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Meta-analysis

High vs low protein intake in chronic critical illness: A systematic review and meta-analysis

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SUMMARY

Background & aims: Patients with persistent organ dysfunction after the first week of intensive care unit (ICU) admission are considered to have chronic critical illness (CCI). Acquired muscle weakness is a common feature of CCI that is accompanied by loss of muscle mass and electromyographic features of myopathy. Optimizing protein intake may help prevent acquired muscle weakness and/or promote muscle recovery, however, the optimal level of protein intake in CCI is uncertain and there is a lack of consensus in published nutritional guidelines. This systematic review focuses on the impact of high versus low protein intake as part of a nutritional strategy for patients with CCI.

Methods: The terms "protein intake" and "critically ill" were systematically searched in PUBMED, CENTRAL (Cochrane Central Register of Controlled Trials), and WEB OF SCIENCE on 06/01/2023. We included studies that (1) enrolled critically ill adults (aged 18 years or over) who were in the ICU for more than 7 days and that compared (2) protein intake above and below 1.3 gr/kg administered by any route (enteral and/or parenteral), (3) had an intervention period that occurred primarily after the first 7 days of critical illness and (4) reported clinical outcomes including length of ICU and hospital stay, duration of invasive mechanical ventilation (IMV), mortality, ICU acquired infections, muscle mass and physical function. Studies pertaining to elective surgery, those with intervention periods shorter than 7 days or occurring primarily within the first 7 days of critical illness, those measuring only laboratory parameters as outcomes, and safety and feasibility studies were excluded.

Results: Four studies were included ($N = 1730$) in the meta-analysis and systematic review. Higher (>1.3 g/kg/d) versus lower protein intake was associated with a decrease in early mortality (defined as ICU or 28-day mortality) hazard ratio (HR) 0.42 (95 % confidence interval (CI): 0.26–0.70, $P < 0.001$), but had no impact on late mortality (defined as the latest mortality timepoint in each study): HR 0.93 (95 % CI 0.76–1.15, $P = 0.51$). There was no significant difference between intervention and control groups with respect to duration of IMV, duration of ICU or hospital stay, muscle mass, or the incidence of ICU-acquired infections. One study reported improvements in physical function at 3 and 6 months in the intervention group.

Conclusion: After the first week of critical illness, increasing protein intake to >1.3 g/kg/d may improve early mortality but not late mortality or other clinical outcomes. The small number of relevant studies and the heterogeneity of outcomes assessed, weaken these conclusions. Further studies are warranted to discern whether higher protein intake is beneficial in chronic critical illness.

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1. Introduction

After the first week of intensive care unit (ICU) admission, patients with persistent organ dysfunction are considered to have chronic critical illness (CCI) [1]. Emerging evidence suggests that CCI is characterized by dynamic changes in metabolism, emphasizing the need for calibrated adjustments of caloric and protein support [2–4]. Moreover, CCI patients vary with respect to underlying disease processes, levels of inflammation, and resistance to anabolism [5], complicating decision-making around nutritional goals.

Acquired muscle weakness is a common physical problem in patients with CCI. It is associated with increased mortality and contributes to prolonged mechanical ventilation and poor functional outcomes [6–8]. Molecular studies have shown that weakness is accompanied by proteolysis and depressed protein synthesis [9]. Moreover, CCI patients with sustained weakness at 6 months showed impaired quadriceps regrowth [10]. Protein supplementation is a simple strategy that may help rebuild lost muscle mass, however, the optimal dose of protein is unknown and studies of protein intake after the first week of critical illness have been inconclusive [3,4,11].

Currently, the European Society for Clinical Nutrition and metabolism (ESPEN) recommends 1.3 g/kg/d of protein intake by the end of the first week of critical illness [12,13]. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends a range of 1.2–2.0 g/kg/d [14]. Caloric excess is thought to be detrimental during the first week of critical illness as it impedes adaptive responses such as autophagy. Thus, high protein intake (≥1.3 g/kg/d) during early critical illness may be disadvantageous if it is accompanied by overfeeding [2,12]. Recent studies have shown that published guidelines are generally followed by clinicians, although protein intake ≥1.3 g/kg/d is rarely achieved [15–17] Systematic reviews of high protein intake during the first week of critical illness have failed to demonstrate significant benefit [18], however, a large database study that included over 20,000 patients reported that a standard protein intake of 0.8–1.2 g/kg/d from days 5–11 of ICU admission was associated with a lower hazard of in-hospital death relative to a low protein intake (<0.8 g/kg/d) or a high protein intake (>1.2 g/kg/d) [19].

For patients with CCI, there are currently no guidelines with respect to ideal protein intake [20]. While high protein intake might be beneficial in promoting muscle recovery, studies to date have been inconclusive. In this systematic review and meta-analysis, we focus on the impact of higher (≥1.3 g/kg/d) versus lower (<1.3 g/kg/d) protein intake in patients with CCI, defined as persistent organ dysfunction beyond 7 days of intensive care unit admission.

2. Methodology

The systematic review was registered in PROSPERO (CRD42023403554) [21].

2.1. Eligibility criteria and exclusion

We included studies that [1] enrolled critically ill adults (18 years or over) who were in the ICU for more than 7 days and compared [2] protein intake above and below 1.3 gr/kg administered by any route (enteral and/or parenteral) [3], had an intervention period occurring primarily after the first 7 days of critical illness and [4] reported clinical outcomes including length of ICU and hospital stay, duration of invasive mechanical ventilation (IMV), mortality, ICU-acquired infections, muscle mass and physical function (Table 1).

Table 1
PICOS criteria for study inclusion.

Parameter	Inclusion Criteria
Population	Adult critically patients admitted to ICU ≥7 days.
Intervention	Protein intake >1.3 g/kg/d after 7 days of critical illness.
Control	Protein intake ≤1.3 g/kg/d after 7 days of critical illness.
Outcome	Clinical (Length of ICU and hospital stay, duration of IMV, mortality, muscle mass and strength)

Studies pertaining to elective surgery, with intervention periods ≤7 days or where more than 50 % of the intervention period occurred during the first 7 days of critical illness, those measuring only laboratory parameters as outcomes, and safety and feasibility studies were excluded.

2.2. Sources and search strategy

The terms “protein intake” and “critically ill” were systematically searched in PUBMED, CENTRAL (Cochrane Central Register of Controlled Trials), and WEB OF SCIENCE on 06/01/2023. Language restrictions were not imposed. This review was confined to the preceding ten years (2013–2023). Studies involving paediatric patients were excluded.

2.3. Study selection, quality assessment and data collection

Search results were exported to Mendeley Desktop (version 1.19.8), where duplicates were eliminated. Two authors (SC, AT) independently assessed titles and abstracts obtained during the search. Discrepancies in study inclusion were adjudicated by a third author (AM), who conducted the final review of selections. The chosen articles were independently analysed by the same authors, and the risk of bias was evaluated using RevMan 5.4, according to the methods described in the Cochrane Handbook [22].

For studies presenting continuous outcomes without means and standard deviations, attempts were made to contact the corresponding authors to obtain this data. If unsuccessful, these studies were excluded from the meta-analysis and included only in the systematic review.

The following outcomes were included in the meta-analysis:

1. Early mortality (defined as ICU or 28-day mortality)
2. Late mortality (defined as the final mortality timepoint in each study)

Other outcomes, including duration of ICU and hospital stay, duration of mechanical ventilation (MV), infections, muscle mass, muscle strength, and PCS-SF36 (Physical Component Summary - Short Form 36) were assessed in only some studies and were therefore included in the systematic review but not the meta-analysis.

Meta-analyses were performed in RevMan 5.4 (Cochrane IMS, Oxford, UK). Due to the small number of studies, we selected a fixed-effects model with odds ratio as the measure of effect. Heterogeneity among studies was quantified using I^2. A p-value less than or equal to 0.05 was considered significant, and values between 0.05 and 0.20 were considered as trending towards significance.

3. Results

The systematic search identified 853 titles from three sources: PubMed (n = 442), CENTRAL (n = 29), and Web of Science (n = 382). Study selection is detailed in the PRISMA 2020 flowchart

(Fig. 1). Study exclusion was principally due to protein doses that did not meet the specified inclusion criteria or units of measurement that were not comparable (i.e. protein intake measured as a percentage of protein target or as total grams) (Table 2). Ultimately, four studies were included in the meta-analysis and systematic review [23–26] (Table 3).

3.1. Summary of studies

The four studies included 1730 patients, with sample sizes ranging from 42 to 1301 patients. The studies are summarized in Table 3. The population included patients from Asia (6 countries), Europe (2 countries), South America (2 countries), Central America (4 countries), North America (2 countries) and Australasia (1 country). Three of the studies included medical and surgical patients while one study included only surgical patients [25]. All studies used enteral nutrition, with parenteral nutrition supplementation only when necessary to achieve protein targets. In 2 studies, parenteral amino acids were used to help meet required protein targets [23,25]. Additionally, 1 study administered a 24 g protein supplement to patients undergoing continuous renal replacement therapy [25].

Intervention periods varied between studies. In one study, the intervention commenced on day 5 of ICU admission and continued until day 14 [26]. In a second study, the intervention started on day 4 and continued until day 28 [23]. In the third study, the intervention started after hemodynamic stabilisation and continued at least 20 days [25]. Finally, in the retrospective study, protein intake was assessed from day 7 of ICU admission until ICU discharge. Protein goals were progressively achieved in three studies [24–26] while in the fourth study, the same protein dose was prescribed throughout the intervention period [23].

With respect to caloric goals, two of the prospective studies used indirect calorimetry to determine metabolic needs. The third did not use indirect calorimetry but overfeeding was discouraged [23]. The retrospective study provided data on caloric intake but did not provide data on indirect calorimetry [24].

Differences in protein intake (g/kg/d) between the groups were documented in all four studies. In the 3 randomised controlled trials (RCTs), protein intake was reported as 1.5 g/kg/d ± 0.5 vs 1.0 g/kg/d ± 0.4 [25], 1.6 g/kg/d ± 0.5 vs 0.9 g/kg/d ± 0.3 [23], and 1.48 g/kg/d vs 1.19 g/kg/d in the intervention and control groups, respectively [26]. In the retrospective study, protein intake was 1.6 g/kg/d ± 0.3 versus 0.9 g/kg/d ± 0.2 [24] in the intervention and control groups, respectively. Notably, in all 4 studies, the higher protein intake group received protein doses exceeding observed protein intake levels in routine clinical practice [27].

3.2. Outcomes

Outcomes reported included hospital and ICU mortality, mortality at 60 and 90 days, hospital and ICU length of stay, duration of

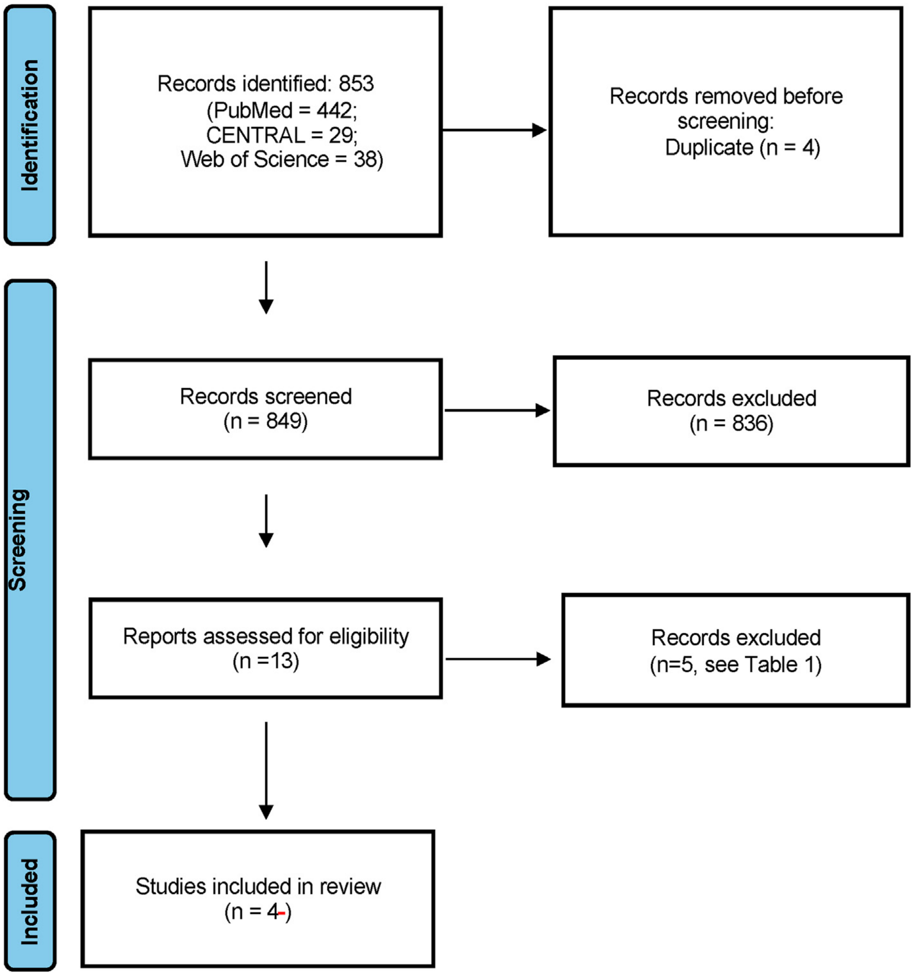


Fig. 1. Study selection PRISMA 2020 flowchart.

Table 2
Reasons for study exclusion.

Reason for exclusion	First author: Title
Safety study	O'Keefe, GE: Increasing enteral protein intake in critically ill trauma and surgical patients
Protein intake not measured in g/kg	Compher, C: Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: A multicenter, multinational observational study Hartl, WH: Protein intake and outcome of critically ill patients: Analysis of a large international database using piece-wise exponential additive mixed models
Protein doses lower than 1.3 g/kg/d in both comparator groups.	Matejovic, M: Medical nutrition therapy and clinical outcomes in critically ill adults: a European multinational, prospective observational cohort study (EuroPN) Huang, SW: The impact of higher protein intake in patients with prolonged mechanical ventilation

Table 3
Characteristics of the included studies.

Study Author/Year (Study Acronym)	Study design	Type of population	Type of nutrition	Intervention period (or data collection period in non-experimental studies)	Protein administered in the "high intake"/ control group (g/kg/d)	N (intervention/control)
Suzuki,2020	Retrospective Single centre	Surgical and medical	EN + PN to hit targets according to medical criteria	Day 7 of ICU admission to ICU discharge	1.6 ± 0.3/0.9 ± 0.2	206 (111/95)
Azevedo, 2021	Clinical trial Single centre	Surgical and medical	EN + PN to hit targets from the 7th day	Days 5–14 of ICU admission	1.48 (1.25–1.64)/1.19 (0.96–1.26)	181 (87/94)
Dresen, 2021	Clinical trial Single centre	Surgical	EN + PN + AA	For at least 20 days after hemodynamic stabilization	1.5 ± 0.5/1.0 ± 0.4	42 (21/21)
Heyland, 2023 *(EFFORT)*	Clinical trial Multicentre	Surgical and medical	EN + PN + AA	Days 4–28 of ICU admission	1.6 (SD 0.5)/0.9 (SD 0.3)	1301 (645/656)

EN: Enteral Nutrition; PN: Parenteral Nutrition; AA: Amino acids.

mechanical ventilation, muscle mass, grip strength and ICU-acquired infections. The main outcomes are presented in Table 4.

3.3. *Mortality*

All studies reported mortality as a primary or secondary outcome ($n = 1730$ patients). This included ICU mortality (2 studies, $n = 223$); 28-day mortality (1 study, $n = 206$); 60-day mortality (2 studies, $n = 1482$); 90-day mortality (2 studies, $n = 387$); and 6-month mortality (1 study, $n = 181$). Early mortality was assessed using ICU mortality or 28-day mortality ($n = 429$) while late mortality was assessed using the final mortality endpoint for each study.

In the meta-analysis of early mortality ($n = 429$), higher daily protein intake ($\geq$1.3 g/kg/d) was associated with a reduction in mortality, yielding a hazard ratio (HR) of 0.42 (95 % confidence interval (CI) 0.26–0.70, $P < 0.001$). Heterogeneity was moderate ($I^2 = 54$ %) (Fig. 2).

In the meta-analysis of late mortality ($n = 1730$), higher daily protein intake ($\geq$1.3 g/kg) was not associated with improved mortality (HR 0.93, 95 % CI 0.76–1.15, $P = 0.51$). High heterogeneity was observed between the studies (I^2 value = 80 %) (Fig. 3).

3.4. *Duration of mechanical ventilation*

All studies reported the duration of invasive mechanical ventilation (IMV). One study reported the results in hours (mean and standard deviation) [25], while two studies reported days (median and interquartile range [IQR]) [23,26]. Additionally, one study measured IMV-free days to day 28 (mean and standard deviation) [24]. None of the studies reported significant differences in duration of IMV between the intervention and control groups. Due to high methodological heterogeneity between studies, a meta-analysis was not conducted.

3.5. *Length of ICU and hospital stay*

All studies reported length of ICU stay. Two studies reported the results as median and IQR, while the others reported mean and standard deviation. No significant differences were observed in ICU length of stay between the intervention and control groups [23–26]. Two studies also reported hospital length of stay, which was similar between the intervention and control groups [23,26]. Result heterogeneity precluded the possibility of a meta-analysis.

3.6. *Physical activity and quality of life*

One study examined physical outcomes, specifically the Physical Component Summary (PCS), of the Short Form 36 (SF-36) scale. Improved scores were reported in the intervention group at 3 and 6 months ($P < 0.05$) [26].

3.7. *Grip strength and muscle mass*

One study assessed muscle strength by testing hand grip at ICU discharge or at day 21 for patients still in the ICU. The intervention group demonstrated increased hand grip strength ($P = 0.05$) [26]. In a second study, the diameter of the quadriceps muscle was evaluated by sonography at study recruitment, 2 weeks and 4 weeks. No statistically significant differences in muscle mass were observed in the intervention and control groups [25].

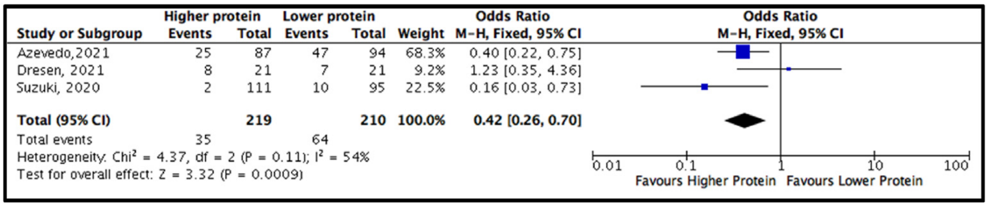
3.8. *ICU-acquired infections*

One study compared ICU-acquired infections, focusing on wound infections and pneumonia. There were no significant differences between the intervention and control groups [25].

Table 4
Outcomes reported in the included studies.

Study author/year	Outcomes	Results
Suzuki, 2020	Mortality at 28 days	Favoured intervention group
	Mortality at 90 days	Favoured intervention group
	ICU length of stay	No difference
	Ventilator-free days to day 28	No difference
Azevedo, 2021	PCS-SF36 at 3 and 6 months	Favoured intervention group
	Hand grip strength at ICU day 21 or ICU discharge	Favoured intervention group
	ICU mortality	Favoured intervention group
	Hospital mortality	Favoured intervention group
	Mortality at 90 days	Favoured intervention group
	ICU length of stay	Favoured intervention group
	Duration of IMV	No difference
Dresen, 2021	Muscle mass	No difference
	ICU length of stay	No difference
	Duration of IMV	No difference
	ICU-acquired infections	No difference
	ICU mortality	No difference
Heyland, 2023 (EFFORT)	Mortality at 60 days	No difference
	Duration of IMV	No difference
	Hospital length of stay	No difference
	ICU length of stay	No difference
	Mortality at 60 days in the subgroup of severe patients with acute kidney injury	Favoured control group

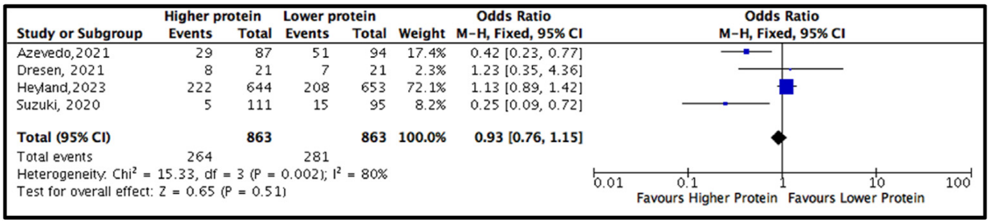
PCS-SF36: Physical Component summary - Short Form 36; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation.



Study or Subgroup	Higher protein Events	Higher protein Total	Lower protein Events	Lower protein Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Azevedo,2021	25	87	47	94	68.3%	0.40 [0.22, 0.75]
Dresen, 2021	8	21	7	21	9.2%	1.23 [0.35, 4.36]
Suzuki, 2020	2	111	10	95	22.5%	0.16 [0.03, 0.73]
Total (95% CI)		**219**		**210**	**100.0%**	**0.42 [0.26, 0.70]**
Total events	35		64			

Heterogeneity: $Chi^2 = 4.37$, df = 2 (P = 0.11); $I^2 = 54\%$
Test for overall effect: Z = 3.32 (P = 0.0009)

Fig. 2. Meta-analysis of early mortality (ICU and 28-day mortality). CI: confidence interval.



Study or Subgroup	Higher protein Events	Higher protein Total	Lower protein Events	Lower protein Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Azevedo,2021	29	87	51	94	17.4%	0.42 [0.23, 0.77]
Dresen, 2021	8	21	7	21	2.3%	1.23 [0.35, 4.36]
Heyland,2023	222	644	208	653	72.1%	1.13 [0.89, 1.42]
Suzuki, 2020	5	111	15	95	8.2%	0.25 [0.09, 0.72]
Total (95% CI)		**863**		**863**	**100.0%**	**0.93 [0.76, 1.15]**
Total events	264		281			

Heterogeneity: $Chi^2 = 15.33$, df = 3 (P = 0.002); $I^2 = 80\%$
Test for overall effect: Z = 0.65 (P = 0.51)

Fig. 3. Meta-analysis of late mortality. CI: confidence interval.

4. Discussion

4.1. Summary of main findings

Higer (≥1.3 g/kg/d) versus lower (<1.3 g/kg/d) protein intake beyond 7 days of ICU admission was associated with a decrease in early mortality but had no impact on late mortality. No significant differences were noted in duration of IMV [24–26], duration of ICU and hospital stay [23,24], grip strength [26], muscle mass, or the incidence of ICU-acquired infections [25]. One study reported improved physical functioning scores at three and six months in the intervention group [26].

4.2. Discussion of main findings

In this meta-analysis and systematic review, we observed a reduction in early mortality (28 days or ICU discharge) in patients with CCI receiving high protein intake (≥1.3 g/kg/day). However, no mortality benefit was observed at 60 and 90 days. This discrepancy was driven by the EFFORT study, the largest of the four studies, which was only included in the late mortality meta-analysis as it did not include data on ICU or 28-day mortality. The intervention in the EFFORT study was initiated earlier than in the other studies, on day 4 of ICU admission. Moreover, rather than gradually increasing protein doses until the target was achieved, the EFFORT study used a full protein dose from the first day of the intervention. Previous studies have reported that high protein intake in the acute phase of critical illness can have adverse effects and this may have contributed to the lack of mortality benefit observed in EFFORT [23]. The EFFORT investigators noted that some subgroups of patients appeared to experience worse outcomes from higher protein intake, namely those with acute kidney injury. This finding, combined with previous evidence, suggests that high protein intake should be avoided prior to day 7 of ICU admission in patients with severe organ dysfunction [19,28]. A post hoc analysis of the EFFORT study looking at patients with AKI on the 7th day of ICU admission revealed higher mortality at 60 days in the group that received higher protein intake. Interestingly, this unfavourable effect on mortality disappeared in patients undergoing renal replacement [29].

Recently, the PRECISe study randomized 935 critically ill patients to high protein intake (median 1.87 g/kg/d) vs low protein intake (median 1.19 g/kg/d). The primary outcome, quality of life at 180 days, was lower amongst patients in the high protein group [30]. There was also a longer time to hospital discharge for these patients. Given that the median length of ICU stay in PRECISe was only 9 days, the results speak more to the negative impacts of high protein intake during the first week of critical illness, rather than its impact in CCI patients. Unfortunately, no subgroup analysis of CCI patients was included in the study.

Excessive caloric intake in the acute phase of critical illness is known to be detrimental [2,13]. In CCI, however, there is little data to guide ideal caloric intake. Indirect calorimetry is increasingly being used to set calorie goals and was used in two of the studies in this meta-analysis [25,26]. Further studies are required to better understand the interaction between protein intake and caloric intake in chronic critical illness.

During the rehabilitation phase of critical illness, additional strategies to enhance anabolism include exercise and medication (anabolic steroids). Only one of the studie in this meta-analysis explicitly incorporated physical exercise into its protocol [26]. There is a pressing need for studies that investigate the synergistic effects of nutrition and physical exercise in recovery from critical illness [31]. In addition, anabolic steroids have been trialled as a strategy to enhance anabolism amongst CCI patients [32,33]. However, none of the studies in this meta-analysis considered anabolic steroids in their protocols.

Heterogeneity of feeding protocols is a major challenge in nutrition studies. This affects not only the dose and route of administration but also the units in which the protein dose is measured. The most common unit is grams of protein per kg of body weight, however some studies use absolute grams of protein while others use percentage of protein target. Two relevant studies were excluded from this meta-analysis because it was not possible to calculate protein intake in g/kg/d. One of the two studies showed benefit from increased protein intake [34] while the other did not [19]. The importance of standardizing dosing units has been emphasized in the consensus statement on outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness (CONCISE) [35]. Investigators who use atypical dosing units in their studies should still provide results in standardized units for ease of comparability.

4.3. Strengths and limitations

This is the first systematic review to address the topic of high versus low protein intake in CCI, however it has several limitations. The number of included studies was small, with one large study exerting a substantial impact on the results. Additionally, there was significant heterogeneity among the studies with respect to the interventions and outcomes studied. Nevertheless, all studies showed separation in protein intake between the high protein and low protein groups, enabling meaningful comparison.

5. Conclusion

In CCI, high protein intake (>1.3 g/kg/d) may be beneficial for early mortality and functional outcomes. However, it is crucial to identify which patients are most likely to benefit from this practice. Ruther randomized studies of protein reinforcement beyond the acute phase of critical illness are required. Additionally, further exploration of patient-centred functional outcomes, such as physical function and muscle strength, is imperative. Finally, subgroup analyses are required to determine which patients truly benefit, so that protein intake can be personalized as part of an overall recovery strategy.

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Declaration of competing interest

The author, Sílvia Castro, reports receiving speaker fees from Baxter.

References

[1] Marchioni A, Tonelli R, Sdanganelli A, Gozzi F, Musarò L, Fantini R, et al. Prevalence and development of chronic critical illness in acute patients admitted to a respiratory intensive care setting. Pulmonology 2020;26(3): 151–8. https://doi.org/10.1016/j.pulmoe.2019.09.006.

[2] Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care 2016;20(1).

[3] Koekkoek WACK, Van Setten CHC, Olthof LE, Kars JCNH, Van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation : the PROTINVENT retrospective study. Clin Nutr 2019;38(2):883–90. https://doi.org/10.1016/j.clnu.2018.02.012.

[4] Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care 2017;21(Suppl 3):15–25.

[5] Zhang J, Luo W, Miao C, Zhong J. Hypercatabolism and anti-catabolic therapies in the persistent inflammation, immunosuppression, and catabolism syndrome. Frontiers in nutrition, 9. Frontiers Media S.A; 2022.

[6] Voiriot G, Oualha M, Pierre A, Salmon-Gandonnière C, Gaudet A, Jouan Y, et al. Chronic critical illness and post-intensive care syndrome: from pathophysiology to clinical challenges. Ann Intensive Care 2022;12(1). https://doi.org/10.1186/s13613-022-01038-0.

[7] Landi F, Bear DE, Cederholm T, Malafarina V, Welch AA. Muscle loss: the new malnutrition challenge in clinical practice. Clin Nutr 2018. https://doi.org/10.1016/j.clnu.2018.11.021.

[8] Raymond A, Zanten H Van, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness : practical guidance for the ICU , post-ICU , and long-term convalescence phases. Crit Care 2019;23(368):1–10.

[9] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013 Oct 16;310(15): 1591–600.

[10] Dos Santos C, Hussain SNA, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay: a pilot study. Am J Respir Crit Care Med 2016 Oct 1;194(7): 821–30.

[11] Heyland DK, Stapleton R, Compher C. Should we prescribe more protein to critically ill patients?. Nutrients, 10. MDPI AG; 2018.

[12] Singer P, Reintam A, Berger MM, Alhazzani W, Calder PC, Casaer M, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2018:1–32 (October).

[13] Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive care unit. Clin Nutr 2023 Sep 1;42(9):1671–89.

[14] Compher C, Bingham AL, McCall M, Patel J, Rice TW, Braunschweig C, et al. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: the American Society for Parenteral and Enteral Nutrition. J Parenter Enteral Nutr 2022;46(1):12–41.

[15] Matejovic M, Huet O, Dams K, Elke G, Vaquerizo Alonso C, Csomos A, et al. Medical nutrition therapy and clinical outcomes in critically ill adults: a European multinational, prospective observational cohort study (EuroPN). Crit Care 2022 Dec 1;26(1).

[16] De Waele E, Jakubowski JR, Stocker R, Wischmeyer PE. Review of evolution and current status of protein requirements and provision in acute illness and critical care. Clin Nutr 2021;40(5):2958–73. https://doi.org/10.1016/j.clnu.2020.12.032.

[17] Berger MM, Burgos R, Casaer MP, De Robertis E, Delgado JCL, Fraipont V, et al. Clinical nutrition issues in 2022: what is missing to trust supplemental parenteral nutrition (SPN) in ICU patients? Crit Care 2022;26(1):1–5. https://doi.org/10.1186/s13054-022-04157-z.

[18] Lee ZY, Yap CSL, Hasan MS, Engkasan JP, Barakatun-Nisak MY, Day AG, et al. The effect of higher versus lower protein delivery in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2021 Dec 1;25(1).

[19] Hartl WH, Kopper P, Bender A, Scheipl F, Day AG, Elke G, et al. Protein intake and outcome of critically ill patients: analysis of a large international database using piece-wise exponential additive mixed models. Crit Care 2022 Dec 1;26(1).

[20] Wischmeyer PE, Bear DE, Berger MM, De Waele E, Gunst J, McClave SA, et al. Personalized nutrition therapy in critical care: 10 expert recommendations. Critical care, 27. BioMed Central Ltd; 2023.

[21] Castro S, Macedo A, Tomé A. The effect of higher than 1,3 gr/kg of protein versus lower intake in chronic critically ill patients. PROSPERO 2023 CRD42023403554 2023. Available from, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023403554. www.abcmedicalg.pt.

[22] Book Series C, Higgins JP, Green S. Cochrane Handbook for systematic reviews of interventions The Cochrane Collaboration ®.

[23] Heyland DK, Patel J, Compher C, Rice TW, Bear DE, Lee ZY, et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial. Lancet 2023 Feb 18;401(10376):568–76.

[24] Suzuki G, Ichibayashi R, Yamamoto S, Serizawa H, Nakamichi Y, Watanabe M, et al. Effect of high-protein nutrition in critically ill patients: a retrospective cohort study. Clin Nutr ESPEN 2020 Aug 1;38:111–7.

[25] Dresen E, Weißbrich C, Fimmers R, Putensen C, Stehle P. Medical high-protein nutrition therapy and loss of muscle mass in adult ICU patients: a randomized controlled trial. Clin Nutr 2021 Apr 1;40(4):1562–70.

[26] de Azevedo JRA, Lima HCM, Frota PHDB, Nogueira IROM, de Souza SC, Fernandes EAA, et al. High-protein intake and early exercise in adult intensive care patients: a prospective, randomized controlled trial to evaluate the impact on functional outcomes. BMC Anesthesiol 2021 Dec 1;21(1).

[27] Ridley EJ, Parke RL, Davies AR, Bailey M, Hodgson C, Pt B, et al. What happens to nutrition intake in the post – intensive care unit hospitalization period ? An observational cohort study in critically ill adults. J Parenter Enteral Nutr 2019;43(1):88–95.

[28] Matejovic M, Huet O, Dams K, Elke G, Vaquerizo Alonso C, Csomos A, et al. Medical nutrition therapy and clinical outcomes in critically ill adults: a European multinational, prospective observational cohort study (EuroPN). Crit Care 2022;26(1):1–14. https://doi.org/10.1186/s13054-022-03997-z.

[29] Stoppe C, Patel JJ, Zarbock A, Lee ZY, Rice TW, Mafrici B, et al. The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial. Crit Care 2023 Dec 1;27(1).

[30] Bels JLM, Thiessen S, Van Gassel RJJ, Beishuizen A, De A, Dekker B, et al. Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and The Netherlands, 404; 2024. www.thelancet.com. https://intensivecare. Available from.

[31] Chapple L Anne S, Parry SM, Schaller SJ. Attenuating muscle mass loss in critical illness: the role of nutrition and exercise. Current osteoporosis reports, 20. Springer; 2022. p. 290–308.

[32] Wischmeyer PE, Suman OE, Kozar R, Wolf SE, Molinger J, Pastva AM. Role of anabolic testosterone agents and structured exercise to promote recovery in ICU survivors. Current opinion in critical care, 26. Lippincott Williams and Wilkins; 2020. p. 508–15.

[33] Anstey MH, Rauniyar R, Fitzclarence E, Tran N, Osnain E, Mammana B, et al. Muscle growth and anabolism in intensive care survivors (GAINS) trial: a pilot randomised controlled trial. Acute and Critical Care 2022 Aug 1;37(3): 295–302.

[34] Compher C, Chittams J, Sammarco T, Nicolo M, Heyland DK. Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: a multicenter, multinational observational study. Crit Care Med 2017 Feb 1;45(2):156–63.

[35] Davies TW, van Gassel RJJ, van de Poll M, Gunst J, Casaer MP, Christopher KB, et al. Core outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness: an international modified Delphi consensus study evaluation (CONCISE). Crit Care 2022;26(1).