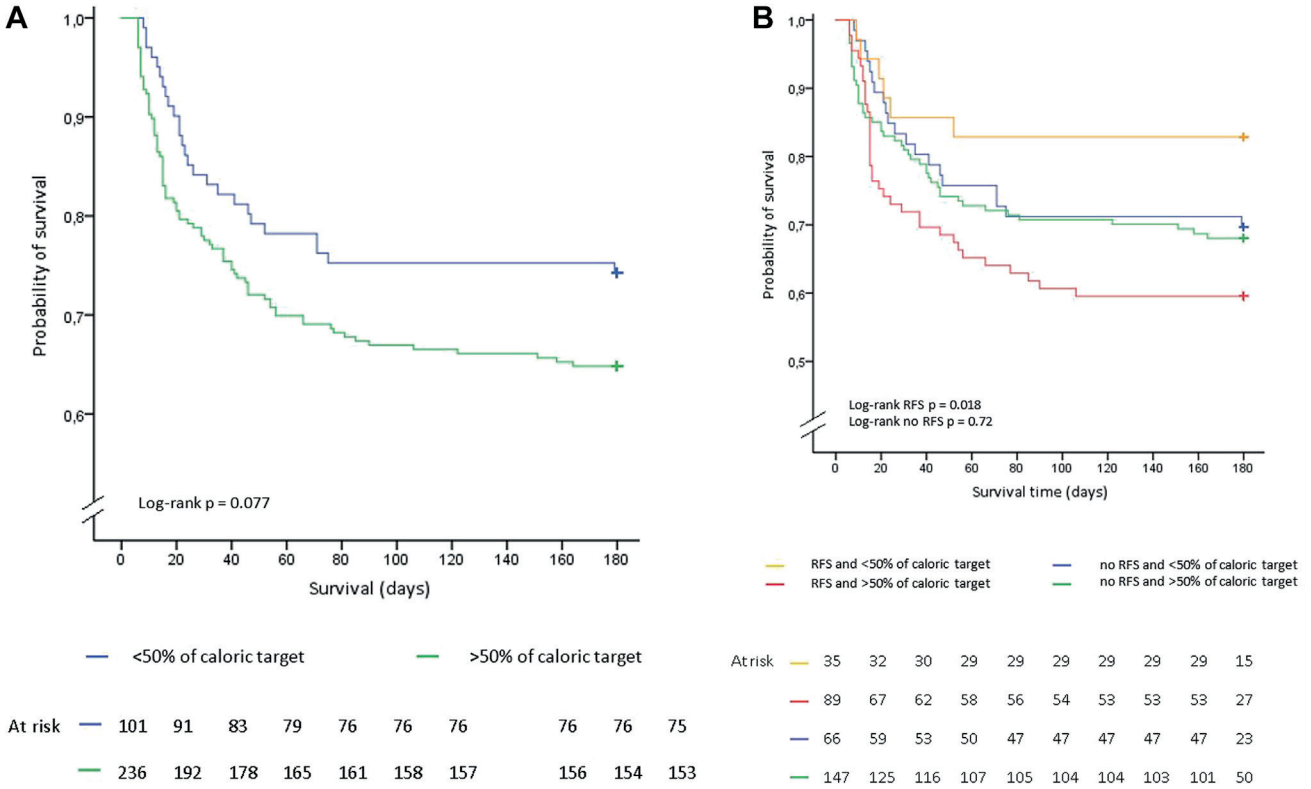
At 6-month in the RFS group 29 (83%) patients receiving <50% of caloric target were alive versus 53 (60%) receiving >50%. In the non-RFS group the numbers were 46 (22%) versus 100 (47%), respectively.

The effect of low caloric intake on overall survival in all patients is depicted in Fig. 3a. The Kaplan–Meier-curve shows a trend towards increased survival for the group with low caloric intake, however this effect was not statistically significant (p = 0.077). In multivariate analyses of all patients no statistically significant effect of low caloric intake on 6-month was found (supplement 1).

In the RFS group 35 patients (28,2%) received less than 50% of their total caloric target during the first 3 days of admission (mean 1403 ± 568 vs 3018 ± 824 kcal/3 days, p = 0.017). Within the RFS group, an increase in overall survival time was seen for the group that received <50% of caloric target compared with the group that received >50% of target censored at day 180 (153.0 (SE 10.1) vs 119.1 (SE 8.0) days, log-rank p = 0.018) (Fig. 3b).

In the group without RFS 66 patients (31,0%) received less than 50% of their caloric target (mean 1236 ± 714 vs 3441 ± 960 kcal, p = 0.028). In this group no differences in survival rates or survival time between the low caloric and normocaloric groups were observed, (log-rank p = 0.72). In multivariate analyses of non-RFS patients no statistically significant effect of low caloric intake on 6-month was observed (supplement 1).

Figure 3| Kaplan-Meier estimates for 180 days follow-up after ICU admission.



A. Survival estimates for the total study population
B. Survival estimates stratified by RFS versus no RFS
Abbreviations: RFS = refeeding syndrome; ICU = intensive care unit

Adjusted 6-month mortality analysis for hypocaloric intake

In the total study population univariate analysis showed a hazard ratio (HR) of 0.68 (95% CI 0.44–1.05, p = 0.08) of low caloric intake compared with the full caloric strategy.

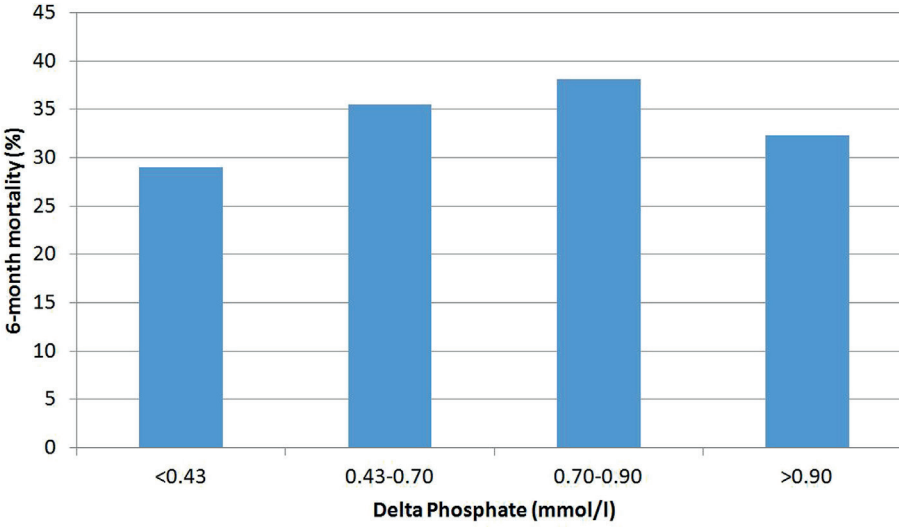
In the RFS group Cox regression univariate analysis showed a HR of 0.38 (95% CI 0.16–0.91, p = 0.03) of low caloric intake compared with an intake of >50% of calculated target. Table 3 depicts the univariate and multivariate HR for caloric intake within the RFS group and the covariates adjusted for. After correction for covariates 'Charlson Comorbidity Index', 'NUTRIC score', 'age on admission', 'Apache-II score', an adjusted HR of 0.39 (95% CI 0.16–0.95, p = 0.037) was found. To ascertain that the model did not violate proportional hazard assumptions, the analysis was done using 100-days survival time.

Table 3| Unadjusted and adjusted hazard ratios (HR) for factors associated with 6-month mortality according to univariate and multivariate COX regression

	RFS population			
Variable	**Univariate COX regression**		**Multivariate COX regression**	
	HR (95%CI)	**P value**	**HR (95%CI)**	**P value**
Caloric intake < 50% target*	0.38 (0.16-0.91)	0.03	0.39 (0.16-0.95)	0.037
Charlson Comorbidity Index	1.23 (1.07-1.40)	0.003	1.14 (0.94-1.38)	0.19
NUTRIC score	1.34 (1.09-1.64)	0.006	0.89 (0.62-1.27)	0.51
Age on ICU admission	1.05 (1.01-1.08)	0.004	1.03 (0.99-1.07)	0.12
APACHE-II score	1.07 (1.01-1.12)	0.014	1.10 (1.02-1.19)	0.017

Abbreviations: RFS = refeeding syndrome; CCI = Charlson Comorbidity Index, NUTRIC = nutrition risk in critically ill, APACHE-II score = acute physiology and chronic health evaluation.
* compared with >50% of target (reference group)

Figure 4| 6-Month mortality by drop in serum phosphate in RFS group.



Abbreviations: Drop = maximum drop in serum phosphate level from baseline, RFS = refeeding syndrome.

DISCUSSION

We did not find significant differences in clinical outcome including mortality, duration of mechanical ventilation or ICU and hospital LOS comparing critically ill patients with and without refeeding syndrome. Results are in contrast with retrospective findings by Coskun and coworkers, who showed that RFS was associated with increased mortality and ICU LOS [11]. Divergent findings may be due to our relatively small study population or to the fact that Coskun only included medical ICU patients with high rates of comorbidities (70%) and malignancies (20%). Also, not all patients were mechanically ventilated. This may have attributed to the high overall mortality rate (75%). Furthermore, the definition of RFS used was different (drop in phosphate levels <0.80 mmol/L; excluding 25% of their initial cohort because hypophosphatemia was present on admission). Intuitively higher cut-off of phosphate levels may lead to smaller differences in clinical endpoints, however the opposite is observed in our results and those of Coskun [11]. Coskun found no differences in mortality between patients with severe hypophosphatemia (<0.32 mmol/L) and those without [11]. Moreover, we did not find any association between the magnitude of decline in phosphate levels and 6-month mortality. Furthermore, other conditions may cause hypophosphatemia in ICU patients, including sepsis. A Chinese observational study found that 77.6% of ICU patients developed hypophosphatemia at any time during ICU admission. Serum phosphate levels were negatively associated with

mortality, but only had prognostic value when levels were <0.40 mmol/L [21]. In addition, Shor found an OR of 7.98 for mortality in patients with sepsis and severe hypophosphatemia (<0.32 mmol/L) compared with other septic patients [22]. Therefore differences in mortality risk observed in studies may at least in part be due to other causes of hypophosphatemia interfering with the RFS diagnosis. Lastly, nutritional interventions used by Coskun were different from our cohort as almost all of our patients were enterally fed compared with only 50% of patients in Coskun's cohort. Zeki showed refeeding hypophosphatemia to be more common during enteral than parenteral feeding [23]. Thus differences in clinical outcomes between Coskun and our study may be attributed to differences in patient populations, RFS definitions and nutritional interventions.

Subgroup analysis: hypocaloric vs normocaloric intake

We observed a non-significant trend towards benefits of low caloric intake in all patients. A recent meta-analysis of randomized controlled trials [24], assessing normocaloric versus intentional hypocaloric nutritional support did not demonstrate differences in risk of acquired infections, hospital mortality, LOS or duration of mechanical ventilation among general ICU patients. However, no data were available on 6-month mortality.

As in non-critically ill patients, caloric restriction and slow progression of caloric intake is recommended to prevent the sequelae of RFS. Strikingly, also among ICU patients we found remarkable benefits favouring lower intake, associated with a reduced 6-month mortality risk and increase in overall survival time compared with higher intake. This is consistent with the findings by Doig who demonstrated a significant increase in overall survival time as well as a decrease in 60-day mortality in patients with restricted caloric intake during the management of RFS [16].

The benefits of caloric restriction are poorly understood. Phosphate is fundamental in multiple intracellular biochemical processes and hypophosphatemia may result in cellular dysfunction. Hypophosphatemia has been reported an independent risk factor for the development of infections, sepsis and septic shock [25, 26]. Increased insulin resistance associated with RFS, also observed in our population, could add to the risk of infection and sepsis [27]. Mechanisms of hyperglycemia and hyperinsulinemia, compatible with an increased insulin resistance among RFS patients have been well described in an article of Obeid et al. [28].

It may be expected that metabolic and biochemical disturbances occur shortly after development of RFS. Indeed, our results show that more potassium and insulin supplementation was needed in the RFS group within the first days of the

development of RFS. However, when inspecting our survival probability graphs, we observed a difference in overall survival time starting, and increasing, from about the fifteenth day after ICU admission. This may suggest that survival of patients with RFS is not only influenced by acute abnormalities, but also by prolonged effects of nutritional support and/or changes in metabolic processes.

Incidence of RFS

Although not frequently studied in the ICU, we have shown an incidence of RFS of 36.8% in our study population. These results are concordant with the prospective cohort study by Marik and Bedigian [5]. They found an incidence of 34% using similar definitions in a comparable ICU population. Coskun found a higher incidence (52%) using a different definition of RFS (RFS was defined as a drop in phosphate levels below 0.80 mmol/L). Strikingly baseline characteristics were not useful to identify patients that subsequently will develop RFS. Although baseline potassium and magnesium levels were significantly lower in RFS patients, clinical discrimination will be impossible due to the major overlap between groups.

Strengths and weaknesses

Because the early clinical features of RFS are non-specific among ICU patients, we used simple and objective diagnostic criteria. We manually screened serum phosphate data to identify RFS patients. Other major possible causes of hypophosphatemia were accounted for by our exclusion criteria.

Other strengths are the number of covariates taken into account and the long follow-up period (6 months). Data extraction from our PDMS provided detailed information on nutritional intake and laboratory results. Also, non-nutritional calories derived from glucose or propofol infusion were included into the analyses [29].

Limitations of our study and its retrospective study design include the unintentional hypocaloric intake applied, potentially leading to selection bias and residual confounding. However, it would be expected that sicker patients would have received less calories, with the direction of bias still favouring our hypothesis. Since our ICU protocol strongly emphasizes the early commencement of feeding, with an observed median time of 5.6 h to start nutritional support, a small proportion of patients have received less than 50% of their energy target, resulting in small study groups (Fig. 1). Generalization of study results should be done with caution. Our inclusion criteria have selected patients with a high severity of illness and prolonged ICU LOS, possibly reducing the external validity.

Suggestions for further research and clinical practice

Prospective trials are warranted to elucidate reasons for the reduced mortality risk associated with caloric restriction in larger groups. The results of our study do not suggest that early full feeding benefits all ICU patients, as no benefits were seen in the total group nor in the non-RFS group that received more than 50% of caloric target during the first 3 days. As low caloric intake seems to benefit patients with RFS and is not worse in patients without refeeding syndrome we suggest to either monitor RFS by daily phosphate level measurements for 3 days after the commencement of nutritional support to detect patients with RFS, or to use low caloric intake (<50% of target) in all patients during the first 3 days. This suggestion is further supported by a recent meta-analysis by Al-Dorzi et al. [30] that even suggested a possible benefit of a lower caloric intake during critical illness in the early phase. In our current ICU nutrition protocol, we gradually increase nutrition intake by 25% of target per day in all patients to reduce the risk of developing RFS or the risk of overfeeding, as endogenous energy production cannot be counteracted by exogenous calorie administration. However, when RFS is diagnosed, nutrition support is reduced to an intake of 25% of the caloric target for 48 h, we correct electrolyte disturbances and administer thiamine, before gradually advancing to target in daily steps of 25% of caloric target.

CONCLUSIONS

Refeeding syndrome defined by feeding induced hypophosphatemia is common among adult ICU patients on prolonged mechanical ventilation, however not predictable by baseline characteristics. Low caloric intake (<50% of target) is associated with a substantial reduction in 6-month mortality risk in those patients that develop refeeding syndrome within 72 h after the start of nutritional support. This effect is not observed in all patients and patients without refeeding syndrome. Findings support caloric restriction in refeeding syndrome patients during critical illness.

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SUPPLEMENTARY DATA

Supplementary table 1| Multivariate survival analyses on the effect of caloric intake in the total study population

Variable	Univariate COX regression		Multivariable COX regression*		Multivariable COX regression$	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Caloric intake < 50% target*	0.68 (0.44 – 1.05)	0.08	0.67 (0.43 – 1.04)	0.08	0.65 (0.42 – 1.02)	0.06
Charlson Comorbidity Index	1.22 (1.14 – 1.30)	<0.001	1.14 (1.03 – 1.25)	0.009	1.16 (1.05 – 1.28)	0.004
NUTRIC score	1.47 (1.31 – 1.64)	<0.001	1.05 (0.87 – 1.27)	0.63	1.07 (0.86 – 1.33)	0.54
Age on ICU admission	1.05 (1.03 – 1.07)	<0.001	1.02 (0.997 – 1.04)	0.09	1.02 (0.99 – 1.04)	0.20
APACHE-II score	1.10 (1.07 – 1.13)	<0.001	1.08 (1.03 – 1.12)	0.001	1.08 (1.03 – 1.13)	0.001
Admission type	1.69 (1.12 – 2.57)	0.01			1.22 (0.77 – 1.93)	0.40
BMI	0.96 (0.93 – 1.00)	0.048			0.95 (0.92 – 0.99)	0.008
SOFA-score	1.07 (1.001 – 1.14)	0.048			0.97 (0.89 – 1.06)	0.54

* without correction for SOFA score, BMI and admission type
$ with correction for SOFA score, BMI and admission type
Abbreviations: RFS = refeeding syndrome; CCI = Charlson Comorbidity Index, NUTRIC = nutrition risk in critically ill; APACHE-II score = acute physiology and chronic health evaluation.

Supplementary table 2| Multivariate survival analyses on the effect of caloric intake in the non-RFS population

Variable	Univariate COX regression		Multivariable COX regression*		Multivariable COX regression$	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Caloric intake < 50% target*	0.91 (0.54 – 1.53)	0.72	0.87 (0.51 - 1.49)	0.62	0.98 (0.56 – 1.70)	0.94
Charlson Comorbidity Index	1.22 (1.12 – 1.32)	<0.001	1.14 (1.01 – 1.28)	0.03	1.14 (1.01 – 1.29)	0.04
NUTRIC score	1.52 (1.33 – 1.75)	<0.001	1.10 (0.87 – 1.40)	0.42	1.13 (0.85 – 1.50)	0.39
Age on ICU admission	1.05 (1.02 – 1.07)	< 0.001	1.01 (0.98 – 1.04)	0.43	1.02 (0.98 – 1.05)	0.38
APACHE-II score	1.11 (1.07 – 1.14)	< 0.001	1.08 (1.02 – 1.13)	0.006	1.08 (1.02 – 1.14)	0.01
SOFA score	1.11 (1.02 – 1.20)	0.02			0.97 (0.86 – 1.09)	0.60
Admission type	1.74 (1.01 – 2.98)	0.045			1.27 (0.68 – 2.39)	0.45
Phosphate on admission	1.52 (0.94 – 2.44)	0.09			0.96 (0.58 – 1.60)	0.88

* without correction for SOFA score, Phosphate on admission and Admission type
$ with correction for SOFA score, Phosphate on admission and Admission type

6

CHAPTER

Is refeeding syndrome relevant for critically ill patients?

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Curr Opin Clin Nutr Metab Care. 2018;21(2):130-137

ABSTRACT

Purpose of review

To summarize recent relevant studies regarding refeeding syndrome (RFS) in critically ill patients and provide recommendations for clinical practice.

Recent findings

Recent knowledge regarding epidemiology of refeeding syndrome among critically ill patients, how to identify ICU patients at risk, and strategies to reduce the potential negative impact on outcome are discussed.

Summary

RFS is a potentially fatal acute metabolic derangement that ultimately can result in marked morbidity and even mortality. These metabolic derangements in ICU patients differ from otherwise healthy patients with RFS, as there is lack of anabolism. This is because of external stressors inducing a hypercatabolic response among other reasons also reflected by persistent high glucagon despite initiation of feeding. Lack of a proper uniform definition complicates diagnosis and research of RFS. However, refeeding hypophosphatemia is commonly encountered during critical illness. The correlations between risk factors proposed by international guidelines and the occurrence of RFS in ICU patients remains unclear. Therefore, regular phosphate monitoring is recommended. Based on recent trials among critically ill patients, only treatment with supplementation of electrolytes and vitamins seems not sufficient. In addition, caloric restriction for several days and gradual increase of caloric intake over days is recommendable.

INTRODUCTION

Refeeding syndrome (RFS) is a potentially fatal acute metabolic derangement that can lead to marked morbidity and mortality [1]. RFS is induced by reintroduction of nutrients (carbohydrates) after prolonged starvation [1]. The relevance of RFS for critically ill patients has not been well understood [1]. Recent ICU studies have provided insights in the epidemiology, how to identify patients at risk, and strategies to improve outcome.

EPIDEMIOLOGY

As an uniform definition is lacking the true incidence and mortality rate of RFS among ICU patients is unknown. In a systematic review on 38 studies addressing RFS definitions only two definitions were used more than once [2]. Most commonly hypophosphatemia (with cutoff levels varying from 0.16 mmol/l or >30%) is used either alone or combined with clinical symptoms [2]. In absence of other symptoms hypophosphatemia after refeeding is referred to as refeeding hypophosphatemia [3,4– 6]. In critically ill patients, the refeeding hypophosphatemia incidence is reported to be 34–52% [3,4,5]. Mortality and morbidity of RFS during critical illness has not been studied well. This may be because of variable definitions [2], unfamiliarity of clinicians with RFS, and the complex interplay between acute illness and RFS [1]. RFS symptoms may be falsely attributed to other clinical diagnoses. Frequent causes of death because of RFS are cardiac arrhythmias, cardiac failure, and pulmonary edema [7]. Prevalence, morbidity, and mortality of 68 anorexia nervosa ICU patients were studied [8]. Seven patients developed RFS of which only two survived. All five deaths were attributed to RFS [8]. More recent trials focusing on refeeding hypophosphatemia in critically ill patients show divergent results ranging from no difference in outcomes to significantly increased mortality in patients with refeeding hypophosphatemia, because of differences in definitions used, study populations studied and treatments instituted [3,4–6,9].

PATHOPHYSIOLOGY

RFS reflects changes from catabolic to anabolic metabolism in malnourished or starved patients upon reintroduction of oral, enteral, or parenteral feeding [1,10–12]. Understanding of RFS requires description of the physiology of nutritional states [11]. The interplay between hormonal and metabolic changes caused by RFS and interactions with the metabolic state induced by critical illness should be taken into account, limiting extrapolation of information from other populations [1].

Catabolism and starvation in health

During starvation, metabolism switches from marked carbohydrate utilization (anabolic state) to preferentially protein and fat metabolism (catabolic state) to produce glucose and energy [10,11,13,14]. In pure starvation, without an external stress response (i.e. anorexia nervosa), this mainly results in increase of fat metabolism (>90% of energy) whereas protein stores are largely protected to maintain lean body mass (LBM) as long as possible [10,11]. During early fasting glucagon secretion increases, which triggers the cyclic AMP cascade conferring glycogen breakdown, inhibition of glycogen and fatty acid synthesis, and induction of hepatic gluconeogenesis. The influx and utilization of glucose by muscle and adipose tissues are decreased because of low insulin levels. Muscle and liver cells switch from glucose substrate to fatty acids utilization, released from adipose tissue at an increased rate (lipolysis), in order to maintain blood–glucose levels [15].

Within 24 h liver glycogen stores are depleted and metabolic changes occur to provide enough energy to vital organs [11]. This facilitates sufficient glucose substrate to brain, kidneys, and erythrocytes (tissues absolutely dependent on these fuels). Gluconeogenesis from glycerol and amino acids is the only pathway to maintain blood–glucose levels when glycogen stores are depleted. However, during prolonged fasting protein stores are preserved as long as possible, as breakdown will lead to loss of muscle mass and function [15]. Glucose oxidation switches to fatty acids oxidation and ketone bodies. The heart and brain slowly commence using ketone bodies instead of glucose for metabolism [15]. In addition, basal metabolic rate is reduced by approximately 25% and the liver decreases gluconeogenesis (thereby preserving muscle protein) [10,11].

During prolonged fasting (starvation) intracellular minerals, vitamins, and trace-elements become depleted as the intracellular compartment contracts. Renal excretion is reduced to limit further losses [10,15].

Stress induced catabolism in critically ill patients

In addition to preexistent undernourishment, external stressors induce a hyper-metabolic state [16], through activation of the pituitary–adrenal axis to release catecholamines and cortisol. In addition, glucagon secretion, insulin resistance, and lipolysis are increased and anabolic hormones are decreased (growth hormone, testosterone) [16,17]. The purpose is to rapidly mobilize energy, mainly via protein breakdown. There is no attempt to conserve energy or protein, but rather to rapidly generate energy from protein stores at the expense of LBM reductions [16,18]. A marked increase in metabolic rate is found and an increase in conversion of amino

acids to glucose through gluconeogenesis [16,18]. Rapid skeletal muscle breakdown is observed [16,18]. In these patients, ketosis is limited, indicating that fat is not the major energy source [18].

Refeeding induced anabolism

Upon refeeding, metabolism switches from protein and fat to carbohydrate utilization (anabolism) [13]. This leads to sudden demand of inorganic phosphate for ATP synthesis, potassium for intracellular glucose transport, magnesium for synthesis reactions, and thiamine for carbohydrate and amino acid oxidation [10,14]. Moreover, insulin levels peak inducing electrolyte shifts to intracellular compartments leading to hypokalemia, hypophosphatemia, hypomagnesemia, and retention of sodium and water causing fluid overload [10,11,13], potentially leading to congestive heart failure and pulmonary edema [13].

Refeeding critically ill patients

Because of persistent catabolism during critical illness [16], RFS may be obscured. This is supported by progressive loss of muscle even when carbohydrate supplementation fulfills energy requirements [16]. Thiessen investigated the role of glucagon in catabolism and muscle wasting in critical illness and found elevated plasma glucagon concentrations in proportion to illness severity. Moreover, glucagon concentrations could not be lowered by administration of glucose and insulin, indicating altered metabolism (persistent catabolism not able to convert to anabolism by glucose administration nor by high insulin levels). Finally, amino acid supplementation increased glucagon concentrations further thereby stimulating gluconeogenesis, glycogenolysis, proteolysis, and lipolysis [17]. The main difference comparing ICU patients with otherwise healthy patients with RFS is the lack of anabolism in the ICU population [17]. Therefore, critical illness should be studied separately.

CLINICAL SYMPTOMS AND BIOCHEMICAL CHANGES IN REFEEDING SYNDROME

RFS has been described in released concentration camps prisoners during World War II, presenting with heart failure, neurologic complications with convulsions, and coma following refeeding [19]. Clinical symptoms are associated with metabolic changes concurrent with refeeding and are presented in Table 1. Specific biochemical changes are discussed hereafter.

Table 1| Clinical signs and symptoms of refeeding syndrome

	Signs and symptoms	Elektrolytes or vitamins depleted
Neurologic	Central pontine myelinolysis	
	(Wernicke's) encephalopathy	PO_4^{3-}, B1
	Coma	PO_4^{3-},Mg^{2+}
	Delirium	PO_4^{3-},Mg^{2+},B1
	Ataxia and tremor	PO_4^{3-},Mg^{2+}, K^+, Ca^{2+}
	Tetany	Mg^{2+}, K^+, Ca^{2+}
	Peripheral neuropathy	B1
	Paresthesia	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Paralysis	Mg^{2+}, K^+, Ca^{2+}
Cardiac	Arrhythmias	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Congestive heart failure	PO_4^{3-}, B1
	Sudden death	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Reduced cardiac contractility	PO_4^{3-}
Respiratory	Respiratory failure and ventilator dependency due to diaphragm fatigue	PO_4^{3-}, Mg^{2+}, K^+
	Pulmonary oedema	PO_4^{3-}
	CO_2 retention	Mg^{2+}
Hematologic	Anemia	PO_4^{3-}
	Leukocyte and platelet dysfunction	PO_4^{3-}
	Trombocytopenia	PO_4^{3-}
	2,3-DPG	PO_4^{3-}
Metabolic	Hyperglycemia	
	Hyperinsulinemia	
	Sodium and water retention	
	Lactic acidosis	B1
Renal	Acute tubular necrosis	PO_4^{3-}
	Acute kidney injury	PO_4^{3-}, K^+
	Osmotic diuresis	PO_4^{3-}
	Poor tubular concentration	PO_4^{3-}, K^+
Musculoskeletal	Weakness	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Myalgia	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Rhabdomyolysis	K^+
	Osteomalacia	PO_4^{3-}

	Signs and symptoms	Elektrolytes or vitamins depleted
Hepatic	Liver failure or function test abnormalities	
Gastrointestinal	Constipation	PO_4^{3-}, Mg^{2+}, K^+, Ca^{2+}
	Nausea and vomiting	K^+
	Ileus	K^+
Immunologic	Immunosuppression and increased risk of infections	
Psychiatric	Korsakov's psychosis	B1

Abbreviations: B1 = thiamine; Ca^{2+} = calcium; K^+ = potassium; Mg^{2+} = magnesium; PO_4^{3-} = phosphate

Phosphate

Hypophosphatemia is the major feature of RFS [10,11]. Phosphate is essential for various metabolic functions and a component of nucleic acids that form DNA/RNA and of ATP that carries the energy required for cellular functions [7,10,20]. Phosphate is also part of 2,3-DPG, which promotes the dissociation of oxygen from hemoglobin [11]. In addition, phosphate is essential for phagocytosis, chemotaxis, platelet aggregation, excitation-stimulus response coupling, and nervous system conduction. Hypophosphatemia is commonly encountered in the ICU, with an all-cause incidence of 30–59% [5].

Potassium

Potassium plays a critical role in the excitability of skeletal, cardiac, and smooth muscle [20,21]. It is important for nerve function, blood pressure control, and in maintaining acid–base balance and osmotic integrity of cells [10,11,20]. Potassium imbalances in ICU patients have been studied retrospectively among 10 451 patients. A hypokalemia incidence of 22% was found. A U-shaped relationship between potassium level and in-hospital mortality ($P < 0.001$) was found, with in-hospital mortality rates more than 40% in patients with severe hypokalemia or hyperkalemia (6.5 mmol/l). Increased potassium variability was independently associated with adverse outcomes [22].

Magnesium

Magnesium is a mandatory cofactor for over 300 enzymes, for ATP to be biologically active and for stabilizing DNA/RNA structures [23,24]. Magnesium is involved in nerve conduction, muscle relaxation, and cell membrane stabilization [23,24]. Severe hypomagnesemia may also induce hypocalcemia because of inhibition of

parathormone (PTH) secretion and increased PTH resistance [10,11]. Recent ICU reviews of all-cause hypomagnesemia show an incidence of 18–65% on ICU admission and associated higher risk of mortality, risk for mechanical ventilation, and increased length of ICU stay [12,23–25].

Thiamine

The active form of thiamine, thiamin pyrophosphate, is an essential cofactor in metabolic pathways such as conversion of pyruvate to acetyl-coenzyme A before entering the TCA cycle, decarboxylation of 2-oxoacids, and activity of transketolase in the pentose–phosphate pathway [26]. All are important for ATP production. Thiamine also has antioxidant properties [26]. Normally, thiamin demands are about 0.5 mg/ day and steady-state whole body stores are estimated at 30 mg [26,27].

Thiamin cannot be synthesized by humans and has a short half-life, thus thiamin levels are highly dependent on intake. In malnutrition, cell stores are usually depleted within 15–20 days [26]. Thiamine deficiency is common among critically ill patients (ranging from 10 to 40%) and is associated with increased morbidity and mortality [26,27]. Moreover, supplementation of thiamine has been associated with decreased mortality. An observational study showed thiamine deficiency (< 100 nmol/l) in 39.7% of patients at ICU admission [27].

Acute thiamin deficiency may be induced by carbohydrate administration in malnourished patients enhancing increased cellular thiamine utilization [10]. In thiamine deficiency, a combined enzyme defect results in aerobic metabolism impairment and insufficient ATP generation [26]. In addition, pyruvate is converted into lactate (as it is unable to enter the TCA-cycle), resulting in hyperlactatemia and lactic acidosis [26].

As thiamine-dependent metabolic pathways are present in almost all human cells, it can affect many organ systems and if untreated lead to metabolic coma and death [26]. Thiamin deficiency induced by refeeding can also worsen hypomagnesemia, hypokalemia, and hypophosphatemia associated with increased renal losses, because of insufficient ATP generation and oxidative stress damaging renal tubular cells [14].

Trace-elements and vitamins

Depletion of trace-elements and vitamins such as copper, selenium, vitamin B6, and vitamin B12 have been described in case reports of starvation [10]. It remains unclear whether these deficiencies are clinically relevant in RFS.

RISK FACTORS

European (NICE) guidelines indicate risk factors for RFS (Table 2) [28]. Higher age greater than 70 years, low (pre)albumin, higher nutritional intake, low insulin-like growth factor-1, NRS 2002 at least three points and enteral feeding are supposed risk factors [2]. However, studies investigating the diagnostic value of this screening tool show low sensitivity (30%) in general hospitalized patients [10,29]. In a recent study refeeding hypophosphatemia among ICU patients with prolonged mechanical ventilation, no cases were related to any of these risk factors nor to admission type, Charlson comorbidity index, NUTRIC, SOFA, or APACHE II scores [3]. Refeeding hypophosphatemia was significantly associated with admission hypomagnesemia and hypokalemia in several recent studies, however the absolute differences in magnesium and potassium levels were too small to be applicable to identify ICU patients at risk for RFS [3,4,30].

As the correlation between risk factors and occurrence of RFS in critically ill patients remains unclear, regular phosphate monitoring is recommended (Table 3).

Table 2| Criteria to identify high risk of developing refeeding problems among non-ICU patients according to NICE

Patient has one or more of the following:
• BMI less than 16 kg/m^2
• Unintentional weight loss greater than 15% within the last 3–6 months
• Little or no nutritional intake for more than 10 days
• Low levels of potassium, phosphate or magnesium prior to feeding.
Or patient has two or more of the following:
• BMI less than 18.5 kg/m^2
• Unintentional weight loss greater than 10% within the last 3–6 months
• Little or no nutritional intake for more than 5 days
• A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Note: Data from [28]

Table 3| Diagnosis of refeeding hypophosphatemia and refeeding syndrome during critical illness

• No ICU admission characteristics are indicative of later development of RH or RFS
• Daily phosphate measurement during initiation phase of nutrition support (up to 72 hours)
• Phosphate drop is suggestive of RH or RFS: serum phosphate level decreased to below 0.65 mmol per liter within 72 hours of commencing nutritional support. Change required to be greater than 0.16 mmol per liter decrease from any previous level. Exclusion reasons: hypophosphataemia due to other reasons such as ongoing dialysis, recent parathyroidectomy, or treatment for hyperphosphataemia.

TREATMENT

Glucose administration

Glucose administration initiated before nutrition may lead to severe complications [10]. Glucose administration induces insulin secretion, which normally should lead to an anabolic response. During critical illness-induced catabolism, glucose and insulin interact differently as insulin resistance is common and high glucagon levels are present [17]. Combined elevated glucagon levels, glucose administration, and insulin resistance may lead to hyperglycemia, resulting in hyperosmolar nonketotic coma, ketoacidosis, osmotic diuresis, and dehydration [10,13,17]. Furthermore, hyperglycemia increases the infection risk and impairs immune function [13] and leads to higher respiratory quotients resulting in increased carbon dioxide production. This may lead to hypercapnia and respiratory acidosis and failure [10].

Electrolyte replacement

NICE guidelines do not recommend electrolyte supplementation before feeding initiation, but rather alongside with refeeding as to not delay energy replacement [28]. Levels of phosphate, magnesium, and potassium should be measured daily during refeeding until stable and supplementation aims at normophosphatemia, normokalemia, and normomagnesemia to prevent complications [28,31]. Few studies have addressed effects of electrolyte supplementation and outcomes of RFS in ICU patients. In a recent case–control study, phosphorus supplementation was shown to decrease the incidence of new onset cardiac arrhythmias in septic patients with hypophosphatemia (< 0.77mmol/l) on ICU admission (38 vs. 63%, P = 0.04) [32]. When systematically reviewed, no relationship between magnesium supplementation and mortality in ICU patients with hypomagnesemia was found [12]. However, a recent study of 143 ICU patients shows magnesium supplementation to correct asymptomatic hypomagnesemia to be associated with a lower incidence of acute kidney injury [relative risk (RR) 0.27; 95% confidence interval (CI), 0.11–0.64) and hospital, but not ICU, mortality (RR 0.28; 95% CI, 0.12–0.65) [33]. In addition, magnesium supplementation in Indian ICU patients showed a decrease in the need (52.1 vs. 65.6%) and duration of mechanical ventilation (36.6 vs. 58.8 h, P = 0.04) and lower mortality in the supplemented group (22.9 vs. 39.6%, P = 0.01) [34].

Thiamine supplementation

Acute thiamine deficiency may cause lactic acidosis and neurological impairment (i.e. Wernicke encephalopathy). Recent case series report thiamin deficiency induced by parenteral nutrition and rapid reversal of symptoms after thiamine

supplementation [14,35,36]. Guidelines and recent reviews recommend minimum daily thiamine supplementation of 100–300 mg. Supplementation should be started before feeding initiation and continued for 7–10 days [10,28,31].

Caloric restriction

In case of high risk of RFS, hypocaloric feeding is recommended to prevent complications of RFS [10,2,37]. Until recently, this statement was largely based on theoretical and anecdotal evidence and expert opinion. However, recently several studies have addressed hypocaloric feeding during RFS in both critically ill and noncritically ill patients [37,38].

A recent systematic review shows that five studies demonstrate preventive effects of hypocaloric feeding on development, morbidity, and mortality of RFS whereas six did not [2]. Three of the five positive studies were (largely) performed among critically ill patients and of the six negative studies, only one is performed in the ICU (other studies in patients with anorexia nervosa) [2]. Since then, of two studies performed among critically ill patients, not included in this review, one more shows significant benefits of hypocaloric feeding on survival rate during RFS [3,5].

Doig and colleagues performed the first randomized trial in adult ICU patients developing refeeding hypophosphatemia within 72 h of refeeding comparing standard nutritional support and protocolized caloric restriction (500 kcal/day) [6]. Although the primary endpoint was negative, full caloric feeding was reported to induce harm reflected by higher mortality rates at hospital discharge (risk difference 9.2%; 95% CI, 0.7–17.7; P = 0.017), and at 60 days (risk difference 12.3%; 95% CI, 3.9–20.7; P = 0.002) and 90 days (risk difference 8.7%; 95% CI, 0.04– 17.0; P = 0.041) after enrolment [6]. Furthermore, more major infections (16 vs. 8%; P = 0.02) and airway or lung infections (32 vs. 21%; P = 0.03) were reported during full feeding compared with caloric restriction [6]. Concurrent with these findings, a retrospective cohort study reported increased survival of ICU patients with refeeding hypophosphatemia that received hypocaloric feeding (< 50% of target) compared with those receiving normal intake (HR 0.39; 95% CI, 0.16–0.95; P = 0.037) [3]. In contrast, a post-hoc analysis of the PERMIT trial did not show benefits of permissive underfeeding compared with standard feeding on 90-day mortality and ICU-associated infections in post-hoc identified patients with refeeding hypophosphatemia [39].

Based on a single RCT [6], supplementation of electrolytes and vitamins alone seems insufficient, and caloric restriction and gradual increase of caloric intake is recommendable (Table 4). Although caloric restriction seems to reduce mortality in

ICU patients with refeeding hypophosphatemia, it may not protect against refeeding hypophosphatemia development as no differences in caloric intake in patients developing refeeding hypophosphatemia and those that do not were observed [3,4,5]. Trials in noncritically ill patients show similar results [37].

Table 4| Treatment of refeeding hypophosphatemia and refeeding syndrome during critical illness

- Supplement phosphate, magnesium and potassium to reach normal plasma levels
- Supplement thiamine at least 100mg daily for 7-10 days
- Restrict caloric intake to a maximum of 500 kcal per day (or maximum 25% of individual caloric target) for 48 hours and then gradually increase caloric intake in daily steps of 25% of target until target is reached

CONCLUSION

Refeeding syndrome has been increasingly studied during critical illness over the past years. Important new findings include differences in metabolic derangements in critically ill patients with refeeding syndrome compared with other RFS patients due to persistent catabolism; and improved outcome when caloric restriction and electrolyte and vitamin supplementation are combined.

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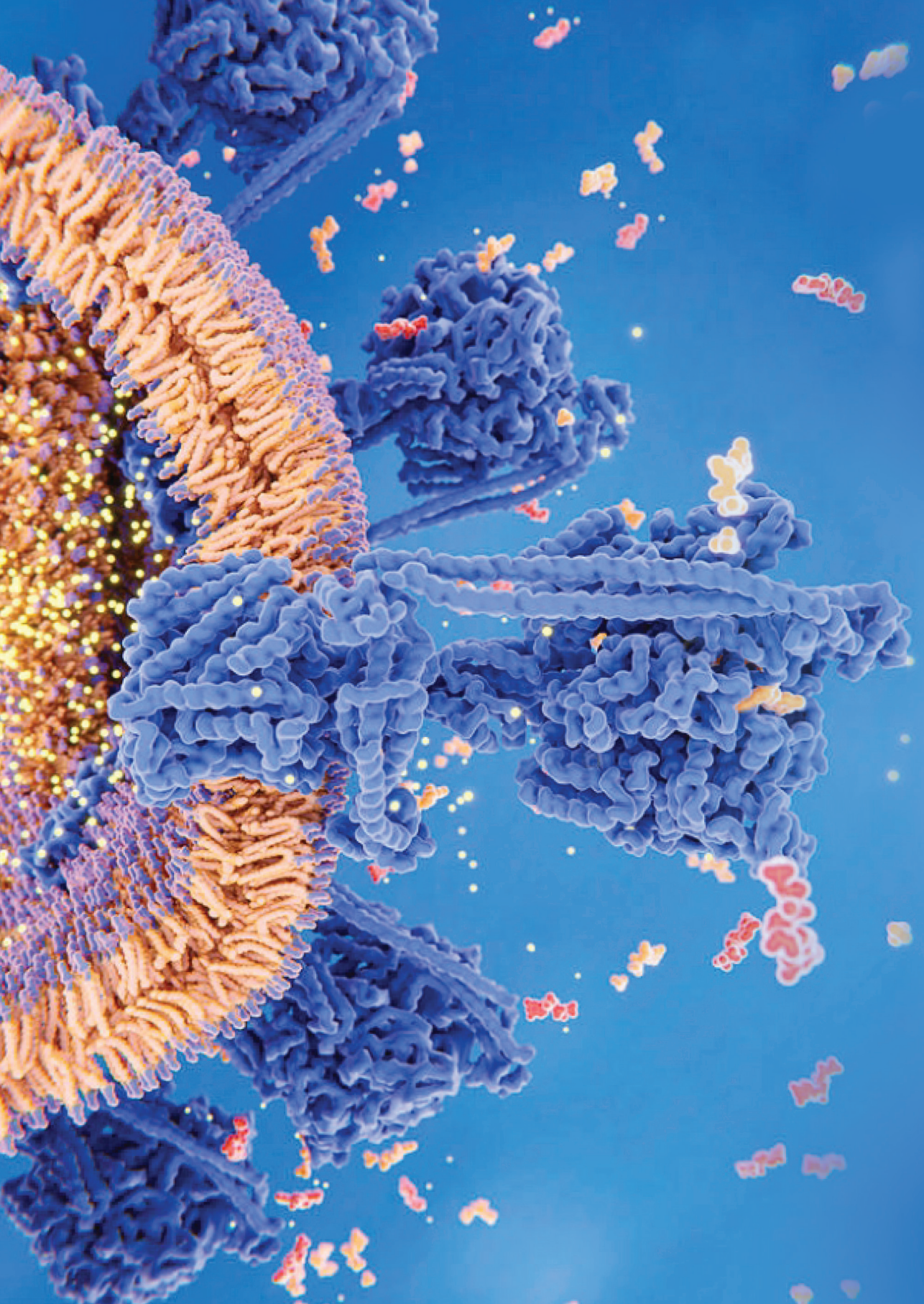

III PART

Pharmaconutrition

7

CHAPTER

Antioxidant Vitamins and Trace Elements in Critical Illness

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A.R.H. van Zanten

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ABSTRACT

This comprehensive narrative review summarizes relevant antioxidant mechanisms, the antioxidant status, and effects of supplementation in critically ill patients for the most studied antioxidant vitamins A, C, and E and the enzyme cofactor trace elements selenium and zinc.

Over the past 15 years, oxidative stress–mediated cell damage has been recognized to be fundamental to the pathophysiology of various critical illnesses such as acute respiratory distress syndrome, ischemia-reperfusion injury, and multiorgan dysfunction in sepsis. Related to these conditions, low plasma levels of antioxidant enzymes, vitamins, and trace elements have been frequently reported, and thus supplementation seems logical. However, low antioxidant plasma levels per se may not indicate low total body stores as critical illness may induce redistribution of antioxidants. Furthermore, low antioxidant levels may even be beneficial as pro-oxidants are essential in bacterial killing.

The reviewed studies in critically ill patients show conflicting results. This may be due to different patient populations, study designs, timing, dosing regimens, and duration of the intervention and outcome measures evaluated. Therefore, at present, it remains unclear whether supplementation of antioxidant micronutrients has any clinical benefit in critically ill patients as some studies show clear benefits, whereas others demonstrate neutral outcomes and even harm. Combination therapy of antioxidants seems logical as they work in synergy and function as elements of the human antioxidant network. Further research should focus on defining the normal antioxidant status for critically ill patients and to study optimal supplement combinations either by nutrition enrichment or by enteral or parenteral pharmacological interventions.

INTRODUCTION

Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) versus the antioxidant defenses [1,2]. Both ROS and RNS are radicals, formed by the reduction of oxygen or nitrogen species [1,2]. As a consequence, these reactive species contain unpaired electrons and therefore are highly reactive with other atoms and molecules [1,3]. Among the ROS the superoxide anion ($\cdot O_2$-), hydroxyl radical ($\cdot$OH) and hydrogen peroxide (H_2O_2) have been frequently studied [1-5]. The most common RNS are nitric oxide (NO$\cdot$) and peroxynitrite (ONOO-)[1-5].

Under normal physiologic conditions, ROS and RNS are constantly formed as a by-product of many biochemical processes, including aerobic cellular respiration [3]. In this process of oxidative phosphorylation oxygen is used as a recipient of electrons from other molecules to generate energy in the form of adenosine triphosphate (ATP) [3]. Oxygen is ultimately reduced to water. However, in 0.1-2.0% of these biochemical processes oxygen is incompletely reduced and intermediary ROS remain [1,3,5].

$$O_2 \rightarrow \cdot O_2 \rightarrow H_2O_2 \rightarrow OH \cdot \rightarrow H_2O$$

Deliberate production of radicals is also performed in normal physiology [3,6]. In the defense against bacteria or fungi the immune system demonstrates an essential feature in order to kill pathogens using radical production in activated phagocytes [3]. Furthermore, small amounts of ROS and RNS are produced to act as signaling molecules that are involved in the regulation of cell proliferation, apoptosis and gene expression [3,6].

The nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complexes are the major sources of ROS-production and can be found in cell membranes, mitochondria, peroxisomes and endoplasmic reticulum [3,4]. NADPH-oxidase is able to generate superoxide radicals by the use of oxygen and cytosolic NAPDH [3,4]. Superoxide is a weak oxidant but can be dismutated into hydrogen peroxide [1,3,5]. Hydrogen peroxide is lipid soluble and can cross cell membranes [1,3,5]. It can inactivate enzymes and damage lipids and DNA [3]. It also reacts with transition metals, like iron and copper, or with superoxide resulting in the formation of the hydroxyl radical [1,3]. The hydroxyl radical is the most aggressive and damaging oxidant, responsible for oxidative damage of most molecules. It can interact with almost all organic and inorganic molecules [1,3,5].

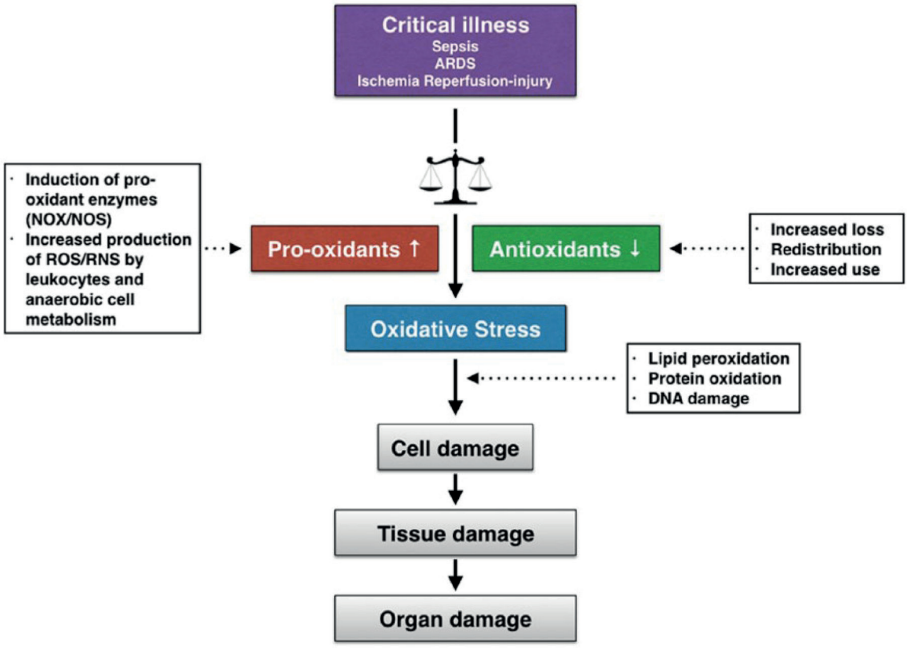
Other important enzymes that produce ROS and RNS are xanthine oxidase and nitric oxide synthase (NOS) [3,5]. Under physiological circumstances endothelial nitric oxide synthase (eNOS) produces small amounts of nitric oxide (NO) [3]. Endogenous

NO is a signaling molecule involved in vasodilatation and neurotransmission [3]. It is also released by phagocytes, where it reacts with superoxide to produce the highly damaging peroxynitrite [3,4]. Furthermore, peroxynitrite can spontaneously decompose into hydroxyl radicals and nitrogen dioxide [3].

The antioxidant network inactivates or scavenges radicals, thereby maintaining the reduction-oxidation balance and prohibiting oxidative damage. However, if antioxidant defenses are limited or production of ROS/RNS is overwhelming and exceeds the defense capacity the balance is disturbed and oxidative stress occurs [1-3,5]. Radicals then react with nonradical molecules like lipids, proteins and DNA. This may result in lipid peroxidation, inactivation of enzymes and DNA base modification, strand breaks, and cross-linking. If the damage is severe, it may ultimately result in cell death, cell damage, tissue damage and organ dysfunction (Figure 1) [1-3,5].

Radical-induced damage caused by oxidative stress has been associated with many acute and chronic illnesses as either a causative agent or a consequence [1-5].

Figure 1| Pathophysiology of oxidative stress in critical illness



During critical illness such as in sepsis, acute respiratory distress syndrome (ARDS), or ischemia-reperfusion injury, the pro-oxidant and antioxidant balance may be disrupted and confer enhanced oxidative stress. Due to induction of prooxidant enzymes and enhanced production of reactive oxygen species by leukocytes

and during anaerobic cell metabolism, the levels of pro-oxidants increase. In contrast, due to increased loss, redistribution, or increased metabolic use, protective antioxidant levels diminish. Oxidative stress, characterized by lipid peroxidation, protein oxidation, and DNA damage, markedly increases. Ultimately, this may lead to cell damage, tissue damage, and ultimately organ damage, decreasing the odds of survival in critical illness.

Abbreviations: NOS, nitric oxide synthase; NOX, nicotinamide adenine dinucleotide phosphate oxidase; RNS, reactive nitrogen species; ROS, reactive oxygen species.

OXIDATIVE STRESS IN THE CRITICALLY ILL

Over the past 15 years, many studies have described oxidative stress in various intensive care unit (ICU) syndromes, including sepsis, acute respiratory distress syndrome (ARDS), cardiogenic shock, multiorgan failure, and diaphragm fatigue [5,7,8]. There is accumulating evidence of increased ROS and RNS production and antioxidant depletion in these syndromes [5,7,9,10].

Sepsis

In sepsis, large amounts of radicals are generated by activated phagocytic cells and upregulated enzymes such as NADPH oxidase in leukocytes and xanthine oxidase and inducible NOS (iNOS) in endothelial cells [4,7]. The increased production of radicals overwhelms the antioxidant defense, and oxidative stress occurs. Furthermore, oxidative stress initiates an additional inflammatory response through the activation of redox pathways for transcriptional activation, for example, increased activation of nuclear factor (NF)–κB and increased circulating inflammatory mediators, including cytokines [7]. This, in turn, leads to production of more ROS/RNS. For example, cytokines chemically attract leukocytes to areas of lipid peroxidation, causing phagocytes to migrate into tissues and release more radicals [5,11].

Radicals cause mitochondrial membrane lipid peroxidation and protein damage, leading to irreversible mitochondrial injury and thereby diminished energy production from oxidative phosphorylation [7,12]. Subsequent cellular, tissue, and organ damage occurs. Oxidative stress–mediated damage to mitochondria appears to be fundamental to the pathophysiology of organ failure in sepsis [4,8,12].

In sepsis, oxidative stress is at least partially responsible for vascular hyporeactivity to catecholamines and increased vascular permeability, causing septic shock.4 The antioxidant glutathione is able to reduce vascular hyporeactivity and endothelial dysfunction. Peroxynitrite, however, interferes with this ability [4]. Moreover, ROS/RNS levels drastically increase during reduced tissue perfusion and induction of the immune response [5].

Besides increased production of ROS and RNS, decreased antioxidant status has been frequently reported in sepsis and other critical illnesses [4,5,7,9,10] This may be caused by losses through body fluids, redistribution, dilution secondary to fluid resuscitation, and inadequate intake [4].

ARDS

ARDS is the result of an uncontrolled acute inflammatory response leading to dysfunction and compromise of the barrier properties of the pulmonary endothelium and epithelium [4,13]. The pulmonary macrophages and endothelium become activated, and subsequently, upregulation of surface expression of adhesion molecules occurs [13]. This leads to neutrophil adhesion and subsequent transmigration from the intravascular space into the alveolus [13]. The activated neutrophil produces inflammatory mediators that include ROS and RNS [4,13]. The parenchymal cells and other leukocytes, such as pulmonary macrophages, also produce ROS and RNS, although in lower amount [13]. Peroxynitrite is produced, causing nitration of proteins such as surfactant, and DNA damage [13]. When patients with ARDS receive O2 therapy, they show enhanced ROS production [4,9,14]. Inhaled NO also contributes to the deficient cellular respiration by reacting with superoxide to form peroxynitrite [4].

Glutathione is the most important antioxidant in the lungs, but glutathione seems to be decreased in the epithelial lining of patients with ARDS [4].

In conclusion, oxidative stress seems to contribute to the pathogenesis of ARDS. This hypothesis was evaluated in multiple studies that report decreased antioxidant and increased pro-oxidant levels in bronchoalveolar lavage fluid and plasma in patients with ARDS [7,15,16]. Also, increased levels of hydrogen peroxide in exhaled breath were reported [17,18].

Ischemia-Reperfusion Injury

Oxidative stress is thought to play a major role in ischemia-reperfusion injury of different organs [19-23]. Hypoxia during ischemia disturbs the generation of ATP in mitochondria, which leads a switch from aerobic to anaerobic cell metabolism. This induces systemic acidosis and accumulation of lactate and intracellular calcium overload, causing activation of intracellular proteases, mitochondrial changes, and a cytokine storm resulting, in tissue injury [19]. If ischemia persists, tissue damage will become irreversible and cell death occurs. Reperfusion of ischemic tissue is essential in restoring aerobic metabolism. However, return of blood flow can result in additional damage, called reperfusion injury [19,20,23].

Reactive oxygen and nitrogen species play a major role in ischemia-reperfusion injury. The production of ROS by mitochondria is increased during ischemia [19,20,23]. Second, a high amount of xanthine dehydrogenase is naturally found in the vascular endothelium. Under hypoxic conditions, this enzyme is converted into xanthine oxidase. Xanthine oxidase catalyzes the production of superoxide from hypoxanthine and molecular oxygen [19-21]. Hypoxanthine is accumulated during ischemia, and molecular oxygen is provided on reperfusion [20,21]. Ischemia and reperfusion also induce the production of superoxide and NO by vascular NADPH oxidase and eNOS [19,20]. In low concentrations, NO has a beneficial effect as it protects the vascular wall from leukocyte and thrombocyte adhesion and leads to vasodilatation. However, in high concentrations, NO is prone to react with superoxide, resulting in the highly reactive peroxynitrite radical. Furthermore, superoxide can induce uncoupling of eNOS. Uncoupled eNOS produces superoxide instead of NO [19].

Direct and indirect effects of ROS/RNS cause tissue damage such as DNA strand breaks and protein and lipid peroxidation. Indirect effects are caused by modulation of cell signaling and control mechanisms. This leads to vascular endothelial dysfunction, leukocyte activation, and adherence and induction of the inflammatory response [19-21,23].

Leukocytes accumulate in the microvasculature, causing obstruction and thereby preventing reperfusion. Moreover, activated leukocytes produce ROS, causing more direct and indirect tissue damage [19-21,23].

ANTIOXIDANTS

An antioxidant is defined as any substance which either (1) prevents the transfer of electrons to and from molecular oxygen and organic molecules, (2) stabilizes organic radicals, or (3) terminates organic radical reactions [8,24]. Antioxidants thereby counteract the effects of reactive oxygen and nitrogen species. The antioxidant network comprises antioxidant enzymes and compounds that interact.

ANTIOXIDANT ENZYMES

Antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and the thioredoxin (TRX) system [25].

SOD

Superoxide dismutases are metalloproteins that catalyze the dismutation of superoxide to hydrogen peroxide and oxygen. There are different SOD subtypes. Copper-zinc

containing superoxide dismutase (SOD_1), uses copper and zinc as cofactors and is present in the cytosol. Manganese containing superoxide dismutase (SOD_2) is found in mitochondria. SOD3 is an extracellular superoxide that uses copper and zinc as cofactors [3,25].

CAT

The enzyme CAT converts hydrogen peroxide into water and oxygen within the cell membrane. It also uses hydrogen peroxide for the oxidation of alcohols and phenols [3,25].

GPx

GPx produces glutathione disulfide and water from hydrogen peroxide. Glutathione disulfide is reduced back to glutathione by glutathione reductase. Thereby regenerating the glutathione system to be used again and again. The glutathione system is found in the cytoplasm and mitochondria. There are 2 forms of the enzyme GPx; one is selenium independent while the other is selenium dependent. Glutathione itself is an endogenous antioxidant compound that is used as a substrate by the glutathione system, but also acts as a direct scavenger of radicals [3,25,26].

TRX System

TRX peroxidase catalyzes the reaction from hydrogen peroxide into water. Oxidized TRX is then reduced by TRX reductase (TrxR). This is a NADPH-dependent reaction. Oxidized ascorbate can also be reduced by TrxR. TrxR uses selenium as a cofactor [3,25,27] .

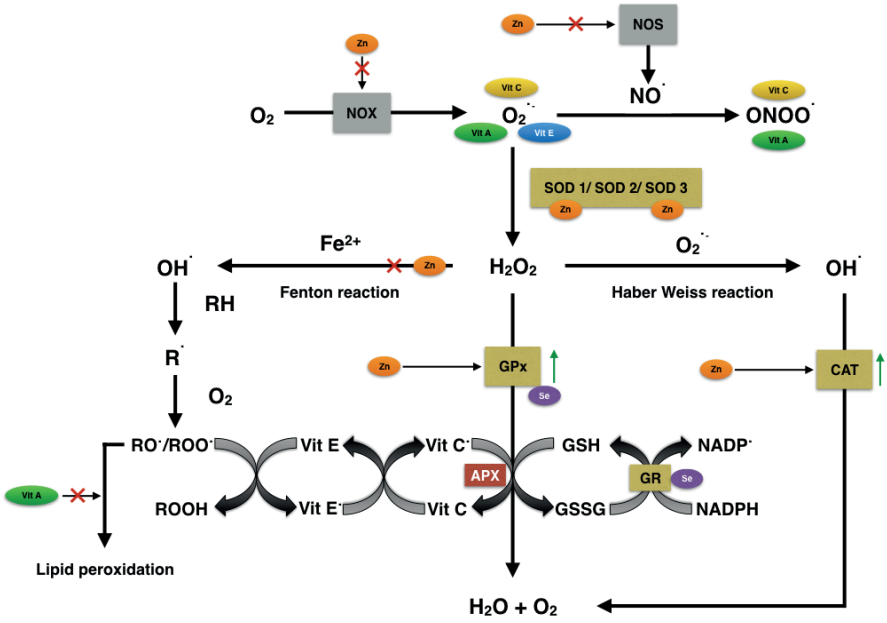
ANTIOXIDANT COMPOUNDS

Antioxidant compounds include antioxidant vitamins, enzyme cofactors, and endogenous antioxidant compounds. Antioxidant vitamins A, C, and E mainly act as radical scavengers. Antioxidant enzyme cofactors include selenium and zinc; they have a complex role and are involved in many processes in the antioxidant network [3,26]. The antioxidant vitamins and enzyme cofactors are reviewed extensively later. Endogenous antioxidant compounds include ubiquinone, α-lipoic acid, bilirubin, serum albumin, ferritin, metallothionein, L-carnitine, uric acid, glutathione, and melatonin. They protect against oxidative damage using 4 mechanisms: (1) sequestration of transition metal ions into complexes, (2) scavenging or quenching free radicals and other ROS and RNS, (3) breaking chain reactions initiated by free radicals, and (4) repairing damaged molecules [3,26].

THE HUMAN ANTIOXIDANT NETWORK

The delicate interplay of oxidants, antioxidants and the antioxidant vitamins A, C and E and the enzymatic cofactor trace elements selenium and zinc are depicted in Figure 2.

Figure 2| The human antioxidant network



(1) Zinc inhibits the pro-oxidative enzymes NOX and NOS; increases the activity of antioxidant enzymes SOD, GPx, and CAT; is a cofactor of SOD1 and SOD3; and competes with transition metals, thereby prohibiting the Fenton reaction and the generation of reactive oxygen species. (2) Selenium is incorporated in GPx and GR, both selenoproteins. (3) Vitamin A is a chain-breaking antioxidant in the process of lipid peroxidation and directly scavenges superoxide, peroxynitrite, and the hydroxyl radical. (4) Vitamin C regenerates vitamin E and directly scavenges water-soluble reactive oxygen species. (5) Vitamin E is a chain-breaking antioxidant in the process of lipid peroxidation and directly scavenges lipid-soluble ROS.

Abbreviations: APX: ascorbate peroxidase; CAT, catalase; Fe2+, iron(II); GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; H2O, dihydrogen monoxide ("water"); H2O2, hydrogen peroxide; NADP*, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NO*, nitric oxide; NOS, nitric oxide synthase; NOX, nicotinamide adenine dinucleotide phosphate oxidase; O2*−, superoxide; OH*, hydroxyl radical; ONOO*, peroxynitrite; R*, alkyl radical; RH, radical-hydrogen; RO*, alkoxy radical; ROO*, peroxy radical; ROOH, hydroperoxide; Se, selenium; SOD, superoxide dismutase; Vit A, vitamin A; Vit C, vitamin C; Vit E, vitamin E; Zn, zinc.

MEASURING OXIDATIVE STRESS IN THE CRITICALLY ILL

Oxidative stress is due to a disturbance in the balance between ROS and antioxidant defenses. Therefore, quantification can be performed by measuring pro-oxidant status, antioxidant status, or both. Because of the very short half-life of reactive oxygen and nitrogen species, direct measurement is difficult. A popular approach in quantifying pro-oxidant status is the measurement of stable by-products that are formed during lipid peroxidation and protein and DNA oxidation. The most used and studied markers are 2 by-products of lipid peroxidation, malondialdehyde and isoprostanes, and a product of DNA oxidation: 8-hydroxydesoxyguanosine [28-31].

Antioxidant status is assessed by the measurement of the consumption of antioxidant compounds and the changes in activity of antioxidant enzymes [28,30,31]. As there is cooperation among different antioxidants in the antioxidant network, measurement of a single compound or enzyme probably does not reflect the real antioxidant capacity. "Total antioxidant capacity" is measured by adding a biological sample to inhibit the transformation of a selected substrate by an in vitro generated free radical [30]. However, this technique does not reflect the pro-oxidants that are produced in vivo.

Measuring oxidative stress remains difficult as there is no single method to characterize the balance of pro-oxidants and antioxidants under clinical conditions [30]. Not only the method itself can be questioned, but also the location where oxidative stress should be measured is a matter of debate. Currently, most markers are assessed in plasma. However, multiple studies show poor correlations between plasma and tissue status of pro-oxidants and antioxidants [28-31].

SELENIUM

Selenium is an essential micronutrient and functions as an enzymatic cofactor of >30 selenoproteins [32-36]. These proteins have numerous biological functions, especially related to redox signaling, the antioxidant defense system, thyroid hormone metabolism, and the humoral and cell-mediated immune response [32]. Selenium homeostasis is controlled by renal regulation. Absorption is not regulated, and bioavailability of dietary selenium is usually high [34]. Adequate selenium intake in humans has been estimated at 50-100 µg/d, with toxic levels occurring >350 µg/d [32,34]. About 60% of selenium in serum is incorporated in selenoprotein P (SePP), 30% is bound to GPx and 5%-10% to serum albumin, and <1% exists as free selenium [32,34,36]. Serum selenium levels are considered normal at 1.0-1.5 µmol/L (7.9-11.8 µg/dL) in healthy adults [35].

Selenium homeostasis changes in systemic inflammatory response syndrome (SIRS) [32,35]. Selenium and selenoproteins in blood are redistributed to tissues involved in protein synthesis and immune cell proliferation [32]. Capillary leakage leads to additional loss of serum selenoproteins to the interstitium [32]. Furthermore, endothelial dysfunction caused by sepsis or ischemia-reperfusion injury leads to binding of SePP to the endothelium [37]. This binding is believed to be a protective mechanism against further oxidative stress injury [37]. In addition, the urinary excretion of selenium increases during a catabolic state, despite low serum selenium plasma concentration [35].

Antioxidant mechanism of selenium

Selenium is incorporated in >30 selenoproteins [32-37]. More than 50% of these selenoproteins exhibit antioxidant activity, of which the GPx family and TRX reductase family are the most well known [34,36]. The GPx family comprises 8 isoforms that catalyze the reduction of various hydroperoxides [32]. GPx acts synergistically with α-tocopherol in antioxidant defense against lipid peroxidation. Thioredoxin reductases (TrxR) include 3 isoforms present in cytosol, mitochondria, and spermatozoa. All isoforms catalyze the reaction from hydrogen peroxide to water [38,39]. In addition, SePP may be protective against endothelial oxidant injury [39].

Selenoproteins also inhibit activation of NF-κB through redox signaling and thereby prohibit a cytokine storm and formation of reactive oxygen and nitrogen species [32].

Various chemical forms of selenium have been identified. Dietary selenium comprises organic compounds such as selenomethionine and selenocysteine, of which the intestine absorbs 90%. Inorganic compounds such as selenite or selenate are more variably absorbed up to levels of 50–90%. When selenium is absorbed by the intestine, it initially exists as free selenium or selenocysteine before it is incorporated into selenoproteins [33]. Intravenous (IV) supplementation of selenium is most efficacious using inorganic compounds, preferably sodium selenite [40]. Selenite is rapidly converted to selenodiglutathione and then reduced to hydrogen selenide to become available for incorporation into selenoproteins (ie, GPx). Selenide is a very active metabolite, which is also converted by methylation. For example, it is converted into dimethyl selenide and trimethyl selenide, which are the best-known excretory metabolites of selenium; they are excreted through lungs and kidneys, respectively, and both have antioxidant properties [36,41]. Selenomethionine could be used intravenously, but it first should be incorporated into other tissue or plasma proteins and needs to be converted to selenocysteine before selenoproteins can be synthesized. Selenomethionine is not currently available for IV use.

Before selenite is converted, it may act as a pro-oxidant and subsequently induce apoptosis and cytotoxicity in activated proinflammatory cells, as well as confer direct virucidal and bactericidal effects [32]. These pro-oxidant effects may be beneficial in the early phase of sepsis [32]. When incorporated into selenoproteins, selenium exhibits an antioxidant effect, mostly by increasing GPx3 levels in plasma. Maximum antioxidant plasma activity of GPx3 is estimated around GPx3 plasma levels of 95 µg/L.

Selenium status in the critically ill

Selenium levels in critically ill patients are most frequently assessed in plasma. Hawker and associates [35] were among the first to report low selenium plasma levels in ICU patients compared with healthy controls. They investigated 175 consecutive patients and assessed mean selenium levels in the first week of ICU admission. Mean selenium levels were significantly lower than those of healthy controls (0.66 ± 0.21 vs 1.05 ± 0.21 µmol/L). Foreceville and coworkers [42] assessed plasma and urinary selenium levels in 134 ICU patients. Mean selenium levels were low in all patients but significantly lower in patients with SIRS (0.62 ± 0.21 vs 0.83 ± µmol/L, P < .001). Furthermore, mean plasma selenium concentrations were negatively correlated to sepsis severity scores. Selenium levels <0.70 µmol/L on ICU admission were associated with 3.5 times higher mortality rates and 3 times higher rates of organ failure. Urinary selenium excretion remained constant despite changes in plasma selenium concentrations [42].

Jang and associates [43] retrospectively investigated the records of 162 patients admitted to a surgical ICU. Mean selenium levels were not significantly different between survivors and nonsurvivors (1.06 ± 0.30 vs 1.0583.3 ± 0.37 µmol/L). However, mean selenium concentrations were significantly different between patients with and without shock (0.99 ± 0.32 and 1.10 ± 0.29 µmol/L, P = .017). Selenium levels were also significantly lower in patients with sepsis in comparison with patients with trauma (0.96 ± 0.34 vs 1.20 ± 0.25 µmol/L, P < .001).

Manzanares et al [44] and Forceville et al [45] investigated the status of selenium and/or specific selenoproteins in critically ill patients in relation to mortality. Forceville and colleagues [45] showed that patients with septic shock or multiorgan failure had 70% lower SePP levels on ICU admission than patients without SIRS. SePP plasma levels were significantly lower in nonsurvivors. Manzanares and coworkers [44] investigated the predictive value of plasma selenium status for ICU mortality. A cutoff value of 60 µg/L showed a specificity of 81.2%. GPx-3 activity was lower in critically ill patients and correlated inversely with severity of sepsis and mortality.

Selenium supplementation in the critically ill

Multiple studies have been performed to assess the effects of selenium supplementation in critically ill patients. Important differences between the studies include supplementation route (parenteral vs enteral), daily dose of selenium (high dose vs low dose), use of a loading bolus, patient selection (septic vs nonseptic patients), and supplementation of other antioxidants (monotherapy vs antioxidant cocktails) [46-52].

Parenteral selenium monotherapy in critical care

Multiple studies have been performed with conflicting results. Seven recent meta-analyses also show divergent outcomes [46-49]. This may be because the methodological quality of the included trials in all meta-analysis varied considerably. In Tables 1 and 2, we show the meta-analyses and included trials on selenium supplementation. The heterogeneity of the study designs made it difficult to conduct a proper and valid analysis. The results should therefore be interpreted with caution.

Table 1| Randomized Controlled Trials Studying Selenium Supplementation vs Placebo in Critical Illness

Study	Year	Patient characteristics	Number of patients	Risk ratio of mortality [95% CI]	Loading dose	Mono-therapy
Kuklinski [abc]	1991	Acute necrotising pancreatitis	17	0.07 [0.00 – 0.98][a]	no	yes
Zimmerman [a,b,c,e,f,g]	1997	ICU patients with SIRS & MOF	40	0.38 [0.12 – 1.21][c]	yes	yes
Berger [a]	1998	Burns > 30% TBSA	20	3.00 [0.14 – 65.91][f]	no	no
Saito [b]	1998	Subarachnoid hemorrhage	286	0.78 [0.38 – 1.60][e]	no	yes
Yamaguchi [b]	1998	Acute ischemic stroke	300	0.66 [0.31 – 1.42][e]	no	yes
Angstwurm [a,b,c,e,f,g,k]	1999	ICU patients with SIRS	42	0.64 [0.31 – 1.32][b]	no	yes
Porter [a]	1999	ICU patients with penetrating trauma. injury severity score ≥ 25	18	1.00 [0.02 – 45.64][f]	no	no
Ogawa [b]	1999	Acute Middle Cerebral Artery Occlusion	99	1.30 [0.35 – 4.91][c]	no	yes
Berger [a,b,c]	2001	ICU patients with trauma	32	1.20 [0.12 – 11.87][g]	no	no
Lindner [a,b,c]	2004	ICU patients with acute pancreatitis	67	1.82 [0.47 – 7.02][e]	no	yes
Angstwurm [a,b,c,e,f,g,k]	2007	ICU patients	238	0.79 [0.60 – 1.06][c]	yes	yes
Berger [a]	2007	Burns > 20% TBSA	21	0.91 [0.07 – 12.69][f]	no	no
Forceville [a,b,c,e,f,g,k]	2007	ICU patients with Septic Shock	60	1.01 [0.58 – 1.76][c]	no	yes
Mishra [a,b,c,e,f,g,k]	2007	ICU patients with Sepsis	40	0.89 [0.46 – 1.73][a]	no	yes
Berger [a]	2008	ICU patients	200	1.54 [0.52 – 4.54][a]	no	no
Montoya [b,c,f,g]	2009	ICU patients with sepsis	68	0.75 [0.29 – 1.93][b]	yes	yes
El-Attar [a]	2009	COPD patients	80	2.00 [0.19 – 21.19][a]	no	no
Gonzalez [a,e]	2009	ICU patients	68	0.75 [0.29 – 1.93][b]	no	yes
Andrews [a,b,c,f,g]	2011	ICU patients	502	1.00 [0.78 – 1.28][a]	no	yes
Manzanares [a,b,c,e,f,g]	2011	ICU patients	31	0.64 [0.18 – 2.23][a]	yes	yes
Valenta [a,b,c,e,f,g,k]	2011	ICU patients with SIRS or Sepsis	150	0.79 [0.48 – 1.32][c]	no	yes
Heyland [a,e]	2013	ICU patients	1218	1.06 [0.90 – 1.24][b]	no	no

Study	Year	Patient characteristics	Number of patients	Risk ratio of mortality [95% CI]	Loading dose	Mono-therapy
Janka [b]	2013	ICU patients with sepsis	72	0.72 [0.45 – 1.15][c]	no	yes
Woth [a]	2014	ICU patients with sepsis & MOF	40	0.74 [0.40 – 1.38][d]	yes	yes
Chelckeba[l]	2015	ICU patients with sepsis	54	0.78 [0.38 – 1.60][c]	yes	yes
Bloos [a]	2016	ICU patients with severe sepsis or septic shock	1180	1.12 [0.92 – 1.36][f]	yes	yes

a) Canadian guidelines [52], b) Allingstrup and Afshari [50]—Cochrane review, c) Huang et al [47], d) ICU mortality, e) American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine guidelines [49], f) Alhazzani et al [46], g) Landucci et al [51], h) 28-day mortality, i) unspecified, j) 3-month mortality, k) Kong et al [48], l) Hospital mortality, m) 20-day mortality, n) 14-day mortality

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; MOF, multiorgan failure; SIRS, systemic inflammatory response syndrome; TBSA, total body surface area.

Table 2| Meta-Analyses Comparing Selenium Supplementation vs Placebo in Critical Illness

Meta-analysis	Year	Patient characteristics	Number of patients	Risk ratio of Mortality [95% CI]
Huang et al [47]	2013	ICU patients with sepsis	965	0.83 [0.70 – 0.99][a]
Alhazanni et al [46]	2013	ICU patients with sepsis	792	0.73 [0.54 – 0.98] [a b]
Kong et al [48]	2013	ICU patients with sepsis	530	0.89 [0.73 - 1.07] [a]
Landucci et al [51]	2014	Critically ill patients	921	0.84 [0.71 – 0.99] [c]
Canadian Guidelines [52]	2015	Critically ill patients	3918	0.99 [0.90 – 1.08] [a]
Allingstrup and Afshari - Cochrane review [50]	2015	Critically ill patients	1391	0.82 [0.72 – 0.93] [a]
ASPEN/SCCM Guidelines [49]	2016	Critically ill patients	1888	0.94 [0.84 – 1.06] [a]

a) unspecified, b) odds ratio, c) 28-day mortality
Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; CI, confidence interval; ICU, intensive care unit; SCCM, Society of Critical Care Medicine.

Alhazzani et al [46] Huang et al [47] and Kong et al [48] all conducted meta-analyses, including studies on parenteral selenium supplementation in ICU patients with sepsis. Alhazanni et al [46] and Huang et al [47] found a statistically significant reduction in mortality (OR, 0.73; 95% CI, 0.54–0.98; P = .33 and risk ratio [RR], 0.83; 95% CI, 0.70–0.99; P = .04), but Kong and colleagues [48] did not (RR, 0.89; 95% CI, 0.73–1.07; P = .21).

In addition, the American Society for Parenteral and Enteral Nutrition (ASPEN) in collaboration with the Society of Critical Care Medicine (SCCM) recently updated their guidelines regarding selenium supplementation in sepsis. They performed a meta-analysis of 9 studies involving 1888 patients and found no significant difference in mortality (RR, 0.94; 95% CI, 0.84–1.06; P = .32), ICU length of stay, hospital length of stay, or duration of mechanical ventilation between study patients and controls. They conclude that a recommendation regarding selenium supplementation in sepsis cannot be made due to conflicting studies [49].

The latest Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT) has not been published yet. However, the preliminary results were incorporated into the Canadian Critical Care Nutrition practice guidelines. From the available data, we have estimated the RR and 95% CI for mortality to be 1.12 (95% CI, 0.92–1.36; P = .28). These results confirm the lack of efficacy of selenium supplementation in sepsis [52].

The Cochrane Collaboration [50] and Landucci et al [51] both conducted systematic reviews of selenium supplementation in ICU patients, thus including both sepsis and nonsepsis patients. Both showed a significant reduction in overall mortality (RR, 0.82; 95% CI, 0.72–0.93 and RR, 0.84; 95% CI, 0.71–0.99, respectively) [50,51]. However, the analysis performed by the Cochrane Collaboration was classified as very low quality of evidence due to high risk of bias in most included trials. The 28-day and 90-day mortality rates were not significantly different between intervention and control groups. Length of ICU stay, the duration of ventilation, and length of hospital stay were also not significantly different. In addition, no effect of selenium supplementation on infectious morbidity was found [50]. In the systematic review performed by Landucci and coworkers [51] the mortality reduction was only found at 28 days, but no significant differences were observed regarding 6-month mortality, nor were any significant differences found between length of ICU stay, nosocomial pneumonia, or renal failure [51].

Finally, the Canadian Clinical Practice Guidelines recently downgraded their recommendations on parenteral selenium supplementation based on the analysis of 20 studies. They advise not to use high-dose selenium supplementation in critically

ill patients, as there is no reduction in overall mortality, length of ICU stay, length of hospital stay, or rate of infections. Subgroup analysis of selenium monotherapy in critically ill patients also failed to show a significant reduction in mortality (RR, 0.90; 95% CI, 0.78 –1.04; P = .17) [52].

High dose vs. low dose selenium

A significant reduction in mortality in patients with sepsis who received high-dose parenteral selenium therapy (>1000 μg/d) was found in a meta-analysis performed by Huang and colleagues [47] (RR, 0.77; 95% CI, 0.61–0.99; P = .04). Low-dose selenium supplementation had no effect on mortality. However, a subgroup analysis in the most recent Canadian Clinical Practice Guidelines showed no effects on mortality from neither high-dose (>500 μg/d; RR, 0.97; 95% CI, 0.85–1.12; P = .70) nor low-dose supplementation (RR, 0.94; 95% CI, 0.67–1.33; P = .75) [52].

Loading dose

Early administering of a bolus may cause a transient pro-oxidative effect that may be beneficial in sepsis [32,45]. Subgroup analysis of the meta-analysis performed by Landucci et al [51] and the Canadian Critical Care Nutrition [52] group showed no effect of a loading dose on mortality (RR, 0.79; 95% CI, 0.52–1.17; P = .13 and RR, 0.90; 95% CI, 0.73–1.10, P = .31). In a meta-analysis of septic patients receiving a loading dose, a significant reduction in mortality was found compared with patients not receiving this bolus (RR, 0.73; 95% CI, 0.58–0.94; P = .01). However, all trials that administered a loading bolus also had longer overall duration of selenium supplementation (>7 days). Longer duration of selenium supplementation by itself was associated with a reduction in mortality. It is not clear whether either one or both factors are necessary in mortality reduction [47].

Enteral selenium supplementation

No studies of enteral selenium monotherapy in critically ill patients have been performed to our knowledge. Enteral supplementation of selenium in antioxidant cocktails is addressed later. It should be taken into account that administering selenium together with ascorbic acid significantly lowers the enteral absorption of selenium. Selenite is reduced by ascorbic acid to elemental selenium, which cannot be used. Therefore, administering selenium concomitantly with ascorbic acid potentially undermines the treatment effect [36].

ZINC

Zinc is an essential trace element required for the normal function of the immune system, glucose control, neurocognitive function, wound healing, and oxidative stress responses [53-58].

The Recommended Daily Allowance (RDA) for healthy individuals is 4–15 mg.54 Zinc is a cofactor of >300 enzymes and plays an important role in DNA synthesis, cell proliferation, protein synthesis, and cell membrane integrity [53,55,57-59]. Zinc homeostasis is controlled by intestinal absorption and intestinal and renal excretion [53,55]. There is no storage system for zinc, and thus adequate intake and narrowly regulated excretion are mandatory [59]. Plasma zinc levels are considered normal at >11 μmol/L (72 μg/dL) in healthy patients [53].

However, the normal regulatory mechanisms are impaired during the systemic inflammatory response [49]. Low plasma concentrations of zinc are often found in critically ill patients [54]. The decrease in plasma concentration is partially caused by acute redistribution from plasma to other tissues and increased losses [54,57]. Zinc is predominantly bound to serum albumin and subsequently leaks from plasma if vascular permeability is increased, as seen in sepsis [54]. Zinc is also sequestered into the liver and spleen to enhance acute phase protein and immune cells synthesis [53,57]. It is thereby, however, depleted from other organs. The urinary excretion of zinc is increased in acute inflammation, causing further decrease in plasma zinc concentrations [49,51,52]. In addition, administration of propofol edetate disodium, a frequently used sedative, is associated with enhanced urinary excretion of zinc [60]. Moreover, poor nutrition may induce zinc deficiency in critically ill patients [54].

The decrease of plasma zinc in acute inflammation may be a protective response, as bacteria require zinc for proliferation [49,52]. However, zinc deficiency impairs the immune response as it leads to decreased T- and B-cell maturation; lymphopenia; impaired T-cell, natural killer–cell, and phagocytic cell function; and an altered cytokine response [49,52,53]. Zinc deficiency also modifies the barrier functions of the skin, lungs, and gastrointestinal tract [53]. In the lungs, it also changes the lipid metabolism, which may lead to pulmonary edema [61]. Zinc also plays an important role in antioxidant defense, and thus zinc deficiency may disturb the oxidant-antioxidant balance and induce oxidative stress. As oxidative stress is thought to play an important role in the pathophysiology of organ failure, zinc deficiency may indirectly contribute to organ dysfunction.

Antioxidant mechanism of zinc

Zinc is no true antioxidant as it is redox inert and thus does not directly interact with ROS [59]. It does, however, play an important role in antioxidant defense in a number of ways. First, zinc increases the activation of antioxidant enzymes such as SOD, GPx, and CAT [57,59,62]. It acts as a direct cofactor of SOD types 1 and 3, being incorporated in the enzyme [62]. Zinc also stimulates the synthesis of glutathione and thereby acts as an indirect cofactor of GPx. In animal studies, zinc supplementation increased the concentrations of glutathione. Some also have reported an increase in the amount of SOD, but results are conflicting [62,63]. Gene expression of these antioxidant proteins is regulated by nuclear respiratory factor 2 (Nrf2). Zinc may have a role in gene expression of these proteins as it upregulates Nrf2 [57].

Second, zinc inhibits important pro-oxidant enzymes such as NADPH oxidase, iNOS, and N-methyl-D-aspartate (NMDA) [62]. NMDA is found in neuronal cells. In case of zinc deficiency, NMDA promotes an increase in intracellular calcium concentrations, which subsequently leads to activation of NADPH oxidase and NOS [62].

Third, zinc competes with redox-active transition metals such as iron and copper for certain binding sites (cell membranes, proteins) and thereby prohibits them from catalyzing the formation of free radicals and the initiation of lipid peroxidation. When zinc binds to these sites, copper and iron are forced to undergo hydrolytic polymerization and become unreactive structures [24,57,62,64].

Fourth, zinc binds to sulfhydryl groups of proteins and thereby protects them from oxidation [24,57,63].

The fifth way zinc influences the antioxidant network is by binding to thionein proteins forming metallothionein (MT), a scavenger of radicals. Zinc supplementation increases the expression of thionein [57,62,63].

Other indirect ways in which zinc reduces oxidative stress include inhibiting NF-κB, which leads to reduced activation of cytokines and pro-oxidant enzymes [56]. Zinc also indirectly reduces hyperglycemia, and thereby oxidative stress, by enhancing glucose transport into cells, promoting phosphorylation of insulin receptors, and catalyzing the conversion from proinsulin into insulin [62].

Zinc status in the critically ill

Because of altered zinc metabolism during the systemic inflammatory response, the diagnosis of true zinc deficiency is difficult in critically ill patients. Cander and coworkers

[53] assessed plasma zinc levels in critically ill patients 24 hours after ICU admission. Only 11% of patients had normal zinc levels. Plasma zinc levels were significantly lower in patients with Sequential Organ Failure Assessment (SOFA) scores of 8 or higher (6.74 ± 1.63 vs 9.17 ± 2.76 µmol/L). However, no difference between survivors and nonsurvivors in plasma zinc levels was demonstrated. Another study by Besecker and coworkers [64] reported lower plasma zinc levels in septic patients compared with nonseptic patients admitted to the ICU (6.96 ± 2.8 vs 8.75 ± 2.8 µmol/L). Both groups showed significantly lower plasma zinc levels than healthy controls. The need for higher dosages of vasopressors was also associated with lower zinc levels in this study. Linko and collaborators65 conducted a large prospective observational study in 551 patients with respiratory failure. In total, 95.8% of patients had low plasma zinc levels at ICU admission. The median (range) plasma zinc levels in noninfectious, septic, and septic shock patients were 5.0 µmol/L (3.1-7.1), 5.1 µmol/L (3.5-7.3), and 3.8 µmol/L (2.6-5.9), respectively. The levels of zinc decreased with increasing severity of cardiovascular organ dysfunction and were lower in operative patients than in nonoperative patients. No differences in plasma zinc levels between survivors and nonsurvivors were found. Furthermore, baseline zinc levels were not associated with ventilatory support duration or ICU length of stay.

Zinc supplementation in the critically ill

Zinc can be supplemented intravenously, enterally, or orally. Intravenous solutions provide 100% bioavailability. In contrast, absorption of oral or enteral supplements depends on the administered form of zinc. Zinc complexes in which zinc is bound to aspartate, cysteine, histidine, or methionine obtain the highest absorption [59].

Zinc supplementation has been frequently studied in critically ill patients but mostly in combination with other micronutrient supplements. Only 1 study, by Young and coworkers [57], evaluated the effects of zinc monotherapy in critically ill patients. They conducted a randomized controlled trial in 68 mechanically ventilated patients with severe closed head injury. In the intervention group, zinc was administered as zinc sulfate as part of standard parenteral nutrition (PN) for 15 days. After 15 days, patients were given oral zinc for a total of 3 months after injury. One-month mortality was higher in the control group (26% vs 12%, P = .09). Zinc supplementation was associated with an improved rate of neurologic recovery, as indicated by differences in Glasgow Coma Scale scores between the supplemented and control groups at day 15 (P = .005), day 21 (P = .02), and day 28 (P = .09).

Heyland and coworkers [55] performed a systematic review on zinc supplementation in critically ill patients. They included 4 randomized controlled trials. Zinc supplementation was associated with a trend toward reduction in mortality (RR, 0.63;

95% CI, 0.25–1.59; P = .33) and ICU length of stay (–0.35 days; 95% CI, –0.85–0.15, P = .17). However, 3 of the 4 included randomized controlled trials were performed in critically ill patients receiving a cocktail of micronutrients rather than zinc alone.

VITAMIN A

Vitamin A is an essential vitamin for many functions throughout the body, including vision, cellular proliferation and differentiation, immune function, reproduction, gene transcription, and antioxidant activity [66-68].

Vitamin A is the name of a group of fat-soluble retinoids and carotenoids [66-68]; α-, β-, and γ-carotene are retinol precursors, of which β-carotene is the most potent [69]. Retinol functions as the storage form of vitamin A and can be converted into other activated forms such as retinoic acid and retinal [66,69]. Vitamin A is absorbed by the small intestine. Intestinal cells can convert retinol precursors into retinol [65]. Retinol is mainly stored in the liver (around 50%-85%) [66,68]. Because retinol is the storage form of vitamin A, serum retinol concentrations are used as indication for vitamin A status. Serum levels are considered normal when >0.70 µmol/L (20 µg/dL) in healthy individuals [70]. Serum β-carotene levels are considered normal between 0.74 and 3.72 µmol/L (40–200 µg/dL) [71]. When excessive quantities of retinol are ingested, vitamin A toxicity can occur (acute intake of >0.2 g or chronic intake of >0.01 g) [72].

Vitamin A metabolism may alter in critically patients. In healthy individuals, vitamin A is excreted in bile [68,73]. However, during acute infection, significant amounts of retinol and retinol-binding protein (RBP) are excreted in urine [73]. Stephensen and coworkers [73] reported that one-third of patients with acute infection excreted >1.75 µmol/d, which is equivalent to 50% of the daily recommended allowance. Acute renal failure and fever were independently associated with excessive urinary retinol excretion [73,74].

Vitamin A deficiency can be caused by poor intake, increased use, or excretion but also be secondary to zinc deficiency [75] Zinc deficiency inhibits the synthesis of RBP in the liver and leads to lower concentrations of RBP and, thus, retinol in plasma [74]. Also, the conversion of retinol to retinal, the active form of vitamin A used by the eye, is dependent on retinol dehydrogenase, which uses zinc as a cofactor [75].

The antioxidant mechanism

Retinol and β-carotene both have antioxidant properties, but β-carotene has markedly more antioxidant potential than retinol [72,76]. β-Carotene is able to scavenge the hydroxyl radical, superoxide anion, and peroxynitrite [67]. Second, it

quenches singlet oxygen and thereby prevents lipid peroxidation [76]. β-Carotene can also bind to transition metals, preventing them from catalyzing the generation of radical oxygen species [76]. Moreover, β-carotene prevents oxidation of retinol [77]. Both retinol and β-carotene act as chain-breaking antioxidants in the process of lipid peroxidation [76]. However, this antioxidant activity is only seen at low partial pressures of oxygen (<20 kPa). At higher oxygen pressures, carotenoids and retinoids lose their chain-breaking potential and instead show an autocatalytic, pro-oxidant effect [76]. Retinol also potentiates the antioxidant effects of ascorbic acid [78].

Vitamin A status in the critically ill

Vitamin A is a lipid-soluble compound, mainly stored as retinol in the liver [66,68]. However, the amount of retinol in serum is frequently used to determine vitamin A status [9,79-81].

Metnitz and coworkers [9] assessed plasma antioxidant and ROS levels in 8 patients with ARDS. The plasma level of retinol was 0.77 ± 0.20 μmol/L in patients with ARDS at the day of diagnosis and 1.19 ± 0.11 μmol/L in healthy controls. Retinol levels normalized within 6 days. β-Carotene plasma levels were 0.08 ± 0.02 μmol/L in patients with ARDS and 1.22 ± 0.22 μmol/L in healthy controls ($P < .001$). β-Carotene plasma levels remained low. Three studies evaluated antioxidant levels in patients with severe sepsis and septic shock at ICU admission and compared them with healthy controls. Retinol and β-carotene levels were significantly lower in patients with severe sepsis and septic shock compared with healthy controls [79-81]. Inadequate retinol levels were found in 65% and inadequate β-carotene levels in 74%–100% of septic patients, respectively [80,81].

Mecocci and coworkers [82] reported that in patients with adequate retinol levels, the conversion of carotenoids to retinol is reduced. This may explain why β-carotene levels are relatively lower than retinol levels in patients with vitamin A deficiency.

Vitamin A supplementation in the critically ill

Supplementation of vitamin A in critically ill patients seems indicated as vitamin A deficiency is common [9,79-81]. However, as β-carotene is a more potent antioxidant than retinol, one may argue that β-carotene should be supplemented in case of vitamin A deficiency [76]. Moreover, high doses of oral β-carotene are unlikely to lead to vitamin A toxicity because the metabolism is highly regulated. This is, however, in contrast with retinol, which is directly absorbed by the cells of the small intestine and may quickly accumulate when supplemented in high dosages [67,72,76].

Supplementation of vitamin A in the forms of retinol, β-carotene, or both has been frequently studied in critically ill patients as part of an antioxidant cocktail. One study, by Matos and coworkers [67], evaluated the effects of retinol monotherapy in 90 patients undergoing coronary bypass grafting surgery. Thirty patients were randomized to the intervention group and given 5000 IU of retinol daily for 21 days. No significant differences in serum retinol or β-carotene levels were found at baseline. After surgery, retinol and β-carotene levels were significantly higher in the supplemented group. A significant reduction in mortality (3.3% vs 8.3%) and ICU length of stay (4.6 vs 8.5 days) in the supplemented group compared with the control group was demonstrated. However, no difference in the duration of mechanical ventilation (2.1 vs 2.7 days) was observed. When the groups were split into those with adequate and inadequate zinc concentrations, a significant drop in pro-oxidant concentrations was observed in the patients with adequate zinc concentrations and vitamin A supplementation but not in those with zinc deficiency.

Corcoran and coworkers [77] assessed the association between changes in serum vitamin concentrations and mortality in critically ill patients. They measured the serum concentrations of β- and α-carotene of 67 patients at ICU admission and subsequently daily until discharge or death. At ICU admission, 41.8% of patients had adequate serum levels. Only 17.9% of patients retained adequate serum concentrations. However, no correlation was found between serum β- and α-carotene levels and mortality (P = .5).

VITAMIN C

Vitamin C, or ascorbic acid, is a water-soluble antioxidant and a cofactor for several enzymes [83]. Its functions include iron and folic acid metabolism, as well as the synthesis of collagen, cortisol, catecholamines, and carnitine [83,84]. Vitamin C is also found in high concentrations in leukocytes and can boost the immune system via several pathways [84,85].

Vitamin C is absorbed by the small intestine and renally excreted [86]. High intake of vitamin C results in a lower intestinal absorption rate [84,86]. High plasma concentrations lead to less tubular reabsorption [84]. Due to active transport, intracellular concentrations of vitamin C are 25- to 80-fold higher than plasma concentrations [87,88]. The highest concentrations are found in neuronal cells and leukocytes [85].

Plasma concentrations of vitamin C are considered normal at >23 μmol/L (0.40 mg/dL) in healthy individuals [85,86]. In critically ill patients, vitamin C metabolism may alter. Oxidative stress induces vitamin C transporter expression on cells, thereby promoting vitamin C transfer from plasma to the intracellular space [87,88].

The antioxidant mechanism

Vitamin C is a strong water-soluble antioxidant. It is able to limit the generation of ROS, directly scavenge ROS/RNS, and repair other oxidized scavengers [85].

Generation of ROS is limited by vitamin C through inhibition of NOX and iNOS. In an aqueous milieu, like in plasma, cells, and the fluid lining of the lungs, vitamin C is able to scavenge or quench superoxide, hydroxyl, peroxyl, and nitroxide radicals. In addition, vitamin C regenerates α-tocopherol from the α-tocopheroxyl radical in membranes and lipoproteins [85,89,90]. α-Tocopherol is the strongest lipid-soluble antioxidant essential for chain breaking of lipid peroxidation. Other oxidized scavengers such as glutathione and urate are also repaired by vitamin C. This, however, leads to generation of the ascorbyl radical, which is a weak pro-oxidant, but has replaced a potentially more damaging radical [85].

Vitamin C indirectly acts as an antioxidant by serving as a substrate for ascorbate peroxidase, which converts hydrogen peroxide into water [85]. Vitamin C also protects the endothelium against phagocyte adhesion and thereby prevents oxidative damage to the endothelium caused by ROS produced by those phagocytes [85].

Vitamin C status in the critically ill

Low circulating levels of vitamin C in critically ill patients have been reported by several investigators, particularly in sepsis and after cardiac arrest [9,80,91-94]. Plasma concentrations become low within 24 hours after injury, and concentrations of <10 μmol/L are described in critically ill patients despite administering of the daily recommended dose of vitamin C [83,95]. Low plasma concentrations are associated with inflammation, severity of organ failure, and mortality [96].

That low plasma concentrations of vitamin C reflect real deficiency and are associated with low intracellular concentrations is supported by the findings that urinary concentrations initially remain low despite high-dose IV supplementation [85]. Moreover, apart from low plasma concentrations, a significant fall in leukocyte vitamin C concentrations was found in patients after myocardial infarction [85,97].

Vitamin C deficiency in critically ill patients may be caused by insufficient intake, acute consumption because of oxidative stress, or increased loss [85].

Vitamin C supplementation in the critically ill

Because of vitamin C deficiency in critically ill patients and the association between deficiency and mortality, supplementation seems rather important. Daily recommended

dosages for healthy individuals are proven insufficient in critically ill patients [83,95]. Long and coworkers [86] found that only dosages of at least 3000 mg/d vitamin C increased serum concentrations in critically ill patients. Two trials were conducted in patients scheduled for cardiac surgery. Bjordahl and coworkers [98] studied 185 patients. Half of the patients received 2 g ascorbic acid by mouth the evening before surgery and 2 g/d by mouth or enteral tube for 5 days, while the others received standard care. There were no differences in ICU length of stay (3.7 vs 4.3, P = .155) or hospital length of stay (10.4 vs 11.7, P = .124). Sadeghpour and associates [99] studied 290 patients in a randomized placebo-controlled trial. The intervention group received 2 g ascorbic acid intravenously immediately before surgery, followed by 1 g by mouth or enteral tube for 4 days. Hospital length of stay was significantly different between the 2 groups (10.17 ± 4.63 days in the intervention group vs 12 ± 4.51 days in the placebo group, P = .01), while no difference in ICU length of stay was found.

Fowler and associates [100] investigated the effects of vitamin C monotherapy in patients with severe sepsis. They compared 2 different doses of IV ascorbic acid (50 mg · kg−1 · 24 h−1 and 200 mg · kg−1 · 24 h−1) with placebo. Plasma ascorbic acid levels in all septic patients at enrollment were subnormal. Ascorbic acid levels in the placebo group fell from 20.2 (11–45) μM at entry to 15.6 (7–27) μM on study day 4. Ascorbic acid levels increased 20-fold in the low-dose treatment group from 16.7 (14–28) μM at baseline to 331 (110–806) μM on day 4. Ascorbic acid levels increased dramatically in patients with high-dose treatment from 17.0 (11–50) μM at baseline to 3082 (1592–5722) μM on day 4. Patients receiving ascorbic acid had significant reductions in SOFA scores vs no reduction in placebo patients. The 28-day mortality was lower in patients randomized to the low-dose vitamin C group (38.1%) vs the high-dose vitamin C group (50.6%) and the placebo group (65.1%). There were no differences in ICU length of stay or ventilator-free days between the 3 groups.

VITAMIN E

Vitamin E is the name of a group of lipid-soluble tocopherols and tocotrienoles of which α-tocopherol is the most biologically active [101,102]. Antioxidant activity is the most important function of vitamin E, but other functions include providing membrane stability and maintenance of an appropriate immune response to infection [103,104]. α-Tocopherol is mainly found incorporated in the cell membrane. The antioxidant activity of α-tocopherol is localized to the head of the molecule, whereas the tail is important for rapid uptake and localization within the cell membrane [105].

Because vitamin E is a lipid-soluble vitamin, the bioavailability depends on lipid metabolism. Vitamin E is absorbed by the intestine and transported to the liver via the lymphatic system in chylomicrons. The chylomicrons are broken down in the

liver, and α-tocopherol is bound to α-tocopherol transfer protein and secreted into the bloodstream [103,104]. Whether vitamin E metabolism changes in critical illness is unclear. In healthy patients, plasma α-tocopherol levels are considered normal at >11.5 µmol/L (4.95 mg/mL) in case of normal levels of serum lipids [106].

The antioxidant mechanism

α-Tocopherol is considered the most important lipid-soluble antioxidant in cell membranes [89,101,105,107]. It protects cell membranes from lipid peroxidation by breaking the lipid radical chain reaction [88,101,105,107]. It also acts as a direct scavenger of superoxide and the hydroxyl radical [101,105,107]

Vitamin E status in the critically ill

α-Tocopherol is a lipid-soluble compound, mainly present in cell membranes. However, α-tocopherol status is usually assessed by measurement in plasma. The correlation of plasma levels with tissue levels is not clearly established. Moreover, plasma concentrations of α-tocopherol are strongly associated with their carrier lipids (cholesterol and triglycerides), and thus changes in lipid status influence α-tocopherol status. It is proposed that measurement of red blood cell α-tocopherol concentrations will prove a more reliable indicator of α-tocopherol tissue status. In animal studies, a good correlation between red blood cell and tissue concentrations has been found [108]. Many investigators have reported decreased α-tocopherol levels in critically ill patients [80,91-94]. However, when standardized for changes in plasma lipids, no decrease or even an increase in α-tocopherol plasma levels was found [105,108]. One study reported similar red blood cell α-tocopherol concentrations corrected for hemoglobin in critically ill patients compared with healthy controls [108].

Corcoran and coworkers [77] assessed the association between changes in serum vitamin concentrations and mortality in critically ill patients. They measured the serum concentrations of α-tocopherol of 62 patients at ICU admission, then daily until discharge or death. At ICU admission, 58.1% had adequate serum levels and 51.6% retained adequate levels. No correlation was found between serum α-tocopherol levels and mortality (P = .23).

Vitamin E supplementation in the critically ill

Like other antioxidants, vitamin E supplementation in critically ill patients is mainly studied as part of antioxidant cocktails. Few have investigated the effects of vitamin E monotherapy.

Two studies evaluated the effects of vitamin E supplementation in a perioperative setting. Bartels and coworkers [102] administered an IV solution containing 1800 IU vitamin E or placebo to 68 patients the day before elective partial liver resection. ICU length of stay was significantly shorter in the vitamin E group, but no differences in hospital length of stay were found. Serum vitamin E concentrations increased after administration of vitamin E infusion and declined in both treatment groups after surgery. However, vitamin E deficiency was prevented in the vitamin E group. Lassnigg and associates [101] administered 4 IV doses of 270 mg vitamin E or placebo to patients between 16 hours before and 48 hours after elective cardiac surgery. Infusion of vitamin E caused normalization of vitamin E plasma concentrations during and after surgery but had no effect on the Simplified Acute Physiology Score II (SAPS II), ICU length of stay, hospital length of stay, or 30-day mortality.

A study comparing serum α-tocopherol levels in healthy volunteers and patients with ARDS after oral/enteral supplementation of 1 g/d α-tocopherol showed doubled serum levels in healthy controls after only 1 dose but no or only a mild increase in serum levels in patients with ARDS after 5–10 days [109].

The effect of vitamin E on the production of superoxide was evaluated ex vivo in venous blood of ICU septic and nonseptic patients. The superoxide production was significantly higher, and the ratio of vitamin E to lipids was significantly decreased in septic patients. Vitamin E induced an ex vivo inhibition of superoxide production of 20% [110].

ANTIOXIDANT COCKTAILS

Several antioxidant cocktails have been studied in critically ill patients. The combination of vitamin C and E has been most extensively studied.

Vitamin C and E combination therapy

Because ascorbic acid regenerates α-tocopherol, combination therapy of these antioxidant vitamins may be more beneficial than monotherapy with either one alone. A randomized, double-blind, placebo-controlled trial was performed by Crimi and coworkers [107] among 216 ICU patients. In total, 105 patients received enteral supplementation with ascorbic acid (500 mg/d) and α-tocopherol (400 IU/d) for 10 days. A significant reduction in 28-day mortality was observed in the intervention group (45.7% vs 67.5%, $P < .05$). In addition, the duration of mechanical ventilation was shorter (6.2 vs 8.9 days, $P = .05$). No significant differences were observed between the length of hospital stay, incidence of ARDS, and incidence of multiorgan dysfunction. Another randomized, double-blind, placebo-controlled

trial was conducted by Howe and associates [111] in 72 critically ill patients. The intervention group received ascorbic acid (1000 mg/8 hours) and α-tocopherol (1000 IU/8 hours) for 28 days or until cessation of mechanical ventilation. Duration of mechanical ventilation was significantly reduced (mean 10 vs 19 days, P = .02). All-cause mortality (33% vs 45%), length of ICU stay (12.9 vs 19.1 days), and hospital length of stay (21.1 vs 22.6 days) were not significantly different between groups. Nathens and coworkers [112] performed a randomized, prospective trial in 595 patients. They showed that α-tocopherol and ascorbate reduced the development of pulmonary morbidity (ARDS, pneumonia) by 19% (95% CI, 10%–40%) and organ failure by 57% (95% CI, 4%–81%) and showed a trend toward a reduction in 28-day mortality in a cohort of severely ill surgical patients, the majority of whom were trauma patients. These benefits translated into a reduction of duration of mechanical ventilation and ICU length of stay. No adverse effects attributable to the antioxidants were observed. Specifically, administration of high-dose ascorbate (1000 mg ascorbic acid given intravenously tid for the shorter of the duration of ICU stay or 28 days or α-tocopherol 1000 IU tid per nasogastric or orogastric tube) did not increase the risk of renal failure or coagulopathy. A limitation of this trial was the lack of a placebo and blinding, potentially introducing bias into the evaluation of the end points.

LARGE RANDOMIZED CONTROLLED TRIALS AND RECENT META-ANALYSIS

In the most recent meta-analysis by Manzanares and coworkers [113] on 21 RCTs including 2531 patients treated with antioxidant trace elements and/or vitamins vs placebo (via enteral, parenteral, or both routes), it was demonstrated that these antioxidants may significantly decrease mortality (RR, 0.82; 95% CI, 0.72–0.93; P = .002) and reduce mechanical ventilation days (weighted mean difference [WMD], −0.67; 95% CI, −1.22 to −0.13; P = .02) and are associated with a trend toward reduced infectious complications (RR, 0.88; 95% CI, 0.76–1.02; P = .08). The treatment effect may be greatest in patients with greater severity of illness, defined as a lacebo group mortality of at least 10% (RR, 0.79; 95% CI, 0.68–0.92; P = .003).

In addition, the recently updated ASPEN/SCCM guidelines state that antioxidant vitamins and trace minerals may improve critically ill patient outcome. They analyzed 15 trials, including 1572 patients, and found that antioxidant and trace element supplementation was associated with a significant reduction in overall mortality (RR, 0.8; 95% CI, 0.70–0.92; P = .001). However, no significant reduction in infectious complications, ICU or hospital length of stay, and duration of mechanical ventilation was found. The ASPEN and SCCM organizations value the quality of evidence to support supplementation of antioxidants and trace elements as low; however, both

organizations still recommend its use in critically ill patients as supplementation seems to be safe. However, the MetaPlus trial and other trials published after 2011 were not included. Therefore, this recommendation may be outdated as only studies before 2014 were evaluated [49].

Only 4 randomized controlled studies studying antioxidants in critically ill patients with at least 300 included patients are available. The study by Nathens and coworkers [112] on vitamin C and E combination therapy has been discussed earlier in this article.

SIGNET Trial

In the Scottish Intensive care Glutamine or seleNium Evaluative Trial (SIGNET), 502 adult critically ill patients requiring PN were treated with either PN alone or supplemented with parenteral glutamine (20.2 g/d), selenium (500 μg/d), or both for up to 7 days [114].

Selenium supplementation did not significantly affect the primary end point of patients developing a new infection (126/251 vs 139/251; OR, 0.81; 95% CI, 0.57–1.15), except for those who had received ≥5 days of supplementation (OR, 0.53; 95% CI, 0.30–0.93). This may be seen as a positive outcome, but per protocol analyses are valued less important than the intention-to-treat analysis, which was negative for the primary end point. Six-month mortality was not significantly different for selenium (107/251 vs 114/251; OR, 0.89; 95% CI, 0.62–1.29). Length of stay, days of antibiotic use, and modified SOFA score were not significantly affected by selenium supplementation.

REDOXS Trial

In the REducing Deaths due to OXidative Stress (REDOXS) blinded 2-by-2 factorial trial, 1223 critically ill adults in 40 ICUs in Canada, the United States, and Europe who had multiorgan dysfunction and were receiving mechanical ventilation were randomized to receive supplements of glutamine, antioxidants, both, or placebo. Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally [115]. The primary outcome was 28-day mortality. Antioxidants had no effect on 28-day mortality (30.8% vs 28.8% with no antioxidants; adjusted OR, 1.09; 95% CI, 0.86–1.40; P = .48) or any other secondary end point. There were no differences among the groups with respect to serious adverse events (P = .83).

In a post hoc analysis, Heyland and coworkers [116] showed that the 28-day mortality rates in the placebo, glutamine, antioxidant, and combination arms were 25%, 32%, 29%, and 33%, respectively. After adjusting for prespecified baseline covariates, the

adjusted OR of 28-day mortality vs placebo was 1.5 (95% CI, 1.0–2.1; P = .05), 1.2 (95% CI, 0.8–1.8; P = .40), and 1.4 (95% CI, 0.9–2.0; P = .09) for glutamine, antioxidant, and glutamine plus antioxidant arms, respectively. It is noteworthy that alanyl-glutamine dipeptide, a synthetic drug, was administered "off label" in this study and at much higher doses than the manufacturers and regulatory agencies recommend. In addition, the general ICU study population included patients with diminished renal or hepatic failure, although the product literature advises against its use in patients with renal and hepatic failure. In the post hoc subgroup analysis, both glutamine and antioxidants appeared most harmful in patients with baseline renal dysfunction. No subgroups suggested reduced mortality with supplements.

MetaPlus trial

The MetaPlus study, a randomized, double-blind, multicenter trial, was conducted from February 2010 through April 2012, including a 6-month follow-up period in 14 ICUs in the Netherlands, Germany, France, and Belgium [95]. A total of 301 adult patients who were expected to be ventilated for >72 hours and to require enteral nutrition (EN) for >72 hours were randomized within 48 hours of ICU admission to high-protein EN enriched with immune-modulating nutrients (IMHP: glutamine, ω-3 fatty acids, selenium, and the antioxidant vitamins C, E, and zinc; n = 152) vs standard high-protein EN (HP; n = 149) continued during the ICU stay for a maximum of 28 days and included in an intention-to-treat analysis, performed for the total population as well as predefined medical, surgical, and trauma subpopulations.

There were no statistically significant differences in incidence of new infections according to the Centers for Disease Control and Prevention (CDC) definitions between the groups: 53% (95% CI, 44%–61%) in the IMHP group vs 52% (95% CI, 44%–61%) in the HP group (P = .96). No statistically significant differences were observed in other end points, except for a higher 6-month mortality rate in the medical subgroup: 54% (95% CI, 40%–67%) in the IMHP group vs 35% (95% CI, 22%–49%) in the HP group (P = .04), with a hazard ratio of 1.57 (95% CI, 1.03–2.39; P = .04) adjusted for age and Acute Physiology and Chronic Health Evaluation II (APACHE II) score comparing the groups. Thus, IMHP compared with HP did not improve infectious complications or other clinical end points and may be harmful as suggested by increased adjusted mortality at 6 months. These findings do not support the use of IMHP nutrients in these patients. Due to the design, it is difficult to conclude whether the increased mortality effects in medical patients are due to the glutamine dipeptide, fish oil, or antioxidant components of the IMHP feed or due to toxic by-products generated by interactions between the supplements.

DISCUSSION

While reviewing the literature on antioxidant vitamins and trace elements, we have encountered divergent outcomes with respect to the impact on plasma levels, biomarkers, intermediate or surrogate end points, and clinically relevant end points. Results vary from no effect on outcomes to clear benefits, but also increased harm has been reported. These observations may, at least in part, be due to 1 or more of the following (confounding) aspects involved.

For some antioxidant vitamins and trace elements, we lack rigorous information on the (normal) status of these micronutrients in critically ill patients and their association with outcomes such as morbidity and mortality. If these data are lacking or are imprecise with respect to cutoff levels, we can question whether low admission levels really reflect deficiency and are associated with increased morbidity and mortality.

To make matters more complex, in case of an association between low plasma antioxidant levels and outcome, is this due to a more causal inference or just representing an epiphenomenon indicating the severity of disease? Plasma micronutrient levels can be low due to losses through body fluids, redistribution, altered protein binding, dilution secondary to fluid resuscitation, and inadequate intake. Low plasma levels therefore do not per se indicate low total body stores of the micronutrient tested or supplemented. During redistribution or incorporation of antioxidants (as, for example, selenium is incorporated in selenoproteins), it is not unlikely that low plasma levels indicate an effective response to oxidative stress. In other situations, a reduced antioxidant status may be essential (ROS are used for bacterial killing), and as such, low antioxidant levels may be seen as part of an adaptive response.

Moreover, we lack well-documented information on dose-response relations of antioxidants in critically ill patients. In other words, if we aim to normalize plasma levels, what are the optimal dosages to achieve that target? From the MetaPlus study, we learned that the antioxidant micronutrients supplemented through enriched enteral feeds did increase the plasma levels of some of those micronutrients significantly after 4 days, but this was not observed in all micronutrients. Although in some patients, a significant increase was noted, all plasma levels remained below the normal reference values despite supplementation. Were the dosages used then too low? Could the delivery through enriched EN have played a role? What is the biological availability of these antioxidants through enteral delivery compared with parenteral supplementation? Many basic questions have not been answered at present. And could interactions between antioxidants have reduced the bioavailability as has been described for enteral vitamin C and selenium?

Most studies with clinical end points do not report baseline and follow-up plasma levels of the studied antioxidant vitamins and trace elements. This makes interpretation hard, as there is no proof of concept with respect to adherence to the intervention, knowledge of deficiency severity, or absence of low levels in the study groups. Furthermore, the response to the intervention in terms of impact on plasma levels then is lacking. This may hamper extrapolation of observations and reduces the external validity. Moreover, rarely effects on total antioxidant status or downstream biomarkers have been addressed in clinical studies among critically ill patients. This may be relevant as for selenium, it has been shown that only high-dose selenium supplementation did incur relevant upregulatory effects on the glutathione system in the critically ill [32,36].

With respect to healthy persons, we know the normal status of antioxidant levels in blood and how to keep these levels into the normal range by food intake with consumption of the RDAs. The exact RDAs for antioxidants, trace elements, and vitamins in ICU patients are not known. Many patients have low admission plasma levels. During ICU stay, this may worsen, as RDAs are only available in 1500 mL (about 1500 kcal) of EN, and many critically ill patients have lower actual intakes. In PN, trace elements and vitamins always have to be added.

Therefore, it seems logical to at least supplement RDA levels during critical illness, but it is probable that higher dosages should be used to confer beneficial effects. However, high-dose supplementation may induce hypervitaminosis and antioxidant toxicity [117,118].

A post hoc analysis of the REDOXS trial showed a significant association of harm between renal failure and selenium supplementation, among other antioxidants. This may suggest that inefficient excretion may lead to accumulation of antioxidants and more specific selenium, potentially inducing such toxicity that it may increase long-term mortality after supplementation. This should caution use of high-dose antioxidant vitamins and trace elements in patients with renal and/or hepatic dysfunction. As the antioxidant vitamins and trace elements supplementation association curve with outcome most likely will be U-shaped and probably will not overlap exactly for individual antioxidants, combining the optimal supplementation dosages is essential. We found that supplementation of a single vitamin or antioxidant may confer less or no benefits in case another is deficient. Metabolic pathways are functioning optimally when substrates and cofactors are available in optimal combinations. Therefore, it is likely that these micronutrients cannot be studied like typical pharmaceuticals using a single intervention and a placebo. Or at least it is plausible that supplementation with combined micronutrients may lead to other outcomes than single interventions.

Last, there is an ongoing debate whether it is important to mitigate the inflammatory response in critical illness as many if not all anti-inflammatory intervention trials in ICU patients were negative over the past decades. It has been observed that most ICU patients do not die early but late during the immunoparalysis phase of illness with persisting organ dysfunction and nosocomial infections. Timing and duration of supplementation therefore are essential. Some antioxidants have been shown to reduce inflammatory response by blunting the proinflammation. This may be a wrong approach when an immunoparalysis phenotype is dominant.

Finally, studies in ICU patients are heterogeneous with respect to the patients' diagnoses, comorbidities, and severity of illness, preexisting nutrition status, refeeding risk, and medications affecting micronutrient levels. In large randomized trials, these aspects can be partially circumvented, but residual confounding always persists. Furthermore, the relevant baseline factors are not always clearly reported, and outcome is not only affected by antioxidant vitamins and trace elements but also can be seen as a summation of all therapeutic interventions (eg, lung-protective ventilation in ARDS, early nutrition, timing and adequacy of antibiotics in case of infections). It is very likely that the impact of micronutrients plays a limited role in the outcome of the critically ill. Therefore, the signal-to-noise ratio could be a strong confounding factor to identify the real benefits of antioxidant vitamins and trace elements supplementation.

FUTURE PERSPECTIVES

Over the past 15 years, various research groups have investigated antioxidant vitamins and trace elements supplementation in critically ill patients. This has markedly added to our knowledge, but the number of large well-designed studies is limited and several questions remain unanswered.

First, it is unclear when, how, and where to measure antioxidant and pro-oxidant markers to get the most accurate indication of the actual antioxidant status in critically ill patients. Second, it is not clear what the target level of antioxidants should be in these patients. Should we aim for certain biochemical targets like restoring plasma and tissue levels? What dosages of supplements should be used to achieve these targets? And how do these biochemical targets relate to clinical end points such as morbidity and mortality?

Moreover, it should be considered that by supplementation of micronutrients, we intend to strengthen the antioxidant defense. However, most antioxidant activity is performed by antioxidant enzymes and not by antioxidant vitamins and trace elements. Therefore, micronutrient supplementation may play a limited role in clinical outcome.

Future research should focus on defining the “normal” antioxidant status and the role of antioxidant vitamins and trace elements to maintain this delicate balance during critical illness and to find optimal combinations and dosages for antioxidant vitamins and trace elements in EN and PN administration.

When the RDAs for healthy persons are considered a relevant target to aim for during critical illness, it is important to notice that many patients receiving EN and all patients taking PN do not meet these targets without supplementation, and potential deficiency may emerge. Following this reasoning, low-dose multivitamin and trace elements supplementation may be justified and seems to be safe for all critically ill patients until enteral or oral feeding can meet the demand.

Since strong evidence that pharmacological supplementation with antioxidant vitamins and trace elements improves outcome is not available, and some studies even have shown harm, at present, high-dose supplementation cannot be recommended.

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8

CHAPTER

Micronutrient deficiencies in critical illness

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ABSTRACT

Background & aims

Low micronutrient levels in critical illness have been reported in multiple studies. Because of the antioxidant properties of various micronutrients, micronutrient deficiency may augment oxidative stress in critical illness. However, it remains unclear whether micronutrient concentrations in ICU patients are different from those in healthy age-matched controls. It is also unclear whether micronutrient deficiency develops, worsens, or resolves during ICU admission without supplementation.

Methods

We prospectively studied a cohort of adult critically ill patients. Micronutrient levels, including selenium, β-carotene, vitamin C, E, B1 and B6 were measured repeatedly during the first week of ICU admission. We compared the micronutrient concentrations at ICU admission to those of healthy age-matched controls. In addition, associations between micronutrient concentrations with severity of illness, inflammation and micronutrient intake were investigated.

Results

Micronutrient blood concentrations were obtained from 24 critically ill adults and 21 age-matched healthy controls. The mean micronutrient levels at admission in the ICU patients were: selenium 0.52 μmol/l, β-carotene 0.17 μmol/l, vitamin C 21.5 μmol/l, vitamin E 20.3 μmol/l, vitamin B1 129.5 nmol/l and vitamin B6 41.0 nmol/l. In the healthy controls micronutrient levels of selenium (0.90 μmol/l), β-carotene (0.50 μmol/l), vitamin C (45 μmol/l) and vitamin E (35.5 μmol/l) were significantly higher, while vitamin B1 (122 nmol/l) and B6 (44 nmol/l) were not significantly different between patients and controls. Selenium, vitamin B1 and vitamin B6 levels remained stable during ICU admission. Vitamin C levels dropped significantly until day 5 ($p < 0.01$). Vitamin E and β-carotene levels increased significantly on days 5-7 and day 7, respectively ($p < 0.01$). Micronutrient levels were not associated with severity of illness, CRP or micronutrient intake during the admission.

Conclusions

At admission, ICU patients already had lower plasma levels of selenium, β-carotene, vitamin C and vitamin E than healthy controls. Vitamin C levels dropped significantly during the first days of ICU admission, while β-carotene and vitamin E levels increased after 5-7 days. No association between micronutrient levels and severity of illness, C-reactive protein (CRP) or micronutrient intake was found. Progressive enteral tube feeding containing vitamins and trace elements does not normalize plasma levels in the first week of ICU stay. This was a hypothesis generating study and more investigation in a larger more diverse sample is needed.

INTRODUCTION

Low blood micronutrient levels in critical illness have been reported in multiple studies, possibly indicating micronutrient deficiencies. Because of the antioxidant properties of various micronutrients, these micronutrient deficiencies may augment oxidative stress in critical illness. Over the past 20 years, oxidative stress-mediated cell damage has been recognised to play a fundamental role in the pathophysiology of various critical illnesses such as acute respiratory distress syndrome (ARDS), ischemia-reperfusion injury, and multiple organ dysfunction syndrome (MODS) [1].

If micronutrient deficiency worsens oxidative stress, micronutrient supplementation may be beneficial in critical illness. However, studies investigating micronutrient supplementation effects in intensive care unit (ICU) patients show conflicting results [2,3]. This is further complicated because most studies evaluated micronutrient cocktails rather than the effect of a single nutrient. Aggregation of the results of these heterogeneous studies suggest a reduction of overall mortality [3]. Recent guidelines, therefore, recommend micronutrient supplementation in ICU patients up to 5-10 times the dietary recommended intake (DRI) in healthy adults [4], but the evidence is limited.

In addition, it remains unclear 1) whether low micronutrient levels in critical illness are different from levels in healthy matched controls and 2) what the course of micronutrient levels is during ICU admission in the absence of supplementation. Due to the large differences in micronutrient levels that have been described in healthy people [5], as well as decreasing micronutrient levels with increasing age [6], it is essential to know whether micronutrient levels in critical illness correspond with micronutrient levels of healthy controls of the same age and population, to determine whether they are genuinely lower in patients. Furthermore, it is crucial to know the natural course of micronutrient levels in critically ill patients as this may guide the investigation and application of possible therapeutic interventions.

We performed a prospective cohort study in critically ill patients before implementing the current nutrition guidelines [4,7]. As active micronutrient supplementation was not the standard of care, patients only received micronutrients from the standard composition of enteral nutrition (EN). This study determined the serum micronutrient levels of selenium, β-carotene, vitamin C, vitamin E and blood levels of vitamin B1 and B6 during the first week of ICU admission and compared these with the micronutrient concentrations of healthy age-matched controls. We also quantified a possible association between micronutrient levels and severity of illness, inflammation and enteral micronutrient intake during ICU admission.

MATERIALS AND METHODS

We performed a prospective observational study in critically ill patients. This study was performed in the mixed medical-surgical adult ICU of Gelderse Vallei Hospital Ede, The Netherlands between July 1st, 2002 and December 1st,2002. Patients were included when they were admitted to the ICU and were > 18 years of age. Exclusion criteria were chronic kidney failure (creatinine > 177 µmol/l, peritoneal or haemodialysis), chronic liver failure (portal hypertension, histologically proven hepatic cirrhosis or oesophageal varices), or receiving parenteral nutrition.

We asked 21 volunteers to participate in the control group. To recruit a control group with a similar age and dietary pattern as the patient group, relatives of the patient were asked to participate. If no relatives were available or did not agree to participate, patients with a similar age admitted to the general hospital wards without an underlying illness confounding micronutrient status were recruited. Volunteers were excluded when they had taken fortified foods or supplements in the previous 14 days.

The ethics committee of Gelderse Vallei Hospital (Ede, The Netherlands) and Wageningen University and Research (Wageningen, The Netherlands) approved the research protocol. All volunteers and patients, or in case of impaired consciousness, the patients' relatives, gave written informed consent.

Clinical management

Patients participating in the study received usual intensive care treatment. According to Gelderse Vallei Hospital-specific standard operational procedures and protocols, the team of physicians, ICU nurses and dieticians performed clinical management, including nutritional support. The Harris-Benedict formula was used to calculate daily energy requirements. No additional vitamins or trace elements supplementation other than enteral nutrition was performed. Our local protocol for enteral nutritional support included four types of standard enteral nutrition with a slightly different composition regarding proteins, fibers and micronutrients and total amount of energy. Changes from one type to another were never based on micronutrient concentrations in the patient nor on the amount of micronutrients in the enteral nutrition.

Sample size

The number of ICU patients needed to include in this pilot study was estimated at 21, based on a power calculation of the most variable vitamin, vitamin C (between-person-variation 15 %; power 0.90; α 0.05) [8].

Data collection

Baseline characteristics were obtained from a questionnaire (in both patients and volunteers) and the individual patient files. The characteristics assessed by questionnaire were medical history, weight, height, smoking status, alcohol consumption and use of medication and micronutrient supplementation. The patient characteristics obtained from the patient files included type and amount of feeding, daily fluid balance, transfusions (blood and plasma), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, C reactive protein (CRP), medications and micronutrient supplementation calculated from nutrition intake. Collected data were de-identified and stored on a secure hospital computer.

Laboratory tests

In patients, blood was sampled at 0, 12, 24, 36, 48, 72, 96, 120 and 144 hours after ICU admission. The micronutrients selenium, ß-carotene and vitamins C and E were measured in serum on every interval. The vitamins B1 and B6 were determined in haemolysed EDTA blood at the first, fourth and seventh time point. Besides measurements of the micronutrients in blood in ICU patients, other laboratory measurements were determined. All measurements are shown in supplement A. In the control group, only one sample was drawn to assess micronutrient status.

Data analysis and statistical considerations

Descriptive data are reported as means and standard deviation (SD) or median and interquartile range (IQR) in case of skewed distributions, or as frequencies and percentages when appropriate. A p-value <0.01 was considered statistically significant.

The primary analysis comparing patient baseline micronutrient levels to the controls was performed using an independent-samples t-test in case of a normal distribution and a Mann-Whitney U test in case of non-normality.

The course of micronutrient levels during ICU admission was shown graphically. Differences between time points were analysed separately for each micronutrient through mixed model regression analysis, taking into account the within-subjects' correlation. An autoregressive covariance was used, and the model was adjusted for multiple comparisons by Bonferroni correction.

We also evaluated the associations of SOFA-scores, CRP, and micronutrient intakes in the ICU on micronutrient levels during ICU admission. These associations were analysed separately for each micronutrient through mixed model regression analysis,

taking into account the within-subjects' correlations. The dependent variable was divided by median split.

IBM SPSS Statistics for Windows, version 25.0 (IBM Corporation, released 2017, Armonk, New York, USA) was used to perform analyses.

RESULTS

During the study period, 106 patients were admitted to the ICU, of whom 24 were included according to the in- and exclusion criteria. Besides, 21 volunteers were willing to participate in the control group; three were excluded because of vitamin supplement intake in the past 14 days.

Baseline characteristics are shown in Table 1. Full baseline laboratory results are shown in supplement B. The median ages were 65.5 and 66.0 years in the patient and control groups, respectively. Most patients and controls were male (66.7% and 54.6%). In the ICU group, median SOFA and APACHE II scores were 7 and 20, respectively. Twelve patients were admitted because of medical reasons (50%) and twelve because of emergency or (complicated) elective surgery (50%). The in-hospital mortality was 37.5%.

Table 1| Baseline characteristics

		ICU patients (n=24)	**Controls (n=18)**
Gender (female)	N (%)	8 (33.3)	8 (44.4)
Age (years)	Median [IQR]	65.5 [62.5 – 71.8]	66 [61 – 72]
BMI on admission (kg/m2)	Median [IQR]	25.1 [22.0 – 26.9]	25.4 [24.1 -29.3]
Malnourished (<18.5)	N (%)	1 (4.2)	0 (0)
Normal (18.5 – 24.9)	N (%)	10 (41.7)	7 (38.9)
Overweight (25 – 29.9)	N (%)	11 (45.8)	9 (50.0)
Obese (30 – 34.9)	N (%)	2 (8.3)	2 (11.1)
Morbidly obese (>35)	N (%)	0 (0)	0 (0)
Admission type			
Medical	N (%)	12 (50.0)	NA
Surgical	N (%)	12 (50.0)	NA
Smoking status (yes)	N (%)	10 (45.5)*	2 (11.1)
Alcohol consumption (yes)	N (%)	13 (61.9)*	15 (83.3)
Nutrition in ICU			
Enteral nutrition	N (%)	22 (91.7)	NA
Parenteral nutrition	N (%)	0 (0)	NA
No nutrition	N (%)	2 (8.3)	NA
SOFA score on admission	Median [IQR]	7 [4 – 9.75]	NA

		ICU patients (n=24)	Controls (n=18)
APACHE II score on admission	Median [IQR]	20 [15.8 - 28.5]	NA
In-hospital mortality	N (%)	9 (37.5)	NA
Mechanical ventilation	N (%)	24 (100)	NA
ICU length of stay	Median [IQR]	5 [3 – 13]	NA

Abbreviations: ICU: intensive care unit; IQR: interquartile range; n: number; SD: standard deviation; SOFA: sequential organ failure assessment; APACHE: Acute Physiology And Chronic Health Evaluation; NA: not applicable.

Primary outcome

Baseline micronutrient levels in ICU patients and controls are shown in Table 2. Selenium, β-carotene, vitamin C and vitamin E levels were significantly lower in ICU patients than in controls ($p < 0.001$). Vitamin B1 and B6 levels were not significantly different in ICU patients and controls.

Table 2| Baseline micronutrient levels in ICU patients and controls

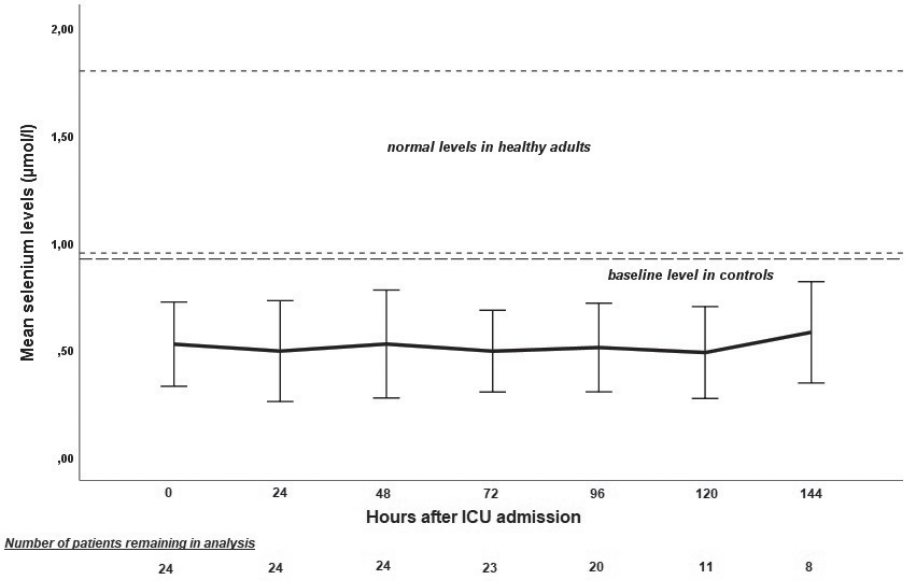
Micronutrient	ICU	Controls	p-value
Selenium (µmol/l)	0.52 ± 0.20	0.90 ± 0.16	<0.0001
b-Carotene (µmol/l)	0.17 [0.08-0.26]	0.50 [0.25-0.57]	<0.0001
Vitamin C (µmol/l)	21.5 [8.5-32.0]	45 [28.8-64.8]	0.001
Vitamin E (µmol/l)	20.3 ± 8.3	35.5 ± 8.3	<0.0001
Vitamin B_1 (nmol/l)	130 [107-169]	122 [105-132]	0.383
Vitamin B_6 (nmol/l)	41 [37-56]	44 [41-61]	0.497

Note: Results are depicted as mean ± standard deviation or median [interquartile range] as appropriate.

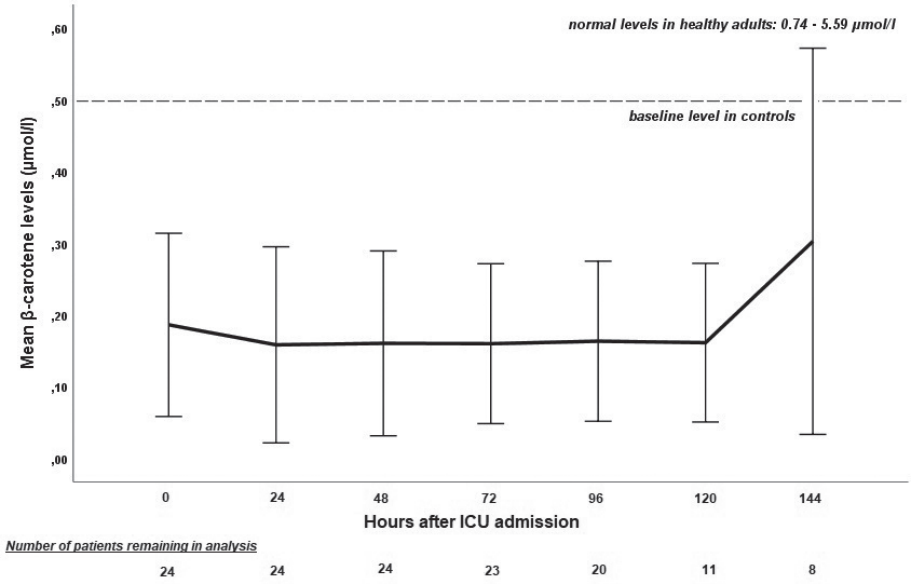
Course of micronutrient levels during ICU admission

Micronutrient levels during the first week of ICU admission are shown in figure 1A-1F. Selenium levels remained stable and low. β-carotene levels remained below normal values but increased significantly on day 7 ($p < 0.01$). Vitamin C levels remained below normal values and dropped significantly from day 1 until day 5 ($p < 0.01$) of ICU admission. Vitamin E levels remained within normal values and increased significantly on days 5-7 ($p < 0.01$). Vitamin B1 and vitamin B6 levels remain stable and within the normal range.

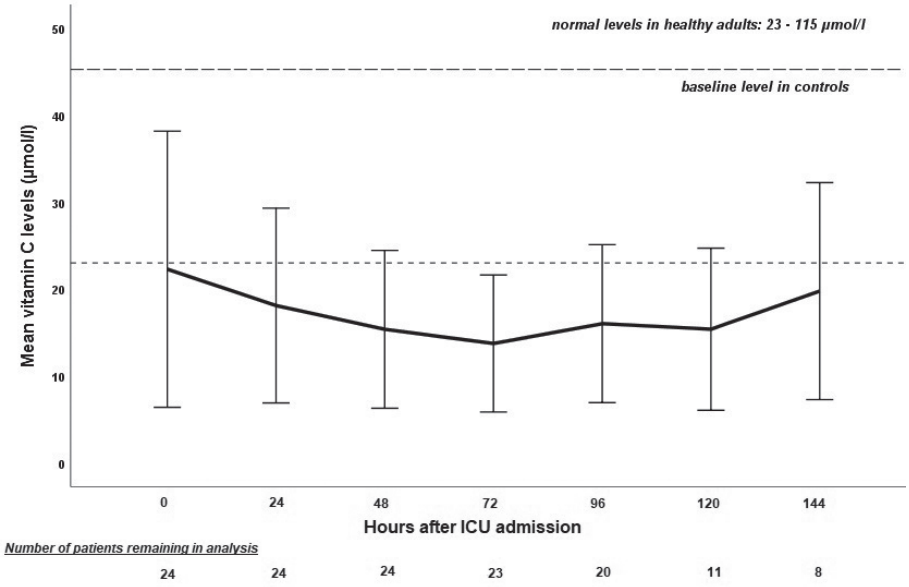
Figure 1| Mean micronutrient levels during ICU admission
A Selenium



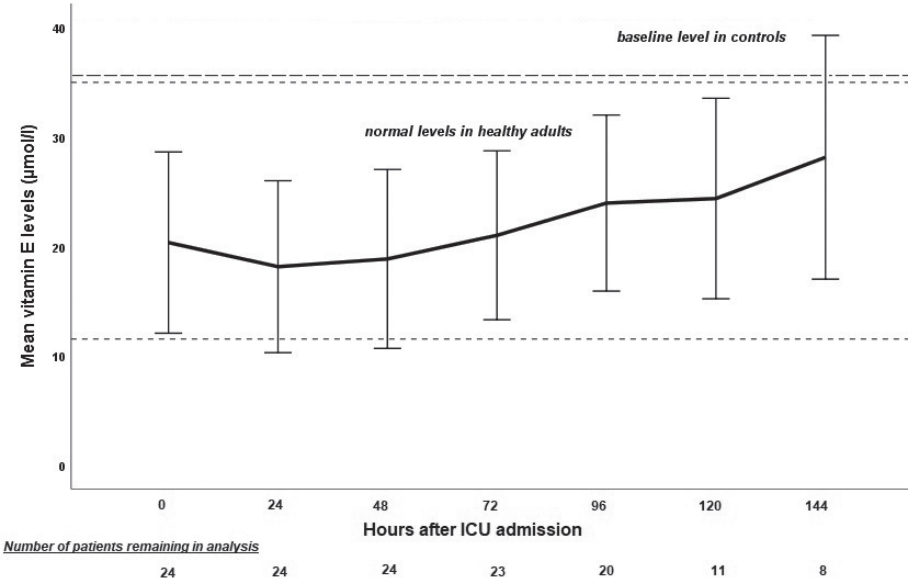
B β-carotene



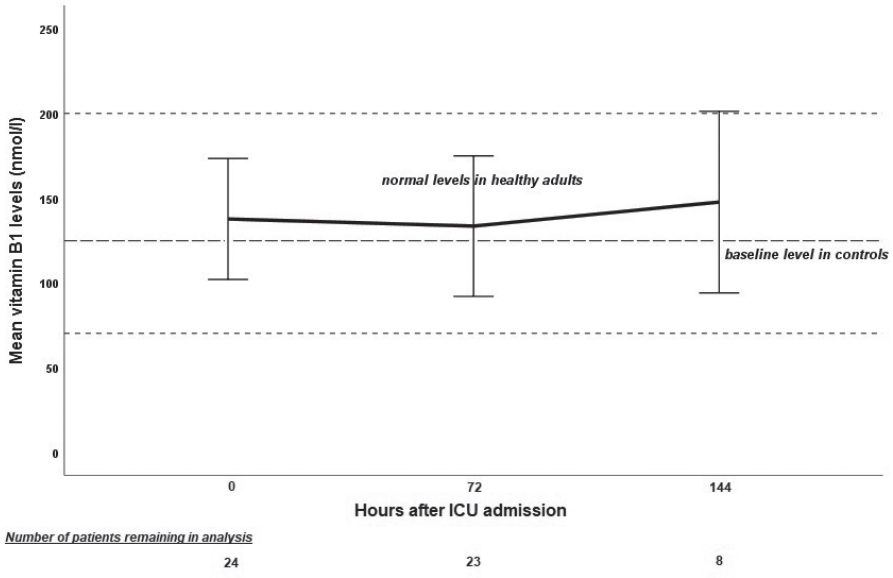
C Vitamin C



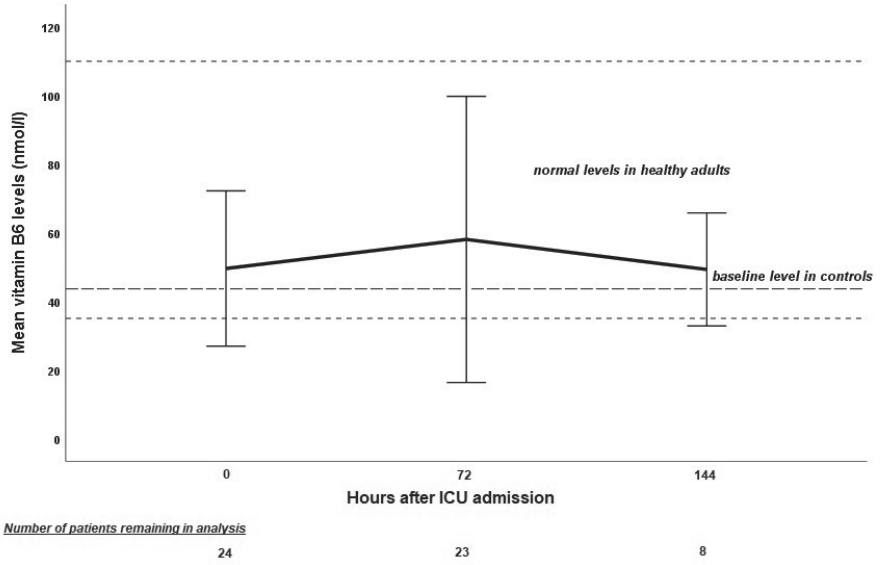
D Vitamin E



E Vitamin B1



F Vitamin B6

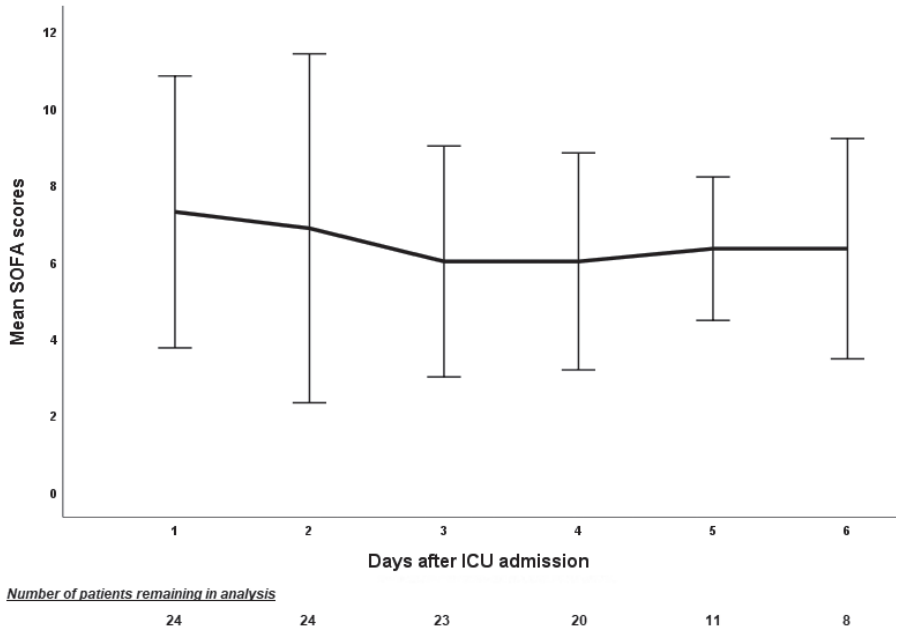


Abbreviations: ICU: intensive care unit. **Note:** error bars represent ± one standard deviation.

Effect of severity of illness on micronutrient levels

Severity of illness was assessed through daily SOFA scores (Fig 2). No significant associations were found between micronutrient levels and SOFA scores (selenium p=0.562, β-carotene p=0.155, vitamin C p=0.528, vitamin E p=0.044).

Figure 2| Mean SOFA scores during ICU admission

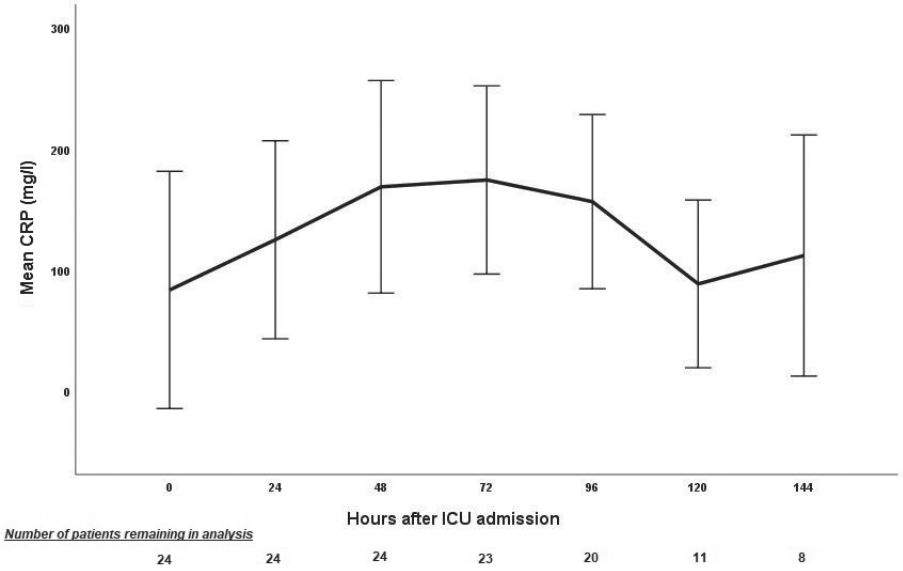


Abbreviations: SOFA: sequential organ failure assessment, ICU: intensive care unit.

Effect of CRP on micronutrient levels

CRP levels during ICU admission are shown in figure 3. No significant associations between micronutrient levels and CRP were found (selenium p=0.400, β-carotene p=0.377, vitamin C p=0.064, vitamin E p=0.552,).

Figure 3| Mean CRP levels during ICU admission

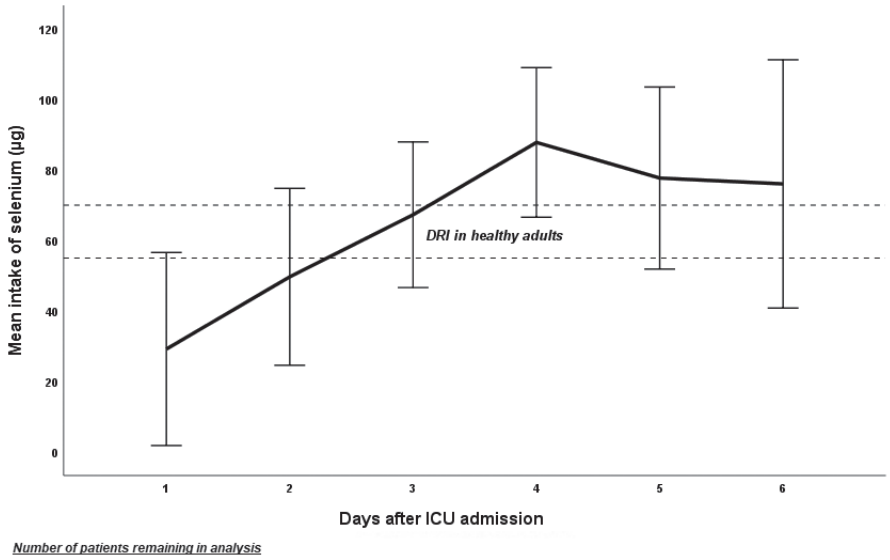


Abbreviations: CRP: C reactive protein, ICU: intensive care unit.

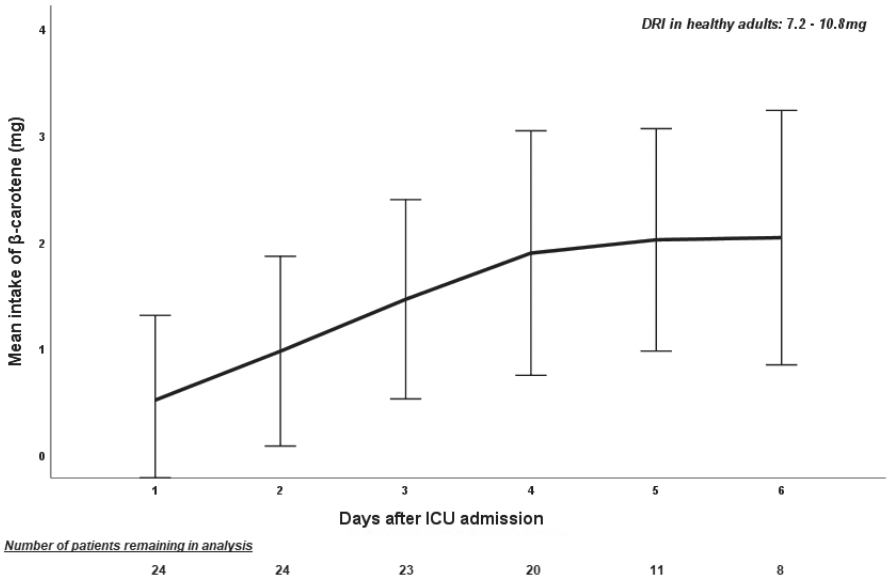
Effect of micronutrient intake in the ICU on micronutrient levels

Micronutrient intake during ICU admission is shown in figure 4A-4F. The micronutrients were part of standard enteral nutrition (no additional supplements were used during the study period). No associations between individual micronutrient intake and blood micronutrient concentrations were observed over time (selenium p=0.621, β-carotene p=0.708, vitamin C p=0.255, vitamin E p=0.792, vitamin B1 p=0.694, vitamin B6 p=0.964).

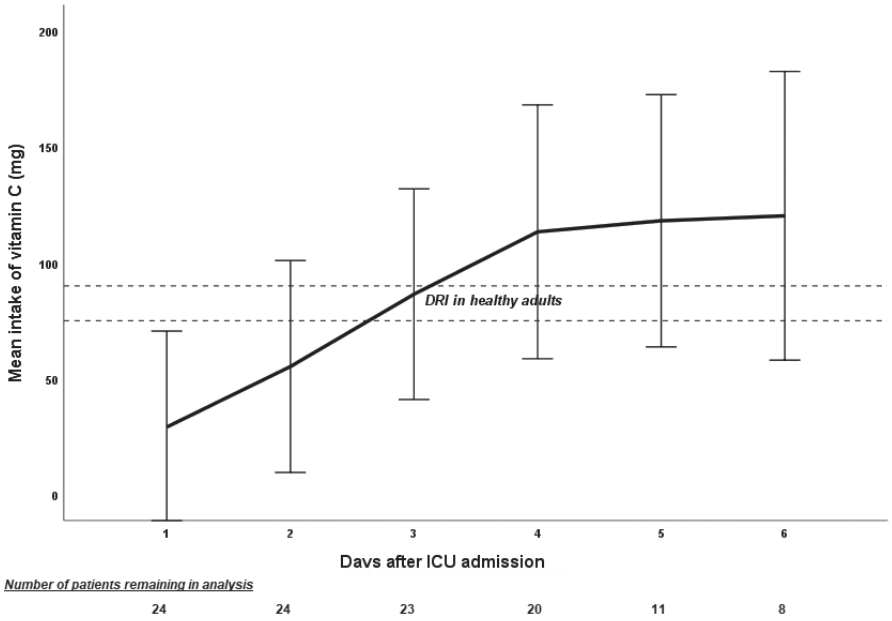
Figure 4| Mean micronutrient intake during ICU admission
A Selenium



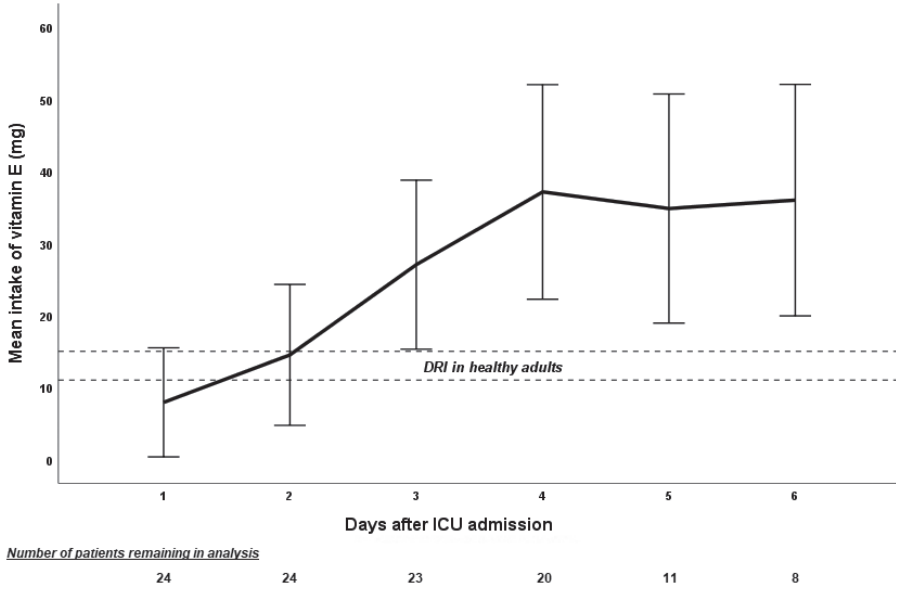
B β-carotene



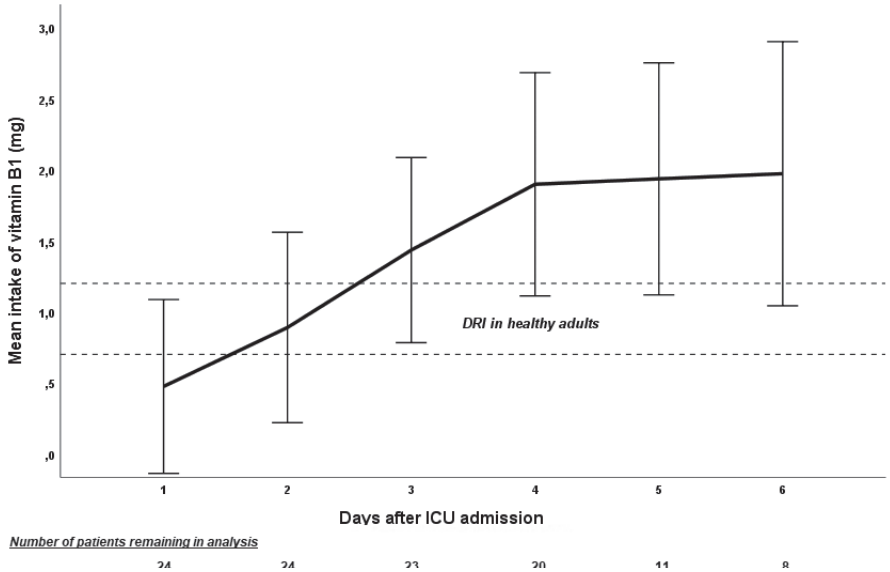
C Vitamin C



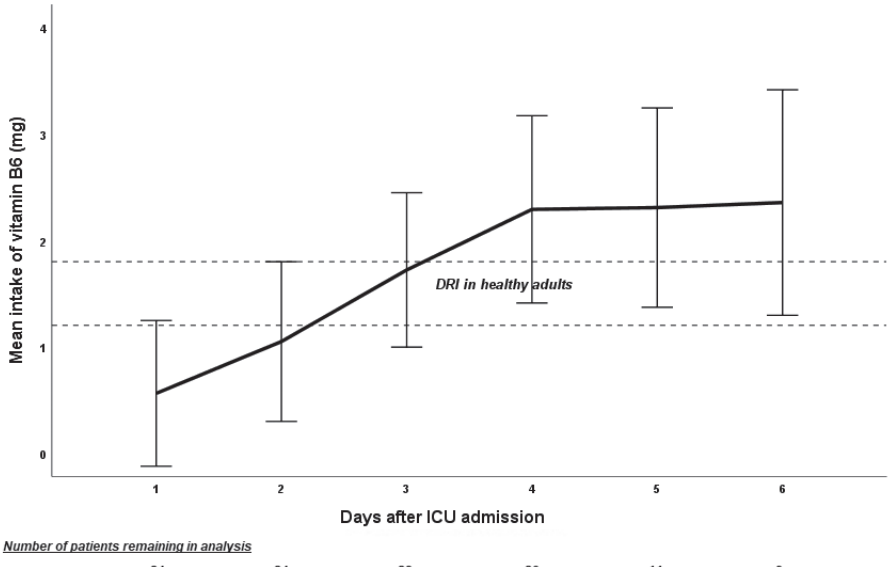
D Vitamin E



E Vitamin B1



F Vitamin B6



Abbreviations: DRI: dietary reference intake; ICU: intensive care unit

DISCUSSION

We prospectively studied micronutrient blood levels in 24 critically ill adults and compared those with micronutrient levels in 21 healthy age-matched controls (Table 2). The micronutrient levels of selenium, β-carotene, vitamin C and vitamin E were significantly lower in ICU patients than in healthy controls. Vitamin B1 and B6 levels were within normal range and not significantly different between the patient and control groups.

Vitamins and trace-elements have numerous essential functions throughout the body, as described in our earlier reviews [1, 9]. Therefore, low blood levels may manifest the critical illness (patho)physiology, rather than intake deficiency. Low micronutrient levels in critical illness may be caused by redistribution, altered protein binding, increased losses through bodily fluids (urine, blood, sweat, ascites, pleural fluid), increased metabolic use, and dilution secondary to fluid resuscitation [1].

Selenium

Selenium levels on ICU admission were significantly lower than in healthy controls in this study. Other studies report similar findings [10,11]. The low selenium levels are the result of changes in selenium metabolism in critical illness. Selenium and selenoproteins are redistributed to tissues involved in protein synthesis and immune cell proliferation. Capillary leakage and no urinary excretion reduction, despite low serum levels, lead to an additional loss of selenium [1,10]. Selenium supplementation, in low and high dosages, as monotherapy or part of a combination of micronutrients, has been studied in large randomized trials [12, 13]. However, no beneficial effects on mortality, ICU length of stay, ventilation duration or infectious complications have been found in these trials nor in a meta-analysis of 21 trials studying selenium supplementation in ICU [14].

Mean selenium levels in healthy controls in this study are also lower than the international reference range for selenium, and this is per other studies of selenium status in the Dutch population [5].

β-carotene

β-carotene levels were relatively low in this study with a mean of 0.17 μmol/l in critically ill patients and 0.50 μmol/l in healthy controls. The normal range of β-carotene serum levels has been reported to be 0.04 – 2.26 μmol/l [15].

Low levels of β-carotene have been earlier reported in patients with ARDS (mean 0.08 μmol/l vs 1.22 μmol/l in healthy controls [16]). The conversion of carotenoids to

retinol is increased in patients with vitamin A deficiency; so low plasma values may indicate real vitamin A deficiency [17]. In addition, vitamin A metabolism is altered in critical illness; significant amounts of retinol and retinol-binding protein are excreted in urine (while it usually is mainly excreted in bile) [1]. Stephensen et al. reported 33% of patients with acute infection excreted > 50% of the DRI of vitamin A [18]. Few studies have been performed on vitamin A supplementation (monotherapy), one study by Matos et al. showed a reduction in mortality and ICU length of stay [19].

Vitamin C

We found a significant decline in vitamin C levels during the first four days of ICU admission. This is in accordance with other studies reporting a rapid decline in vitamin C levels after initial injury [20,21].

Vitamin C supplementation has been studied in large trials, both as single interventions and combined with other vitamins and steroids [22,23]. In the Metaplus trial, enteral supplementation of vitamin C did not lead to normalization of plasma levels [23]. However, high dose intravenous supplementation (up to 200mg/kg/day) has shown to increase plasma levels to normal and supranormal levels in a small phase I trial [24]. . More importantly, no improvements in significant clinical endpoints have been reported in recent randomised trials [22-25].

Vitamin E

Vitamin E levels remain within normal range; however, are significantly lower than in healthy controls in this study. A decrease in vitamin E serum levels has been frequently reported in critically ill patients [1,26]. However, when standardised for serum lipids changes, no decrease or even an increase in vitamin E levels was found [27]. Concurrent with these findings, we observed an increase in vitamin E levels during the first week of ICU admission.

Vitamin B1

The incidence of thiamin deficiency in critically ill patients is supposedly 10-30% [9, 28-30]. However, none of the patients included in our study, nor the healthy controls, had any sample with a thiamin level below the normal value (< 70 nmol/l). A lower mortality rate has been reported in ICU patients with severe thiamine deficiency (< 7 nmol/l) receiving thiamin supplementation. In patients with no deficiency, no benefit of thiamin has been shown [28].

Vitamin B6

Only one previous study has investigated vitamin B6 intake and status in critically ill patients [31]. Vitamin B6 levels were measured prospectively in 94 critically ill patients on day 1 and 14 of ICU admission. In accordance with our findings, the authors of this study found vitamin B6 status to be within normal values on ICU admission (42 nmol/l). However, a significantly lower vitamin B6 level was found on day 14 than on day 1, although intake was high and even increased during ICU admission (>10x DRI). Also, urinary excretion of vitamin B6 was significantly higher on day 14, although blood levels were lower. We found no significant change in vitamin B6 levels during the first week of ICU admission in this study, but we have no measurements after 14 days. Our findings may thus not be contradictory, as vitamin B6 levels may decline only after the first week of ICU admission.

Inflammation, the severity of illness and micronutrient levels

We observed no associations between CRP nor SOFA scores and micronutrient levels in this study. However, previous studies on vitamin C supplementation show low plasma concentrations associated with severity of illness, inflammation and mortality [1, 21]. Also, selenium levels were negatively correlated with CRP [32] and associated with mortality, organ failure and sepsis severity scores in other studies. Our measurements may have been too early to see an effect of declining inflammation (as CRP and SOFA scores were still high at the end of the study). In addition, our study was not primarily powered for these analyses. Therefore the study population may have been too small to observe such an effect.

No previous studies have investigated the association between CRP nor severity of illness and vitamin E or β-carotene levels.

Micronutrient intake and micronutrient levels

We observed no associations between micronutrient intake and micronutrient levels during ICU admission. It is possible that the micronutrient intake from EN in this study was too limited to influence actual serum micronutrient levels in ICU patients (i.e., the daily dose of micronutrients is too low to normalise levels). However, multiple studies with high dose micronutrient supplementation have also been unable to normalise micronutrient blood levels [22, 31]. This may indicate that micronutrient blood levels are mainly influenced by other processes (i.e., increased metabolic use, redistribution, increased losses), and intake may play a minor role [1].

Strengths and weaknesses

Micronutrient status of critically ill patients was compared with healthy age-matched controls from the same geographical area. As micronutrient levels in healthy adults decline with age and differ widely between geographical regions, matching patients accordingly reduces the risk of falsely interpreting micronutrient levels in ICU patients as (ab)normal.

We were also able to show the course of micronutrient levels during the first week of ICU admission in the absence of supplementation. This "natural" course has not been extensively investigated before.

However, our study has several limitations. The study population was small and from a single-centre, resulting in low statistical power for our secondary analysis. Therefore, this study should be seen as a hypothesis generating study. Secondly, vitamin E levels were not standardised for serum lipid status. As serum triglyceride levels were lower in patients on ICU admission than in controls, the significant difference between mean vitamin E levels may be (partially) explained by this. Finally, the study was performed in 2002 thus indicating a long delay in manuscript preparation. Recently, the relevance of the data was reconsidered as this study was performed without additional micronutrient supplements and therefore shows the "natural course" of micronutrient concentrations in ICU patients. Nowadays, as many ICUs use additional micronutrients this study would be hard to perform in 2021. We do not think the delay has influenced the validity of our results.

CONCLUSION

Patients already showed lower plasma levels of selenium, β-carotene, Vitamin C and Vitamin E than healthy controls on ICU admission. Vitamin C levels dropped significantly during the first days of ICU admission, while β-carotene and vitamin E levels increased after 5-7 days. Selenium levels remained stable. Vitamin B1 and B6 levels on ICU admission were comparable with healthy age-matched controls and remained stable. No associations between micronutrient levels and severity of illness, CRP or micronutrient intake were found. Progressive enteral tube feeding containing vitamins and trace elements does not normalize plasma levels in the first week of ICU stay. When treatment objectives are to normalise plasma concentrations of the studied micronutrients only tube feeding is not sufficient and pharmacological supplementation should be considered.

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9

CHAPTER

Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: A systematic review and meta-analysis

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ABSTRACT

Introduction

As fish oil exerts anti-inflammatory and immunomodulatory properties which may be beneficial for critically ill patients, multiple RCTs and meta-analysis have been performed. However, controversy remains as to whether fish oil enriched enteral nutrition can improve clinical outcomes in adult critically ill patients in intensive care units.

Methods

A systematic literature search was conducted. The primary outcome was 28-day mortality. Secondary outcomes were ICU and hospital mortality, ICU and hospital length of stay, ventilation duration and infectious complications. Predefined subgroup and sensitivity analyses were performed.

Results

Twenty-four trials, enrolling 3574 patients, met the inclusion criteria. The assessment of risk of bias showed that most of included studies were of moderate quality. The overall results revealed no significant effects of enteral fish oil supplementation on 28-day, ICU or hospital mortality. However, ICU LOS and ventilation duration were significantly reduced in patients receiving fish oil supplementation. Furthermore, subgroup analysis revealed a significant reduction in 28-day mortality, ICU LOS and ventilation duration in ARDS patients but not in other subgroups. When comparing high with low quality trials, significant reductions in 28-day mortality and ventilation duration in low but not high quality trials were observed. Regarding ICU LOS a significant reduction was observed in high quality trials whereas only a trend was observed in low quality trials. No significant effects on hospital LOS or infectious complications were observed in overall or subgroup analyses.

Conclusions

Enteral fish oil supplementation cannot be recommended for critically ill patients as strong scientific evidence for improved clinical benefits could not be found. There is a signal of mortality benefit in ARDS patients, however results are based on low quality studies. Further research should focus on the relation between the individual critically ill patients' immune response, the administration of fish oil and clinical outcomes.

INTRODUCTION

Fish oil (FO) has gained great interest as dominant source of ω-3 polyunsaturated fatty acids (PUFAs), more specifically eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). It has been suggested that EPA and DHA may attenuate the production of pro-inflammatory lipid mediators and cytokines, modulate the activity of nuclear receptors and expression of nuclear transcription factors (factor-kappa B, NF-κB; peroxisome proliferator-activated receptor γ, PPAR-γ; intracellular adhesion molecule 1, ICAM-1) and act as precursors of resolvins which in turn attenuate inflammation [1, 2]. Thus, FO exerts anti-inflammatory and immunomodulatory properties [3, 4], that may potentially confer improved clinical outcomes of critical illness.

Over the past 30 years, several randomized controlled trials have been performed addressing the clinical effects of fish-oil supplementation among critically ill patients. Conflicting results have been reported, ranging from clinical benefit to possible harm. Recently, several meta-analysis have been performed regarding fish-oil containing nutrition in critically ill patients. The effects of enteral fish-oil containing formulas in ARDS patients was studied in two recent meta-analysis [5, 6]. In both, no significant effects on mortality or ventilator free days and ICU free days were found. Manzanares and coworkers recently studied effects of intravenous fish-oil lipid emulsions in critically ill patients [7]. In a meta-analysis of 10 randomized controlled trials (RCTs) no effect on overall mortality was found, however a significant reduction in infections was observed. Furthermore, a recent meta-analysis of 17 RCTs by Lu and colleagues on parenteral and enteral fish oil supplementation in critically ill patients with sepsis showed significant reductions in ICU length of stay (LOS) and duration of mechanical ventilation. No effects on mortality were observed [8]. The value of peri-operative fish-oil supplementation was studied by Langlois and coworkers in a meta-analysis of 19 RCTs on cardiac surgery patients [9]. A significant reduction in hospital LOS as well was the occurrence of postoperative atrial fibrillation was found. However, no effects on ICU LOS, mortality or duration of ventilation were observed.

Fish oil supplementation has also been addressed in international guidelines. The ESPEN guidelines suggest a benefit of fish oil lipid emulsions in ARDS, but have not been updated since 2009 [10]. The more recent ASPEN guidelines withhold to recommend fish oil due to conflicting data [11]. The Canadian Clinical Practice Guidelines advise consideration of enteral formulas containing fish oils in patients with ARDS/ALI as associations with its use and reduction in 28-day mortality were found [12].

The purpose of the current study was to provide an up-to-date systematic review and meta-analysis of all RCTs of fish-oil containing enteral nutrition addressing relevant clinical outcomes in critically ill patients.

METHODS

Search Strategy and Study Identification

A systematic review was conducted to identify all relevant randomized clinical trials published before January 2018 in MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. We used the following medical subject headings or keywords “fish oils”, “docosahexaenoic”, “eicosapentaenoic”, “omega-3”, “lipid emulsions”, “intensive care”, “critical illness”, “critically ill”, “enteral nutrition” and “randomized”. In addition, citations of the selected RCTs were checked in Web of Science and references of the selected RCTs were manually searched for additional original studies. The search was restricted to English articles only and abstracts from scientific meetings were not accepted for inclusion into this systematic review.

Study Selection Criteria/Eligibility criteria

Only trials meeting the following characteristics were included:

1. Study design: randomized clinical, parallel group, controlled trials (RCTs).
2. Study population: critically ill adult patients (>95% of patients >18 years of age).
3. Intervention: Enteral supplementation of fish oil (ω-3 fatty acids) or fish oil containing enteral nutrition compared with a control or placebo intervention.
4. Study outcomes must have included one of the following: mortality, ICU or hospital length of stay (LOS), duration of mechanical ventilation and infectious complications.

Those trials performed in elective surgery patients or only reporting biochemical, metabolic, immunologic or nutritional outcomes were excluded.

Two authors (WK and VP) independently performed methodological quality assessment of the studies. The risk of bias was assessed by using a data abstraction form with a scoring system from 0 to 14 scoring the components recommended by the Cochrane Collaboration including: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data (including ITT analysis); selective reporting; and other sources of bias [13]. Scores of 9-14 were regarded as high quality (Level I) and 0-8 as low quality (Level II). Any disagreement was resolved by consensus.

Data synthesis

The primary outcome of the systematic review was 28-day mortality. Separately, we analyzed data reported as ICU or hospital mortality. When mortality was unspecified, data were not included in data analysis. Secondary outcomes included infections,

ventilation duration and ICU and hospital LOS. We used definitions of infections as defined by the authors in their original articles. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5%) to distinguish them from patients with elective surgery who were also cared for in some ICUs, but had a low baseline mortality rate (<5%).

We combined data from all trials to estimate the pooled risk ratio (RR) with 95% confidence interval (CI) for mortality and infectious complications and overall weighted mean difference (WMD) with 95% CI for LOS and duration of ventilation. When studies reported only medians with interquartile ranges, these were converted to means and standard deviations according to the Cochrane guidelines. Pooled RRs were calculated using the Mantel-Haenszel test, and WMDs were estimated using the inverse variance approach. The random-effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimations. All data analysis was conducted using Review Manager (RevMan) 5.3 software [14]. Whenever possible, studies were aggregated on an intention-to-treat basis. Statistical heterogeneity was measured and quantified using the I2 test and the Mantel–Haenszel $\chi 2$ test. Statistical heterogeneity was predefined at I2 >50 % or $p<0.05$. Sensitivity analysis was used to assess the sources of heterogeneity. Publication bias was assessed for all analyses after visual inspection of funnel plots. We considered $p<0.05$ to be statistically significant and $p<0.10$ as the indicator of a trend.

Subgroup analysis

A predefined subgroup analysis was performed to investigate whether there were difference in treatment effect among patients with sepsis, ARDS or trauma. Additionally, we compared older (< 2010) and newer studies on treatment effects. We also assessed the effect of trial quality on outcome, as trials with lower quality may demonstrate a greater treatment effect than those with higher quality.

RESULTS

Study identification and selection

The literature search identified 58 potentially eligible trials [15-72]. We excluded 34 trials for the following reasons: (1) patients not considered to be adult critically ill patients (n=6) [39-44]; (2) no clinical outcomes meeting inclusion criteria (n=2) [45,46]; (3) parenteral fish oil administration (n=8) [47-54]; (4) duplicate studies, reviews of published trials or subgroups of included studies (n=4)[55-58]; (5) published as abstracts (n=8) [59-66]; (6) papers published in a language other than English(n=6) [67-72], (Figure 1).

Finally, 24 RCTs, with a total number of 3574 patients, met the inclusion criteria and were included in this systematic review [15-38]. In total, 1787 patients were treated with enteral FO supplementation and 1787 patients with a control feed. The results were based on data derived from the included studies, depicted in Table 1 and 2. We reached 100% agreement for inclusion of the trials. The mean methodological score was 8.5 (range, 3 to 13). Details of methodological quality are shown in Figure 2.

Figure 1| Flowchart

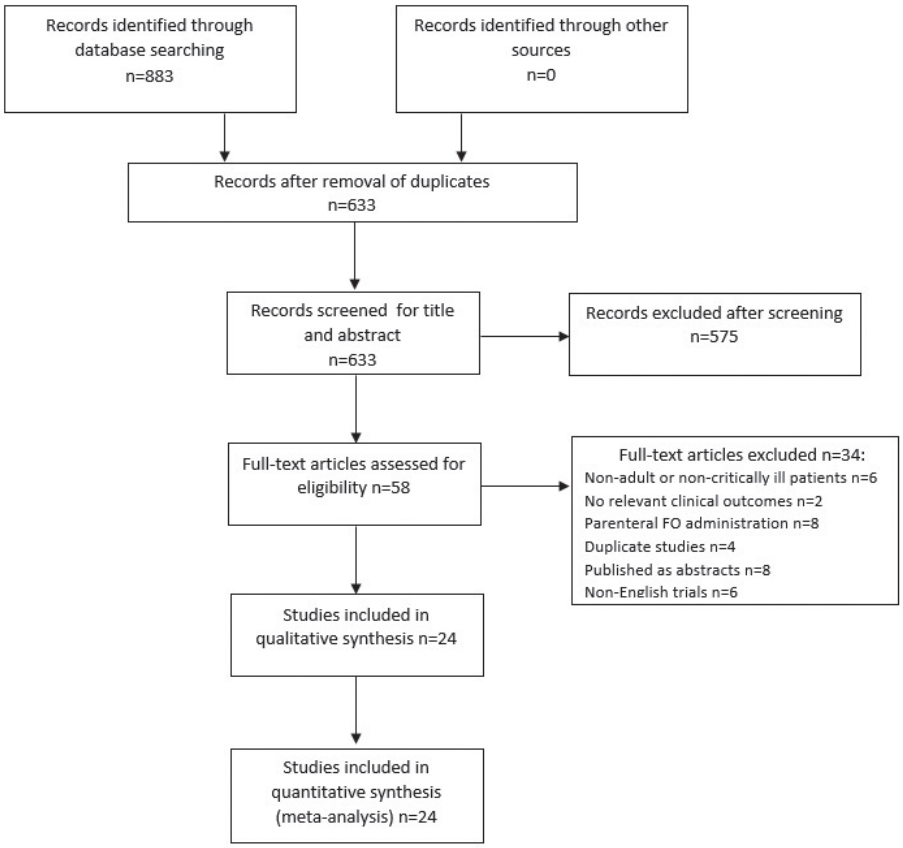


Table 1| Randomized Clinical Trials evaluating enteral fish oil supplementation in ICU patients

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Atkinson 1998	ICU patients N = 390	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** Isocaloric isonitrogenous EN identical in vitamin & trace element profiles.	**ICU** 80/197 **HOS** 95/197	**ICU** 74/193 **HOS** 85/193	**ICU** 6 (0-103) **HOS** 12 (0-187)	**ICU** 6 (0-282) **HOS** 13 (0-289)	4 (0-101)	4 (0-204)
Bower 1995	ICU patients with SIRS/ Sepsis N = 326	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control**: isonitrogenous EN with similar protein-fat-carbohydrate distribution and vitamin/trace element profile.	**HOS** 23/147	**HOS** 10/132	**HOS** 21	**HOS** 26	NR	NR
Elamin 2012	ICU patients with ARDS N = 22	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric isonitrogenous EN identical in protein-fat-carbohydrate distribution and vitamin/ trace element profiles.	**28-day** 0/9	**28-day** 1/8	**ICU** 12.8	**ICU** 17.5	6.7	8.2
Gadek 1999	ICU patients with ARDS N = 146	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Isocaloric, isonitrogenous EN identical in protein-fat-carbohydrate distribution	**HOS** 11/70	**HOS** 19/76	**ICU** 11 ± 0.9 **HOS** 27.9 ± 2.1	**ICU** 14.8 ± 1.3 **HOS** 31.1 ± 2.4	9.6 ± 0.9	13.2 ± 1.4
Galban 2000	ICU patients with sepsis N = 181	**Intervention:** EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** High caloric EN with similar protein-fat-carbohydrate distribution.	**ICU** 17/89	**ICU** 28/87	**ICU** 18.2 ± 12.6	**ICU** 16.6 ± 12.91	12.4 ± 10.4	12.2 ± 10.3
Grau-Carmona 2011	ICU patients with sepsis and ARDS N = 160	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** low fat, high carbohydrate EN	**28-day** 11/61	**28-day** 11/71	**ICU** 16 (11-25)	**ICU** 18 (10-30)	10 (6-14)	9 (6-18)

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Hosny 2013	ICU patients with sepsis N = 75	**Intervention:** EN (unspecified) supplemented with DHA+EPA 3dd 3g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Intervention:** EN (unspecified) supplemented with DHA+EPA 3dd 1g, Vit C 1000mg/d, Vit E 800IU/d, selenium 100 ug/d vs **Control:** EN (unspecified) without supplements.	**28-day** 8/25 11/25	**28-day** 10/25	**ICU** 11.6 ± 6.1 13.6 ± 4.1	**ICU** 13.9 ± 4.2	6.7 ± 3.83 8.4 ± 4.63	10.9 ± 6.3
Jakob 2017	ICU patients N = 90	**Intervention:** High protein, low carbohydarate EN with high omega-3 FA 3.6g/L vs **Control:** Low protein, high carbohydrate EN with low omega-3 FA 2.9g/L.	NR	NR	**ICU** 7.0 (5.3-8.7) **HOS** 31.0 (27.0-35.0)	**ICU** 10.0 (6.6-13.4) **HOS** 36.0 (29.9-42.1)	6.2 (4.8-7.7)	7.0 (4.7-9.3)
Kagan 2015	ICU patients with severe trauma N = 120	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** high fat, low carbohydrate EN, isocaloric and similar in protein and macronutrient composition.	**28-day** 8/62	**28-day** 5/58	**ICU** 19.5 ± 15.3 **HOS** 33.1 ± 25.7	**ICU** 16.4 ± 11.3 **HOS** 27.1 ± 17.3	NR	NR
Kieft 2005	ICU patients N = 597	**Intervention:** EN supplemented with arginine, glutamine and EPA 0.8g/L/DHA 0.3g/L vs **Control:** isocaloric control EN	**28-day** 93/302 **ICU** 84/302 **HOS** 114/302	**28-day** 82/295 **ICU** 78/295 **HOS** 106/295	**ICU** 7.0 (4.0-14.0) **HOS** 20.0 (10.0-35.0)	**ICU** 8.0 (5.0-16.0) **HOS** 20.0 (10.0-34.0)	6.0 (3.0-12.0)	6.0 (3.0-12.0)

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Kudsk 1996	ICU patients with emergency celiotomy N = 35	**Intervention:** high protein EN with arginine, glutamine and omega-3 1.1 g/L vs **Control:** isocaloric, isonitrogenous EN	**5-day** 1/17	**5-day** 1/18	**ICU** 5.8 ± 1.8 **HOS** 18.3 ± 2.8	**ICU** 9.5 ± 2.3 **HOS** 32.6 ± 6.6	2.4 ± 1.3	5.4 ± 2.0
Mendez 1997	ICU patients with severe trauma N = 59	**Intervention:** EN with arginine and 40% canola oil (omega-3) **Control:** isocaloric, isonitrogenous EN with soy and corn oil	**?** 1/22	**?** 1/21	**ICU** 18.9 ± 20.7	**ICU** 11.1 ± 6.7	?	?
Mesejo 2015	Mechanically ventilated ICU patients with hyperglycemia N = 157	**Intervention:** high protein EN with modified maltodextrin and EPA/DHA 0.68g/L **Control:** high caloric standard maltodextrin EN **Control: i**socaloric modified maltodextrin EN	**28-day** 11/52 13/52 **6-month** 16/52 20/53 18/52	**28-day** 10/53	**ICU** 13 (9-20) **HOS** 27 (18-50)	**ICU** 12 (7-21) 11.5 (7.5-18) **HOS** 25 (17-51) 30.5 (14-46.5)	7 (4-13)	6 (2-11) 6 (3-12)
Parish 2014	ICU patients with ARDS N = 58	**Intervention:** EN (unspecified) + omega-3 soft gels 720mg 3dd **Control:** same EN (unspecified) without soft gels	**28-day** 7/29	**28-day** 9/29	**ICU** 15 ± 3.5	**ICU** 15.6 ± 4.3	**VFD** 6.6 ± 2	**VFD** 6 ± 2.5
Pontes-Arruda 2006	ICU patients with ALI and severe sepsis or septic shock N = 165	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Isocaloric and isonitrougenous EN	**28-day** 26/83	**28-day** 38/82	**ICU-free days** 10.8 ± 1.1	**ICU-free days** 4.6 ± 0.9	**VFD** 13.4 ± 1.2	**VFD** 5.8 ± 1.0

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Pontes-Arruda 2011	ICU patients with sepsis N = 115	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric, isonitrogenous, low fat, high carbohydrate EN	**28-day** 15/57	**28-day** 16/58	**ICU** 7 (4-12) **ICU-free days** 21.1 ± 4.7 **HOS** 9 (6-14) **HOS-free days** 19.5 ± 7.8	**ICU** 13 (9-18) **ICU-free days** 14.7 ± 5.1 **HOS** 19 (13-24) **HOS-free days** 10.3 ± 8.6	7 (4-12)	15 (8-21)
Rice 2011	ICU patients with ALI N = 272	**Intervention:** EN (unspecified) + supplement with omega-3 FA & AOX **Control:** same EN (unspecified) + isocaloric isovolemic carbohydrate rich controls supplement	**60-day** 38/143	**60-day** 21/129	**ICU-free days** 14.0 ± 10.5	**ICU-free days** 16.7 ± 9.5	**VFD** 14.0 ± 11.1	**VFD** 17.2 ± 10.2
Shirai 2015	ICU patients with sepsis induced ARDS N = 46	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** Low caloric, low protein, high carbohydrate EN	**28-day** 3/23	**28-day** 3/23	**ICU** 15 (11-24) **ICU-free days** 13 (0-17)	**ICU** 24 (20-30) **ICU-free days** 4 (0-8)	14 (10-17) **VFD** 14 (11-18)	17 (12-24) **VFD** 11 (3-16)
Singer 2006	ICU patients with ARDS or ALI N = 100	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** isocaloric, isonitrogenous control with similar protein-fat-carbohydrate distribution.	**28-day** 13/46	**28-day** 28/49	**ICU** 13.5 ± 11.8	**ICU** 15.6 ± 11.8	12.1 ± 11.3	14.7 ± 12
Stapelton 2011	ICU patients with ALI N = 90	**Intervention:** EN (unspecified) + 9.75g EPA/d + 6.75g DHA/d **Control:** same EN (unspecified) + saline 0.9% enterally in similar amount	**HOS** 9/41	**HOS** 10/49	?	?	?	?

Study	Population	Intervention	Mortality		Length of stay		Duration of ventilation	
Thiella 2012	ICU patients with pressure ulcers N = 40	**Intervention:** EN supplemented with GLA, antioxidants and EPA 5,3g/L vs **Control:** low-fat, high carbohydrate EN	NR	NR	**ICU** 26.1 ± 14.2	**ICU** 21.1 ± 9.1	NR	NR
Tihista 2017	ICU patients with burns > 15% requiring mechanical ventilation N = 106	**Intervention:** Low-fat EN (unspecified) of which 50% of the fat was replaced by fish-oil **Control:** Low-fat EN (unspecified) without fish-oil	**HOS** 15/53	**HOS** 13/53	**HOS** 52 (29-78)	**HOS** 51 (36-72)	14 (10-28)	18 (11-32)
Weimann 1998	ICU patients with severe trauma N = 32	**Intervention**: EN supplemented with L-arginine, RNA and EPA/DHA 1.7g/L vs **Control:** Isonitrogenous isocaloric EN	**ICU** 2/16	**ICU** 4/13	**ICU** 31.4 ± 23.1 **HOS** 70.2 ± 52.9	**ICU** 47.4 ± 32.8 **HOS** 58.1 ± 30.1	21.4 ± 10.8	27.8 ± 14.6
Van Zanten 2014	ICU patients requiring mechanical ventilation N = 301	**Intervention:** high protein, high fat EN with glutamine, MCT, antioxidants and EPA+DHA 5.0g/L **Control:** isocaloric high protein, low fat EN	**28-day** 31/152 **ICU** 30/152 **HOS** 38/152 **6-months** 53/152	**28-day** 25/149 **ICU** 29/149 **HOS** 33/149 **6-months** 42/149	**ICU** 18 (12-29) **HOS** 30 (21-44)	**ICU** 18 (10-34) **HOS** 30 (20-49)	9 (5-15)	8 (5-15)

Abbreviations: ICU: Intensive Care Unit; HOS: hospital; EN: enteral nutrition; RNA: ribonucleic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; NR: not reported; SIRS: systemic inflammatory response syndrome; ARDS: acute respiratory distress syndrome; GLA: gamma-Linolenic acid; Vit E: vitamin E; Vit C: vitamin C; FA: fatty acids; ALI: acute lung injury; AOX: antioxidants; MCT: medium chain triglyceride; VFD: ventilation free days.

Table 2| Infectious complications in randomized clinical trials evaluating fish oil supplementation in ICU patients

Study	Population	Infections		VAP		Bacteremia		UTI		CRI		Intra-abdominal	
Atkinson 1998	ICU patients N = 390	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bower 1995	ICU patients with SIRS/Sepsis N = 326	0.74 ± 0.97*	0.98 ± 1.27*	NR	NR	9/147	17/132	24/147	30/132	NR	NR	NR	NR
Elamin 2012	ICU patients with ARDS N = 22	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gadek 1999	ICU patients with ARDS N = 146	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Galban 2000	ICU patients with sepsis N = 181	46/89	68/87	11/89	11/87	7/89	19/87	11/89	11/87	10/89	11/89	NR	NR
Grau-Carmona 2011	ICU patients with sepsis N = 160	32/61	34/71	24/61	26/71	6/61	6/71	2/61	5/71	10/61	13/71	4/61	3/71
Hosny 2013	ICU patients with sepsis N = 75	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jakob 2017	ICU patients N = 90	19/46	19/44	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kagan 2015	ICU patients with severe trauma N = 120	NR	NR	25/62	22/58	14/62	3/62	NR	NR	NR	NR	NR	NR

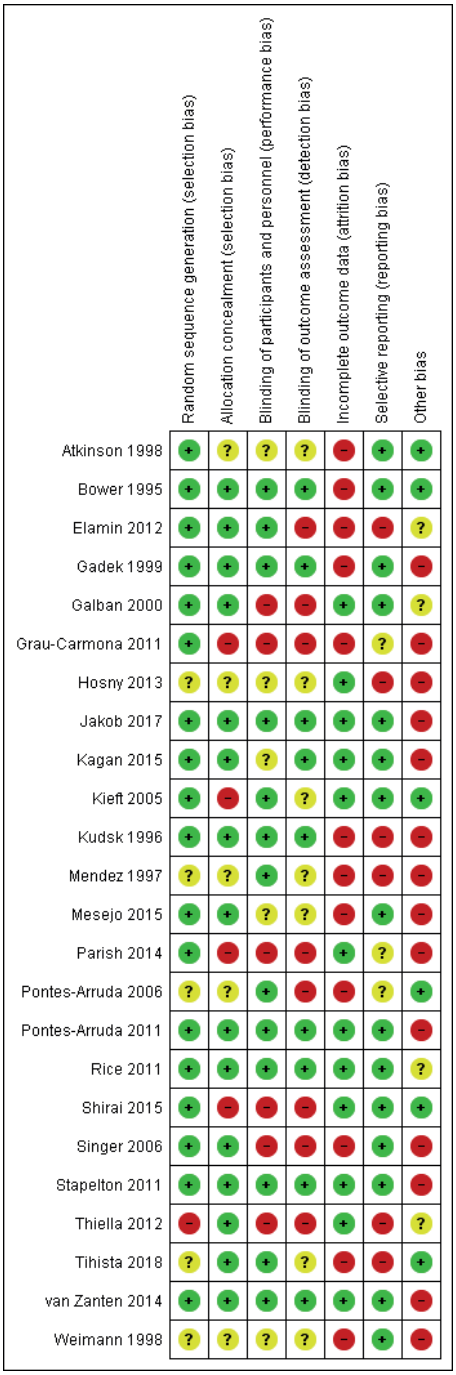
Study	Population	Infections		VAP		Bacteremia		UTI		CRI		Intra-abdominal	
Kieft 2005	ICU patients N = 597	130/302	123/295	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kudsk 1996	ICU patients with emergency celiotomy N = 35	NR	NR	0/16	2/17	1/16	4/17	2/16	6/17	NR	NR	1/16	6/17
Mendez 1997	ICU patients with severe trauma N = 59	19/22	12/21	16/22	11/21	6/22	7/21	3/22	4/21	NR	NR	NR	NR
Mesejo 2015	Mechanically ventilated ICU patients with hyperglycemia N = 157	8/52	23/53 23/52	8/460**	10/392** 6/424**	3/52	1/53 3/52	1/52	1/53 1/52	1/52	1/53 2/52	NR	NR
Parish 2014	ICU patients with ARDS N = 58	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pontes-Arruda 2006	ICU patients with ALI and severe sepsis or septic shock N = 165	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pontes-Arruda 2011	ICU patients with sepsis N = 115	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rice 2011	ICU patients with ALI N = 272	NR	NR	10/143	10/129	16/143	14/129	NR	NR	NR	NR	NR	NR

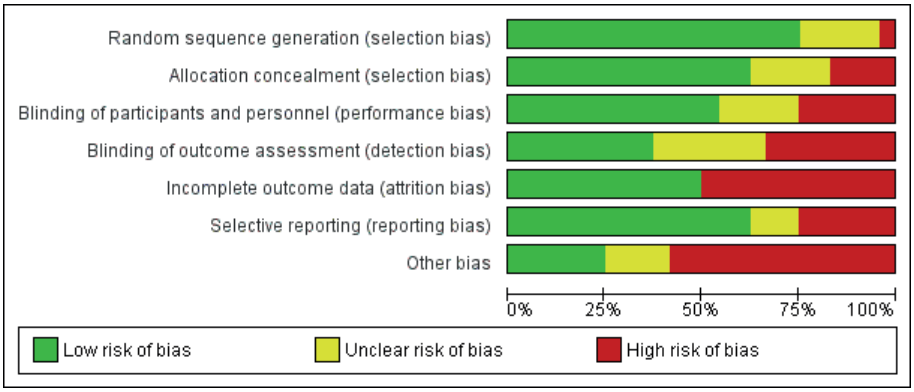
Study	Population	Infections		VAP		Bacteremia		UTI		CRI		Intra-abdominal	
Shirai 2015	ICU patients with sepsis induced ARDS N = 46	10/23	12/23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Singer 2006	ICU patients with ARDS or ALI N = 100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stapelton 2011	ICU patients with ALI N = 90	1/41	1/49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thiella 2012	ICU patients with pressure ulcers N = 40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tihista 2017	ICU patients with burns > 15% requiring mechanical ventilation N = 106	NR	NR	15/53	20/53	7/53	7/53	NR	NR	2/53	6/53	NR	NR
Weimann 1998	ICU patients with severe trauma N = 32	NR	NR	10/16	6/13	1/16	1/13	2/16	1/13	9/16	6/13	NR	NR
Van Zanten 2014	ICU patients requiring mechanical ventilation N = 301	80/152	78/149	56/152	59/149	15/152	12/149	15/152	15/149	NR	NR	NR	NR

* = per patient , ** = per ventilation day

Abbreviations: VAP: ventilator associated pneumonia; UTI: urinary tract infection; CRI: catheter related infection; ICU: intensive care unit; NR: not reported; SIRS: systemic inflammatory response syndrome; ARDS: acute respiratory distress syndrome; ALI: acute lung injury

Figure 2| Risk of bias of RCTs included in meta-analysis



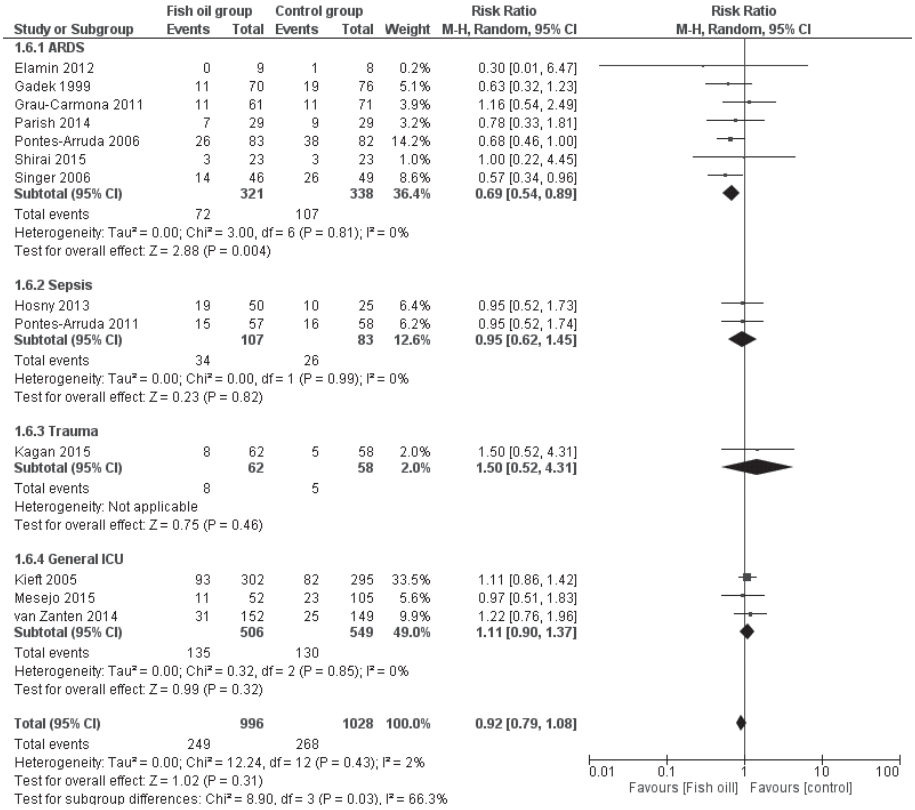


Meta-Analyses of Primary Outcome

Overall effect on 28-day Mortality

After aggregation of the data from 13 RCTs [17,18,20,21,23,24,27-30,32,33,38] evaluating 28-day mortality, no significant reductions in case fatality was found (RR 0.92, 95% CI 0.79 – 1.08; p=0.31; Figure 3). Statistical heterogeneity was not significant (I2 = 2%, p = 0.43).

Figure 3| The effects of fish oil supplementation on 28-day mortality in different ICU populations



Abbreviations: ARDS: acute respiratory distress syndrome; ICU: intensive care unit; CI: confidence interval; M-H: Mantel-Haenszel.

9

Secondary outcomes

Overall effect on ICU and Hospital Mortality

Five and seven RCTs reported the effects of fish oil supplementation on ICU [15,19,24,37,38] and hospital [15,16,18,24,34,36,38]mortality respectively. We pooled the data and found no significant effect on ICU mortality (RR 0.96, 95%CI 0.78–1.18; p=0.69; see figure 1 in [73]) or hospital mortality (RR 1.08, 95%CI 0.95–1.23; p=0.23; see figure 2 in [73]). Heterogeneity was non-significant (I2=27%, p=0.24 for ICU mortality and I2 =0%, p=0.43 for hospital mortality).

Overall effect on ICU length of stay

ICU length of stay was reported in 21 RCTs [15,16-30,32-35,37,38]. A significant reduction in ICU length of stay favouring fish oil supplementation (MD -2.23, 95%CI -3.34, -1.12; p<0.0001; Figure 4) was observed. However, heterogeneity was significant (I2=78%, p<0.0001).

Overall effect on hospital length of stay

Four trials reported hospital LOS [15,18,23,38]. We pooled these data and found no significant effect of fish oil supplementation on hospital LOS (MD -0.52, 95%CI -4.51, 3.48; p=0.80 and heterogeneity was significant (I2 = 56%, p=0.08).

Overall effect on ventilation duration

Aggregation of the data of 19 RCTs [15,18-27,29,30,32-34,36-38] reporting the effects of fish oil supplementation on ventilation duration showed a significant reduction in ventilation duration favouring fish oil (MD -2.08, 95%CI -3.30, -0.85; p=0.0009, Figure 5). However, heterogeneity was significant (I2 =87%, p<0.0001).

Overall effect on infectious complications

After aggregation of data from 11 RCTs [19-22,,24, 26, 27, 32, 34, 36, 38] regarding overall infectious complications no significant effects of fish oil were found (RR 0.96, 95%CI 0.81–1.13; p=0.60). Heterogeneity was significant (I2 =53%, p=0.03). We also pooled data of several specific infectious complications: ventilator associated pneumonia (9 RCTs), bacteraemia (11 RCTs), urinary tract infections (8 RCTs) and catheter related infections (5 RCTs). However, no significant effect of fish oil was found in any of these analyses.

Risk of Publication Bias in Included Trials

Upon visual inspection of funnel plots no indications for publication bias were found.

Sensitivity Analysis

We conducted sensitivity analyses to investigate the effects of intention to treat analysis (vs per protocol analysis), different enteral nutrition formulas and outcome measures reported as medians and IQRs. No significant effects were observed.

Subgroup analyses

Of the 13 RCTs that investigated the effects of enteral fish oil supplementation on 28-day mortality, 7 were performed in ARDS patients[17,18,20,28,29,32,33], 2 in sepsis patients [21,30], 1 in trauma patients [23] and 3 in heterogeneous groups of ICU patients [24,27,38]. Although the overall treatment effect was not significant, aggregation of the data from the 7 trials performed in ARDS patients did show a significant reduction in 28-day mortality, favouring fish oil supplementation (RR 0.69, 95%CI 0.54–0.89, p=0.004, Figure 3). In the other subgroups no significant effects were found. Moreover, ICU LOS and ventilation duration were also significantly reduced in ARDS patients but not in the other subgroups (Figure 4 and 5). No significant differences between subgroups were found regarding ICU mortality, hospital mortality, hospital LOS and infectious complications.

Old versus new studies

Nine of the 13 RCTs investigating the effects of enteral fish oil supplementation on 28-day mortality were published between 2010 and 2015 [17,20,21,23,27,28,30,32,38]. No significant differences in 28-day mortality were observed when these were compared with the four studies published between 1999 and 2009 (p=0.16, see figure 3 in [73]) [18,24,29,33]. No significant differences between old and new studies were found regarding ICU mortality, hospital mortality, hospital LOS and infectious complications.

Effect of study quality on outcomes

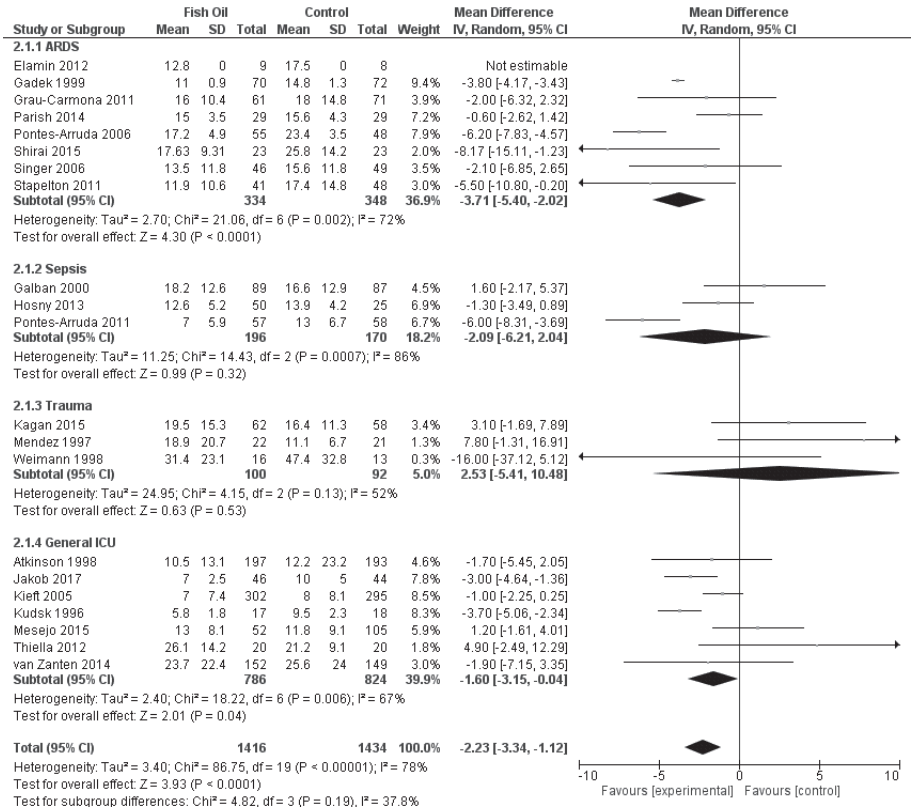
While low quality trials did show a decrease in 28-day mortality with fish oil supplementation (RR 0.77, 95% CI 0.61 – 0.96, p=0.02), high quality trials did not (RR 1.07, 95% CI 0.88 – 1.30, p=0.51, see figure 4 in [73]). In addition, duration of ventilation was significantly shorter in fish oil supplemented patients in low quality trials (p=0.03), but not in high quality trials (p=0.05). Furthermore, in high quality trials ICU LOS was significantly reduced (p=0.002) in fish oil supplementation while this effect was non-significant in low quality trials (p=0.07). No differences were observed between Level 1 and 2 trials regarding ICU and hospital mortality and infectious complications. Hospital LOS was only reported in high quality trials.

Post-hoc analysis of adverse events and tolerability

In order to evaluate the risk-to-benefit ratio of omega-3 supplementation we performed a post-hoc analysis of adverse events and tolerability. Adverse events are systematically reported in 5 studies. No difference was observed between adverse events in patients with and without omega-3 supplementation (RR 1.04, 95% CI 0.96-1.13, p=0.34), see

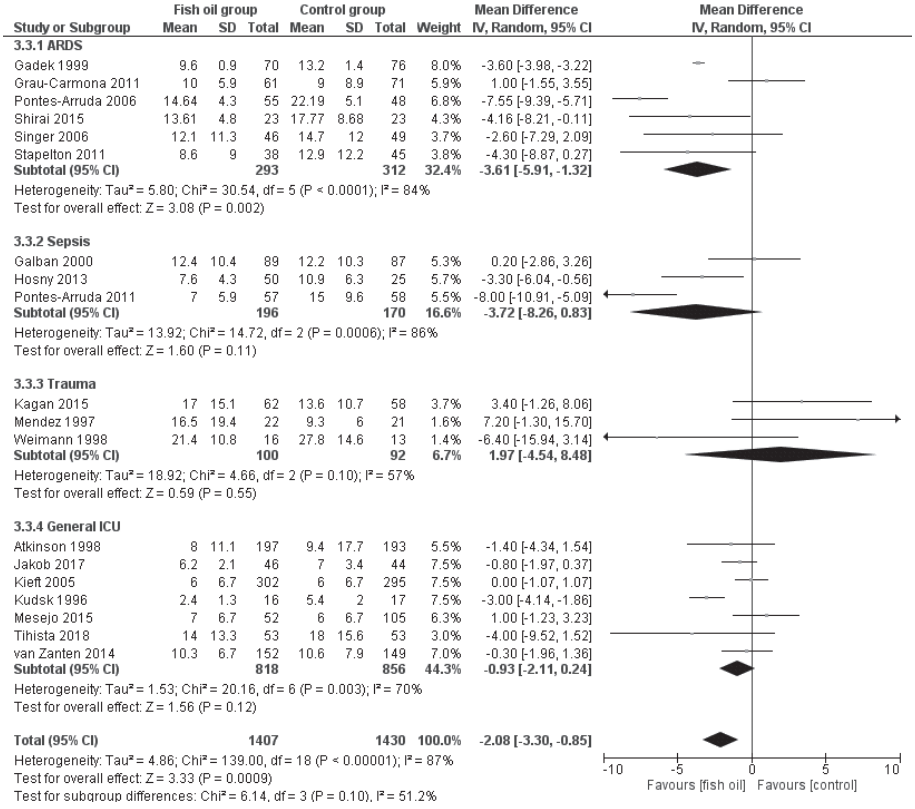
figure 5 in [73]. Tolerability of omega-3 was assessed by incidence of nausea/vomiting, dyspepsia, high GRV, aspiration, diarrhea, constipation, abdominal distention, ileus, pancreatitis, calories delivered, tube replacement rates, achievement of feeding target, triglyceride levels, prokinetics use and overall GI complications (see table 3 in [73]). No significant differences were observed between groups.

Figure 4| The effects of fish oil supplementation on ICU length of stay in different ICU populations



Abbreviations: ARDS: acute respiratory distress syndrome; ICU: intensive care unit; CI: confidence interval; SD: standard deviation; IV: inverse variance.

Figure 5| The effects of fish oil supplementation on ventilation duration in different ICU populations



Abbreviations: ARDS: acute respiratory distress syndrome; ICU: intensive care unit; CI: confidence interval; SD: standard deviation; IV: inverse variance.

DISCUSSION

We systematically reviewed 24 eligible RCTs evaluating the effects of enteral fish oil supplementation in ICU patients [15-38]. The overall results showed no effects on 28-day, ICU or hospital mortality, but length of ICU stay and ventilation duration were significantly reduced by enteral fish oil supplementation. However, upon inspection of the results retrieved from our subgroup analysis, the significance of these findings seems largely due to the benefits found in the ARDS subgroup (i.e. decrease in 28-day mortality, ICU LOS and duration of ventilation). These results should be interpreted with caution as 6 out of 7 ARDS studies were of low methodological quality [17,20,28,29,32,33].

Three recent meta-analysis evaluated the effects of enteral fish oil supplementation specifically in ARDS patients [5,6,74]. No effects on mortality were found and either none or a small reduction in ICU LOS and ventilation duration were reported. In addition, Manzanares et al. recently published the results of a systematic review of parenterally administered fish oil in critically ill patients [7]. They concluded that although no significant effects on mortality were found, fish oil containing lipid emulsions may be associated with a reduction in infections and also could be associated with a reduction in duration of ventilation and hospital LOS. It is however difficult to compare parenteral with enteral administration as the bioavailability of enteral administered fish oil is hard to predict especially in critically ill patients in whom pharmacokinetics are changing during the course of the illness. Moreover, pharmacodynamics including local effects of enteral fish oil on gut immunity may be important, however this assumption is purely speculative. Contemplating the results of recent meta-analysis, including our own, it remains unclear whether fish oil supplementation is beneficial. A closer look at the individual clinical trials shows even larger differences in clinical outcomes. These conflicting results may be, at least partially, explained by two factors. Study populations were heterogeneous and ranged from general ICU patients to specific groups like elective surgical patients admitted to the ICU, severe trauma patients and patients with sepsis or ARDS. Furthermore, study designs are variable demonstrated by differences in method of administration (i.e. parenteral vs enteral, continuous vs bolus, FO as a component of nutrition vs a separate supplement), amount and composition of the (par)enteral nutrition studied as well as the composition of the control feeds.

However, we should also investigate the possibility of a (patho)physiological explanation as for why studies find conflicting results. Dysregulation of the immune response in critical illness has long been the target of development of new therapeutic interventions. The anti-inflammatory and immunomodulatory effects of fish oil have been established in multiple studies. Downregulation of pro-inflammatory mediators

(i.e. cytokines and adhesion molecules) as well as a decrease in the cellular immune response have been widely reported [75-87]. Moreover, a meta-analysis by Pradelli et al showed that the amount of fish oil supplemented in clinical trials led to a significant increase in EPA and DHA plasma levels, which was associated with a significant reduction in IL-6 and a shift in the generation of leukotrienes indicating an anti-inflammatory response in vivo [88]. These findings are important as they suggest that bioavailability of enteral fish oil and the induction of an anti-inflammatory effect are not a problem. The consequently reported immunological response to fish oil supplementation may however be the key to the differences in clinical outcomes found in individual trials [75-87]. The (patho)physiological immunological response to critical illness is different between individual patients and over time, ranging from an extensive hyperinflammatory response to severe immunosuppression. The persistent inflammatory immunosuppressed catabolic syndrome as described by Hotchkiss et al. and Rosenthal et al. suggests diverging immunological phenotypes of multiple organ failure including early deaths due to overwhelming inflammation and late deaths due to both intractable inflammation-induced organ injury or persistent immunosuppression and recurrent infections [89,90]. Whereas the anti-inflammatory effects of fish oil may be beneficial during hyperinflammation it may also be potentially harmful in case of pathophysiological immunosuppression. This may for instance explain why in a post-hoc analysis of the Metaplus trial increases of plasma (EPA+DHA)/LCP-ratios from baseline to day 4 were associated with increased adjusted mortality risk at 6 months independent of baseline levels in the predefined subgroup of medical patients. The exposure of the fish oil supplementation in this study was long (median 12 days) and may have aggravated an immunosuppressed phenotype [38].

Additionally, it may be further illustrated by the differences in clinical outcome effects between old and new studies. Although not significantly different, a marked trend towards better mortality outcome was observed in earlier studies, while no effect was seen in recent studies. When calculating the placebo group mortality large differences were found (32.9% in studies < 2010, 19.6% in studies > 2010). This may suggest that the anti-inflammatory effects are of most benefit to the sickest patients but may be harmful in less severely ill critically ill patients.

Strengths and Limitations

A large number of RCTs were included in this meta-analysis, providing a large number of patients which strengthens the results. However, the studies included have several methodological differences which may influence the outcomes. These include differences in control feeds used, additional immunomodulatory contents (i.e. antioxidants and arginine/glutamine), dose and timing of fish oil supplementation.

Furthermore, we only subtracted data reported in the original papers but were unable to contact the authors to complete missing data. Moreover, the effects of omega-3 supplementation may depend on baseline EPA and DHA levels and on EPA and DHA levels reached. However, only 6 of 24 studies reported plasma levels. As they were reported in different manners it was not possible to analyse them systematically. EPA and DHA levels are reported in Table 1 in [73].

CONCLUSIONS

Based on the results of this meta-analysis enteral fish oil supplementation cannot be recommended for critically ill patients as strong scientific evidence for improved clinical benefits could not be found. There is a signal of mortality benefit in ARDS patients, however results are based on low quality studies. Therefore, enteral fish oil feeds may be considered in patients with ARDS. Further research should focus on the relation between the individual critically ill patients' immune response, the administration of fish oil and clinical outcomes.

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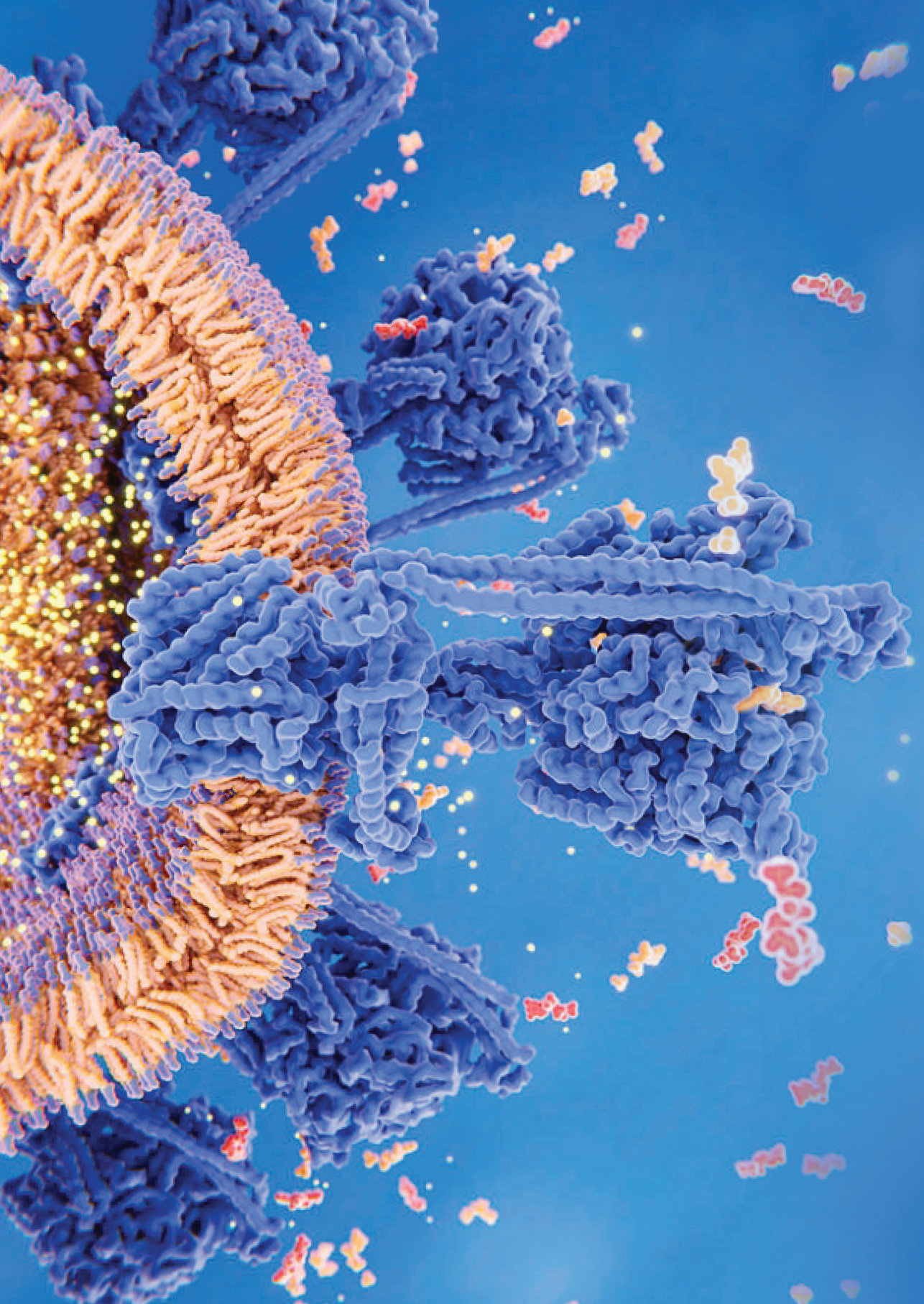

IV PART

Future perspectives for nutrition in the ICU

10

CHAPTER

Nutrition in the ICU: New Trends vs Old-Fashioned Standard Enteral Feeding?

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ABSTRACT

Purpose of review

The narrative review aims to summarize the relevant studies from the last 2 years and provide contextual information to understand findings.

Recent findings

Recent ICU studies have provided insight in the pathophysiology and time course of catabolism, anabolic resistance, and metabolic and endocrine derangements interacting with the provision of calories and proteins. Early provision of high protein intake and caloric overfeeding may confer harm. Refeeding syndrome warrants caloric restriction and to identify patients at risk phosphate monitoring is mandatory. Infectious complications of parenteral nutrition are associated with overfeeding. In recent studies enteral nutrition is no longer superior over parenteral nutrition. Previously reported benefits of glutamine, selenium, and fish oil seem to have vanished in recent studies; however, studies on vitamin C, thiamine, and corticosteroid combinations show promising results.

Summary

Studies from the last 2 years will have marked impact on future nutritional support strategies and practice guidelines for critical care nutrition as they challenge several old-fashioned concepts.

INTRODUCTION

Nutrition support during critical illness aims to improve survival, limit loss of lean body mass, and improve functional outcomes.

Preferably, nutrition dose, composition, and timing are customized to the dynamic metabolic derangements occurring during critical illness. Lack of information on admission patient characteristics (i.e. sarcopenia) and metabolic responses complicate interpretation and application of findings from large trials.

Recent studies have provided pathophysiological insights in protein and energy metabolism and relevance of nutritional interventions for specific ICU populations.

NEW PATHOPHYSIOLOGICAL INSIGHTS

Early during critical illness inflammatory mediators and hormones induce catabolism reflected by elevated cytokine levels and catabolic hormones including cortisol and glucagons [1,2,3]. Endogenous glucose production is enhanced up to 1200 kcal/day [4]. Skeletal muscle protein breakdown is increased [1]. Proteolytic pathways are stimulated. Mitochondrial dysfunction, neuromuscular innervation dysfunction, and calcium homeostasis dysregulation occur [5,6]. All mechanisms contribute to derangements of muscle metabolism [5].

Anabolic resistance, defined as failure of normal anabolic stimuli to induce messenger RNA translation of cellular protein, is increased [6,7]. Higher amino acid levels are needed to achieve similar protein synthesis [6,7]. Anabolic resistance increases with age, leading to 0.8% annual muscle loss (sarcopenia) [7]. Many patients experience lean body mass loss before ICU admission, associated with worse outcomes [7]. Muscle disuse and immobilization increase anabolic resistance [6,8]. Anabolic stimuli and hormone levels (i.e. growth hormone, testosterone) decrease and contribute to enhanced catabolism [6].

Catabolism, anabolic resistance, and lack of anabolic stimuli lead to rapid and severe loss of muscle mass and function in the first weeks of ICU stay [1]. Low muscle quantity and quality on admission assessed by computer tomography are associated with increased mortality and disability rates [9,10 ,11]. Protein breakdown cannot be suppressed by nutritional interventions or insulin. High amino acid dosages may - in the context of increased levels of the catabolic hormone glucagon - enhance hepatic amino acid catabolism [3,12].

Physical therapy may improve anabolic resistance, and early mobilization is associated with improved functional recovery and earlier ICU and hospital discharge [6,7,13]. This creates an anabolic window in which protein supplementation may be more effective [6]. Pulsatile protein administration has been proven to achieve better total-body protein synthesis in non-ICU patients [7]. Pulsatile administration has not been studied in the ICU. Higher protein dosages (2.0-2.5 g/kg/day) may be necessary to achieve optimal muscle protein synthesis [7,8,14]. Specific amino acids have been proven to stimulate anabolic signals by acting as indirect substrates for the mammalian target of rapamycin (mTOR) [6,15]. The mTOR complex is considered the central regulator that integrates nutrient signals, anabolic growth factors such as insulin, cellular energy status, and the oxidative stress level of cells and is particularly sensitive to arginine, leucine, and glutamine (GLN) [7]. Other anabolic interventions include intensive insulin therapy, oxandrolone, and propranolol [15].

Although decreasing catabolism is observed in most ICU patients after 3-4 days, it may persist longer [15,16]. The pathophysiological mechanisms of chronic critical illness and multiorgan failure have recently been summarized as persistent inflammation, immunosuppression and catabolism syndrome [15,16].

CALORIC REQUIREMENTS

As both underfeeding and overfeeding may induce increased morbidity and/or mortality targeting optimum caloric goals is essential. Overfeeding is associated with hyperglycemia, hyperlipidemia, infection risk, and liver steatosis, whereas underfeeding is associated with infection risk and loss of muscle mass and function [17].

The American society for parenteral and enteral nutrition (ASPEN) and the European society for clinical nutrition and metabolism (ESPEN) provide evidence-based guidelines on clinical nutrition designed by world renowned experts [18,19]. Guidelines recommend determining energy requirements to establish caloric goals, ideally, using indirect calorimetry [18]. When indirect calorimetry is unavailable, the use of predictive or weight-based equations is recommended. Although the accuracy of equations ranges from 40 to 75% compared with indirect calorimetry, none of the over 200 equations appears superior to another [18,20-22]. Oshima et al.[23], found calculating energy expenditure based on CO2 measurements (VCO2*8.19 = 24-h energy expenditure) compared with indirect calorimetry inferior. However, superiority of indirect calorimetry over predictive equations has not been established [24]. Weight-based equations recommend 20-25 kcal/kg/day in the acute phase followed by 25-30 kcal/kg/day during recovery [25] or 25-30 kcal/kg/day during the complete ICU stay [18].

Zusman et al.[26] assessed outcomes related to caloric adequacy (percentage of administered calories divided by resting energy expenditure [REE] from indirect calorimetry). The optimum was 70% (significant mortality decrease with caloric increase from 0 to 70% and significant mortality increase >70%). Feeding more than 70% of REE was associated with increased length of stay (LOS) and ventilation duration.

Weijs et al.[27] found that energy overfeeding (>110% of REE) was independently associated with increased mortality in nonseptic patients (odds ratio 1.89). Petros et al.[28], studied normocaloric (75.5% of REE) versus hypocaloric (42.2% of REE) enteral nutrition. No significant mortality differences were observed, however hypocaloric feeding was associated with more nosocomial infections. In contrast, the PERMIT trial by Arabi et al.[29], assessing normocaloric (71% of REE) versus hypocaloric (46% of REE) enteral nutrition did not report differences in nosocomial infections, or any significant differences in mortality, feeding intolerance or ICU/hospital LOS.

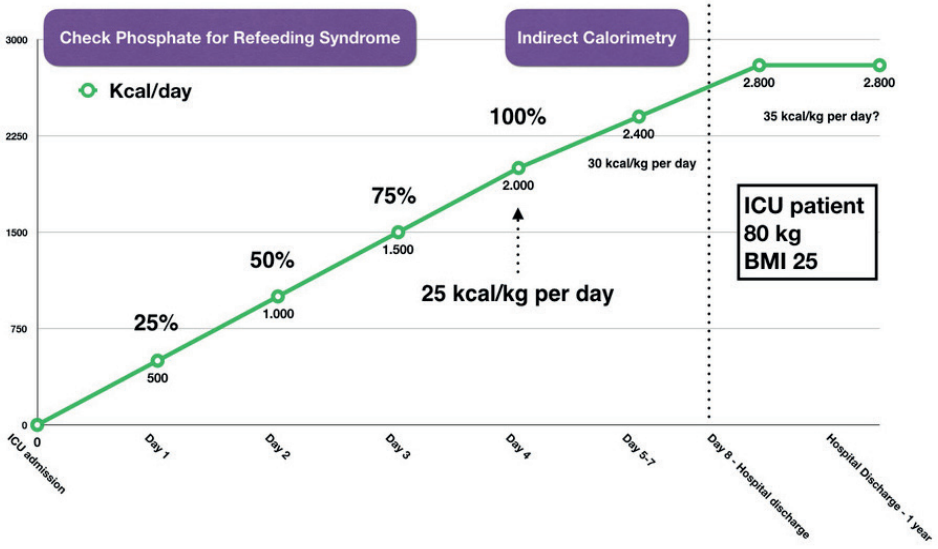
In the EAT-ICU randomized controlled trial (RCT) effects of early goal-directed nutriton (EGDN) versus standard care were studied [30]. EGDN aimed at providing 100% of nutritional requirements based on indirect calorimetry and 24-h urinary urea excretion using enteral nutrition and supplemental parenteral nutrition (SPN). In the standard care group, enteral nutrition was aimed at 25 kcal/kg/day, and if not met by day 7, SPN was started. In the EGDN group, 91% of REE was administered versus only 56% in the standard care group. No significant differences in mortality, severe adverse events, LOS, or physical outcomes were found [30]. Singer et al.[31], stated that 56 and 91% of target REE are associated with the same mortality rate when evaluating the U-shaped survival curve found by Zusman et al.[26], the first caused by underfeeding, the second by overfeeding. Targeting 100% of REE within 24 h after admission may have induced overfeeding, as endogenous energy production was not taken into account.

Cahill et al.[32], studied best achievable nutritional goals in relation to guidelines in a large observational study. Mean caloric adequacy was poor (59% of REE). Similarly, a recent Latin-American study still showed poor feeding adequacy reflected by 40% of patients achieving less than 90% of target [33]. Moreover, most studies targeting normocaloric intake report actual intakes around 70% of REE suggesting that using enteral nutrition aiming at 100% results in optimal actual achievements of around 70% [27-29]. Studies investigating improvement strategies to achieve nutritional goals show significant increase in caloric delivery when SPN is used versus enteral nutrition alone [34].

Dynamic and variable metabolic responses during critical illness warrant regular assessment of REE. Importantly, there is a time-dependent optimum for administered calories because of variable endogenous energy production. This optimum is

individual and related to specific diseases and patient characteristics as reflected by differences encountered among septic and nonseptic patients [27] and those with high and low BMI [34 ,35]. We suggest to gradually increase caloric intake over days to prevent early overfeeding (Fig. 1).

Figure 1| Energy targets during critical illness



In this example a weight-based equation (25 kcal/kg/day) is used to commence feeding aiming to reach target on day 4. This patient with an actual body weight of 80 kg has a daily target of 2000 kcal. After day 4, indirect calorimetry can be used to estimate resting energy expenditure to recalibrate the optimal caloric target. During the post-acute phase of ICU stay higher caloric intakes may be used.

PROTEIN REQUIREMENTS

Determination of protein requirements during critical illness is difficult, and most recommendations are based on pragmatic trials [18].Weight-based equations are commonly used. ASPEN guidelines recommend protein supplementation of 1.2-2.0 g/kg body weight/day [18].

Emerging evidence suggests that protein intake is more relevant for outcomes than caloric intake. Observational studies suggest benefits from high protein intake [36,37]. Recently, three RCTs have compared low versus high protein with similar

caloric intake [38-40]. All showed advantages of more proteins including less fatigue, greater muscle strength, improvement in sequential organ failure assessment scores, less hyperglycaemic events, and shorter duration of respiratory failure [38-40]. No differences in mortality or LOS were observed [38-40]. However, in two of the three trials no effect on primary outcomes was found including ICU discharge hand-grip strength and duration of renal dysfunction [38,39]. In a more recent observational study adequate protein (>90% of 1.2 g/kg/day) and sufficient caloric intake (25 kcal/kg/day) in ventilated patients compared with inadequate protein intake and sufficient caloric intake was associated with improved weaning rates, more ventilator-free days, lower ICU and hospital mortality, and increased 60-day survival [41].

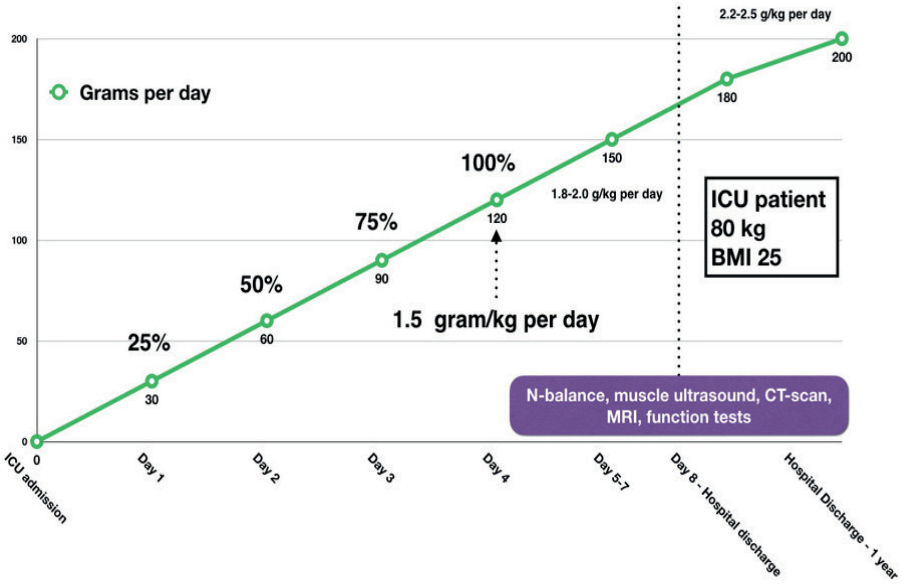
Concordant with these findings, high protein intake (1.2 versus 1.0 g/kg and 0.8 g/kg) on day 4 in the prospective study by Weijs et al.[27], was associated with lower mortality, whereas early overfeeding (>110% of REE) was associated with higher mortality rates. Positive effects of high protein intake were only significant in nonseptic patients. Analysis by Elke et al.[42], however, demonstrated reduced mortality and more ventilator-free days with early higher protein and caloric intake in patients with sepsis and severe pneumonia. Also harm has been reported [43,44]. The INTACT RCT randomized acute lung injury patients to intensive medical nutrition therapy or standard nutrition care. The trial was terminated early for higher mortality in the intervention group (40 versus 16%). This effect was initially attributed to both early high caloric and protein intake with actual nutritional intakes of 0.95 versus 0.58 g/kg/day proteins and 25.4 versus 16.6 g/kg/day calories [45]. However, in a post hoc analysis comparing survivors with nonsurvivors, the mean protein intake was higher in survivors (0.91 versus 0.79 g/kg/d, non significant) with no differences in caloric intake [46]. Several reviews and opinion papers suggested to increase protein targets to 1.2-1.8 g/kg/day, with some even suggesting doses as high as 2.0-2.5 g/kg/day [2,8,14].

Casaer et al.[44] observed time-dependent associations of protein intake and clinical outcomes, based on post hoc analyses of the EPANIC trial, with harmful effects of protein intake during the first 3 days of ICU admission, inducing an autophagy deficient phenotype. Thus, early enhanced caloric loading may lead to overfeeding and early high protein intake may be harmful as well, possibly associated with autophagy. Moreover, protein effects may be divergent in individual patients with renal or hepatic failure, refeeding syndrome (RFS) and high or low nutritional risk score [14].

Hoffer et al.[8], suggested several strategies including assessing the rate of body nitrogen loss to predict minimum protein requirements or to evaluate muscle mass. Kreymann et al.[47], suggested use of energy/nitrogen ratios in optimizing the balance between energy and protein intake. None are standard of care.

Therefore, we suggest to gradually increasing protein intake over days and aim for later higher protein intake (Fig. 2).

Figure 2| Protein targets during critical illness



Abbreviations: CT, computed tomography.

In this example a weight-based equation (1.5 g/kg/day) is used to commence feeding aiming to reach target on day 4. This patient with an actual body weight of 80 kg has adaily target of 120 g of protein. Monitoring optimal protein intake after day 4 is experimental. Several strategies have been suggested such as N-balance, muscle ultrasound (m. quadriceps), CT-scan or MRI studies to estimate lean body mass, or function tests. None have been proven useful to guide protein targeting. During the post-acute phase of ICU stay higher protein intakes are associated with improved outcomes.

ENTERAL VERSUS PARENTERAL NUTRITION

Controversy exists on whether enteral nutrition still is preferred over parenteral nutrition. Timing of total parenteral nutrition and SPN is also debated.

When enteral nutrition is contraindicated or not tolerated ESPEN guidelines advise to start parenteral nutrition within 24-48 h of ICU admission, whereas ASPEN guidelines recommend this only for patients at high nutritional risk [18,19], whereas in others parenteral nutrition should be withheld for 7 days [18]. ESPEN guidelines recommend

SPN in all patients receiving less than their targeted enteral nutrition after 2 days, whereas ASPEN guidelines only recommend SPN if patients are unable to meet more than 60% of nutritional requirements after 7-10 days [18,19].

Early enteral nutrition is considered superior for gut immunity, and to preserve gastrointestinal mucosal function and integrity [24]. In a minority (10-20%) of ICU patients enteral nutrition is not feasible or tolerated enhancing the risk of underfeeding.

Early parenteral nutrition allows for higher nutritional adequacy without potential harms and benefits to the gut. However, parenteral nutrition is associated with higher rates of infectious complications [43]. Elke et al.[48] performed a meta-analysis of 18 RCTs comparing enteral nutrition with parenteral nutrition. The association of parenteral nutrition with increased infection risk was only seen when patients received significantly more calories, but not when enteral nutrition and parenteral nutrition groups had similar caloric intakes [48]. Similarly, the CALORIES trial, which compared enteral nutrition and parenteral nutrition with similar caloric intake, and the NUTRIREA-2 trial comparing enteral nutrition and parenteral nutrition in ventilated patients with shock reported no differences in mortality rates [49,50]. However, in the NUTRIREA-2 trial enteral nutrition was associated with higher rates of vomiting, diarrhea, bowel ischemia, and acute colonic pseudoobstruction, whereas parenteral nutrition was associated with higher caloric and protein adequacy [50].

Timing of SPN has been investigated in several trials. A systematic review of RCTs and observational studies found no differences between early and late SPN regarding in-hospital mortality and contradicting results on LOS, infection rates, duration of ventilation, and muscle wasting [51]. A pilot RCT comparing enteral nutrition and enteral nutrition and SPN in ICU patients with BMIs less than 25 and more than 35 [34] reported no differences in mortality, Barthel index and handgrip strength despite higher caloric and protein intake in the SPN group [34].

Based on recent trials parenteral nutrition seems no longer inferior to enteral nutrition. However, early full nutrition (i.e. 100% of REE) is harmful and parenteral nutrition can lead to higher caloric achievements increasing overfeeding risk. In enteral nutrition (without SPN) 100% of REE is rarely achieved. Adjustment of caloric targets or 'low dose' parenteral nutrition (aiming at 70% of target) may provide an alternative to enteral nutrition. When no contraindications or intolerance to enteral nutrition is present, enteral nutrition is still preferred for the beneficial effects on the gut. In specific patient groups enteral nutrition may lead to rare but severe gastrointestinal complications [50].

REFEEDING SYNDROME

RFS is a potentially fatal acute metabolic derangement (including hypophosphatemia, hypokalemia, fluid overload and thiamine deficiency) reflecting changes from catabolism to anabolism in malnourished patients upon refeeding [52]. The complex interplay of metabolic derangements in RFS and critical illness has not been clarified.

A uniform definition of RFS is lacking. Most commonly used definitions include refeeding hypophosphatemia (varying cutoff levels between <0.32 and 1.00 mmol/l, or drops from baseline phosphate >0.16 mmol/l or >30%), either alone or in combination with clinical symptoms [53]. ICU refeeding hypophosphatemia incidence is estimated at 34-52% [54,55-56].

Contrasting risk factors for RFS among general ward patients, identification among ICU patients remains difficult [57]. We investigated proposed risk factors of refeeding hypophosphatemia and found no significant associations, except for hypokalemia and hypomagnesemia on admission [54]. Although significant, differences in these electrolytes levels were too small to be helpful [54,55,58]. Therefore, phosphate monitoring is mandatory.

Electrolyte and vitamin (especially thiamin) replacement and hypocaloric feeding is recommended for patients at risk of developing RFS [57]. The first RCT in adult ICU patients developing refeeding hypophosphatemia comparing standard nutritional support and caloric restriction (500 kcal/day) showed benefits of caloric restriction concerning infections and mortality rates [59]. We showed increased 6-month survival among refeeding hypophosphatemia patients on hypocaloric feeding (<50% of target) [54]. However, permissive underfeeding has not been shown to be beneficial in patients who developed refeeding hypophosphatemia in the post hoc analysis of the PERMIT trial regarding 90-day mortality and ICU-associated infections [29]. Moreover, hypocaloric feeding may not protect against RFS development as no differences in caloric intake in RFS patients and those without were observed [56].

IMMUNONUTRITION

The efficacy of immunonutrients has been studied frequently [60,61,62,63]. GLN supplementation may be beneficial through inducing protein anabolism via mTOR [7]. However, studies have showed conflicting results ranging from no effect or small benefits to increased mortality [64]. A post hoc analysis of the MetaPlus trial found associations of higher baseline GLN levels and increased 6-month mortality, but not between plasma GLN level changes and mortality [65]. Ziegler et al.[61], studied parenteral nutrition with GLN supplementation in surgical ICU patients. No

differences in in-hospital and 6-month mortality or adverse events were observed compared with placebo [61].

Previous guidelines recommended enrichment of nutrition with omega-3 fatty acids. Recent updates suggest fish oil not to be used routinely [66]. New data showed possible harm (6-month mortality) of fish oil supplementation [65] Reviews and meta-analyses show no effect on mortality and possible reductions in ICU LOS in sepsis patients treated with fish oil [67,68].

Selenium supplementation has been studied extensively [69]. A RCT by Bloos et al.[62], evaluated sodium selenite in patients with severe sepsis or septic shock. No significant differences in 28-day mortality or adverse events were observed. Hospital LOS was significantly shorter in patients receiving sodium selenite [62]. Selenium is no longer recommended.

Marik et al.[63], published a before-after study on micronutrient supplementation. In severe sepsis and septic shock patients high-dose vitamin C (6 g daily), thiamine (400 mg daily), and hydrocortisone supplementation (200 mg daily) were compared with control patients. Significant benefits on hospital mortality and duration of vasopressor use were observed with this combination [63]. Effects of combined therapy with vitamin C and hydrocortisone on human lung microvascular endothelial barrier function were investigated after lipopolysaccharide administration. Neither vitamin C nor hydrocortisone alone was beneficial. However, the combined use reversed the lipopolysaccharide-induced barrier dysfunction [70]. Although promising, these studies need confirmation in larger prospective trials.

CONCLUSION

Recent ICU studies have provided insight in the pathophysiology and time course of catabolism, anabolic resistance, and metabolic and endocrine derangements interacting with the provision of calories and proteins. Early provision of high protein intake and caloric overfeeding may confer harm. RFS warrants caloric restriction and to identify patients at risk phosphate monitoring is mandatory. Infectious complications of parenteral nutrition are associated with overfeeding. In recent studies enteral nutrition is no longer superior over parenteral nutrition. Previously reported benefits of GLN, selenium and fish oil seem to have vanished in recent studies, however studies on vitamin C, thiamine, and corticosteroid combinations show promising results.

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11

CHAPTER

General discussion and future perspectives

W.A.C. Koekkoek

GENERAL DISCUSSION

The optimization of nutritional support in the intensive care unit (ICU) is impeded by limited evidence on the nutritional needs of critically ill patients. This thesis aimed to improve the understanding of the nutritional needs of ICU patients.

Estimation of the optimal caloric target in the acute phase of critical illness

As acute illness results in severe metabolic stress, with detrimental effects on muscle mass and function, it is important to start metabolic evaluation and nutritional support already in the acute phase of illness [1-3]. Metabolic evaluation often limited to an estimation of caloric and protein requirements in clinical practice. However, the course of energy expenditure during critical illness is complex and influenced by many individual and iatrogenic factors as well as different metabolic phases of critical illness [4]. Therefore, frequent assessment of energy expenditure can be used to optimize nutritional support. Indirect calorimetry is the only reliable method for estimating energy expenditure in current practice. Energy expenditure should not be estimated by VCO2-derived methods as they are nor accurate nor precise and do not provide an alternative for indirect calorimetry (chapter 2). Although frequently used, existing predictive equations to estimate energy expenditure are also unreliable in ICU patients. Because indirect calorimetry is not always feasible, the development of better and dynamic predictive models for energy expenditure (chapter 3) may be helpful in determining nutritional goals in daily practice.

A reliable estimation of energy expenditure is only the first step in determining the optimal caloric target. The percentage of the estimated energy expenditure that reflects the optimal caloric feeding target is still under debate [4,5]. In the past decade, a paradigm shift has taken place, from aggressive to more cautious early feeding [4-7]. This paradigm shift results from clinical studies reporting increased mortality associated with overfeeding in the acute phase of ICU admission [8,9] and a better understanding of the factors influencing the course of energy expenditure and energy demand in critical illness. Factors favoring a gradual increase of nutritional support include endogenous energy production, which cannot be abolished by exogenous nutrient and insulin administration, and the refeeding syndrome [10]. As no bedside method is yet available to estimate endogenous energy production, and because the diagnosis of refeeding syndrome is complicated [11], the optimal exogenous caloric target in the acute phase remains a more or less calculated guess.

Does optimal protein intake change during critical illness?

Different metabolic phases of critical illness have been described, such as the early acute, late acute, post-acute, post-ICU and post-hospital phases. Theoretically, it is plausible that the required protein intake differs in each metabolic phase of critical illness. However, there is no clinical marker to identify transition into the next metabolic phase and the duration of the different metabolic phases is likely to differ in every individual patient. In chapter 4 timing of protein intake was investigated. We found the lowest six month mortality in patients with a gradually increased protein intake. Recently, another cohort study was published [12] reporting increased survival in patients with overall high protein intake, compared with overall low protein intake and a gradual increase of protein intake. An explanation for the different results may be found in the population studied. Another recent study investigated which patients would benefit most from early high protein intake. Early high protein intake (>1.2g/kg/day on days 2-4) compared with early normal or low protein intake (<1.2g/kg/day on days 2-4) was associated with a lower 60-day and six-month mortality in patients with a low muscle-skeletal area and low muscle density, but not in patients with a normal or low muscle-skeletal area without low muscle density [13]. Furthermore, in another study from our own group, we found a robust time-dependent effect of protein intake in patients without sepsis but not in patients with sepsis. In patients without sepsis, early high protein intake (>1.2g/kg/day on days 1-3) and late low protein intake (<0.8g/kg/day on days 4-7) were associated with higher 6-month mortality compared with early low and late high protein intake [14].

Although multiple randomized controlled trials (RCTs) have compared protein dose in critically ill patients over the past years, none have investigated time-dependent effects of protein doses [15-23]. As most RCTs include patients within 24-72 hours after ICU admission and start the intervention (i.e. high protein vs lower protein) somewhere in this time window, possible time-dependent effects of protein intake are hard to investigate in the early acute phase of critical illness. However, these time-dependent effects may the many negative or even conflicting results of studies evaluating protein intake.

To complicate things further, while we are trying to optimize nutrition in the first days of ICU admission, nutrition is often suboptimal for weeks in the post-ICU and post-hospital phase. Recent studies report low nutritional adequacy after extubation and ICU discharge, with protein intake reaching only 27%-46% of target [24-25]. As research thus far has largely focused on the acute phase of critical illness, these new studies evaluating intake in the post-acute/post-ICU/post-hospital phase are of high interest. Better protein (and energy) provision in the post-acute and post-ICU phase may significantly improve long-term clinical outcomes.

Antioxidant micronutrients and micronutrient deficiencies

The relationship between micronutrient blood concentrations and total body stores, alters during critical illness (chapter 7). This alteration may well be an effective adaptive response, as redistribution of antioxidants to the intracellular compartment may reduce the harmful effects of excessive reactive oxygen species on mitochondrial function and increase the amount of reactive oxygen species in the bloodstream to improve bacterial killing [26]. We showed that in the absence of micronutrient supplementation, other than in standard enteral nutrition, the course of micronutrient blood concentrations in the first week of ICU admission differs for each nutrient studied (chapter 8). This variability may reflect the changes in micronutrient metabolism during critical illness.

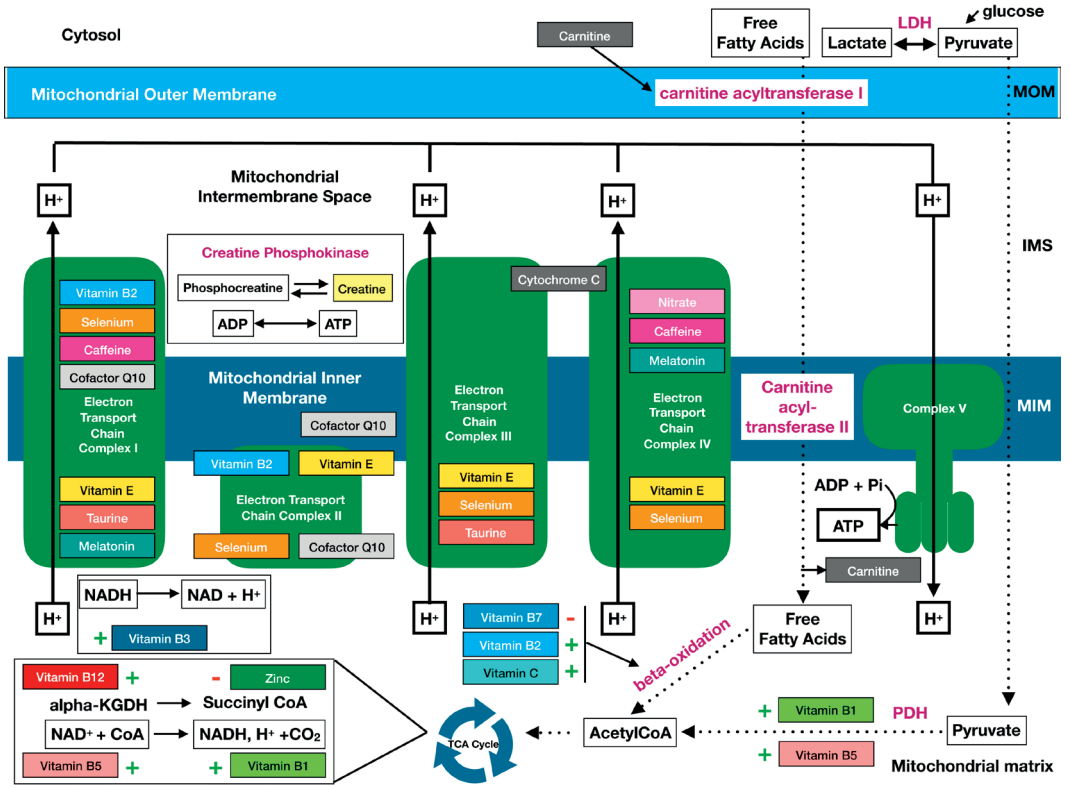
Most clinical trials have focused on either supplementing one micronutrient to normal or supranormal levels, or a combination of micronutrients that had a low blood concentration in earlier studies [27]. However, normalization of blood concentrations may not be the optimal target. The cascade of oxidative stress-mediated damage ultimately leads to (multi-)organ damage, starting with mitochondrial damage [28]. Therefore, restoration of mitochondrial damage, regeneration of mitochondrial function, and possibly preventing mitochondrial dysfunction may be more promising targets to investigate.

The potential beneficial role of vitamin C in critically ill patients has gained specific interest in recent years. The theoretical potential of vitamin C (including antioxidant capacity, improvement of microcirculation and immune modulation) in combination with low vitamin C blood concentrations reported in critically ill patients and a large mortality benefit in a retrospective cohort study [29] lead to numerous clinical trials. However, multiple randomized controlled trials have failed to demonstrate clinical benefits of intravenous vitamin C monotherapy [30-32].

The human antioxidant network consists of multiple enzymes, cofactors and vitamins (chapter 7). It is likely that the antioxidant properties of the total antioxidant network increase when substrates and cofactors are available in optimal combinations. Supplementation of a single antioxidant micronutrient may confer less or no benefits in case another is deficient.

A recent Bayesian multiple treatment comparisons meta-analysis tried to identify the ideal combination of antioxidants for improvement of clinical outcomes. Combinations of selenium, zinc, copper and/or vitamin E were ranked the best treatments for reduction of mortality, infection risk, ventilator days and ICU length of stay [33].

Figure 1| An overview of relevant nutrients in bioenergetics mitochondrial processes



Abbreviations: a-KGDH = alpha-ketoglutarate dehydrogenase; ATP = adenosine triphosphate; CoA = coenzyme A; CO2 = carbon dioxide; CoQ = coenzyme Q; NAD(H) = Nicotinamide adenine dinucleotide (reduced); PDH = pyruvate dehydrogenase; Vit = vitamin.
Reproduced with permission from [34].

OPTIMIZING CRITICAL CARE NUTRITION: SUGGESTIONS FOR CLINICAL PRACTICE

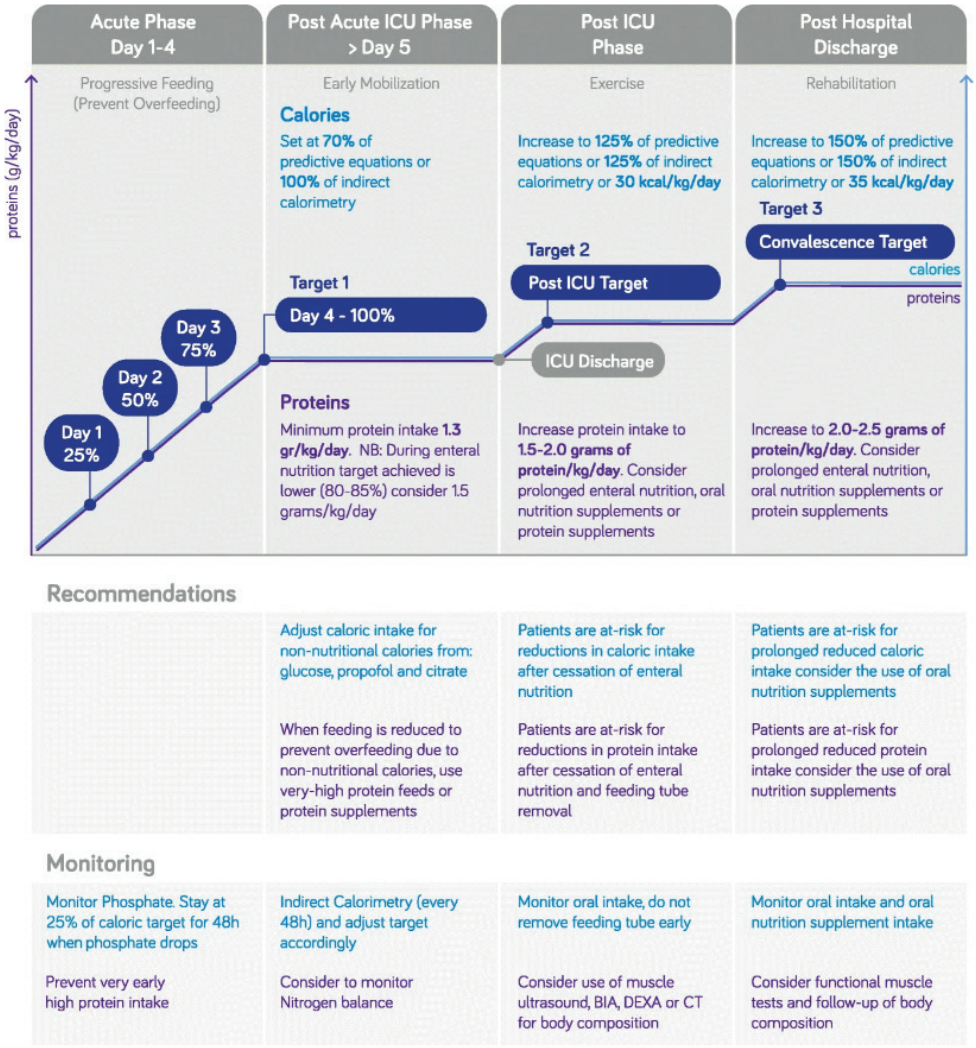
Optimizing critical care nutrition starts with recognition of the importance of this component of ICU care. This thesis has shown that a continuous evaluation of nutritional goals during ICU stay and adjustment of nutritional support to patient needs are likely to improve patient outcomes. Although these interventions are already part of standard care in several ICUs, the importance of metabolic and nutritional evaluation and intervention deserves more attention in our daily clinical practice.

Specific clinical recommendations for critically ill patients based on the main findings of this thesis include:

1. Estimate energy expenditure by indirect calorimetry, as alternative methods (VCO2 and predictive equations) are unreliable
2. In absence of indirect calorimetry, use predictive equations to estimate energy expenditure roughly and adjust the target by taking individual patient factors influencing energy expenditure into account
3. Gradually increase protein intake in critically ill patients as this is associated with the best patient outcomes
4. Do not postpone initiation of feeding or discard the importance of low dose nutrition in the early phase of critical illness, as underfeeding in any phase is associated with the worst patient outcomes
5. In case of refeeding hypophosphatemia, caloric restriction should be implemented in addition to electrolyte and vitamin supplementation to improve patient outcomes
6. Low serum levels of micronutrients do not implicate need for aggressive supplementation
7. Standard enteral supplementation of fish oil is NOT recommended, as there is no prove of clinical benefits at this time

Our group proposed a practical approach to provide proteins and calories during the phases of critical illness and convalescence in 2019. In the end, this approach may not be optimal for every critically ill patient, but based on current knowledge, this approach confers the least harm [30].

Figure 2| Practical approach to provide proteins and calories during the phases of critical illness and



Abbreviations: g/kg/day grams of proteins per kilogram per day, kcal/day total kilocalories per day, BIA bioelectrical impedance analysis, DEXA dual-energy X-ray absorptiometry, CT computed tomography scanning. Reproduced with permission from [35].

OPTIMIZING CRITICAL CARE NUTRITION: SUGGESTIONS FOR FURTHER RESEARCH

In order to optimize nutrition in critically ill patients, we must better understand (1) the underlying metabolic pathology and requirements in the different phases of critical illness (acute, post-acute, post-ICU and post-hospital), (2) the differences in metabolic pathology and requirements between critically ill patients and (3) the metabolic response to nutritional interventions. Based on this knowledge we can (4) adjust nutritional goals and interventions for individual patients in all phases of critical illness.

Specific suggestions regarding further research

1. *Estimation of energy expenditure*
   a. How can we estimate endogenous energy expenditure in the individual patient in clinical practice?
   b. Can indirect calorimetry be replaced by a dynamic predictive model?

2. *Optimal protein intake*
   a. How can we identify differences in protein requirement between patients and within patients during the course of critical illness?
   b. How can we optimize protein (and caloric) adequacy in the post-ICU phase?

3. *Refeeding syndrome*
   a. Does macronutrient composition (proteins, carbohydrates, fats) of nutrition influence clinical outcomes in patients with refeeding hypophosphatemia?
   b. What is the pathophysiological mechanism of hypophosphatemia in patients with refeeding syndrome?
   c. Is mitochondrial dysfunction and antioxidant status similar in patients with and without refeeding syndrome?

4. *Antioxidants, micronutrients and mitochondrial dysfunction*
   a. How does mitochondrial (dys)function develop during critical illness?
   b. Is mitochondrial dysfunction a causal factor in ICU-acquired weakness?
   c. Can mitochondrial damage be prevented or restored by combinations of micronutrients?
   d. Is micronutrient intake adequate to support bioenergetic restoration in the post-acute phase?

5. *Immunonutrition*
    a. What are the pharmacokinetics and –dynamics of enterally administered fish oil compared to parenterally administered fish oil? Can this explain the difference in patient outcomes?
    b. How does enteral fish oil supplementation affect the immune system? How does the immune response on enteral administered fish oil differ from parenterally administered fish oil?

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A

APPENDICES

SUMMARY

Critically ill patients may lose one kilogram muscle mass per day in the first ten days of intensive care unit (ICU) admission. This profound loss of muscle mass is likely to contribute to the long term impairment in physical function observed in many ICU survivors. Optimal nutritional support during and after ICU admission is important as it has been associated with improving clinical outcomes. Ideally, nutritional support reduces the loss of muscle mass in the early phases of ICU admission and later on encourages muscle anabolism and recovery leading to better functional outcomes.

PART I – Estimating the optimal caloric target

The caloric needs of ICU patients change during ICU admission. Adequate estimation of energy expenditure is important for determination of a caloric target. Indirect calorimetry is the gold standard method to estimate resting energy expenditure, but its use is limited in clinical practice. An alternative method of estimating energy expenditure has been proposed based on the carbon dioxide consumption (VCO_2) measured by the mechanical ventilator. This is reported to show better accuracy than predictive equations, which generally have poor predictive performance.

The predictive performance of the energy expenditure estimated by ventilator-derived carbon dioxide consumption ($EEVCO_2$) compared with the energy expenditure estimated by indirect calorimetry was determined in **chapter 2.** In a prospective cohort of 31 mechanically ventilated patients receiving artificial nutrition 414 paired measurements were obtained. The mean estimated $EEVCO_2$ was 2134 kcal/24 hours and the mean estimated energy expenditure by indirect calorimetry was 1623 kcal/24 hours. We concluded that $EEVCO_2$, compared with indirect calorimetry, overestimates actual energy expenditure and the overall predictive performance of the $EEVCO_2$ is poor. Although the reliability is acceptable, bias is significant, and the precision and accuracy rates are unacceptably low. Predictive equations, although inaccurate, may even predict energy expenditure better compared with $EEVCO_2$.

In order to optimize estimations of energy expenditure in absence of indirect calorimetry factors that influence energy expenditure have to be identified. Neuromuscular blocking agents conceptually lower energy expenditure, but have not been extensively investigated. A cohort of 122 adult critically ill patients requiring invasive mechanical ventilation and treatment with continuous infusion of cisatracurium for at least 12 hours was studied in **chapter 3.** Mean energy expenditure was significantly lower after cisatracurium infusion (1974 kcal/day before cisatracurium vs 1888 kcal/day after cisatracurium), although the magnitude of the effect was small. It was associated with overfeeding in only a minority of patients and therefore, in most patients, no reductions in caloric prescription are necessary. In

addition, sepsis and higher body temperature were associated with increased energy expenditure in this cohort.

PART II – Nutritional dose and timing of initiation

This part of the thesis focusses on the optimal macronutrient composition and nutritional dose in the first week of ICU admission. Studies implied no harm of hypocaloric feeding when protein requirements are met. Therefore, optimal protein provision may be more important than caloric adequacy. A possible time-dependent association of protein intake and clinical outcome has been suggested. We investigated this association in a retrospective cohort study, reported in **chapter 4**. In total 455 patients, who were mechanically ventilated for at least 7 days were included. Overall low protein intake, i.e. < 0.8g/kg/day during the first 7 days of ICU admission, was associated with the highest ICU, in-hospital and 6-month mortality (40.0%, 48.6%, 48.6%). In addition, a time-dependent effect of protein intake in critically ill patients was observed. High protein intake (> 0.8g/kg/day) during the first 3 days of ICU admission was associated with increased ICU, in-hospital and 6-month mortality (22.2%, 33.3%, 42.7%). Lowest 6-month mortality was found when increasing protein intake from <0.8g/kg/day on day 1-2 to 0.8-1.2g/kg/day on day 3-5 and >1.2g/kg/day after day 5 (23.4%).

Energy intake during refeeding syndrome is heavily debated in critically ill patients. The incidence of refeeding syndrome and the associations between caloric intake and clinical outcomes were studied in a retrospective cohort of 337 critically ill mechanically ventilated patients in **chapter 5.** Refeeding syndrome was diagnosed by the occurrence of new onset hypophosphatemia (<0.65 mmol/l) within 72 hours of the start of nutritional support, 124 (36.8%) developed refeeding syndrome. Between the two groups, no statistical significant differences in clinical outcomes were observed. However, within the refeeding syndrome group, a reduced 6-month mortality risk for low caloric intake (<50% of target) was seen compared with normal intake, adjusted Hazard Ratio 0.39, (95% CI 0.16–0.95, p = 0.037). In patients without refeeding syndrome no significant difference in 6-month mortality risk was observed between low or normal caloric intake.

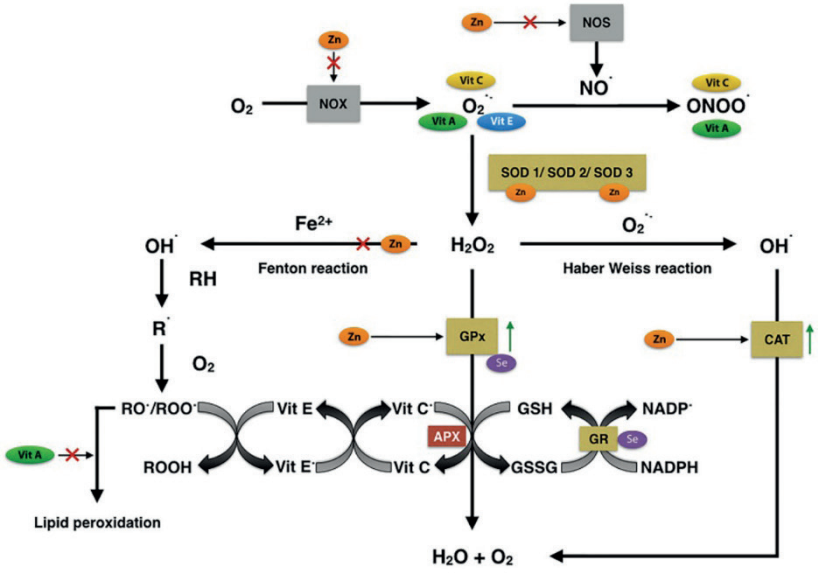
The current knowledge of refeeding syndrome in critically ill patients regarding epidemiology, identification of patients at risk and strategies to reduce potential negative impact on outcome is reviewed in **chapter 6.** Refeeding syndrome is a potentially fatal acute metabolic derangement that ultimately can result in marked morbidity and even mortality. These metabolic derangements in ICU patients differ from otherwise healthy patients with refeeding syndrome, as there is lack of anabolism. This is because of external stressors inducing a hypercatabolic response

among other reasons also reflected by persistent high glucagon despite initiation of feeding. Lack of a proper uniform definition complicates diagnosis and research of refeeding syndrome. However, refeeding hypophosphatemia is commonly encountered during critical illness. Based on recent trials among critically ill patients, only treatment with supplementation of electrolytes and vitamins seems not sufficient. In addition, caloric restriction for several days and gradual increase of caloric intake over days is recommendable.

PART III – Pharmaconutrition

Macro- and micronutrient supplements are the focus of interest of this part of the thesis. We present an extensive review of antioxidant mechanisms, antioxidant status and effects of supplementation of antioxidant vitamins and trace-elements in critically ill patients in **chapter 7.** The disturbed balance between pro-oxidants and antioxidants is considered as oxidative stress. Oxidative stress leads to cell damage, tissue damage and ultimately (multi)organ damage and failure. Restoring the pro-oxidant/antioxidant balance may therefore reduce cell and organ damage and restore cell and organ function. The human antioxidant network consist of enzymes, antioxidant vitamins and enzyme cofactors (i.e. trace-elements) and endogenous antioxidant compounds. The delicate interplay between oxidants and the antioxidant network is depicted in figure 1.

Figure 1 – The human antioxidant network



Low plasma levels of antioxidant enzymes, vitamins, and trace elements have been frequently reported in critically ill patients and thus supplementation seems logical. However, low antioxidant plasma levels per se may not indicate low total body stores i.e. true deficiency as critical illness may induce redistribution of antioxidants. The current evidence on supplementation of vitamin A, C, E and enzyme cofactor trace elements selenium and zinc, either combined or alone, in critically ill patients was reviewed. Results are conflicting as some studies show clear benefits, whereas others demonstrate neutral outcomes and even harm.

Blood micronutrient concentrations in the first week of ICU admission in the absence of micronutrient supplementation are the object of the prospective cohort study in **chapter 8.** Patients only received micronutrients through standard enteral nutrition. Micronutrient levels, including selenium, β-carotene, vitamin C, E, B_1 and B_6 were measured repeatedly during the first week of ICU admission in 24 critically ill patients. The micronutrient concentrations at ICU admission were compared to those of healthy age-matched controls. Most mean micronutrient levels were significantly lower in the ICU patients compared to the healthy controls (selenium 0.52 µmol/l vs 0.90 µmol/l, β-carotene 0.17 µmol/l vs 0.50 µmol/l, vitamin C 21.5 µmol/l vs 45 µmol/l and vitamin E 20.3 µmol/l vs 35.5 µmol/l), while vitamin B1 (129.5 nmol/l vs 122 nmol/l) and B6 (41 nmol/l vs 44 nmol/l) were not significantly different between patients and controls. Selenium, vitamin B1 and vitamin B6 levels remained stable during ICU admission. Vitamin C levels dropped significantly until day 5 ($p < 0.01$). Vitamin E and β-carotene levels increased significantly on days 5-7 and day 7, respectively ($p < 0.01$). Therefore, progressive enteral tube feeding containing vitamins and trace elements does not normalize plasma levels in the first week of ICU stay. When treatment objectives are to normalize plasma concentrations of the studied micronutrients only tube feeding is not sufficient and pharmacological supplementation should be considered. In addition, no associations between micronutrient levels and severity of illness, CRP or micronutrient intake were found.

A systematic review and meta-analysis of 24 trials studying the effects of enteral fish oil supplementation on clinical outcomes in critically ill patients is described in **chapter 9.** Overall, no significant effect of enteral fish oil supplementation on 28-day, ICU or hospital mortality was observed. However, ventilation duration and ICU length of stay were significantly reduced in patients receiving fish oil supplementation. When comparing high with low quality trials, significant reductions ventilation duration in low but not high quality trials were observed. Regarding ICU length of stay a significant reduction was observed in high quality trials whereas only a trend was observed in low quality trials. Furthermore, subgroup analysis revealed a significant reduction in 28-day mortality, ICU LOS and ventilation duration in ARDS patients but

not in other subgroups. However, the studies included in the ARDS subgroup are mostly of low methodological quality. Therefore, enteral fish oil supplementation cannot be recommended for critically ill patients as strong scientific evidence for improved clinical benefits could not be found.

PART IV – Future perspectives for nutrition in the ICU

We describe new developments and insights in critical care nutrition between 2015-2018 in **chapter 10.** The general discussion of this thesis is presented in **chapter 11**, including a practical approach to provide proteins and calories during the phases of critical illness and convalescence, and specific suggestions for further research.

NEDERLANDSE SAMENVATTING

Patiënten op de intensive care (IC) verliezen tot één kilogram spiermassa per dag in de eerste tien dagen van IC opname. Dit forse spiermassaverlies draagt waarschijnlijk bij aan de langdurige fysieke beperking die wordt waargenomen bij veel patiënten die de IC overleven. Optimale voeding gedurende en na IC opname is belangrijk en geassocieerd met betere klinische uitkomsten. Idealiter reduceert voeding het spiermassaverlies in de vroege fase van IC opname en stimuleert voeding spieropbouw en -herstel in een latere fase, waardoor de functionele uitkomst verbetert.

DEEL 1 – Het inschatten van de optimale hoeveelheid calorieën

De energiebehoefte van IC patiënten verandert gedurende IC opname. Om de optimale hoeveelheid calorieën te bepalen die aan een IC patiënt moet worden gegeven is het belangrijk het energieverbruik nauwkeurig in te schatten. Indirecte calorimetrie is de gouden standaard methode om energieverbruik in rust in te schatten, maar wordt weinig gebruikt in de klinische praktijk. Een alternatieve methode die is voorgesteld om het energieverbruik in te schatten is gebaseerd op de koolzuurproductie (VCO_2) gemeten door de beademingsmachine. Vergeleken met voorspelmodellen, die veelal een beperkte voorspellende waarde hebben, wordt een betere nauwkeurigheid van deze methode beschreven. In **hoofdstuk 2** onderzoeken we de voorspellende waarde van het geschatte energieverbruik op basis van koolzuurproductie gemeten door de beademingsmachine ($EEVCO_2$) vergeleken met het door indirecte calorimetrie geschatte energieverbruik. In een prospectief cohort van 31 beademde patiënten die kunstmatige voeding kregen, werden 414 gepaarde metingen gedaan. Het gemiddeld geschatte $EEVCO_2$ was 2134 kcal/24 uur, terwijl het energieverbruik door de indirecte calorimetrie werd geschat op 1623 kcal/24 uur. We concludeerden dat het $EEVCO_2$ het energieverbruik overschat vergeleken met indirecte calorimetrie en dat de voorspellende waarde van het $EEVCO_2$ slecht is. Hoewel de betrouwbaarheid acceptabel is, zijn de precisie, nauwkeurigheid en bias dat niet. Voorspelmodellen lijken het energieverbruik op dit moment beter in te schatten dan het $EEVCO_2$.

Om voorspelmodellen te optimaliseren moeten factoren worden geïdentificeerd die het energieverbruik beïnvloeden. Theoretisch zouden neuromusculair blokkerende medicijnen het energieverbruik moeten verlagen, maar dit is niet eerder uitvoerig onderzocht. **Hoofdstuk 3** beschrijft een cohort van 122 ernstig zieke volwassen patiënten die invasief beademd werden en tenminste 12 uur cisatracurium kregen toegediend via een continue infuus. Het gemiddelde energieverbruik was significant lager gedurende toediening van cisatracurium (1888 kcal/24 uur) dan voorafgaand aan de toediening (1974 kcal/24 uur), hoewel de effectgrootte beperkt was. Bij een minderheid van de patiënten was het gebruik van voorspelmodellen, niet gecorrigeerd

voor neuromusculair blokkerende medicijnen, geassocieerd met overvoeding. Bij de meeste patiënten was het niet nodig de calorische intake te reduceren wanneer neuromusculair blokkerende medicijnen werden gebruikt. Als bijkomende bevindingen werden zowel sepsis als een verhoogde lichaamstemperatuur geassocieerd met een toename in het energieverbruik in dit patiënten cohort.

DEEL 2 – De voedingsdosering en het moment van starten van voeding

In dit gedeelte onderzoeken we de ideale macronutriële samenstelling en opbouw van voeding in de eerste week van IC opname. Recente studies impliceren dat hypocalorisch voeden niet schadelijk is wanneer aan de eiwitbehoefte wordt voldaan. Optimale eiwitvoorziening zou dan ook belangrijker kunnen zijn dan het behalen van een calorisch target. Daarnaast wordt een mogelijke tijdsafhankelijke associatie van eiwitinname en klinische uitkomst gesuggereerd. Wij onderzochten deze associatie in een retrospectief cohort van 455 IC patiënten die minimaal 7 dagen invasief werden beademd **(hoofdstuk 4).** Een algehele lage eiwitinname, d.w.z. < 0,8 g/kg/dag gedurende de eerste 7 dagen van IC-opname, was geassocieerd met de hoogste IC-, ziekenhuis- en 6-maanden mortaliteit (40,0%, 48,6%, 48,6%). Bovendien werd een tijdsafhankelijk effect van eiwitinname bij ernstig zieke patiënten waargenomen. Een hoge eiwitinname (> 0,8g/kg/dag) tijdens de eerste 3 dagen van IC-opname was geassocieerd met verhoogde IC-, ziekenhuis- en 6-maanden mortaliteit (22,2%, 33,3%, 42,7%). De laagste mortaliteit na 6 maanden werd gevonden bij verhoging van de eiwitinname van <0,8 g/kg/dag op dag 1-2 tot 0,8-1,2 g/kg/dag op dag 3-5 en >1,2 g/kg/dag na dag 5 (23,4%).

De calorische intake tijdens het refeedingsyndroom wordt bediscussieerd bij ernstig zieke patiënten. De incidentie van het refeedingsyndroom en de associaties tussen calorie-inname en klinische uitkomsten werden bestudeerd in een retrospectief cohort van 337 ernstig zieke beademde patiënten (**hoofdstuk 5).** De diagnose refeedingsyndroom werd gesteld wanneer er sprake was van een nieuw ontstane hypofosfatemie (< 0.65 mmol/l) binnen 72 uur na de start van voeding. Het refeedingsyndroom werd bij 124 (36,8%) vastgesteld. Tussen de patiëntengroepen met en zonder refeedingsyndroom werden geen statistisch significante verschillen in klinische uitkomsten waargenomen. Binnen de groep met het refeedingsyndroom werd er echter bij de patiënten met een lage calorie-inname (<50% van het doel) een significant lager sterfterisico na 6 maanden gezien vergeleken met de patiënten met normale calorie-inname (HR 0,39). Bij patiënten zonder het refeedingsyndroom werd geen significant verschil in sterfterisico na 6 maanden waargenomen tussen lage of normale calorie-inname.

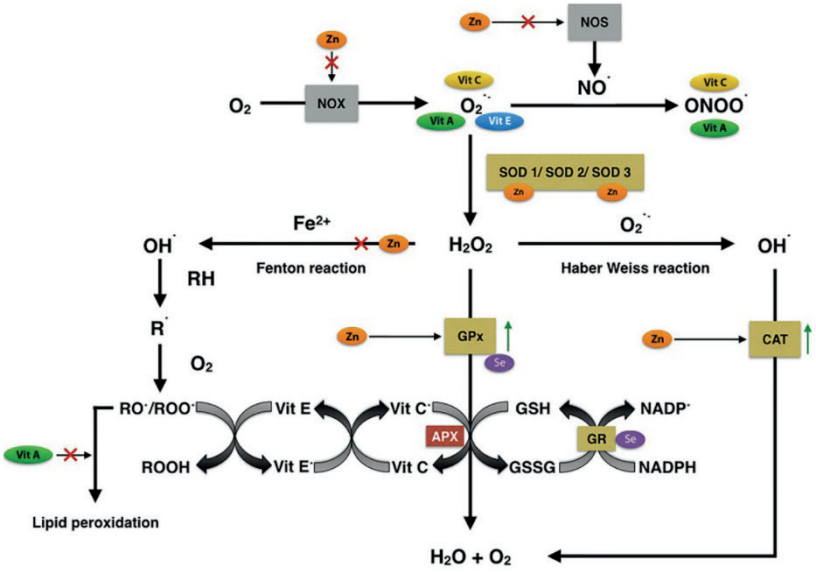
De huidige kennis over het refeedingsyndroom bij ernstig zieke patiënten met betrekking tot epidemiologie, identificatie van patiënten die risico lopen en strategieën om mogelijke negatieve gevolgen te beperken, wordt besproken in **hoofdstuk 6**. Refeedingsyndroom is een potentieel fatale acute metabole stoornis die uiteindelijk kan resulteren in duidelijke morbiditeit en zelfs sterfte. De metabole stoornissen bij IC-patiënten verschillen van verder gezonde patiënten met het refeedingsyndroom, omdat er geen anabolisme is bij IC patiënten. Externe stressoren veroorzaken een hyperkatabole respons, hetgeen wordt weerspiegeld door een persisterend hoge concentratie glucagon in het bloed ondanks de start van voeding. Het ontbreken van een goede uniforme definitie bemoeilijkt de diagnose en het onderzoek van het refeedingsyndroom. Refeeding-hypofosfatemie komt echter vaak voor bij IC patiënten. Op basis van recente onderzoeken bij ernstig zieke patiënten lijkt alleen behandeling met suppletie van elektrolyten en vitamines niet voldoende. Aanvullend is een caloriebeperking en een geleidelijke verhoging van de calorie-inname uitgespreid over meerdere dagen aan te bevelen.

DEEL 3 – Farmaconutritie

Dit deel van het proefschrift onderzoekt de toegevoegde waarde van micro- en macronutriënten bij IC patiënten. In **hoofdstuk 7** geven we een beschrijvend overzicht van antioxidantmechanismen, antioxidantstatus en effecten van suppletie van vitaminen en sporenelementen met antioxidante eigenschappen bij ernstig zieke patiënten.

Oxidatieve stress is gedefinieerd als een verstoorde balans tussen pro-oxidanten en antioxidanten. Oxidatieve stress leidt tot celbeschadiging, weefselbeschadiging en uiteindelijk orgaanbeschadiging en orgaanfalen. Theoretisch kan herstel van de pro-oxidant/antioxidant-balans cel- en orgaanschade verminderen en de cel- en orgaanfunctie herstellen. Het menselijke antioxidantnetwerk bestaat uit enzymen, antioxidantvitaminen en enzymcofactoren (d.w.z. sporenelementen) en endogene antioxidantverbindingen. Het delicate samenspel tussen oxidanten en het antioxidantnetwerk is weergegeven in figuur 1.

Figuur 1 – Het humane antioxidantnetwerk



Lage plasmaspiegels van antioxidante enzymen, vitamines en sporenelementen zijn vaak gemeld bij ernstig zieke patiënten en daarom lijkt suppletie logisch. Lage plasmaspiegels van antioxidanten wijzen echter niet perse op een lage hoeveelheid antioxidanten in het lichaam. Bij ernstig zieke patiënten kan er redistributie van antioxidanten naar de weefsels optreden. Het huidige wetenschappelijke bewijs voor suppletie van vitamine A, C, E en enzym-cofactor-spoorelementen selenium en zink, hetzij gecombineerd of alleen, bij ernstig zieke patiënten werd onderzocht middels literatuuronderzoek. De resultaten zijn echter tegenstrijdig, aangezien sommige onderzoeken duidelijke voordelen laten zien van suppletie, terwijl anderen geen effect of en zelfs schade rapporteren.

In de prospectieve cohortstudie in **hoofdstuk 8** bestuderen we de concentraties van micronutriënten in het bloed in de eerste week van IC-opname. Patiënten kregen alleen micronutriënten via standaard enterale voeding, maar geen extra suppletie. De concentraties van micronutriënten, waaronder selenium, β-caroteen, vitamine C, E, B1 en B6, werden herhaaldelijk gemeten tijdens de eerste week van IC-opname bij 24 ernstig zieke patiënten. De micronutriëntenconcentraties bij opname op de IC werden vergeleken met die van gezonde controles van dezelfde leeftijd. De meeste gemiddelde micronutriëntenconcentraties waren significant lager bij de IC-patiënten vergeleken met de gezonde controles (selenium 0,52 µmol/l versus 0,90 µmol/l,

β-caroteen 0,17 µmol/l versus 0,50 µmol/l, vitamine C 21,5 µmol/l versus 45 µmol /l en vitamine E 20,3 µmol/l versus 35,5 µmol/l), terwijl vitamine B1 (129,5 nmol/l vs 122 nmol/l) en B6 (41 nmol/l vs 44 nmol/l) niet significant verschilden tussen patiënten en controles. De selenium-, vitamine B1- en vitamine B6-spiegels bleven stabiel tijdens IC-opname. De vitamine C concentratie daalde aanzienlijk tot dag 5 ($p < 0,01$). Vitamine E- en β-caroteenspiegels namen significant toe op respectievelijk dag 5-7 en dag 7. We concludeerden dat wanneer het doel is om de plasmaconcentraties van de bestudeerde micronutriënten te normaliseren alleen sondevoeding niet voldoende toereikend is en farmacologische suppletie moet worden overwogen. We vonden geen verbanden tussen de micronutriënten concentraties in het bloed en de ernst van de ziekte, CRP of de inname van micronutriënten.

Hoofdstuk 9 betreft een systematische review en meta-analyse van 24 studies waarin de effecten van enterale visoliesuppletie op de klinische uitkomsten bij IC patiënten werden bestudeerd. Er werd geen significant effect van enterale visoliesuppletie op de 28-dagen, IC- en ziekenhuismortaliteit waargenomen. De duur van de beademing en de verblijfsduur op de IC waren echter significant korter bij patiënten die visoliesuppletie kregen. Bij het vergelijken van onderzoeken van hoge kwaliteit met onderzoeken van lage kwaliteit, werd een significante verkorting van de beademingsduur waargenomen in onderzoeken van lage maar niet van hoge kwaliteit. Met betrekking tot de verblijfsduur op de IC werd een significant kortere verblijfsduur waargenomen in onderzoeken van hoge kwaliteit, terwijl er slechts een trend werd waargenomen in onderzoeken van lage kwaliteit. Bovendien onthulde een subgroep analyse een significante vermindering van de mortaliteit na 28 dagen, ICU ligduur en beademingsduur bij ARDS-patiënten, maar niet bij andere subgroepen. De onderzoeken die zijn opgenomen in de ARDS-subgroep zijn echter meestal van lage methodologische kwaliteit. Wij concluderen dan ook dat wij enterale visoliesuppletie niet kunnen aanbevelen bij het ontbreken van sterk bewijs voor klinische voordelen.

DEEL 4 – Een blik op de toekomst

In **hoofdstuk 10** beschrijven we nieuwe ontwikkelingen en inzichten in voeding op de intensive care tussen 2015-2018 en in **hoofdstuk 11** worden alle resultaten uit dit proefschrift bediscussieerd en in perspectief van de huidige wetenschappelijke literatuur gezet. Daarnaast werd een praktische benadering gedeeld om eiwitten en calorieën op te bouwen tijdens de verschillende fasen van kritieke ziekte en herstel. Tenslotte worden specifieke onderzoeksvragen voor toekomstig onderzoek gesuggereerd.

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CURRICULUM VITAE

Wilhelmina Aria Christina (Kristine) Koekkoek was born December 6th 1990 in Zuilichem, the Netherlands. She lived there with her parents until 1993, when they moved to Woudenberg and her sister Helene was born. Kristine graduated from the Corderius College (Gymnasium) in Amersfoort in 2008, after which she moved to Utrecht to study medicine at the University of Utrecht.

During her medical training she got the opportunity to do an elective internship in pediatrics in Dar-es-Salaam (Tanzania) and participated in multiple research protjects (HIV drug resistance, vascular wall anomalies of the Circle of Willis, and the availability of antidotes for toxicologic emergencies).

After six years she graduated in 2014 and worked as a resident in the department of intensive care in *De Gelderse Vallei hospital* in Ede. Here, she started the research that has resulted in this thesis. After being admitted to the specialization in internal medicine at the *University Medical Centre Utrecht* in 2016, she worked as a resident in both the department of internal medicine and intensive care in *De Gelderse Vallei hospital* in Ede.

In 2019 she returned to the *University Medical Centre Utrecht* to complete her training in internal medicine. In 2021 Kristine started her fellowship intensive care under supervision of Dr. Monika Kerckhoffs. She aims to complete this fellowship in 2023.

Kristine lives in Woudenberg, is married to Jozef Jan Vonhof and has two children: Lucas (2018) and Eileen (2020).