

Protein and energy delivery in critically ill adult patients and the impact on nutritional and patient-centred outcomes

Kate Emily Fetterplace BNut&Diet

Student number: 944244

ORCID ID: 0000-0002-1094-1619

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Melbourne Medical School, Royal Melbourne Hospital

Department of Medicine and Radiology

University of Melbourne

Abstract

Adult patients who survive critical illness are known to be at risk of several adverse health consequences, including substantial muscle loss, impaired muscle function and reduced quality of life. While nutrition interventions for critically ill patients may attenuate muscle loss, this therapeutic approach remains unproven. Evidence published by others over the period of this PhD program challenged the existing orthodoxy that greater overall calorie provision during the acute phase of critical illness improves overall patient outcomes. Accordingly, the PhD candidate specifically investigated the relationship between protein provision in critical illness and patient-centred outcomes. This thesis comprises several discrete but aligned studies, including a systematic and narrative review of the literature, three observational studies, and a pilot parallel group randomised clinical trial (RCT).

The systematic review and meta-analysis established that current practice guidelines recommending the amount of enteral protein are not based on strong evidence. Moreover, there is a lack of high-quality data about the impact of protein provision on functional outcomes that are important to patients.

The narrative review evaluated the methodologies and outcomes used to quantify the effect of nutrition therapy in the critically ill. While patient centred and less direct surrogate clinical outcomes are increasingly being used in the nutrition literature, there remains substantial variation in the tools used and the outcomes selected.

In a prospective observational study of patients surviving an intensive care unit (ICU) admission following serious trauma, it was identified that many of the outcomes that would be desirable to measure were not feasible after ICU discharge in this patient cohort. In contrast, it was feasible to implement these methodologies in ICU in a separate cohort of critically ill patients, and cumulative nutrition deficits in the latter study were associated with inferior nutritional and patient-centred outcomes, including the presence of malnutrition and ICU-acquired weakness and greater loss of fat-free mass.

To evaluate whether it was feasible to increase the enteral protein received by at-risk ICU patients to the doses recommended in practice guidelines, and establish point estimates for the impact of this strategy on patient-centred outcomes, a parallel group RCT was conducted. This single-centre single-blinded pilot trial compared an intervention of a

‘volume-based’ enteral feeding protocol with protein supplementation to usual care. The intervention delivered greater amounts of protein and energy than received by the usual care group, and this was associated with attenuation of muscle loss and reduced prevalence of malnutrition in survivors at ICU discharge. These data are novel, describing the first successful delivery of enteral protein within current guideline recommendations and a consequent favourable effect on muscle mass.

Based on this program of work, a multi-centre randomised clinical trial is required to explore the signals observed in these studies, and to generate robust evidence regarding optimal provision of enteral protein during critical illness and the impacts on functional recovery and quality of life in those who survive.

Declaration

This is to certify that:

- i. the thesis comprises only my original work towards the PhD except where indicated in the preface;
- ii. due acknowledgement has been made in the text to all other material used;
- iii. the thesis is fewer than 100,000 words in length, exclusive of tables, figures, bibliographies and appendices.

Kate Fetterplace

June 2020

Preface

This is to certify that this thesis contains content that is substantially unchanged from the content of multi-author papers either published or are currently under review (Chapters 2-8). The following statement outlines the contribution of all authors to their respective chapters:

1) Chapter 2 (Study 1) – **Fetterplace K**, Gill BMT, Chapple LS, Presneill JJ, MacIsaac CM, Deane AM. 'Systematic review with meta-analysis of patient-centered outcomes, comparing international guideline recommended enteral protein delivery to usual care'. Journal of Parenteral and Enteral Nutrition 2019, DOI: 10.1002/jpen.725.

- a) Fetterplace K was responsible for 80% of this work; she contributed to the concept and study design, and was primarily responsible for the literature review and database searching, data acquisition and analysis, drafting the manuscript for publication and responding to the editor's feedback.
- b) Deane A assisted with the concept and study design and revising the initial draft manuscript for publication.
- c) Gill B was the second reviewer and assisted with the literature review and data acquisition.
- d) Presneill J assisted with the statistical analysis of the results.
- e) All authors contributed to study design and revising the manuscript for submission.

2) Chapter 3 (Study 2) – **Fetterplace K**, Ridley EJ, Beach L, Ali Abdelhamid Y, Presneill JJ, MacIsaac CM, Deane AM. 'Quantifying response to nutritional therapy during critical illness: implications for clinical practice and research? A narrative review'. Accepted June 19th 2020, Journal of Parenteral and Enteral Nutrition.

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- b) Deane A contributed to the concept and design and reviewed the initial manuscript draft.
 - c) All other authors contributed equally to study design and revising the draft manuscript for publication.

- 3) Chapter 4 (Study 3) – **Fetterplace K**, Corlette L, Ali Abdelhamid Y, Presneill JJ, Paris M, Stella D, Mourtzakis M, MacIsaac CM, Deane AM. ‘Assessment of muscle mass using ultrasound compared to computed tomography in critically ill adult patients’. Under review, Australian Critical Care.
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 - b) Corlette L assisted with data acquisition and analysis and revised the manuscript for submission.
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 - b) Beach L contributed to the study design and concept, ethics approval process, recruitments of participants and data acquisition.

- c) Presneill J and Edbrooke L assisted with statistical analysis.
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- b) Wittholz K was the lead author on this study; Fetterplace K was responsible for mentoring her to conduct her first study. Kym was pivotal to the study concept and design, ethics approval, data acquisition and drafting the manuscript.
- c) Deane A assisted Fetterplace K in the process of mentoring a junior colleague to conduct her first study and contributed to the study design.
- d) Presneill J assisted with the statistical analysis.
- e) Clode M contributed to data acquisition.
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6) Chapter 7 (Study 6) – **Fetterplace K**, Deane AM, Tierney A, Beach L, Knight LD, Rechnitzer T, Forsyth A, Mourtzakis M, Presneill J, MacIsaac C. ‘Targeted full energy and protein delivery in critically ill patients: A study protocol for a pilot randomised control trial (FEED Trial)’. Pilot and Feasibility Studies 2018; 4:52. DOI: 10.1186/s40814-018-0249-9

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- b) Deane A contributed to the study design and was responsible for revising the initial draft manuscript.
- c) All other authors contributed to study design and revised the manuscript for publication.

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- b) Deane A contributed to the study design and was responsible for revising the initial draft manuscript.
- c) Beach L and Gill B contributed to the data acquisition.
- d) Presneill J assisted with the statistical analysis.
- e) All authors contributed to the concept and study design and revised the manuscript for publication.

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Acronyms and abbreviations

APACHE:	Acute Physiology and Chronic Health Evaluation
BIS:	Bioimpedance spectroscopy
BMI:	Body Mass Index
CONSORT:	Consolidated Standards for Reporting of Trials
CT:	Computed Tomography
CSA:	Cross sectional area
DXA:	Dual-energy X-Ray Absorptiometry
ECOG:	Eastern Cooperative Oncology Group (ECOG) performance status HRQoL: Health-related quality of life
EER:	Estimated energy requirements
EN:	Enteral nutrition
EQ-5D:	EuroQol-5D
FFM:	Fat free mass
HGS:	Handgrip strength
Ht:	Height
iADL:	Instrumental activities of daily living
IBW:	Ideal body weight
ICU:	Intensive care unit
ICUAW:	Intensive care unit acquired weakness
IQR:	Interquartile range
Kg:	Kilograms
L3:	3 rd lumbar vertebra
LOS:	Length of stay
MEE:	Measured energy expenditure
MF-BIA:	Multi-frequency Bioimpedance

MRC-SS:	Medical Research Council sum score
MUAC:	Mid upper arm circumference
MV:	Mechanically ventilated
OR:	Odds ratio
PFIT-s:	Physical function in Intensive Care Test–scored
PN:	Parenteral nutrition
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QMLT:	Quadriceps muscle layer thickness
RCT:	Randomised controlled trial
RQ:	Respiratory quotient
SD:	Standard deviation
SF-36:	Short Form-36
SF-BIA:	Single frequency Bioimpedance analysis
SOFA:	Sequential Organ Failure Assessment
SGA:	Subjective global assessment
US:	Ultrasound
WHODAS:	World health organization disability assessment schedule

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Dissemination of research

The research described in this thesis was disseminated in the following publications and presentations.

Oral abstract presentations

- | | |
|-----------|--|
| Nov 2019 | Australasian Society of Parenteral and Enteral Nutrition Conference 2019 (Adelaide) – ‘A systematic review with meta-analysis of patient-centered outcomes comparing international guideline recommended enteral protein delivery to usual care’ |
| June 2019 | Melbourne Health Research week 2019 – A systematic review with meta-analysis of patient-centered outcomes comparing international guideline recommended enteral protein delivery to usual care’ |
| Jan 2018 | American Society of Parenteral and Enteral Nutrition Conference (Las Vegas) – ‘Targeted full energy and protein delivery in critically ill patients: A pilot randomised control trial (FEED Trial)’ |
| June 2018 | Melbourne Health Research Week – ‘targeted full energy and protein delivery in critically ill patients: A pilot randomised control trial (FEED Trial)’ (June 2018) |

Invited presentations

- | | |
|----------|---|
| Feb 2020 | AuSPEN Advanced Nutrition Course (Melbourne), ‘Nutrition support in critical illness’ |
| Feb 2020 | AuSPEN Advanced Nutrition Course (Melbourne), ‘Nutrition Assessment Workshop for ultrasound and bioimpedance’ |
| Oct 2019 | World Congress of Critical Care 2019 (Melbourne), ‘Protein: Does dose matter?’ |

May 2019	Nestle Critical Care Event (Melbourne), 'Protein provision in critical illness and functional outcomes'
Nov 2018	AuSPEN National Conference (Sydney), 'Targeted full energy and protein delivery in critically ill patients: A pilot randomised control trial (FEED Trial)'
May 2018	Metabolism and Nutrition in Intensive Care Course (Melbourne), 'What requirements do you target?'
Oct 2017	Nutricia Sarcopenia Road Show (Melbourne), 'Nutritional management of sarcopenia'

Invited presentations at virtual events

April 2020	Dietitian Connection Webinar (Abbott), 'GI function in critical illness and managing intolerance'
Mar 2020	Podcast – Journal of Parenteral and Enteral Nutrition, 'A systematic review with meta-analysis of patient-centered outcomes comparing international guideline recommended enteral protein delivery to usual care'
Nov 2018	Dietitians Connections Webinar (Nestle), 'How to meet protein requirements'

Poster presentations

Nov 2018	AuSPEN Conference 2018 – Nutrition related outcomes in multi-trauma patients following intensive care unit discharge (November 2018)
Nov 2016	AuSPEN conference 2016 – 'Measured energy expenditure to determine cumulative calorie deficit and associations with functional outcomes in critically ill'

Awards

- Jan 2020 Journal of Parenteral and Enteral Nutrition – **Top cited article 2018-2019**, for ‘Targeted full energy and protein delivery in critically ill patients: A pilot randomised control trial (FEED Trial)’.
- Dec 2019 Royal Melbourne Hospital - **Excellence in Allied Health** award winner 2019
- Nov 2019 Australasian Society of Parenteral and Enteral Nutrition Conference 2019 – **Travel Grant** for the top-scoring abstract.
- Jan 2018 American Society of Parenteral and Enteral Nutrition Conference 2018 – **Harry Vars Promising Investigator Award**.
- June 2019 Journal of Parenteral and Enteral Nutrition – **Top 20 downloaded articles 2017-2018**, for ‘Targeted full energy and protein delivery in critically ill patients: A pilot randomised control trial (FEED Trial)’.
- Nov 2017 Australasian Society of Parenteral and Enteral Nutrition Conference 2017 – **David Russell Award** for the most significant contribution to clinical practice.

Published manuscripts included in this thesis

- 1) **Fetterplace K**, Gill BMT, Chapple LS, Presneill JJ, MacIsaac CM, Deane AM. ‘Systematic review with meta-analysis of patient-centered outcomes, comparing international guideline recommended enteral protein delivery to usual care’. Journal of Parenteral and Enteral Nutrition 2020; 44(4):610-620. DOI: 10.1002/jpen.725. PMID: 31617220
- 2) **Fetterplace K**, Beach LJ, MacIsaac CM, Presneill JJ, Edbrooke L, Parry SM, Rechnitzer T, Curtis R, Berney S, Deane AM, Denehy L. ‘Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes

- in survivors of critical illness'. *Journal of Human Nutrition and Dietetics* 2019; 32(6):702-12.
- 3) Wittholz K, **Fetterplace K**, Clode M, George ES, MacIsaac CM, Judson R, Presneill JJ, Deane AM. 'Measuring nutrition related outcomes in a cohort of multi-trauma patients follow intensive care unit discharge'. *Journal of Human Nutrition and Dietetics* 2020; 33(3):414-422. DOI: 10.1111/jhn.12719 PMID: 31788891
 - 4) **Fetterplace K**, Deane AM, Tierney A, Beach L, Knight LD, Rechnitzer T, Forsyth A, Mourtzakis M, Presneill J, MacIsaac C. 'Targeted full energy and protein delivery in critically ill patients: A study protocol for a pilot randomised control trial (FEED Trial)'. *Pilot and Feasibility Studies* 2018; 4:52. DOI: doi.org/10.1186/s40814-018-0249-9 PMID: 2948196
 - 5) **Fetterplace K**, Deane AM, Tierney A, Beach LJ, Knight LD, Presneill JJ, Rechnitzer T, Forsyth A, Gill BMT, Mourtzakis M, MacIsaac C. 'Targeted full energy and protein delivery in critically ill patients: A pilot randomized controlled trial (FEED Trial)'. *Journal of Parenteral and Enteral Nutrition* 2018; 42(8):1252-1262. DOI: 10.1002/jpen.1166.
 - 6) **Fetterplace K**, Ridley EJ, Beach L, Ali Abdelhamid Y, Presneill JJ, MacIsaac CM, Deane AM. 'Quantifying response to nutritional therapy during critical illness: implications for clinical practice and research? A narrative review'. Accepted for publication 18th of June 2020, *Journal of Parenteral and Enteral Nutrition*.
 - 7) **Fetterplace K**, Corlette L, Ali Abdelhamid Y, Presneill JJ, Paris M, Stella D, Mourtzakis M, MacIsaac CM, Deane AM. 'Assessment of muscle mass using ultrasound compared to computed tomography in critically ill adult patients'. Under review, May 2020, *Australian Critical Care Journal*.

Published manuscripts during candidature not included in this thesis

- 1) Chapple L, **Fetterplace K**, Ridley E. 'Nutrition of for critically ill patients with COVID-19'. *ICU Management and Practice* 2020; 20(1):2-57

- 2) **Fetterplace K**, Holt D, Udy A, Ridley E. 'Parenteral nutrition in adults during acute illness: a clinical perspective for clinicians'. *Internal Medicine Journal* 2020; 50(4):403-411. DOI: doi.org/10.1111/imj.14786

- 3) Tatu-Babet OA, **Fetterplace K**, Lambell K, Miller E , Deane AM, Ridley EJ. 'Is energy delivery guided by indirect calorimetry associated with improved clinical outcomes in critically ill patients? A systematic review'. *Nutrition and Metabolic Insights* 2020, DOI: doi.org/10.1177/1178638820903295

- 4) Baldwin CE, **Fetterplace K**, Beach L, Kayambu G, Paratz J, Earthman C, Parry SM. 'Early detection of muscle weakness and functional limitations in the critically ill: A retrospective evaluation of bioimpedance spectroscopy'. *Journal of Parenteral and Enteral Nutrition* 2019, DOI: doi.org/10.1002/jpen.1719

- 5) Hay T, Deane A, Rechnitzer T, **Fetterplace K** et al., 'The hospital-based evaluation of laxative prophylaxis in ICU (HELP-ICU): A pilot cluster-crossover randomized clinical trial'. *Journal of Critical Care* 2019; 52:86-91. DOI: [doi:10.1016/j.jcrc.2019.04.010](https://doi.org/10.1016/j.jcrc.2019.04.010)

Chapter 1: Introduction

1.1 Thesis overview

This thesis describes a research program that generated literature reviews and studies which have been published in, accepted by or are currently under review at peer-reviewed journals. It includes a systematic review and meta-analysis, a narrative review of methodologies, three observational studies and a pilot randomised controlled trial (RCT). Each chapter represents a defined research project. At the start of each chapter, a summary outlines why the project was undertaken and how it links to the overall topic. Whilst the research papers and chapters are presented in this thesis in order for the reader to follow a logical progression of information, note that this was not the order in which the projects were conducted. This thesis concludes with a summary of the research findings, the strengths and limitations of the research, suggested future directions, and recommendations.

1.2 Research problem and significance

Worldwide, the numbers of people who require intensive care admissions continues to rise. Each year there are over 190,000 admissions to intensive care across Australian and New Zealand hospitals (ANZICS, 2019). Over the last two decades mortality rates have fallen due to ongoing improvements in medical therapy; however, there is an increasing awareness that those who survive an episode of critical illness frequently develop substantial muscle loss and weakness, reduced functional ability and lower health-related quality of life up to five years after discharge (Cuthbertson B. H et al., 2010; Herridge, 2009; Kress, 2014). While mortality remains the gold standard for assessing the effects of all treatments in critical care, including nutritional therapy, there is growing interest in therapies that not only increase survival but will improve other outcomes that are important to survivors. Intuitively, optimal nutrition therapy may reduce mortality and improve the quality of survivorship due to attenuation of the muscle loss and disability that occurs during an episode of critical illness; however, this remains to be determined.

Critical illness induces a 'stress' response that is characterised by the secretion of neuroendocrine hormones and pro- and anti-inflammatory cytokines. This milieu causes marked changes to the metabolism of energy, protein and lipids, which results in increased catabolism and substrate utilisation and resistance to anabolic processes (Preiser et al., 2014). These adaptive processes are associated with a rapid depletion of body stores, muscle wastage, weight loss and anorexia. Observational data suggests that patients lose approximately 20% of muscle mass within two weeks of commencement of an episode of critical illness, and muscle loss is greatest in those patients who have the greatest severity of illness – quantified as multi-organ failure (Puthucherry et al., 2013). Nutrition provision during critical illness cannot completely prevent these processes, but there is general agreement that nutrition plays a key role in the provision of adequate substrates, hence attenuating muscle loss (Preiser et al., 2015).

The current international critical care nutrition guidelines recommend that protein should be provided at a level of 1.2–2.0g/kg/day and that energy delivery should be guided by measured energy expenditure determined with indirect calorimetry or, in the absence of measuring energy expenditure, approximately 25–30kcal/kg per day (McClave et al., 2016; Singer et al., 2018). There is general consensus that these targets should be based on actual weight, but for patients who are overweight or obese, ideal body weight or an obesity-adjusted weight should be used (Singer et al., 2018). However, until recently little high-quality RCT data was available to support these recommendations. Furthermore, older international observational datasets have reported that critically ill patients receive significantly less nutrition than the international guidelines recommend, with patients only meeting approximately 50% of protein and 60% of energy targets, but contemporaneous local data are scarce (Ridley et al., 2018).

Historically, the critical care nutrition literature has mostly focused on energy or calorie provision. Prior to the commencement of this PhD program, three large RCTs, two investigating the use of initial trophic enteral feeding versus full enteral feeding and the other investigating early versus late parenteral nutrition (n=894, 1,000 and 4640

respectively), challenged this dogma (Arabi et al., 2011; Casaer et al., 2011; Rice et al., 2012). Moreover, toward the end of this program another large RCT (n=4,000), conducted in the same region in which the work described in this thesis was conducted (thereby having external validity to this research), showed that there were no differences in outcomes in those randomised to receive 100% or 70% of estimated energy requirements (TARGET Investigators*, 2018). Taken together, these data suggest that the amount of energy delivered in the acute phase of critical illness has negligible effect on mortality (Casaer et al., 2011; Heyland et al., 2017; Rice et al., 2012; TARGET Investigators*, 2018). However, there remained insufficient evidence about the effects of protein or optimising nutrition provision (protein and energy) and outcomes other than mortality that are important to survivors of critical illness (Bear et al., 2017; Heyland et al., 2016). Accordingly, as data become available during this PhD candidature, there was an increasing focus on the role of protein and a transition away from energy delivery.

1.3 Research objective

The research presented in this thesis examined protein and energy provision in critically ill adult patients and explored patient-centred outcomes following critical illness and the associations between nutrition provision and these outcomes. The specific aims of the research were to:

- a) systematically review the literature to estimate the effect of enteral protein delivered according to international guidelines, compared to usual care, on patient centred-outcomes (Chapter 2);
- b) review the current available evidence to describe the methods used, and outcomes available, to quantify the response to nutrition therapy in critically ill patients (Chapter 3);
- c) explore the precision of minimally invasive techniques that can be used in critically ill people to assess muscle mass (Chapter 4);

- d) determine nutritional deficits in critically ill patients in relation to estimated requirements and measured energy expenditure, and to explore associations between cumulative energy deficit and patient-centred outcomes (Chapter 5);
- e) Determine the feasibility of assessing patient-centred outcomes in a specific cohort of critically patients following ICU discharge and to explore the relationships between nutritional provision and these outcomes (Chapter 6).
- f) To determine whether a high-protein enteral nutrition intervention delivers greater protein and energy than usual care to critically ill patients and to evaluate the effect on patient-centred outcomes (Chapter 7 and 8).

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Chapter 2: Systematic literature review of protein provision in critical illness

2.1 Chapter summary

This systematic literature review is an important piece of work that makes a substantial contribution to this field of research. The manuscript was published (in print) in May 2020 (appendix 1). This systematic review was undertaken in the second half of this PhD program, rather than (as is traditional) at its commencement. For this reason, the review does include the pilot RCT (chapters 7 and 8), which forms part of this thesis.

This is the first systematic review and meta-analysis to compare the effect on patient-centred outcomes of protein provision consistent with international guidelines and amounts of protein provided as part of standard care. This review was undertaken to summarise the available evidence about the effect of protein provision on patient-centred outcomes.

2.2 Systematic review

A systematic review with meta-analysis of patient-centered outcomes, comparing international guideline recommended enteral protein delivery to usual care

Kate Fetterplace^{1,2} APD BNutrDiet, Benjamin MT Gill¹ APD MDiet, Lee-anne S. Chapple^{3,4} APD PhD, Jeffrey J. Presneill^{2,5} MBBS PhD, Christopher MacIsaac^{2,5} MBBS PhD, Adam M. Deane^{2,5} MBBS PhD.

1. Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia
2. The University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Parkville, Australia
3. Discipline of Acute Care Medicine, School of Medicine, University of Adelaide, Australia
4. Intensive Care Research, Royal Adelaide Hospital, Adelaide, Australia
5. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Australia

Corresponding author

Ms Kate Fetterplace^{1,2} BNutDiet, APD

Senior Dietitian, Royal Melbourne Hospital

Allied Heath, Royal Melbourne Hospital

Grattan St Parkville, Victoria, Australia 3050

Phone: +61 3 9342 7440

Fax +61 3 9342 8440

Email: Kate.Fetterplace@mh.org.au

Statement of authorship

K Fetterplace and AM Deane equally contributed to the conception and design of the research; L. Chapple and C. MacIsaac contributed to the design of the research; K Fetterplace, BMT Gill, L Chapple and AM Deane, JJ Presneill contributed to the acquisition and analysis of the data; K Fetterplace, JJ Presneill and AM Deane contributed to the interpretation of the data; and K Fetterplace and AM Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of interest

AMD or his institution have received honoraria, travel grants or project grant funding from Baxter, Cardinal Health, Fresenius Kabi, GSK, Medtronic and Nutricia. AMD has participated on advisory boards for Lyric Pharmaceuticals and Takeda. KF has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi, Nutricia and Nestle Health Science (not related to this study). LC has received project grant funding from Nutricia.

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2.3 Abstract

Background: International guidelines recommend that protein be administered enterally to critically ill patients at doses between 1.2-2.0 g/kg per day. Observational data indicate that patients frequently receive less protein. The aim of this systematic review was to evaluate patient-centered outcomes with guideline recommended enteral protein compared to usual care.

Methods: A systematic review was performed of randomized controlled trials including critically ill adult patients provided predominately enteral nutrition with mean protein at ≥ 1.2 g/kg per day (intervention) and < 1.2 g/kg per day (comparator). Random effects models were applied for outcomes reported in ≥ 3 trials.

Results: Of 1375 abstracts, 69 full-text articles were reviewed and six trials meet the inclusion criteria, including 511 patients. The intervention group received a mean (SD) of 1.3 (0.08) g/kg per day and the comparator group received 0.75 (0.15) g/kg per day protein. Insufficient data were available for meta-analyses on the primary outcome (muscle mass or strength). According to our meta-analyses mortality at 28 days (5 studies) [RR 0.92 (95% CI 0.63 to 1.35), $p = 0.66$] and the durations of ICU (6 studies) and hospital admission (4 studies) were similar between the intervention and comparator; with some uncertainty due to sample sizes and heterogeneity.

Conclusion: There are insufficient data to conclude if protein provision within the current international guideline recommendations improves outcomes. In a limited dataset, enteral protein intakes near the lower level of current recommendations, does not appear to reduce admission duration or mortality when compared to usual care in critically ill.

2.4 Introduction

Recommendations from international critical care guidelines suggest that critically ill patients should receive at least 1.2 g/kg body weight per day of protein via the enteral route (Hurt et al., 2017; McClave et al., 2016; Reintam Blaser et al., 2017; Singer et al., 2019). These guidelines were developed on the assumption that protein delivery > 1.2 g/kg body weight per day may reduce morbidity and mortality (Hurt et al., 2017). However, observational data suggests that many patients do not meet these recommended protein targets, with several studies reporting that during usual critical care management patients only receive a mean of 0.6-0.8 g/kg per day protein, presumably due to interruptions to feeding, intolerance and limited availability of higher protein formulas (Bellomo et al., 2014; Compher et al., 2017; Deane et al., 2019; Nicolo et al., 2016; Ridley et al., 2018).

During critical illness the frequent occurrence of muscle loss is associated with inferior patient-centered outcomes (Hurt et al., 2017). Inflammatory mediators, coupled with inactivity, may drive an imbalance between protein breakdown and synthesis (Liebau et al., 2015; Preiser et al., 2015), with rapid muscle loss of up to 1-2% of lean body mass per day (Liebau et al., 2015; Wandrag et al., 2015). It remains unclear whether increased delivery of protein may stimulate protein synthesis and attenuate this muscle loss (Liebau et al., 2015), or otherwise favorably influence important patient-centered outcomes, including acute illness duration and mortality, or functional capacity and quality of life in survivors (Allingstrup et al., 2012; Hurt et al., 2017; Yeh et al., 2017).

The aim of this systematic literature review was to evaluate data from all eligible randomized clinical trials to estimate the effect of enteral protein delivered according to international guideline recommendations (i.e. ≥ 1.2 g/kg per day) when compared to the care usually administered (i.e. < 1.2 g/kg per day). The outcomes of interest were muscle mass and strength, duration of ICU and hospital admission, requirement for transfer to a rehabilitation facility, physical function, quality of life and mortality.

2.5 Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009) and methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011) and the Centre for Research and Dissemination (CRD's) Guidance ("Centre for Reviews and Dissemination. System Reviews: CRDs guidance for undertaking reviews in health care," 2009). The protocol was registered on PROSPERO (registration CRD42018109924).

The research question was: "In critically ill adult patients (population), does protein delivery equal to or greater than 1.2 g/kg per day of ideal body weight (IBW) via enteral nutrition (intervention), when compared to less than 1.2 g/kg per day of IBW (comparator), influence patient-centered outcomes (outcome)?" All of the study procedures were undertaken by the lead author (KF), with a second reviewer (BG) independently completing title and abstract screening, full-text review, quality assessment and data extraction, with a third and fourth reviewer (AMD and LC) resolving any conflicts and discrepancies between the first and second reviewers. Endnote reference manager software program (version X7.8, USA: Thomas Reuters, 2014), Covidence 2018 (www.covidence.org) and Review Manager (version 5.3), were used to undertake the review and track processes.

2.5.1 Inclusion and exclusion criteria

Studies were included if they:

- Were randomized clinical trials;
- Included only adult patients (≥ 18 years);
- The participants were admitted to an intensive care unit with the majority receiving mechanical ventilation;
- One group received greater than or equal to 1.2 g/kg ideal body weight (IBW) per day of protein via predominately enteral nutrition (more protein cohort), whereas

the other group received less than 1.2 g/kg IBW per day of protein (less protein cohort);

- The difference in protein delivery between the two groups was statistically different (significance set at the 0.05 level); and
- At least one of the pre-defined outcomes was reported as a primary or secondary outcome.

Studies were excluded if:

- Protein provided was exclusive parenteral nutrition;
- Protein provision was due to glutamine supplementation or other immune enhancing amino acids such as arginine; and
- The original article could not be located or it was not available in English.

‘Predominately enteral’ protein was a definition used for this systematic review to identify studies that clearly provided nutritional therapy via the enteral route in preference to parenteral nutrition. Whilst parenteral nutrition, either as total or supplemental nutritional support, was not an exclusion criterion, studies were only included if parenteral nutrition was administered when the enteral route was not possible or insufficient. This approach to use ‘predominately enteral’ was taken because it is in line with current international guidelines and local practice (McClave et al., 2016; Ridley et al., 2018). This is in contrast to the use of parenteral nutrition as part of initial therapy, which does not represent usual care and the route of protein administration (i.e. intravenous) may be a potential confounding variable (Derde et al., 2012). The threshold protein provision of ≥ 1.2 g/kg was based on IBW, to try to account for studies which included participants with body mass indices (BMIs) greater than the healthy weight range. Ideal body weight was selected as there is uncertainty about what weight (actual or ideal) should be used to dose protein (Weijs et al., 2012).

2.5.2 Search strategy

A systematic search of the literature was conducted using four databases, MEDLINE (Ovid SP, from 1948 to current), EMBASE (OVID SP, from 1948 to current), the current issues of

the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL, EBSCOhost, from 1948 to current), including studies published up until 9th November 2018. The search strategy was refined to exclude infant and pediatric patients and animals. No other restrictions or limits were placed on the search strategy. The search terms used included all variations of critical ill, intensive care, critical care, nutritional support, enteral nutrition, nasogastric, nasojejunal, dietary protein, protein and amino acids. A full sample of the MEDLINE search strategy is included in supplemental appendix 1. Additionally, reference lists from relevant reviews and guidelines were checked and the Medline search was repeated on the 15th of March 2019 for any additional studies for inclusion (Davies ML et al., 2017; Ferrie et al., 2013; Lambell et al., 2018; McClave et al., 2016; Singer et al., 2019).

2.5.3 Outcome measures

The major outcomes of interest were: muscle mass at ICU or hospital discharge, assessed using ultrasonography of any muscle, such as quadriceps muscle layer thickness as described by Tillquist and colleagues (Tillquist et al., 2014), or any other validated technique such as computed tomography and bioimpedance (Price & Earthman, 2019); or muscle strength at ICU or hospital discharge, assessed using handgrip dynamometry or any other validated technique (Hermans et al., 2012). The secondary outcomes were physical function at ICU discharge, quality of life at any time point, the requirement for transfer to a rehabilitation facility, mortality at any time point, duration of ICU and hospital admission, and incidence of diarrhea. Following the systematic review and extraction of trials it became apparent that only the outcomes of mortality, duration of ICU and hospital admission and incidence of diarrhea provided sufficient data to be included in the meta-analysis.

2.5.4 Data extraction and risk of bias

Data extraction was completed independently by two reviewers (KF and BG). Data collection included study characteristics (author, year of publication, patient inclusion criteria, trial objectives, intervention and control methods, protein and energy targets, characteristics of

participants, protein and energy provision, and all reported outcomes of interest). The corresponding authors of relevant publications were contacted to clarify missing data and protein provision if it was not documented in g/kg IBW per day and the mean BMI was above the healthy weight range. Each included study was assessed independently by the first and second reviewer for risk of bias in random sequencing generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting and other sources of bias using The Cochrane Risk of Bias Tool (Higgins, 2011), with AMD providing assessment when required for consensus.

2.5.5 Data handling and statistical analysis

Binary data are presented as proportions or percentages. If original studies reported mortality at different time points, all were noted, however 28-day mortality was selected for analysis as the most complete outcome data. For continuous variables; mean and standard deviations (SD) were directly recorded, and median with interquartile range [IQR] data were converted prior to analysis to approximate mean (SD) data as described by Wan and colleagues (Wan et al., 2014). All included studies reported protein and energy provision in g/kg per day and kcal/kg per day; where actual weight was reported and the mean BMI was within the healthy weight range ($\text{BMI } 18.5\text{-}25 \text{ kg/m}^2 \leq 65 \text{ years}$, $22 - 27 \text{ kg/m}^2$ if $>65 \text{ year}$) the reported mean (SD) protein dose was used in data analyses; if actual weight was reported and the mean BMI was above the healthy weight range, then calculations were done to assess the protein provision based on IBW (defined as the upper end of the healthy weight range); if studies reported IBW or an adjusted IBW for the protein dose this was used in the data analyses. One author was contacted (Jakob et al., 2017) to further assess their data to confirm that protein was provided at a level of 1.2g/kg IBW per day in the intervention.

Random effects meta-analyses were applied to the outcomes of mortality and length of admission using the package “metan” in Stata statistical software (version 15.1, College Station Texas, USA). Effect estimates for mortality are presented as risk ratios (RR) with 95%

confidence intervals (CIs) and the effect estimates of length of stay are reported as standardized mean differences (SMD) with 95% CI. Variation in RR and SMD attributable to heterogeneity was summarized for each of these outcomes using the I^2 statistic.

2.6 Results

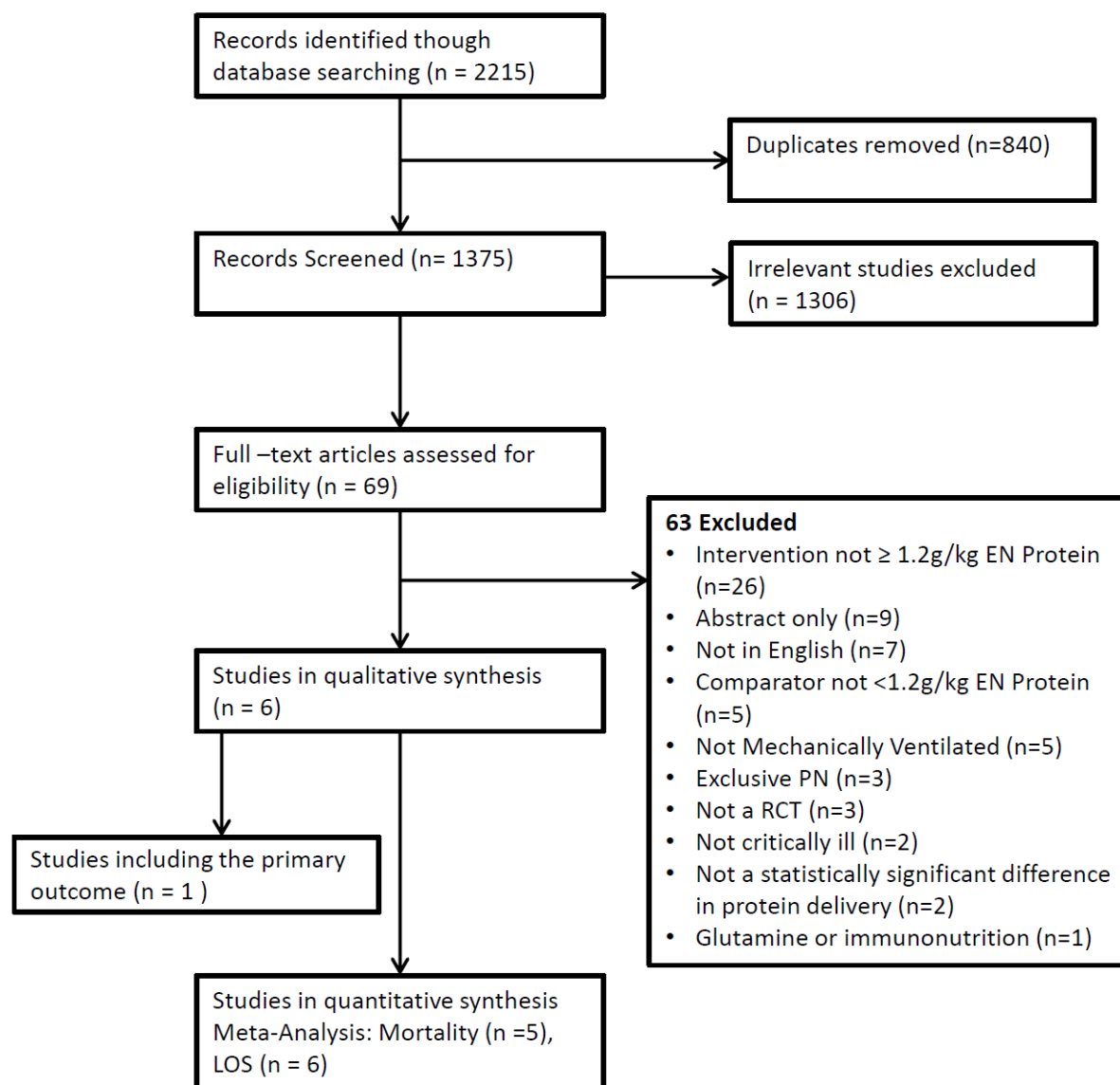
There were 2215 records identified from the database searching and no additional papers from other sources. After duplicates and irrelevant papers were excluded based on titles and abstracts alone, 69 papers underwent full-text review. Six trials were eligible for inclusion, which included 511 patients (Figure 1: PRISMA diagram) (Allingstrup et al., 2017; Eyer et al., 1993; Fetterplace et al., 2018; Jakob et al., 2017; Rugeles et al., 2013; van Zanten et al., 2018).

2.6.1 Study and patient characteristics

The included trials were conducted over a range of years and in various regions (three from Europe, and one each from the United States of America, South America and Australia) from 1993 to 2018. The study objectives and interventions varied, however all studies except that of Eyer and colleagues (Eyer et al., 1993) aimed to deliver protein within the guidelines range from the outset in the intervention group and below the guidelines range in the comparator group. In order to meet the higher protein requirements, all studies incorporated the use of a higher protein enteral formula, with two studies also using supplemental protein powder (Rugeles 2013 and Fetterplace 2018). Three studies aimed to deliver standardized amounts of energy between groups (Jakob 2017, Fetterplace 2018 and Van Zanten 2018). Two studies used supplemental parenteral nutrition to meet energy and protein needs (Jakob 2017 and Allingstrup 2017). The full details of the included study methodologies are provided in Table 1. All studies, except Van Zanten and colleagues (van Zanten et al., 2018), were single centre and all studied relatively small cohorts, enrolling between 38 and 199 participants. The mean (SD) ages for the intervention and control groups were 57 (7.9) and 57 (8.3) years. The mean (SD) BMIs for the intervention and control group were 27 (3.7) and 27 (3.4) kg/m² and the mean (SD) Acute Physiology and

Chronic Health Evaluation (APACHE) II scores were 22 (6.0) and 22 (5.4). Details of the participant characteristics in the included studies are provided in Table 2.

Figure 2-1. PRISMA diagram



Abbreviations: Kg: kilogram, EN: Enteral nutrition, PN: Parenteral nutrition, RCT: randomised controlled trial, LOS: Length of Stay

Table 2-1. Summary and methodology of included studies

Author, year, country	Number of centres	Study objective	Methods		Protein Target per day		Energy Target per day	
			Study intervention	Study control	Intervention	Control	Intervention	Control
Allingstrup, 2017, Denmark	1	To assess the effects of individualized energy and protein nutrition optimised by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance) on physical quality of life at 6 months in acutely admitted, adult ICU patients	Standard high protein formula (1.5kcal/ml, 75g protein per 1000ml), with addition of supplemental PN, if required to reach the goals, up to 90 days or discharge	Standard formula (1.0kcal/ml, 38g protein per 1000ml), if calculated goal rate was not met by 7 days supplemental PN was commenced	At least 1.5g/kg actual weight, assessed with urinary nitrogen	Approximately 0.95g/kg actual weight	Measured Energy expenditure	25kcal/kg
Eyer, 1993, USA	1	To assess if early enteral nutrition will attenuate the metabolic response after blunt trauma	Early Nutrition support (Day 0), Peptide based formula (1.33kcal/ml, 58g protein per 1000ml), up to discharge	Late nutrition support (72hr, IV fluid), Peptide based formula (1.33kcal/ml, 58g protein per 1000ml)	1.5 g/kg actual weight	1.5g/kg actual weight (once feeds commenced)	Approximately 34kcal/kg	Approximately 34kcal/kg (once feeds commenced)
Fetterplace, 2018, Australia	1	To determine whether a high protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly-rate-based nutrition protocol critically ill patients without protein supplementation to mechanically ventilated	Standard high protein formula (1.25kcal/ml, 63g protein per 1000ml), with a volume based feeding protocol, plus supplemental protein powder in 3 to 4 bolus per day, for up to 15 days or discharge	Standard formula (1.0kcal/ml, 40g protein per 1000ml)	1.5g/kg IBW Based on BMI for age For BMI > 32 Adjusted IBW was used = IBW + (25% actual – IBW)	Approximately 1.0 g/kg IBW	25kcal/kg IBW Based on BMI for age, For BMI > 32 Adjusted IBW was used = IBW + (25% actual – IBW)	25kcal/kg IBW Based on BMI for age For BMI > 32 Adjusted IBW was used = IBW + (25% actual – IBW)
Jakob, 2017, Switzerland	1	To test the effect of a new enteral formula on the frequency of diarrhea and gastrointestinal tolerance, and on all diarrhea-related costs in ICU long-stayers	High protein enteral ICU specific formula (1.5kcal/ml, 94g protein per 1000ml), for up to 10 days or discharge	Standard formula (1.57kcal/ml, 61g protein per 1000ml)	Approximately 1.55g/kg actual weight	Approximately 0.97g/kg actual weight	25kcal/kg actual weight	25kcal/kg actual weight

Author, year, country	Number of centres	Study objective	Methods	Protein Target per day	Energy Target per day	Author, year, country	Number of centres	Study objective
				Study intervention	Study control	Intervention	Control	Intervention
Rugeles, 2013, Colombia	1	To compare two enteral nutritional regimens in the critically ill patient, and their impact in the development of severe organic failure, as measured with the SOFA	Standard enteral feed (1.3kcal/ml, 66.6g protein per 1000ml), plus supplemental soy protein powder in 2 bolus per day, for up to 7 days or discharge	Standard enteral feed (1.3kcal/ml, 66.6g protein per 1000ml),	1.5g/kg actual weight	Approximately 1.0g/kg actual weight	15kcal/kg actual weight	25kcal/kg actual weight
Van Zanten, 2018, Netherlands	4	To investigate protein and energy intake, gastrointestinal tolerance, and safety of this new polymeric very high protein formula	Very high protein formula (1.25kcal/ml enteral, 100g protein per 1000ml), up to 28 days or discharge	Standard high protein formula (1.25kcal/ml, 63g protein per 1000ml)	Approximately 2.0g/kg IBW	Approximately 1.25g/kg IBW	25kcal/kg IBW For BMI > 30 IBW = 30x(Ht m ²)	25kcal/kg IBW For BMI > 30 IBW = 30x(ht m ²)

Abbreviations: PN, Parenteral Nutrition; IV, Intravenous fluid; IBW, Ideal body weight; BMI, Body mass index; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; Ht, height.

Table 2-2. Participant characteristics of included studies

Author, year	No. randomized		Age, year, Mean (SD)		Sex, n % males		BMI, kg/m2, Mean (SD)		Proportion of Medical admission, n (%)		APACHE II Score, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Allingstrup, 2017	100	99	62 (15.8)	65 (17)	65 (65)	59 (60)	22.7(4.5)	22 (3.8)	52(52)	43 (43)	N/A	N/A
Eyer, 1993	19	19	44 (22)	41 (18)	14 (73)	8 (42)	N/A	N/A	0 (0)	0 (0)	N/A	N/A
Fetterplac, 2018	30	30	55 (13)	57 (16)	23 (77)	21 (70)	30 (7.1)	29 (5.3)	21 (70)	16 (53)	22 (6.2)	20 (5.9)
Jakob, 2017	46	44	64 (17)	61 (17)	33 (72)	28 (64)	29 (7.0)	28 (6.1)	N/A	N/A	28 (8.0)	28 (8.7)
Rugeles, 2013	40	40	53 (20)	56 (20)	22 (55)	24 (60)	24 (3.3)	24 (4.4)	40 (100)	40 (100)	14 (4.8)	15 (6.2)
Van Zanten, 2018	22	22	64 (13)	61 (15)	9 (41)	13 (59)	30 (4.1)	31 (8.4)	8 (36)	9 (41)	25 (5.6)	23 (7.1)

Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation.

2.6.2 Protein and energy provision

The mean duration of the interventions ranged from 7 to 18 days, with an unweighted pooled mean of 11 (3.8) days. All studies included an intervention group that delivered a greater amount of protein (Table 3). The intervention group received a mean (SD) protein delivery of 1.3 (0.08) g/kg per day and the control group received a mean protein delivery of 0.75 (0.15) g/kg per day, with an unweighted pooled mean difference of 0.55 (95% CI 0.40 – 0.71) g/kg per day. Energy provision was variable within the two groups with two studies delivering substantially more energy in the intervention group (Table 3). The intervention group received an unweighted pooled mean of 21 (6.3) kcal/kg per day and the control group received a mean of 17 (3.8) kcal/kg per day, with the mean difference in energy delivery being 3.5 (95%CI -3.3 to 10.2) kcal/kg per day.

Table 2-3. Energy and protein provision of included studies

Author, year	Duration of Intervention mean (SD), days	Delivered protein, mean (SD), g/kg/day		Delivered energy, mean (SD), kcal/kg/day	
		Intervention	Control	Intervention	Control
Allingstrup, 2017	11.3 (12.8)	1.4 (0.42)	0.49 (0.30)	24 (6.6)	14 (6.8)
Eyer, 1993	11.8 (7.9)	1.3 (0.30)	0.9 (0.2)	30 (6)	19 (5)
Fetterplace, 2018	10.6 (8.3)	1.2 (0.30)	0.75 (0.11)	23 (5.7)	21 (3.3)
Jakob, 2017	7 (2.6)	1.2 (0.47)	0.90 (0.20)	20 (7.4)	22 (4.9)
Rugeles, 2013 ^a	9.5 (5.5)	1.4	0.76	12	14
Van Zanten, 2018	18.4 (13.4)	1.3 (0.95)	0.70 (0.32)	16 (11)	15 (6.3)

^aOnly mean figures for protein and energy delivery were reported in the original paper, the author was contacted for clarification of the variance, however this was not provided.

2.6.3 Assessment for risk of bias

The risk of bias assessment for each of the included studies can be visualized (Figure 2 and 3). Four studies were considered of high quality (Allingstrup 2017, Jakob 2017, Fetterplace 2018 and Van Zanten 2018) and two studies were of low quality (Eyer 1993 and Rugeles

2013). Only one study had unequivocally adequate blinding (Van Zanten 2018) and while a second study reported using double blind methodology (Jakob 2017) it was unclear how this was achieved.

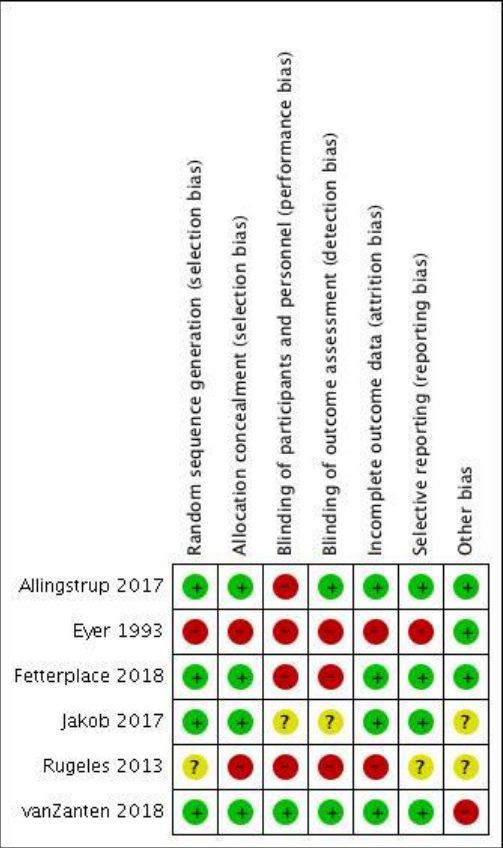


Figure 2-2. Risk of bias summary for each included study

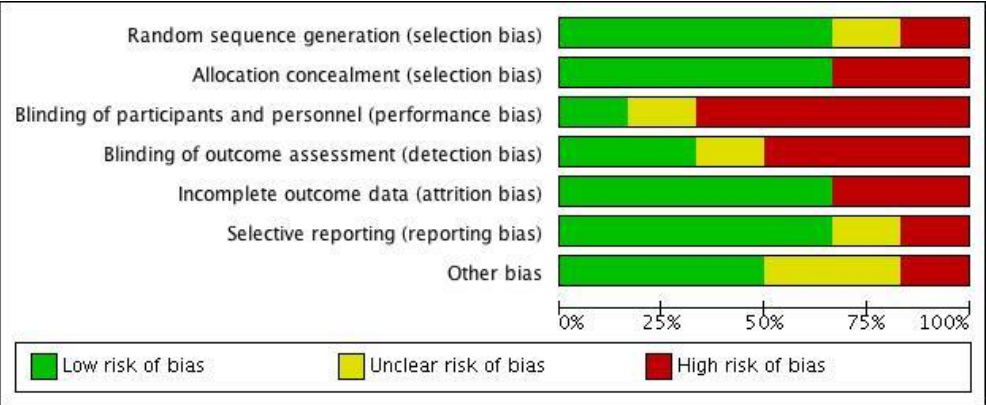


Figure 2-3. Summary of domains for risk of bias for included studies

2.6.4 Outcomes

2.6.5 Functional outcomes

Muscle mass, muscle strength, quality of life and physical function outcomes were reported in only one study. Our group (Fetterplace and colleagues) reported that muscle mass loss, measured using quadriceps muscle layer thickness, was attenuated with greater protein delivery (Fetterplace et al., 2018). There was no difference in muscle strength and physical function; however, inferences were limited by significant amounts of missing data (up to 80% of participants). Allingstrup and colleagues attempted to assess muscle strength but this was abandoned mid-study due to methodological difficulties (Allingstrup et al., 2017). The latter study was the only one to assess quality of life; they found there was no difference between the high and low protein groups at six months post hospital discharge (Allingstrup et al., 2017), however outcome data were missing in 18% of survivors. The requirement for transfer to a rehabilitation facility was only reported by a single study, where greater protein administration did not impact the proportion of patients who required rehabilitation (Fetterplace et al., 2018).

2.6.6 Mortality

The provision of equal to or greater than 1.2 g/kg per day protein did not reduce 28-day mortality (Figure 4. 5 studies, 431 participants) (RR 0.92 95% CI (0.63 to 1.35), $p = 0.66$, $I^2 = 0.0\%$ $p = 0.99$).

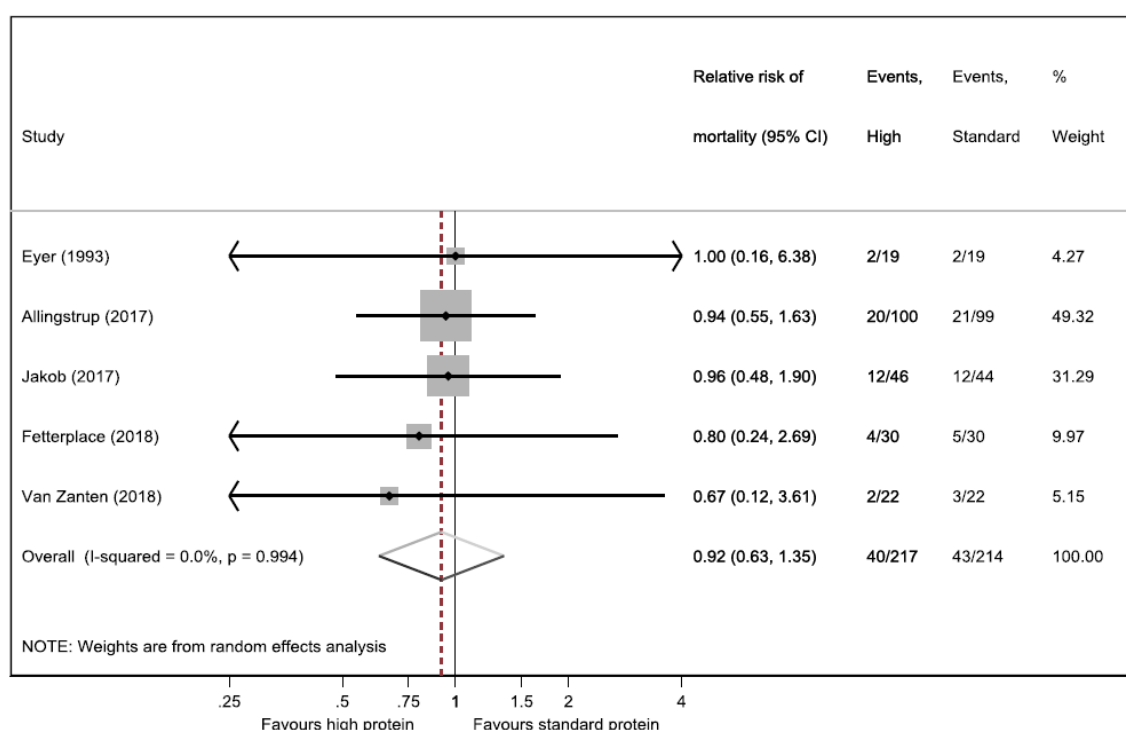


Figure 2-4. Random effects meta-analysis of mortality, sorted by ascending year of publication

Abbreviations: High; Higher protein (intervention group), Standard; Usual protein group (Comparator). Random effects model using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Analysis using Stata command *metan* in Stata version 15.1, College Station Texas, USA.

2.6.7 Length of stay

Greater protein delivery did not reduce length of ICU or hospital admission. The standardized mean difference for length of ICU admission (Figure 5 (6 studies, 511 participants) was 0.01 days (95% CI -0.39 to 0.38, $p = 0.98$, $I^2 = 76\%$, $p = 0.001$), and for hospital length of admission (4 studies, 393 participants) the standardized mean difference was 0.09 days (95%CI -0.29 to 0.11, $p = 0.38$, $I^2 = 76\%$, $p = 0.01$).

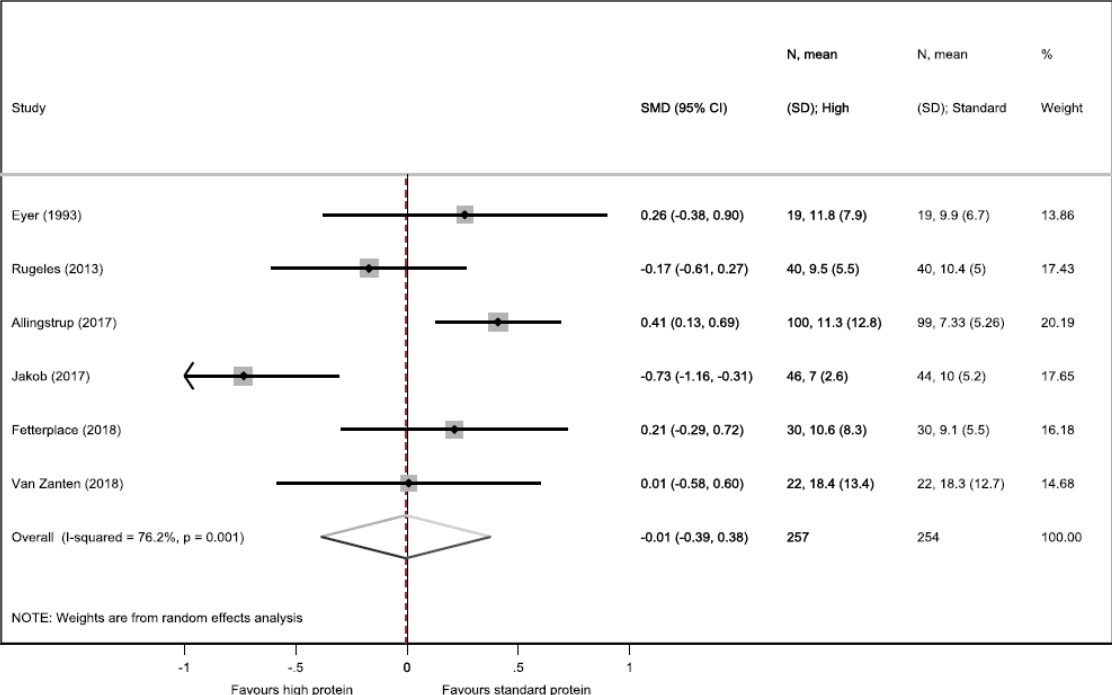


Figure 2-5. Random effect analysis of length of admission, sorted by ascending year of publication

Abbreviations: High; Higher protein (intervention group), Standard; Usual protein group (Comparator). Random effects model returned by using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Analysis using Stata command *metan* in Stata version 15.1, College Station Texas, USA

2.6.8 Diarrhea

Three studies reported the incidence of diarrhea (Jakob 2017, Fetterplace 2018 and Van Zanten 2018). Diarrhea was not significantly different between the 2 groups (RR 0.90 (95%CI 0.71 to 1.1, $p = 0.37$, $I^2 = 0\%$).

2.7 Discussion

This systematic literature review and meta-analysis did not detect any effect on mortality or length of admission with protein provision at the level of international guidelines (≥ 1.2

g/kg IBW per day) when compared to what the majority of patients receive as usual care (< 1.2 g/kg IBW per day). However, confidence in these results is low due to both the small number of participants that have been included in trials (n=511) and heterogeneity of study methodology. Importantly, many of the outcomes of interest, including the major primary outcomes muscle mass and strength, as well as quality of life and the requirement for transfer to a rehabilitation facility, were not sufficiently reported in the original studies to enable meta-analyses. Accordingly, this review highlights the lack of trial data available to evaluate current guideline recommendations regarding optimal enteral protein administration to the critically ill.

Mean protein provision was consistent across the included studies with the intervention group receiving a mean of 1.3 (0.08) g/kg per day of protein; inferring that approximately two thirds of the patients in this group received the minimum recommended amount of protein (≥ 1.2 g/kg per day). Protein delivery was less consistent in the comparator group, with the mean protein delivery ranging from 0.5-0.9 g/kg per day, (mean 0.75 (1.5) g/kg per day), this is reflective of variation in clinical practice (Ridley et al., 2018). This review highlights that to date all studies aiming to achieve higher protein provision with predominately enteral nutrition have only managed to deliver mean protein at the lower end of the current international guidelines recommendations and, therefore, a proportion of patients in the intervention group of this systematic review received less than the recommendations. No randomized controlled trial has successfully delivered protein at the upper end of the international guidelines (i.e. 1.6 -2.0 g/kg per day) to all patients using predominately enteral nutrition and, therefore it is unknown if outcomes would be better or worse if this occurred. It is also uncertain as to whether it is the protein dose *per se* that is important, or whether the route of delivery or type of protein is relevant and what effect calorie intake has on protein utilization or if protein should be delivered as a 'package' of care in combination with exercise (Garza et al., 1976; D. K. Heyland et al., 2019; D. K. Heyland et al., 2017; D. K. Heyland et al., 2018). Furthermore, it remains unclear whether enteral protein digestion and absorption is impaired during critical illness, and how any abnormality impacts delivery of protein and outcome (Liebau et al., 2015).

It should be recognized that energy delivery varied between trials. Energy provision across the high protein group and the comparator group was not standardized and in most of the studies the energy delivery was not in-line with the current guideline recommendations (McClave et al., 2016). Whilst the amount of energy delivered may confound the impact of protein delivery (Compher et al., 2017; J. L. Hoffer et al., 2017; Nicolo et al., 2016), a recent large blinded randomized controlled trial reported that augmented energy delivery (i.e. consistent with international guidelines) when compared to standard care had no impact on mortality or other patient-centered outcomes when similar amounts of protein were administered (Ridley et al., 2018; TARGET Investigators*, 2018a, 2018b). However, functional outcomes for this trial are yet to be published.

The novelty of this systematic review is that only randomized clinical trials that provided predominately enteral protein; within the guidelines range in the intervention group, were included. Accordingly, the intervention group approached what current international guidelines recommend, and the comparator group represents 'usual' clinical care, as established in numerous observational trials in various regions. Three systematic reviews have previously evaluated the impact of protein provision in the critically ill (Davies ML et al., 2017; Ferrie et al., 2013; J. L. Hoffer & Bistrian, 2012). The most recent of these was by Davies and colleagues (Davies ML et al., 2017), who evaluated the effect of two different protein doses on mortality, length of stay, incidence of pneumonia and length of mechanical ventilation. Similar to the current review, they reported that greater protein provision did not appear to influence mortality or any of the other secondary outcomes (Davies ML et al., 2017). However, this review included studies that administered enteral or parenteral nutrition, as well as including studies that administered specific amino acids such as glutamine. This is important as guidelines recommend that parenteral nutrition is reserved for specific cases and trial data suggests outcomes from exogenous glutamine supplementation are worse than with standard care D. Heyland et al. (2013). Hence, including studies using specific amino acids is unlikely to be representative of mixed protein administration. Davies and colleagues also included all studies that delivered two different amounts of protein, irrespective of whether this was within the current guideline recommendations. Of the eight studies included by Davies and colleagues that delivered

predominately enteral nutrition (Braunschweig et al., 2015; Doig et al., 2015; Hsu et al., 2009; Huang et al., 2012; Ibrahim et al., 2002; Kearns et al., 2000; Qiu et al., 2017; Rice et al., 2012), none of these achieved ≥ 1.2 g/kg per day protein in the intervention group (i.e. international guideline recommendations) and < 1.2 g/kg per day in the comparator group. Furthermore, there have been trials recently published in this field, with four out of the six studies included in the current systematic review published after the review by Davies and colleagues (Davies ML et al., 2017). The two systematic reviews conducted prior to Davies and colleagues (Ferrie et al., 2013; J. L. Hoffer & Bistrian, 2012) also incorporated both enteral and parenteral nutrition and multiple study methodologies. In addition, Ferrie and colleagues included studies that were not conducted in the ICU (Ferrie et al., 2013).

2.7.1 Strength and limitations

The main strength of this systematic review is that randomized clinical trials that provided predominately enteral nutrition, with mean protein provision within the current guidelines range in the intervention and similar to usual care in the comparator, were included. This removed potential confounders of parenteral nutrition and immune-modulating amino acids such as glutamine.

There are several limitations to this review. The most substantial limitation is the lack of data available to facilitate analyses for the primary outcomes. Likewise, many of the other secondary outcomes of interest were not able to be included in meta-analyses because of insufficient data; these outcomes included physical function, requirement for rehabilitation and quality of life. Even when there were sufficient data to conduct meta-analyses, such as with mortality, point estimates were limited by an inadequate number of patients, particularly for such a ubiquitous intervention as nutritional therapy (Summers et al., 2016), leading to wide confidence intervals. The duration of ICU and hospital admission point estimates were also limited by small sample sizes as well as significant heterogeneity, resulting in considerable uncertainty in these results. A limitation of meta-analyses includes clinical heterogeneity (Møller et al., 2018); clinical heterogeneity that may have affected the results of this study includes patient factors, pre-morbid nutritional

state and duration of intervention. Lack of data and heterogeneity within existing data may explain why the current international guidelines acknowledge that there is some uncertainty regarding the optimal protein dose (McClave et al., 2016).

2.8 Conclusion

There are insufficient data to conclude if enteral protein provision within the current international guideline recommendations, improves patient-centered outcomes for critically ill patients. In a limited dataset of critically ill patients, mean enteral protein intake at approximately the lower end of the range recommended by international guidelines did not appear to reduce acute admission duration or mortality when compared to usual care. Large methodologically rigorous randomized clinical trials evaluating protein provision within the guideline recommendations, possibly combined with physical therapy interventions, are required to assess the impact on patient-centered outcomes such as functional capacity and muscle mass and strength and, thereby, inform clinical practice.

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2.9.1 Supplementary material for chapter 2

Search Strategy

Search completed 13th November 2018

Database: Ovid MEDLINE(R) ALL <1946 to November 09, 2018> Search Strategy:

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- 1 exp Critical Illness/ or exp sepsis/ or exp respiration, artificial/ or exp critical care/ (244117)
 - 2 (critical* ill* or acute* ill* or icu or intensive care or intensive therapy or critical care or mechanical*ventilat* or sepsis or shock or burn unit* or coronary care or respiratory care).mp. (519027)
 - 3 exp Enteral Nutrition/ (18444)
 - 4 (enteral or nasogastric or nasojejunal or naso-gastric or naso-jejunal or tube feeding or gastric feeding).mp. (35119)
 - 5 exp Dietary Proteins/ or protein*.ti,ab. (2818437)
 - 6 1 or 2 (604104)
 - 7 exp Amino Acids/ (773441)
 - 8 5 or 7 (3382855)
 - 9 ((child* or infant* or p?ediatric* or juvenile* or adolescen* or teen*) not adult*).mp. (2099705)
 - 10 exp animals/ not exp humans/ (4513797)
 - 11 (random* or trial* or placebo).ti,ab. (1570735)
 - 12 (randomized controlled trial or controlled clinical trial).pt. (559057)
 - 13 exp Randomized Controlled Trial/ (471569)
 - 14 11 or 12 or 13 (1714305)
 - 15 exp Nutritional Support/ (42809)
 - 16 3 or 4 or 15 (57512)
 - 17 16 and 8 and 6 (2180)
 - 18 17 not 9 (1807)
 - 19 18 not 10 (1625)
 - 20 19 and 14 (519)
 - 21 from 20 keep 1-519 (519)

Chapter 3: Methods to quantify the response to nutritional therapy during critical illness

3.1 Chapter summary

This narrative review was completed in the latter part of PhD candidature. The manuscript was fully accepted for publication on 18th June 2020. This review was undertaken to explore the methodologies and outcomes used previously in critical care nutrition trials. This review is important because it summarises the patient-centred outcomes used in previous studies, the strengths and limitations of each outcome, and identifies the utility of the outcomes, enabling evaluation the effect of nutrition therapy in the critically ill.

3.2 Narrative review

Quantifying response to nutritional therapy during critical illness: Implications for clinical practice and research? A narrative review

Kate Fetterplace^{1,2} APD, BNut&Diet, Emma J. Ridley^{3,4} APD, PhD, Lisa Beach^{5,6} PT, MPhty, Yasmine Ali Abdelhamid^{2,5} MBBS, Jeffrey J. Presneill^{2,5} MBBS, PhD, Christopher M. MacIsaac^{2,5} MBBS, PhD, Adam M. Deane^{2,5} MBBS, PhD.

1. Department of Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Victoria, Australia
2. The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, Victoria, Australia
3. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, 3004, Australia
4. Nutrition Department, The Alfred Hospital, Commercial Road, Melbourne, 3004, Australia
5. Intensive Care Unit, Royal Melbourne Hospital, Parkville Victoria, Australia

6. Department of Allied Health (Physiotherapy), Royal Melbourne Hospital, Melbourne, Victoria, Australia

Corresponding author

Ms Kate Fetterplace^{1,2} BNutDiet, APD

Senior Dietitian, Royal Melbourne Hospital

Allied Health, Royal Melbourne Hospital

Grattan St Parkville, Victoria, Australia 3050

Phone: +61 3 9342 7440 Fax +61 3 9342 8440

Email: Kate.Fetterplace@mh.org.au

Conflicts of interest

Fetterplace has received conference grants or honoraria from Baxter, Fresenius Kabi, Nutricia, Abbott and Nestle Health Science (not related to this study); Deane has received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study); Ridley has unrestricted research funding from Baxter Healthcare Corporation and has received honoraria from Baxter Healthcare Corporation (United States and Australia) and Nutrica (not related to this research).

Statement of authorship

K Fetterplace, AM Deane equally contributed to the conception and design of the research; EJ Ridley, L Beach, Y Ali Abdelhamid, JJ Presneill and CM MacIsaac contributed to the design of the research; K Fetterplace contributed to the acquisition and analysis of the data; K Fetterplace and AM Deane contributed to the interpretation of the data; K Fetterplace, AM Deane and EJ Ridley drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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3.3 Abstract

Critical illness causes substantial muscle loss that adversely impacts recovery and health related quality of life. Treatments are therefore needed that reduce mortality and/or improve the quality of survivorship. The purpose of this review is to describe both patient centered and surrogate outcomes that quantify responses to nutrition therapy in critically ill patients. The use of these outcomes in randomized clinical trials will be described, and the strengths and limitations of these outcomes detailed. Outcomes used to quantify the response of nutrition therapy must have a plausible mechanistic relationship to nutrition therapy, and either be an accepted measure for the quality of survivorship or highly likely to lead to improvements in survivorship. This review identified that previous trials have utilized diverse outcomes. The variety of outcomes observed is probably due to a lack of consensus as to the most appropriate surrogate outcomes to quantify response to nutrition therapy during research or clinical practice. Recent studies have used, with some success, measures of muscle mass to evaluate and monitor nutritional interventions administered to critically ill patients.

3.4 Background

3.4.1 Why is nutrition therapy important?

Critical illness activates a 'stress' response that is characterized by secretion of neuroendocrine hormones and inflammatory mediators (Preiser et al., 2014). Such messaging induces catabolism and resistance to anabolism, with significant changes in protein, glucose and lipid metabolism (Preiser et al., 2014). The consequence of these physiological changes in critical illness includes substantial muscle wasting, which occurs to a much greater degree than is seen with bed rest alone (Puthucherry et al., 2013). Muscle loss has been associated with less favorable outcomes from critical illness, such as increased mortality rates and complications, muscle weakness, delayed recovery of physical function

and reduced quality of life (Cuthbertson B. H et al., 2010; Herridge, 2009; Kress, 2014; Moisey et al., 2013). Given these consequences of critical illness, some therapies such as nutrition and early rehabilitation, are administered in the intensive care unit (ICU) to attenuate deterioration in functional ability and enhance recovery (Rengel et al., 2019; Turnbull et al., 2016). Intuitively, optimal nutrition therapy may reduce mortality and improve the quality of survivorship with a reduction in disability; however, this remains to be determined.

The optimal nutrition therapy for critically ill patients remains unknown (Bear et al., 2017; Preiser et al., 2015). Recent large randomized clinical trials (RCTs) have challenged the orthodoxy that greater calorie provision during the early phase of critical illness improves outcomes (Arabi et al., 2011; Deane et al., 2020; Rice et al., 2012; TARGET Investigators*, 2018). This has resulted in a shifting focus from the study of calorie provision to other aspects of the composition of nutrition formula, in particular the provision of protein (Hurt et al., 2017). There is also considerable interest in the timing of nutrition therapy and the challenge to align nutrition therapy with the 'phase of illness', with speculation that excessive nutrition during the early phase of critical illness may alter adaptive processes, such as autophagy, which may exacerbate rather than attenuate the impact of critical illness (Preiser et al., 2015). Furthermore many trials of nutrition therapy have focused only on the early period of critical illness, where interventions are generally implemented for a relatively shorter period, and therefore the potential impact of such limited intervention on long term outcomes needs to be considered (E. J. Ridley et al., 2020; Taverny et al., 2019). In a recent systematic review it was identified that there is heterogeneity of outcomes reported in nutrition trials, with limited use of outcomes, other than mortality, that are likely to be important to patients (Taverny et al., 2019). All of these factors make it difficult to assess the effect of nutrition interventions in a confounded environment of complex critical illness and highlights the importance of identifying appropriate outcomes to evaluate nutrition therapy (Bear et al., 2018).

The purpose of this review was to describe outcomes available to quantify the response to nutrition therapy provided to the critically ill (Chapple et al., 2020). While mortality is clearly of extreme importance to seriously ill patients, this review will focus on other outcomes that are relevant to the quality of survivorship. The objectives were to detail the outcomes used, and the strengths and limitations of each of these outcomes. An evaluation of outcomes that are aligned to health service efficiency, such as duration of ventilation and admission, are beyond the scope of this review.

3.5 Methods

A literature review was undertaken to identify RCTs of nutrition therapy in critically ill patients which included at least one of the following outcomes: quality of life, physical function, muscle strength, muscle mass or nutrition related anthropometric measurements. These outcomes were selected as they have a possible mechanistic link to nutrition therapy and they are likely to be important to patients or a surrogate to an important patient outcome. The MEDLINE database (Ovid SP, from 1948 to current) was searched in December 2019, using the following subject headings and key search terms: variations of critically ill, intensive care, critical care, nutrition support, enteral nutrition, nasogastric, nasojejunal, parenteral nutrition, dietary protein, muscle strength, muscle mass, body composition, quality of life, activities of daily living and physical functional performance (Appendix 1). The search was limited to adult patients and papers written in English. All titles and abstracts were reviewed for relevance and reference lists of previous review papers were examined to maximize the likelihood that all relevant RCTs were included (Bear et al., 2017; Davies ML et al., 2017; Fetterplace et al., 2019; Lambell et al., 2018; Emma J. Ridley et al.; Taverny et al., 2019). Seventeen nutrition therapy RCTs in critically ill patients were identified and subsequently one additional paper was added with an updated search in January 2020 (Allingstrup et al., 2017; M. P. Casaer et al., 2013; Michael P. Casaer et al., 2011; Clifton GL et al., 1985; Deane et al., 2020; Doig, Simpson, Bellomo, et al., 2015; Doig, Simpson, Heighes, et al., 2015; Doig et al., 2013; Ferrie et al., 2016; Fetterplace et al., 2018; Gonzalez-Granda et al., 2019; Hermans et al., 2013; Mazaherpur et al., 2016; Needham, Dinglas, Bienvenu, et al.,

2013; Needham, Dinglas, Morris, et al., 2013; Reid et al., 2016; E. J. Ridley et al., 2018; Wischmeyer et al., 2017).

3.5.1 Outcomes and methods available to assess the response to nutrition therapy

Mortality

Mortality is generally considered to be the gold standard for assessing the effects of all treatments, including nutritional therapy, for critically ill patients. This is because the outcome is unequivocally important to patients, it is relatively easy and inexpensive to quantify, and it is not subject to ascertainment bias. For these reasons it is one of the most frequently utilized outcomes in nutrition therapy RCTs (Chapple et al., 2020; Taverny et al., 2019). However, over time ICU mortality rates have reduced. The subsequent reduction in the baseline mortality rates necessitates a larger sample population in order to detect an effect (Summers et al., 2016; Turnbull et al., 2016). This is particularly pertinent for nutrition, which is a low-cost therapy administered to a large number of heterogeneous patients. Population-level effects may be relatively modest, because some groups may benefit to a great degree and others may not. To date the largest sample populations included in critical care nutritional trials have been powered to detect a 3 to 4% absolute reduction in mortality, however, considering the very large numbers who are treated with nutrition therapy, a benefit (or harm) of a 1% reduction (or increase) in mortality would be an important and cost-effective outcome for individuals, populations and healthcare services (Michael P. Casaer et al., 2011; Investigators*, 2018; TARGET Investigators*, 2018). Furthermore, to detect the true effect of nutrition therapy on mortality in a heterogeneous population of critically ill patients, a trial in the tens of thousands of participants may be required or, at the very least, an enriched cohort of several thousand, who are highly likely to respond (Summers et al., 2016). Therefore, the search for appropriate surrogate markers is necessary, unless very large studies can be undertaken.

Other outcomes

Quality of life following critical illness is an extremely important outcome to patients and care givers (Taverny et al., 2019; Turnbull et al., 2016). However the effect of nutrition therapy on this outcome remains uncertain and quality of life is unlikely to be useful in quantifying the effect of nutrition therapy in short term interventions (Oeyen et al., 2010).

Other outcomes may also be relevant even if not immediately considered by patients as crucial to a better survival; these outcomes may be termed 'surrogate outcomes'. A surrogate outcome is defined as an outcome that, while not directly important to patients, is strongly related, either proven or plausible, to an outcome that is important to patients (Fleming & Powers, 2012; Prentice, 1989). For an outcome to be identified as a suitable primary outcome for a trial, the outcome must be considered as important to patients, feasible to measure, subject to minimal bias, and there must be a plausible mechanism linking the intervention to an improvement in the outcome (Fleming & Powers, 2012). It is important to recognize that surrogate outcomes facilitate conduct of 'proof of principle studies' in smaller cohorts prior to studies in larger cohorts. Additionally, the inclusion of surrogate outcomes in trials provides mechanistic understanding of why an intervention might improve a patient-centered outcome (Fleming & Powers, 2012; Taverny et al., 2019).

The patient centered and surrogate outcomes, other than mortality, which have been used in RCTs include: health related quality of life, functional capacity, muscle strength, muscle mass, nutritional status and biochemical markers (Bear et al., 2018; Lambell et al., 2018; Taverny et al., 2019). Not all of these measurements will be directly important to patients; Figure 1 outlines outcomes that nutrition therapy may impact and the likely level of importance to patients (Merriweather et al., 2016; Taverny et al., 2019). Additionally, there are substantial limitations when trying to use some of these parameters as the primary outcome for a RCT. Figure 2 provides suggested criteria for outcomes that may be of use in RCTs of nutrition therapy (Baldwin et al., 2013; Denehy et al., 2011; Fleming & Powers, 2012;

Iwashyna & Netzer, 2012; Merriweather et al., 2016; Oeyen et al., 2010; Turnbull et al., 2016).

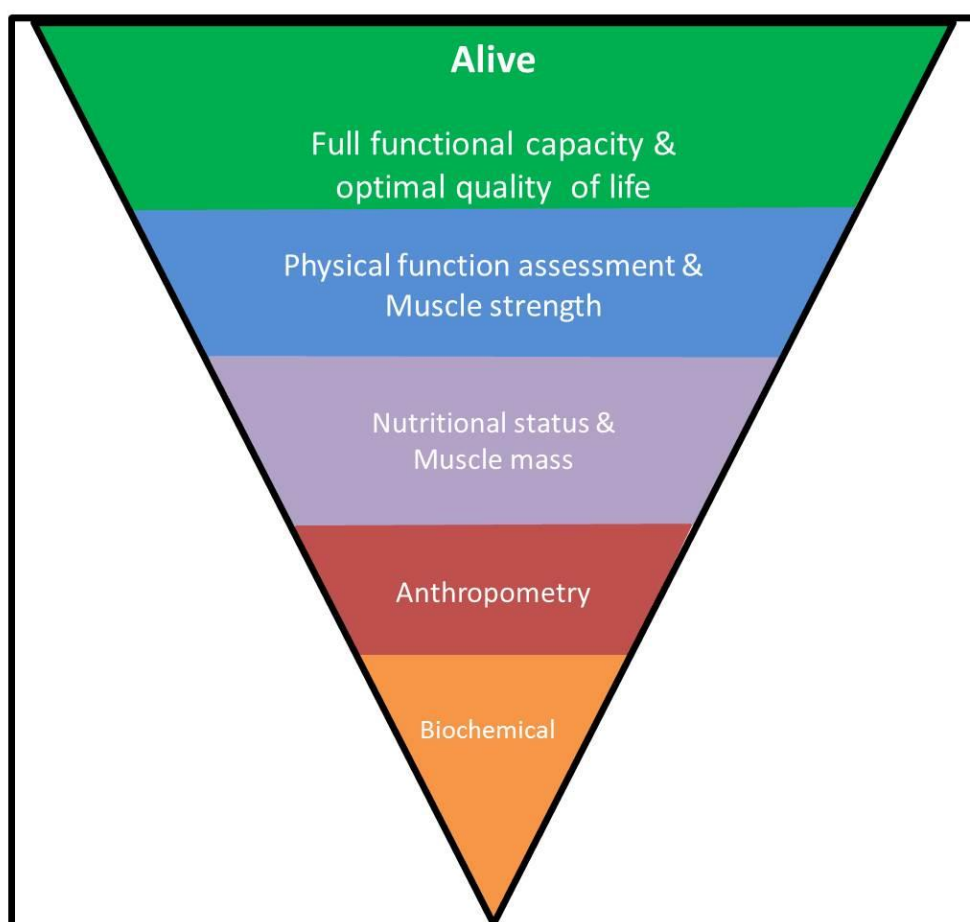


Figure 3-1. Patient centered and surrogate outcomes which have a mechanistic link to nutrition therapy and level of importance to patients

*Level of importance is based on our opinion and available data (Merriweather et al., 2016; Taverny et al., 2019)

Features	Outcomes						
	Mortality	Health related quality of life	Physical function	Muscle strength	Muscle mass	Nutritional status	Anthropometry
Important to patients	+	+	+	–	–	?	–
Easy to measure	+	×	–	–	?	–	–
Reliability	+	?	–	–	?	?	?
Limited ascertainment bias	+	×	×	×	+	?	?
Mechanism	?	?	?	?	+	+	+

Figure 3-2. Important features of outcomes and degree to which the selected outcomes meet these criteria

References: (Baldwin et al., 2013; Denehy et al., 2013; Fleming & Powers, 2012; Iwashyna & Netzer, 2012; Merriweather et al., 2016; Oeyen et al., 2010; Prentice, 1989; Turnbull et al., 2016)

Legend:

- + = the outcome clearly meets the criteria,
- = the outcome somewhat meets the criteria
- ? = it is unclear if the outcome meets the criteria
- × = the outcome does not meet the criteria

The tools to quantify these patient centered and surrogate outcomes, which were utilized in the included studies are provided in Table 1, this is not an exhaustive list of all available tools. A limitation of many of these outcomes is that they can only be used in survivors who are awake and able to participate in the assessment. This means that if death, loss to follow up, or an inability to participate is not randomly distributed between groups, spurious associations may be made and therefore the validity of the results will be diminished. This is of particular concern in critically ill patients due to the nature of their presenting conditions and the requirement for mechanical ventilation. For this reason, measurements that are independent of patient participation, such as muscle mass, and those that have less loss to follow up, have considerable appeal. It should be emphasized that improvements in surrogate outcomes, such as muscle mass, do not currently have any causal link with improved patient centered outcomes, such as survival and quality of life (Genton et al., 2005).

There is variability in the methodology used to quantify outcomes and the time points at which these outcomes are measured (Table 2). Across the studies reviewed, the most commonly reported outcome was physical function (13/18 studies), however over ten different tools have been utilized. This variability makes comparisons between studies challenging. The study characteristics of nutrition therapy RCTs are summarized (Table 3) and the impact on surrogate outcomes are also shown (Figure 3). The studies included mostly heterogeneous critically ill patients, the intervention were not consistent across the studies and in the majority of studies (13/18) the intervention period was for 10 days or less and limited to the ICU and therefore this limits the interpretation of these results.

Table 3-1. Tools to measure patient centered and surrogate outcomes and strength and limitations

Surrogate outcome	Tools	Strengths	Limitations
Health related quality of life	Short Form-36 and RAND-36, EuroQol-5D and EuroQol-5D-L, Eastern Cooperative Oncology Group (ECOG) performance status, Zubrod/WHO Performance Status, Charlson Fatigue Questionnaire, Employment status, Barthel Index, iADLs, WHODAS	Reproducible assessment tools	Population norms not established for all countries, the timing of assessment can affect results, limited to the population who can communicate and engage in follow up
Physical Function	Physical function in ICU test, Functional Status Score for ICU, Physical component SF-36, discharge destination, 6min walk test, 4-m timed walk speed, functional activity score for physical exercise, ICU mobility scale	Validated assessment tools, strong relationship with quality of life	Limited to those who can participate and some tools have subjective components to assessments. No validated assessment which can be utilized across the continuum of care. Assessment tools may not reflect actual daily functionality and quality of life
Muscle Strength	Handgrip strength Medical Research Council Sum Score (MRC-ss)	Handgrip is an objective measurement; MRC has been validated in the critically ill population with excellent inter-rater reliability	Limited to those who can participate, manual muscle testing has elements of subjectivity, regional muscle strength, such as handgrip strength is limited by the lack of standardization in protocols and it may not reflect functional ability or quality of life.
Muscle Mass	Dual –energy X-ray Absorptiometry (DXA) Computed tomography (CT) Bioimpedance techniques (SF-BIA, MF-BIA and BIS) Ultrasound	For all methods limited patient participation is required. Ultrasound is available in all intensive care units and it is minimal invasive.	For all methods further validation is required to confirm predictability of patient centered outcome and edema is likely to present challenges to accuracy. Ultrasound is user dependent and protocols require further validation. CT and DXA provide radiation and require

		BIA and BIS devices are portable and minimal invasive.	transfer out of the ICU. BIA and BIS are depended on device-specific algorithms, which may not be appropriate for the ICU population (none have been validated for critically ill patients)
Nutritional Status	Subjective global assessment (SGA) Global Leadership Initiative on Malnutrition (GLIM) criteria Body mass index (BMI) NUTRIC score (Nutrition risk) Nutrition Risk Screen (NRS)	Minimal patient participation and SGA is a validated assessment tool	Reliant on pre-admission history, SGA incudes subjective components, BMI is not indicative of patient centered outcomes or nutritional status. NUTRIC score and the NRS are not a nutrition assessment tool
Weight	Bed, hoist, chair and stand on scales	Objective and generally widely available	Confounded by fluid status, severity of illness and bed rest. Medical stability and equipment availability limit its use
Other Anthropometry	Mid upper arm circumference Mid arm muscle circumference Skin fold measurements	Objective	Limited data that supports associations with patient centered outcomes and the impact of nutrition therapy. Intra-rater reliability and the presents of edema limits it use.
Biochemical markers	Albumin Pre-albumin Nitrogen balance Urea: Creatinine ratio	Easy to measure, widely available and objective	Lack of data to suggest that nutrition influences change or that these are predictive of patient centered outcomes

Abbreviations: BMI, Body mass index; SF-BIA, Single frequency Bioimpedance analysis; MF-BIA, Multi-frequency Bioimpedance analysis; BIS, Bioimpedance spectroscopy; iADLs, Instrumental Activities of Daily Living; SGA, Subjective Global Assessment; WHODAS, World health organization disability assessment schedule.

References: (Bear et al., 2018; Chapple et al., 2020; Denehy et al., 2013; Earthman, 2015; Fleming & Powers, 2012; Hough et al., 2011; Oeyen et al., 2010; Taverny et al., 2019)

Table 3-2. Summary of tools used to measure patient centered and surrogate outcomes in nutritional therapy randomized control trials

Study	Anthropometry	Biochemical	Muscle Mass	Muscle Strength	Physical function, mental capacity and health related quality of life
Allingstrup (2017) Eat-ICU	Weight and BMI (baseline only)	24-hour urine nitrogen (baseline)		Handgrip strength (failure to complete)	SF-36 (6 months)
Casaer (2011) EPaNIC	Weight, BMI, nutrition risk screen (NRS) (baseline)				6-min walk test (hospital discharge), Independent in all activities of daily living
Casaer (2013) Sub study of EPaNIC	Weight, BMI and nutrition risk screen (baseline) Weight repeat in 11 out of 15 patients		Changes in muscle and fat volume & intramuscular lipid/water content using CT analysis (baseline & approximately day 8)		
Clifton (1985) Head injuries	Weight (baseline and weekly)	Albumin Nitrogen balance			
Deane (2020) TARGET D180	BMI (baseline only)				EQ-5D-5L, return to work, hours worked, effectiveness at work, disability (WHODAS) and Adelaide activities profile (6 months)
Doig (2015) refeeding	BMI, SGA (fat and muscle wastage) (baseline only)	Albumin (baseline)			ECOG performance status and RAND-36 (90 days)
Doig (2015) IV Amino acid	BMI, SGA (fat and muscle wastage) (baseline only)				Zubrod/WHO Performance Status and RAND-36 at 90 days
Doig (2013) Early PN 46	BMI (baseline only), SGA (fat and muscle wastage) and MUAC (baseline and twice weekly in ICU)	Albumin recoded (not reported)			ECOG performance status and RAND-36 (60 days)

Study	Anthropometry	Biochemical	Muscle Mass	Muscle Strength	Physical function, mental capacity and health related quality of life
Ferrie (2016) PN Protein	Weight, NUTRIC score and NRS-2002 (baseline only). MUAC, Tricept skinfold, leg circumference and SGA (baseline, day 3,7)	Nitrogen balance (day 3 and 7)	Ultrasound muscle thickness (biceps, forearm & quadriceps) and CSA of Rectus femoris (baseline, day 3 & day 7)	Handgrip strength (day 7 & ICU discharge)	Fatigue – Charlder Fatigue Questionnaire (day 7 in ICU)
Fetterplace (2018) FEED	Weight, MUAC, SGA (baseline, day 5 and ICU discharge)	Albumin (baseline and ICU discharge)	Ultrasound thickness of quadriceps (baseline, day 5, 10, 15 or ICU discharge)	Handgrip strength and MRC-ss (ICU discharge)	Physical function in ICU test (PFIT) (ICU discharge) and discharge destination (acute hospital discharge)
Gonzalez-Granda (2018) ONCA	Weight, BMI and NUTRIC score (baseline only)		Bioimpedance analysis* (baseline and every 3 days until ICU discharge) Resistance, Reactance, phase angle & body cell mass		
Hermans (2013) Sub study EPaNIC	BMI and nutrition risk score (baseline only)		Skeletal muscle biopsies of the quadriceps (day 8 post randomization)	MRC-ss (repeated 3 x per week until ICU discharge)	
Mazaherpur (2016) Traumatic brain injury	Weight and BMI (baseline, week 1,2,3)	Albumin, nitrogen balance, total protein (baseline, week 1,2,3)			

Study	Anthropometry	Biochemical	Muscle Mass	Muscle Strength	Physical function, mental capacity and health related quality of life
Needham (2013) EDEN sub study	BMI (baseline only)	Albumin (baseline)			SF-36, EQ-5D-3L, functional performance inventory, overall functional activity score for physical exercise, requirement for rehabilitation facility, fatigue interval scale score, hospital anxiety and depression scale, impact of event scale-revised score post traumatic event, then mini mental state examination and employment status (6 and 12 months)
Needham (2013) EDEN sub study 1 year	BMI (baseline, 6 and 12 months)		Percentage fat and muscle area based on MUAC and triceps skinfolds (6, 12 months)	MRC-ss and handgrip strength (6 and 12 months)	6-min walk test, 4-metre timed walk speed (m per sec), standardized performance tests relevant to cognitive domains of acute lung injury survivors (6 and 12 months)
Reid (2016) Target feasibility					SF-36, EQ-5D and employment status (12 months)
Ridley (2018) Supplemental PN	BMI, MUAC (baseline and hospital discharge)			Handgrip strength (hospital discharge)	ICU Mobility scale (hospital discharge), EQ-5D-3L (hospital discharge, 90 days, 6 months)
Wischmeyer (2017) Top-up	BMI, NUTRIC score (baseline only)			Handgrip strength (ICU & hospital discharge)	Barthel Index (admission, hospital discharge), 6-min walk test, SF-36 (90 days and 6 month)

Abbreviations: BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group (ECOG) performance status; EQ-5D, EuroQoL-5D; ICU, Intensive care unit; MUAC, Mid Upper Arm Circumference; MRC-ss, Medical research Council-sum score; SF-36, Short Form-36; SGA, Subjective Global Assessment; WHODAS, World health organization Disability assessment schedule.

*Bioimpedance analysis device - Nutriguard-MS analyzer (Data Input GmbH, Darmstadt, Germany)

Table 3-3. Characteristics of critical care nutrition therapy RCTs which include at least 1 of the selected outcomes, not including mortality

Study	Sample size (n)	Study design	Length of intervention (days)	Nutrition intervention	Mean intervention energy versus control (kcal/kg)	Mean intervention protein versus control (g/kg)	Surrogate outcomes of interest
Allingstrup (2017) Eat-ICU	199	Single center RCT	11	Nutrition guided by indirect calorimetry and nitrogen balance versus standard care	24 (6.6) vs. 14 (6.8)	1.4 (0.42) vs. 0.49 (0.3)	Physical function – ND
Casaer (2011) EPaNIC	4640	Multicenter RCT (7 ICUs)	8	Early versus late parenteral nutrition Calorie Goal (kcal/kg) Male > 60y = 30 Male ≤60y = 34 Female > 60y = 24 Female ≤ 60y = 30	Not available Approximately ³ : 30 vs. 20	Not available Approximately ³ : 1.0 vs. 0.6	Physical function – ND Activities of daily living – ND
Casaer (2013) Sub study of EPaNIC	15	Single center RCT	8	Early versus late parenteral nutrition	Not available (refer to main study Casaer 2011)	Not available (refer to main study Casaer 2011)	Muscle volume ¹ – ND Muscle quality ↓ (increased intramuscular fat)
Clifton (1985) Head injuries	20	Single center RCT	7	High protein versus standard protein both at 150% of measured energy expenditure	52 (11) vs. 48 (8)	2.6 (0.56) vs. 1.5 (0.25)	Nitrogen balance – ND Nitrogen loss ↑ Weight and albumin – ND
Deane (2020) TARGET D180	3815	Multicenter RCT (43 sites)	6	Energy dense formula (1.5kcal) versus standard (1.0kcal) at 24ml/kg ideal body weight	30.2 (7.4) vs. 17.4 (5.5) ideal body weight	1.09 (0.23) vs. 1.09 (0.22) ideal body weight	Quality of life – ND Employment status – ND Disability – ND
Doig (2015) Refeeding	339	Multicenter RCT (13 sites)	7	Standard feeding versus restricted feeding in patients with low phosphate levels	Approximately 1365 vs. 850kcal per day ³	Approximately 55g vs. 32g per day ³	RAND-36 general health score ↑ Other quality of life and physical function – ND

Study	Sample size (n)	Study design	Length of intervention (days)	Nutrition intervention	Mean intervention energy versus control (kcal/kg)	Mean intervention protein versus control (g/kg)	Surrogate outcomes of interest
Doig (2015) IV Amino acid	474	Multicenter RCT (16 sites)	ICU duration (LOS 11 days)	IV amino acid supplementation (up to 2.0g/kg/day) in addition to feeding versus standard care	Approximately 1215 vs. 970 kcal per day ³	Approximately 1.7 vs. 0.7 ³	Quality of life and physical function - ND
Doig 2013) Early PN	1372	Multicenter RCT (31 sites)	ICU duration (LOS 9 days)	Early parenteral nutrition versus Standard	Not provided: Approximately 1300kcal versus 800kcal	Not available	General health status ↑ Quality of life – ND Nutritional status ↑
Ferrie (2016) PN Protein	120	Single center RCT	10	Higher protein parenteral nutrition versus standard protein parenteral nutrition	23.1 (3.9) vs. 24.9 (4.2)	1.1 (0.22) vs. 0.9 (0.21)	Muscle mass (US) - day 7 ↑ Handgrip - day 7 ↑ Nitrogen balance day 3 ↑, day 7 – ND
Fetterplace (2018) FEED	60	Single center RCT	15	Volume based enteral feeding with supplemental protein versus standard care	23 (5.7) vs. 21 (3.3)	1.2 (0.3) vs. 0.75 (0.11)	Muscle mass (US) ↑ Nutritional status ↑ Weight, MUAC, muscle strength, physical function - ND
Gonzalez-Granda (2018) ONCA	40	Single center RCT	17 – 21	Indirect calorimetry directed nutrition provision versus standard care	20.4 (5.7) vs. 20.0 (7.5)	78 (18) g vs. 59 (21) g ¹	Bioimpedance measurements ⁴ – ND
Hermans (2013) Sub study EPaNIC	600 122 biopsy	Multicenter RCT (5 ICUs)	8	Early versus late parenteral nutrition	Not available (refer to main study Casear 2011)	Not available (refer to main study Casear 2011)	Muscle strength on first assessment ↓ Muscle strength ICU discharge – ND Muscle myofibre density and cross-sectional area – ND

Study	Sample size (n)	Study design	Length of intervention (days)	Nutrition intervention	Mean intervention energy versus control (kcal/kg)	Mean intervention protein versus control (g/kg)	Surrogate outcomes of interest
Mazaherpur (2016) Traumatic brain injury	60	Single center RCT (3 arms)	21	Continuous enteral, intermittent enteral versus enteral with supplementary parenteral nutrition	Supplemental PN: 53.1% (18.3) EN intermittent: 32.2% (14.7) EN continuous: 38.5% (19.7) ²	Supplemental PN: 67.7% (16.9) EN intermittent: 17.2% (10.1) EN continuous: 31.8% & (15.1) ²	Weight ↑ (no significant change in sup PN, other decreases) Nitrogen balance ↑ Albumin – ND Total protein – ND
Needham (2013) EDEN sub study	525	Multicenter RCT (41 sites)	6	Full feeding versus initial tropic feeding	Main study: Approximately 1300kcal/day versus 400 kcal per day	Not available	Physical function – ND Mental domain SF-36 ↓ Admission to rehabilitation facility ↓
Needham (2013) EDEN sub study 1 year	174	Multicenter RCT (5 sites)	6	Full feeding versus initial tropic feeding	Main study: Approximately 1300kcal/day versus 400 kcal per day	Not available	Physical function, muscle strength, cognitive impairment – ND (6 months) Walking speed ↑ Executive function ↓ (12 months)
Reid (2016) TARGET feasibility, sub study	79	Multicenter RCT (5 sites)	10	Energy dense enteral formula (1.5 kcal/ml) versus standard enteral formula (1.0 Kcal/ml) delivered at 24ml/kg ideal body weight	Main study: 27.3 (7.4) vs. 19.0 (6.0)	Main study ¹ : 70g (20) vs. 74g (30)	Quality of life and physical function – ND Employment status ↑
Ridley (2018) Supplemental PN	99	Multicenter RCT (6 sites)	7	Supplementary parenteral nutrition with enteral nutrition versus standard care	20.6 (6.3) vs. 13.6 (6.6)	1.0 (0.3) vs. 0.6 (0.3)	Muscle strength, quality of life, mobility and MUAC – ND
Wischmeyer (2017) Top-Up	125	Multicenter RCT (11 sites)	7	Supplementary parenteral nutrition with enteral nutrition versus standard care	90% (16) vs. 72% (25) ²	82% (19) vs. 64% (26) ²	Muscle strength, quality of life and physical function – ND

Abbreviations: CT, Computed tomography, LOS, Length of stay; MUAC, Mid Upper Arm Circumference; RCT, Randomized control trial; PN, Parenteral Nutrition; US, Ultrasound.

Legend: ND = No statistically significant different between the groups, ↓ = the outcome was worsened with the nutrition intervention, ↑ = the outcome was improved with the nutrition intervention

¹g/kg was not available, therefore results reported as gram per day

²energy and protein in kcal/kg and g/kg were not provided; therefore data is presented as percentage of requirements met

³Analysed data was not available, therefore this was estimated for mean daily nutrition delivery graphs

⁴Bioimpedance analysis device - Nutriguard-MS analyzer (Data Input GmbH, Darmstadt, Germany)

	Anthrop- ometry	Muscle Mass	Muscle Strength	Physical function	Quality of life
Allingstrup ⁽²⁴⁾ (2017)				—	—
Casaer ⁽²⁵⁾ (2011)				—	
Casaer ⁽²⁶⁾ (2013)	—	×			
Clifton ⁽²⁷⁾ (1985)	—				
Deane ⁽¹³⁾ (2020)				—	—
Doig ⁽²⁹⁾ (2015)		+		—	+
Doig ⁽²⁸⁾ (2015)				—	—
Doig ⁽³⁰⁾ (2013)	+	+		+	
Ferrie ⁽³¹⁾ (2016)		+	—		
Fetterplace ⁽³²⁾ (2018)	+	+	—	—	
Gonzalez - Granda ⁽³³⁾ (2018)		—			
Hermans ⁽³⁴⁾ (2013)		—	—		
Mazaherpur ⁽³⁵⁾ (2016)	+				
Needham ⁽³⁶⁾ (2013)				—	—
Needham ⁽³⁷⁾ (2013)			—	+	—
Reid ⁽³⁸⁾ (2016)	—			—	—
Ridley ⁽³⁹⁾ (2018)			—	—	—
Wischmeyer ⁽⁴⁰⁾ (2017)			—	—	—

Figure 3-3. Effect of nutrition therapy on selected outcomes according to RCTs

Legend:
 = Nutritional intervention being studied reported to have a beneficial effect on the outcome measured
 = Nutritional intervention being studied reported to have no significant difference on the outcome measured
 = Nutritional intervention being studied reported to have a detrimental effect on the outcome measured

3.6 Utility of each outcome based on available evidence from nutrition RCTs

3.6.1 Biochemical or other biomarkers

Many studies of nutrition therapy have included biochemical measurement to assess the impact of nutrition therapy, including albumin, pre-albumin and nitrogen balance. Albumin and pre-albumin concentrations dramatically reduce during the acute onset of critical illness making interpretation problematic. Likewise, nitrogen balance is affected by the catabolic processes of critical illness and is significantly altered with renal impairment (Frankenfield et al., 1997). Moreover, there is little evidence that these measurements have a causal relationship with improved nutrition status or, more importantly, overall outcome in critical illness (Koretz, 2005). The ideal biochemical measure would be independent of severity of illness and have a clear causal relationship to better outcomes that patients care about. As such, analysis of muscle tissue to determine changes in muscle quality and the assessment of whole-body protein turnover and muscle protein metabolism are appealing but these are impractical for routine clinical care or larger RCTs (Gamrin-Gripenberg et al., 2018; Liebau, Sundstrom, et al., 2015; Liebau, Wernerman, et al., 2015; Price & Earthman, 2019; Puthuchearry et al., 2013).

3.6.2 Standard anthropometry

Anthropometric measurements can be used to estimate baseline lean body mass and nutritional status. These measurements include weight, mid upper arm circumference (MUAC) and skin fold assessments (Heymsfield et al., 1982).

Weight loss is a frequently used outcome in clinical practice to assess the effectiveness of nutrition therapy and has been proposed as a criterion to assess nutritional status (Cederholm et al., 2019). However, substantial fluid shifts due to resuscitation during the acute phase, 'de-resuscitation' in the recovery phase and muscle loss due to bed rest, all limit the utility of weight as an outcome. Observational data suggests that mean loss of body weight is between 3 to 5 kg or approximately 5% of body weight over an intensive

care admission (LA. S. Chapple et al., 2017; Fetterplace et al., 2019). Whilst there are associations between cumulative calorie deficit and weight loss in critical illness, when confounding variables are incorporated into models, associations are either diminished or no longer present suggesting these may not be causal associations (Fetterplace et al., 2019). Whilst smaller single-center RCTs have included weight loss as an outcome (Fetterplace et al., 2018; Kearns et al., 2000; Mazaherpur et al., 2016), larger multi-center RCTs of nutritional therapy have rarely reported change in weight.

Mid upper arm circumference (MUAC) or Mid Arm Muscle Circumference (MAMC) are bedside anthropometric measurements that have been used in observational studies and RCTs. The techniques used to obtain these measurements are described elsewhere (Simpson et al., 2015). In four RCTs of nutrition interventions in critical care, there have been no significant differences in MUAC or MAMC reported as a result of the intervention (Doig et al., 2013; S. Ferrie et al., 2016; Fetterplace et al., 2018; Ridley et al., 2018). Based on the available data it appears that anthropometric measurements probably lack precision to appropriately quantify the impact of nutrition therapy in critical illness (Suzie Ferrie & Tsang, 2018; Simpson et al., 2015) or the impact of critical illness is not reversed with current nutrition interventions.

3.6.3 Nutritional status

The Subjective Global Assessment (SGA) is used in clinical practice to identify nutritional risk on admission to ICU (Gattermann Pereira et al., 2019; Lew et al., 2017). Whilst there are limitations to this technique, the SGA classification correlates with handgrip strength, muscle thickness measurements, hospital length of stay and ventilated days in the critical care setting (S. Ferrie et al., 2016; Reintam Blaser et al., 2020). Deterioration in SGA scores is also associated with greater nutritional deficits in observational datasets of critically ill patients (Fetterplace et al., 2019; H. Kim & Choi-Kwon, 2011). Whether change in SGA is sufficiently sensitive or specific to be useful outcome in RCTs is unknown. A small single center pilot RCT reported attenuated reduction in SGA categories with greater protein provision (Fetterplace et al., 2018). However, in a large multi-center open-label RCT early

parenteral nutrition that increased nutrition provision also attenuated the worsening of SGA scores but had no effect on any patient-centered outcome (Doig et al., 2013). The latter observation suggests that assessing effect of nutritional intervention using the SGA requires circumspect interpretation.

The NUTRIC score has been suggested as a tool to assess nutrition risk on admission to ICU and to identify who will benefit the most from nutrition therapy (Rahman et al., 2016). There are, however, limitations to NUTRIC as a screening tool, and post-hoc analyses of RCTs, the NUTRIC score has not identified any subgroups who benefitted from the nutritional intervention (Arabi et al., 2017; Reintam Blaser et al., 2020). Moreover, the NUTRIC score was not designed to be repeatedly used to assess the impact of nutrition provision.

3.6.4 Muscle mass

Loss of muscle mass during ICU admission has been associated with increased mortality, longer length of stay, increased requirement for rehabilitation, poor physical function and quality of life (L. L. Moisey et al., 2013). Given that it is plausible that a nutritional intervention will attenuate loss of muscle mass, and increased muscle loss is associated with worse patient-centered outcomes, this is an appealing surrogate outcome (Lambell et al., 2018). However, the use of muscle mass does rely on the assumption that greater muscle mass will improve physical function and quality of life (Genton et al., 2005).

Dual-energy X-Ray Absorptiometry (DXA) is widely accepted as the 'reference' method for the assessment of body composition (Mourtzakis et al., 2008) (L. Moisey et al., 2013). DXA has been used in observational studies in the critically ill (LA. S. Chapple et al., 2017; Ishibashi et al., 1998) but its use remains limited, as it necessitates transfer out of the ICU, is costly and exposes the patient to radiation. Several other methodologies have been used to quantify skeletal muscle mass during an ICU admission, including computed tomography (CT), multi-frequency bioimpedance analysis (MF-BIA), bioimpedance spectroscopy (BIS) and ultrasound (C. P. Earthman, 2015; Lambell et al., 2018; Price & Earthman, 2019).

In ambulant patients with cancer, skeletal muscle cross sectional area at the third lumbar vertebra (single slice CT image) is strongly associated with whole-body skeletal muscle measured using DXA (Pearson's linear correlation coefficient $r = 0.94$) (Mourtzakis et al., 2008). Observational studies in the ICU using repeated CT images have suggested that greater energy provision diminishes skeletal muscle loss (Braunschweig et al., 2014) but this technique has been rarely used in RCTs. Due to radiation dose the majority of studies make use of opportunistic imaging, which increases the risk of selection bias. In a cohort study nested within the EPaNIC trial (Michael P. Casaer et al., 2011), authors reported data from 15 patients who had a CT scan soon after admission and a repeat scan one week later (M. P. Casaer et al., 2013). All patients lost substantial muscle volume during the 1 week period and there was no strong evidence of a difference in muscle volume according to study treatment, however, there was an increase in the femoral intramuscular lipid and water content observed in the early PN group (M. P. Casaer et al., 2013). Repeated CT imaging is unlikely to be feasible in clinical practice or larger trials unless radiation dose and the need for transfer out of ICU are addressed.

In healthy populations bioimpedance techniques are considered relatively accurate methods to estimate fat free mass, however in critically ill these techniques are prone to greater errors, particularly when single frequency BIA devices are utilized (Price & Earthman, 2019). MF-BIA and BIS have been used to provide estimates for extracellular, intracellular water and total body fluid, these devices utilize prediction equations which are population specific or algorithms with different resistive constants, respectively to estimate fat-free mass and fat mass (C. Earthman, Traughber, D., Dobratz, J., Howell, W., 2007; C. P. Earthman, 2015; Robert, 1993). In observational studies of critically ill patients, raw bioimpedance values have been associated with nutritional status, skeletal muscle mass (CT measurements, $r \approx 0.6$), sarcopenia and mortality (da Silva et al., 2015; C. P. Earthman, 2015; D. Kim et al., 2019; Kuchnia et al., 2017). Additionally, in critically ill cohorts calorie deficit has been associated with a reduction in fat-free mass (Fetterplace et al., 2019) and impedance raw values (lower phase angle and higher impedance ratio), were reported to be predictive of lower muscle strength scores (both using the SFB7 BIS device (ImpediMed™, Pinkenba, Australia) (Baldwin et al., 2019). The MF-BIA device

(Nutriguard-MS analyser, Data Input GmbH, Darmstadt, Germany) has only been incorporated as an outcome assessment in one single-center nutrition RCT in the ICU (Gonzalez-Granda et al., 2019). The authors reported that in 40 critically ill patients allocated to nutrition support directed by indirect calorimetry with 1.2g/kg protein or usual care, there were no significant differences in any bioimpedance analysis measurements (including fat-free mass and phase angle) between the groups (Gonzalez-Granda et al., 2019). However, this study was limited by a small sample and the energy and protein provision were similar across the two groups. Bioimpedance techniques are promising, but they require further validation in the critically ill.

Ultrasound also overcomes some of the limitations of CT scans, being a portable and non-invasive methodology (C. P. Earthman, 2015). It is, however, operator-dependent, and there is lack of consensus on the most appropriate ultrasound protocol to use and which muscle site to measure (Weinel et al., 2019). In several ICU studies a four-point protocol has been described to measure quadriceps mass (bilateral quadriceps muscle layer thickness (QMLT) (Tillquist et al., 2014). QMLT was reported to be strongly associated with site-specific DXA measures of lean tissue mass in healthy individuals ($r^2 = 0.82$) (Michael T. Paris et al., 2017). In observational studies conducted in the critically ill, moderate associations have been reported between QMLT and DXA total lean mass (Pearson linear correlation coefficient $r = 0.74$) (LA. S. Chapple et al., 2017) and QMLT and CT abdominal skeletal muscle cross sectional area (Pearson's linear correlation coefficient $r = 0.45$) (M. T. Paris et al., 2017). Ultrasound techniques appear to have very good intra-observer agreement but inter-observer agreement is not as strong (Seeger et al., 2015). Alternatives to QMLT include muscle cross sectional area or protocols which incorporate other muscle groups such as the biceps, abdominal muscles and forearm have been suggested to improve prediction of total skeletal muscle mass (Parry et al., 2015; Puthucherry et al., 2013; Seymour et al., 2009).

Observational studies using ultrasound have reported that critically ill patients lose approximately 1-2% of muscle thickness per day in ICU (Puthucherry et al., 2013; C. L. Reid

et al., 2004), however the precision of these estimates is unknown and in other studies intra- and interrater variability has been reported to be larger than this change (Seger et al., 2015). Greater muscle mass at ICU discharge, assessed with ultrasound, has been associated with improved quality of life and functional outcomes (LA. S. Chapple et al., 2017; Parry et al., 2015). Two RCTs have utilized ultrasound to assess change in muscle mass in response to a specific nutritional therapy (S. Ferrie et al., 2016; Fetterplace et al., 2018). In a single center RCT greater parenteral protein administration was associated with greater forearm (mean (SD), 3.2 (0.4) vs 2.8 (0.4) cm, $p < .0001$) and quadriceps muscle thickness (mean (SD) 6.8 (2.1) vs 5.8 (1.9), $p = 0.02$) at day 7 of ICU, but not biceps thickness (S. Ferrie et al., 2016). In another single-center RCT a high protein volume based enteral feeding protocol was associated with attenuated loss of QMLT thickness (0.22cm (95%CI 0.06 -0.38, $p = 0.01$) (Fetterplace et al., 2018). These results support the concept that ultrasound may be a useful modality to assess muscle mass in response to nutritional therapy, however consensus on an optimal protocol is required to improve the precision of this technique, and the high interrater variability needs to be overcome or minimized in order for this methodology to be utilized in multi-centered studies (M. T. Paris et al., 2020).

3.6.5 Muscle strength

The Medical Research Council sum score (MRC-ss) can be used to assess muscle strength and diagnose ICU acquired weakness (score $<48/60$) (Ciesla et al., 2011; De Jonghe et al., 2002). In observational studies cumulative calorie deficit during critical illness has been associated with greater odds of developing ICU-acquired weakness at ICU discharge (Odds Ratio (OR) 2.1, 95%CI 1.4–3.3, $P = 0.001$) (Fetterplace et al., 2019). The MRC-ss has been used in at least three RCTs. In a sub-group of EPaNIC participants (Michael P. Casaer et al., 2011) who were able to cooperate at various assessment points, ICU acquired weakness was diagnosed on day 8 in 127/294 (43%) patients randomized to early PN and 105/305 (34%) patients allocated to late PN (mean difference 9% (95%CI 1 to 16, $p = 0.03$) (G. Hermans et al., 2013). However this difference was not observed at the final assessment at ICU discharge (G. Hermans et al., 2013). In the other two RCTs no significant differences in

MRC-ss were observed with the nutrition interventions (Fetterplace et al., 2018; Needham, Dinglas, Morris, et al., 2013).

Handgrip dynamometry is a measure of volitional force, which quantifies distal muscle strength of the upper limb, and it is easy to perform in patients who are awake and able to follow instructions (Baldwin et al., 2013) (G. Hermans et al., 2012; Vanpee et al., 2011). In the critically ill, weaker handgrip strength is associated with greater mortality (OR 4.5, 95%CI 1.5-13.6, $p = 0.007$) (Ali et al., 2008) but the mechanistic relationship between weakness of distal muscle groups and mortality is not fully understood. Handgrip strength has been reported in several RCTs of nutritional interventions at various time points including ICU discharge, hospital discharge and 6 months after discharge (S. Ferrie et al., 2016; Fetterplace et al., 2018; Ridley et al., 2018; Wischmeyer et al., 2017). Ferrie and colleagues reported handgrip was higher in the group that received greater protein provision via parenteral nutrition (mean SD 21.1 (10.1) vs 18.5 (11.8) kg, $p = 0.03$) at day 7, however there was less strength of evidence that there was a difference at ICU discharge (S. Ferrie et al., 2016). Other RCTs have been limited by a substantial amount of missing data, ranging from 57%-69% of the study population and therefore it is difficult to assess if there was any effect from the nutrition intervention (Fetterplace et al., 2018; Ridley et al., 2018; Wischmeyer et al., 2017). Although the MRC-ss and handgrip dynamometry are both validated tests to assess muscle strength as part of routine care their use is limited to those who are alert and able to obey instructions. Therefore, their use in RCTs is somewhat limited due to missing data.

3.6.6 Physical ability and quality of life

Various tools have been used in RCTs of nutritional therapy to assess physical function, mental capacity, cognition, level of disability and health related quality of life at many different time points (Table 3). In most cases these assessments are completed at 6 or 12-month after discharge and the nutrition intervention did not impact the outcome measured.

Physical function

The physical function in ICU Test (PFIT) score provides a functional assessment in the critically ill population (Denehy et al., 2013; Skinner et al., 2009). It examines four components of endurance, function and strength as previously described (Skinner et al., 2009). In an observational cohort cumulative calorie deficit was associated with lower PFIT scores at ICU discharge (Fetterplace et al., 2019). The PFIT score has been used in one single-center RCT, with no differences seen in associations with the nutrition intervention; however, missing data again limited interpretation, with only 36% (22/60) of the study cohort included (Fetterplace et al., 2018).

Other measurements of physical function that have been used include; the 6-minute walk test, the 4-metre timed walking speed test, the functional performance inventory and the Short Form-36 (SF-36) (physical component). The EDEN trial (Rice et al., 2012) evaluated the effect of initial trophic feeding versus full feeding and in a 12-month follow up study they reported that there was no strong evidence that there was a differences between groups in any physical function outcome measured (6-min walk distance, 4-metre timed walking speed test, or the functional performance inventory) (Needham, Dinglas, Bienvenu, et al., 2013; Needham, Dinglas, Morris, et al., 2013). Similarly in a trial of supplemental parenteral nutrition there was limited evidence that there was a difference between groups for the 6-min walking test at hospital discharge (in 14% of the study population) or in the SF-36 (physical component) score at 6 month follow up (Wischmeyer et al., 2017).

Disability

Functional limitations may lead to disability, which is defined by the restriction in participation through a given social role (Iwashyna & Netzer, 2012). Common measures of disability include discharge destination, assessment of the ability to return to work, and independence in performing activities of daily living. Employment status and the degree of disability have been assessed in three nutrition RCTs (Deane et al., 2020; Needham, Dinglas, Bienvenu, et al., 2013). In a pre-specified 180 day follow up of almost 4000 participants who were randomized to receive 100% or 70% of estimated energy

requirements in the TARGET trial (TARGET Investigators*, 2018), a similar numbers of participants returned to work, with no differences in hours of work (Deane et al., 2020); additionally, there were similar amounts of participants who had no to mild disability according to the World Health Organization Disability Assessment Schedule (WHODAS) (relative risk = 0.99 (95% CI 0.88 to 1.11)) (Deane et al., 2020). Similarly, trophic feeding versus full feeding (Rice et al., 2012) in the ICU did not appear to effect employment status at 6 or 12 moths (Needham, Dinglas, Bienvenu, et al., 2013).

Quality of life

Health-related quality of life (HRQOL) is a multi-dimensional concept which attempts to score participants perception of physical and mental health. The most frequently used tools to assess quality of life in critical care nutrition studies are the 36-Item Short Form Health Survey (SF-36) and the EuroQol (EQ-5D, EQ-5D-3L and EQ-5D-5L). The EuroQol assesses domains of health related quality of life and the SF-36 provides a score for physical function and mental health separately (Oeyen et al., 2010). Observational studies of critically ill patients have consistently reported that health related quality of life following ICU is substantially lower than population norms (LA. S. Chapple et al., 2017; Needham, Dinglas, Bienvenu, et al., 2013; D. B. Reid et al., 2016).

Health related quality of life scores have been included in eight critical care nutrition RCTs. In the 180 day follow up study of patients in TARGET, there was no difference in quality of life (EQ-5D-5L) in survivors (Deane et al., 2020). Likewise, in the EDEN trial, similar quality of life scores (SF-36 and EQ-5D) were reported (Needham, Dinglas, Bienvenu, et al., 2013). In contrast, two separate RCTs have reported small but statistically greater quality of life scores with greater nutrition provision; however, the difference observed is of uncertain importance (Doig et al., 2015; Doig et al., 2013). None of the other studies reported any notable effects on health related quality of life and mental capacity (Allingstrup et al., 2017; Needham, Dinglas, Bienvenu, et al., 2013; D. B. Reid et al., 2016; Ridley et al., 2018; Wischmeyer et al., 2017).

3.6.7 Summary of outcome measures

The standardization of methodology and timing of assessment has merit. However the use of core-outcome sets should not stifle innovation in this field, as better tools to measure the impact of nutrition therapy are required (Arabi & Preiser, 2017). The use and development of tools which do not require significant patient participation and that are straightforward to administer hold the most promise for larger/multi-centered trials, particularly when recruitment includes a proportion of patients admitted to the ICU with a neurological disorder who may have ongoing cognitive impairment. Some of these advancements may include technology to precisely measure body composition at the bedside and techniques or biomarkers that promptly detect muscle loss or weakness (Chan et al., 2018; Teigen et al., 2017). However, it must be noted that improvements in such outcomes may not result in overall enhancements in outcomes which are important to patients such as functional ability or quality of life. When study cohorts are unaffected by cognitive impairment tools which require patient participation may remain more relevant (McNicholl et al., 2019).

3.7 Conclusions

A variety of patient centered and surrogate outcomes have been used to evaluate the effect of nutrition therapy during critical illness. Whilst mortality remains the gold standard outcome for large RCTs, future RCTs may need to include substantially greater numbers of participants than have been used in previous trials if small but clinically relevant differences in mortality are to be detected. Current funding and logistic constraints preventing very large nutrition trials in critical illness supports the continued search for alternative patient-centered and surrogate outcomes for proof of concept and mechanistic studies.

Nutrition therapy has been shown to have varying effects on many patient centered outcomes and there is a lack of constancy in the tools used and limited data is available. Many of the outcomes used have substantial limitations and those which require volitional measurements may confound results. Of the surrogate outcomes, there is considerable interest in muscle mass, however standardized protocols for assessment need to be established. Moreover, a causal relationship needs to be proven between muscle mass

and outcomes which are imported to patients before it can be considered a useful surrogate outcome. Future research should also consider the length of nutrition therapy and the likely impact on long term outcomes.

3.8 References

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3.9 Supplementary material for chapter 3

Literature Search

Database(s): **Ovid MEDLINE(R) ALL** 1946 to March 19, 2020

Search Strategy:

#	Searches	Results
1	exp Critical Illness/ or exp sepsis/ or exp respiration, artificial/ or exp critical care/	261006
2	(critical* ill* or acute* ill* or icu or intensive care or intensive therapy or critical care or mechanical*ventilat* or sepsis or shock or burn unit* or coronary care or respiratory care).mp.	559998
3	exp Enteral Nutrition/	19431
4	(enteral or nasogastric or nasojejunal or naso-gastric or naso-jejunal or tube feeding or gastric feeding).mp.	37444
5	1 or 2	649774
6	((child* or infant* or p?ediatric* or juvenile* or adolescen* or teen*) not adult*).mp.	2217290
7	exp animals/ not exp humans/	4680615
8	exp Nutritional Support/	44652
9	exp Parenteral Nutrition/	23808
10	(parenteral* or feed*).mp.	630030
11	3 or 4 or 8 or 9 or 10	649787
12	Muscle, Skeletal/ or Muscles/ or Body Composition/	318922
13	Physical Functional Performance/	629
14	Muscle Strength/	19186
15	"Activities of Daily Living"/ or "Quality of Life"/	240096
16	(Muscle* or Physical* or Function* or Strength*).mp.	5479297
17	12 or 13 or 14 or 15 or 16	5633714
18	5 and 11 and 17	4543
19	18 not 6	3706
20	19 not 7	2946

Chapter 4: Retrospective observation study of methods to assess muscle mass in critical illness

4.1 Chapter summary

This study was undertaken to explore the validity of ultrasound as a non-invasive technique to measure muscle mass in critically ill patients. Some preliminary data suggests that quantifying change in muscle mass holds promise for the assessment of the effects of nutrition therapy. This study was an analysis of data collected for other studies, and it included data from patients who participated in the RCT within this thesis (chapter 8). This manuscript is currently under review.

4.2 Retrospective observational study

Assessment of muscle mass using ultrasound compared to computed tomography in critically ill adult patients

Kate Fetterplace^{1,2} BNut&Diet, Lucy Corlette⁴ MBBS, Yasmine Ali Abdelhamid^{2,3} MBBS, Jeffrey J. Presneill^{2,3} MBBS, PhD, Michael T. Paris⁵ BSc, Damien Stella^{2,4} MBBS, Marina Mourtzakis⁵ PhD, Christopher MacIsaac^{2,3} MBBS, PhD, Adam M. Deane^{2,3} MBBS, PhD.

1. Department of Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia
2. Department of Medicine and Radiology, Melbourne Medical School, The University of Melbourne, Royal Melbourne Hospital, Parkville, Australia
3. Department of Intensive Care, Royal Melbourne Hospital, Melbourne Australia
4. Department of Radiology, Royal Melbourne Hospital, Melbourne, Australia
5. Kinesiology, University of Waterloo, Waterloo, Canada

Corresponding author

Ms Kate Fetterplace^{1, 2} BNutDiet, APD

Senior Dietitian, Royal Melbourne Hospital

Allied Heath, Royal Melbourne Hospital

Grattan St Parkville, Victoria, Australia 3050

Phone: +61 3 9342 7440

Fax +61 3 9342 8440

Email: Kate.Fetterplace@mh.org.au

Declaration of interests

KF has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi, Nutricia, Abbott and Nestle Health Science (not related to this study). AMD or his institution have received honoraria, travel grants or project grant funding from Baxter, Cardinal Health, Fresenius Kabi, GSK, Medtronic and Nutricia. AMD has participated on advisory boards for Lyric Pharmaceuticals and Takeda. YAA has received honoraria from Baxter Healthcare Corporation.

Authorship declaration

K Fetterplace, AM Deane, CM MacIsaac, and D Stella contributed to the conception and design of the research; M Mourtzakis, Y Ali Abdelhamid and MT Paris contributed to the design of the research; K Fetterplace, L Corlette, and Y Ali Abdelhamid contributed to the acquisition of the data; K Fetterplace and JJ Presneill contributed to the analysis and the interpretation of the data; K Fetterplace and AM Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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None to declare

4.3 Abstract

Background: Preserved skeletal muscle mass identified using computed tomography (CT) predicts improved outcomes from critical illness, however CT images involve a dose of radiation and transfer out of the intensive care unit. This study aimed to assess in critically ill patients the relationship between muscle mass estimates returned by two techniques - a minimally invasive ultrasound technique and CT images at the 3rd lumbar vertebra level.

Methods: All patients were treated in a single Australian Intensive Care Unit. Eligible patients had paired assessments, within a 72 hours window, of muscle mass by ultrasound (quadriceps muscle layer thickness in cm, with maximal and minimal pressure) and CT axial cross-sectional area (cm²).

Results: Thirty-five patients (mean (SD) age 55 (16) years, median [IQR] body mass index (BMI) 27 [25 - 32] kg/m², and 26 (74%) male) contributed 41 paired measurements. Quadriceps muscle thickness using the maximum pressure technique was a strong independent predictor of lumbar muscle cross sectional area. Within a multivariate mixed linear regression model and adjusting for sex, age and body mass index, for every 1 cm increase in quadriceps muscle layer thickness lumbar muscle cross sectional area increased by 35 cm² (95%CI 11 to 59 cm²).

Conclusion: Ultrasound assessment of the quadriceps muscle reasonably predicts the skeletal muscle at the 3rd lumbar vertebra level of critically ill patients. However, there is substantial uncertainty within these regression estimates and this may reduce the current utility of this technique as a minimally-invasive surrogate for CT assessment of skeletal muscle mass.

Key words: critically ill, muscle mass, ultrasound, sarcopenia, nutrition therapy

4.4 Introduction

Reduced skeletal muscle mass, determined by muscle cross sectional area (CSA) at the third lumbar vertebra (L3), using computed tomography (CT), has been shown to be an independent risk factor for increased mortality and morbidity in critically ill patients (Fuchs et al., 2018; Jaitovich et al., 2019; L. Moisey et al., 2013; Weijs et al., 2014). Because of the radiation dose involved with CT imaging and the requirements for moving patients out of the intensive care unit (ICU), CT has limited utility as a widespread and repeatable method to quantify body composition analysis.

Accordingly, minimally-invasive techniques that can be performed at the bedside, such as ultrasound, may be useful to quantify muscle mass as part of usual care or within a clinical trial evaluating nutritional and/or physical therapy (L. S. Chapple et al., 2020; K. J. Lambell et al., 2018; Price & Earthman, 2019; Weinell et al., 2019). Ultrasound is minimally-invasive and protocols using multiple anatomical sites for muscle thickness analysis have been validated against whole body skeletal muscle mass using magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry in healthy individuals (Price & Earthman, 2019; Sanada et al., 2006). However, in the critically ill the most appropriate ultrasound protocol to measure a muscle group, such as quadriceps, remains uncertain (M. T. Paris et al., 2017; Weinell et al., 2019). There is further uncertainty as to whether quadriceps muscle group is a robust estimate of skeletal muscle CSA obtained with CT images, which remains the methodology that has proven associations between muscle mass and outcomes (M. T. Paris et al., 2017; Weinell et al., 2019). Therefore, it remains unclear whether ultrasound is a useful tool to assess for sarcopenia, or if it could be used to monitor the effect of interventions, such as nutrition therapy, in critically ill patients (Weinell et al., 2019).

The primary aim of this study was to explore the relationship between skeletal muscle CSA assessed using CT imaging and quadriceps muscle layer thickness (QMLT) measurements using ultrasound with maximal and minimal pressure. These measurements were obtained from critically ill patients who had a CT scan and QMLT measurements within 72 hours of

each other. The secondary aims were to explore the relationship between sarcopenia determined by CT analysis cut points and QMLT measurements, markers of nutritional status and clinical outcomes. The tertiary aim was to compare two different software techniques to assess muscle CSA so as to validate a methodology that clinicians/researcher with limited access to radiologist expertise.

4.5 Materials and methods

4.5.1 Study design and setting

This single centre retrospective observational study was conducted at a tertiary-referral Australian intensive care unit (ICU) from patients admitted between 2015 and 2019. A local database of patients who had QMLT measurements obtained using ultrasound during ICU admission for another research study was searched (Fetterplace et al., 2018). Data were included from patients if they also had an abdominal CT scan within 72 hours of one of the QMLT measurements (M. T. Paris et al., 2017). All CT scans were performed for clinical purposes other than assessment of muscle mass. Data were excluded if the radiologist (LC) determined that the CT scan images were inappropriate for analysis due to the lack of clarity, artefact or if the patient positioning meant that the skeletal muscle was incompletely visualised. The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2014). This study was approved by the hospital Human Research Ethics Committee (QA2019072) and all of the included patients had provided informed consent to participate in the original studies.

4.5.2 Data collection and procedures

Patients were characterised by age, sex, admission category, and Acute Physiology and Chronic Health Evaluation II (APACHE II Score). Nutrition related data included admission weight according to bed scales (Hill-Rom[®], Indiana USA), body mass index (BMI), energy and protein requirement assessed by the dietitian, average provision of energy and protein during ICU stay, and nutritional status on ICU admission and discharge assessed by

the Dietitian using the Subjective Global Assessment (Detsky et al., 1987). Outcome characteristics included ICU and hospital length of stay, length of mechanical ventilation, discharge destination and mortality. Nutrition provision was delivered in line with the relevant trial or unit protocol. The majority of patients (>75%) were enrolled in a randomised clinical trial aimed to determine whether a volume-target enteral protocol with supplemental protein, delivered greater amounts of protein and energy to critically ill patients compared with usual care (Fetterplace et al., 2018).

4.5.3 Ultrasound measurements of quadriceps muscle layer thickness

All ultrasound measurements were undertaken by one of two trained operators (KF or YA); initial measurements were within 72 hours of ICU admission and any subsequent measurements were between days 5 to 7 of ICU stay or at ICU discharge. A portable ultrasound device (Sonosite S-ICU™) with a multiple frequency transducer (13-6MHz, 6cm) was used to obtain all images. The methods to obtain the QMLT measurements were carried out as previously described (LA. S. Chapple et al., 2017; Fetterplace et al., 2018; M. T. Paris et al., 2017; Tillquist et al., 2014). Two linear muscle measurements were completed at two points; the midpoint between the Anterior Superior Iliac Spine (ASIS) and the upper pole of the patella and at the point two thirds between the ASIS and the top of the patella. Bilateral linear average QMLT measurements (four measurements), for minimal pressure and maximal pressure, were recorded separately, if available. Figure 1 provides comparison between the minimal pressure and pressure ultrasound measurements. The time and date of the QMLT measurements were recorded.

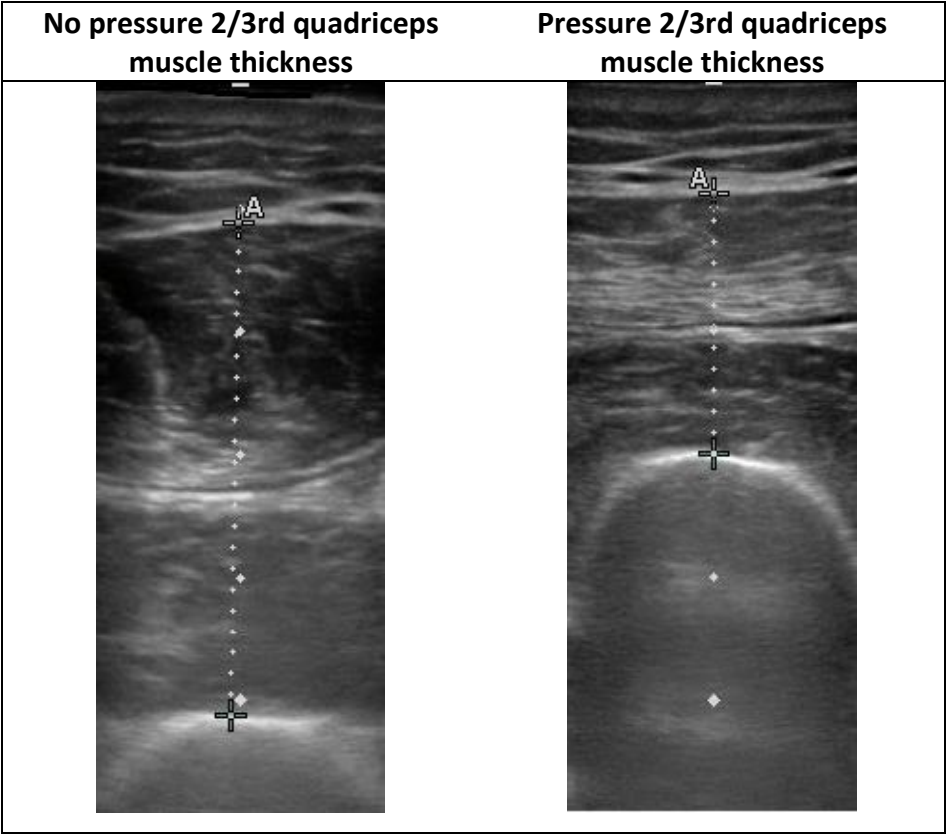


Figure 4-1. Quadriceps muscle layer thickness no pressure measurement compared to pressure measurement at 2/3rd between the ASIS and the top of the patella

*Images are from the subject at the same time point

4.5.4 Computed tomography skeletal mass cross sectional area

A radiologist (LC) reviewed all available abdominal CT scans to assess for resolution and clarity and to ensure that all components of the skeletal mass could be assessed at the level of L3. If the scan was deemed to be suitable, the scan was downloaded for analysis using the syngo.Via advanced visualisation software, version VB30A, Siemens Healthineers GmbH program (Forchheim, Germany). A single CT slice (5mm thickness) at the level of L3 was identified for analysis and then the skeletal muscle was individually selected by the radiologist using the multi-modality reading workflow tool called “Region Growing through Hounsfield Unit thresholding”. This is a method, which has been approved by the U.S. Food and Drug Administration (FDA) to precisely determine tissue volumes (Hounsfield unit -30 to 150 for muscle). The cross-sectional muscle volume (cm^3) for the selected 5mm CT slice was recorded and converted to cross sectional area (cm^2) by dividing the volume by the CT scan slice thickness. As a comparison the CT images were analysed using another method that has previously been reported in the nutrition literature (Michael T. Paris et al.). The latter technique required de-identified unanalysed single slice Digital Imaging and Communications in Medicine (DICOM) files to be analysed using the Automated Muscle and Adipose Tissue Composition Analysis (AutoMATiCA) program (Michael T. Paris et al.). This program provided an automated analysis for skeletal muscle CSA. The comparison between the two methods is provided (Figure 2). Patients were categorised as having sarcopenia if the skeletal muscle CSA was $<110 \text{ cm}^2$ for women and $<170 \text{ cm}^2$ for men (Weijs et al., 2014). The time and date of the scans was recorded and matched with the most approximate QMLT measurement.

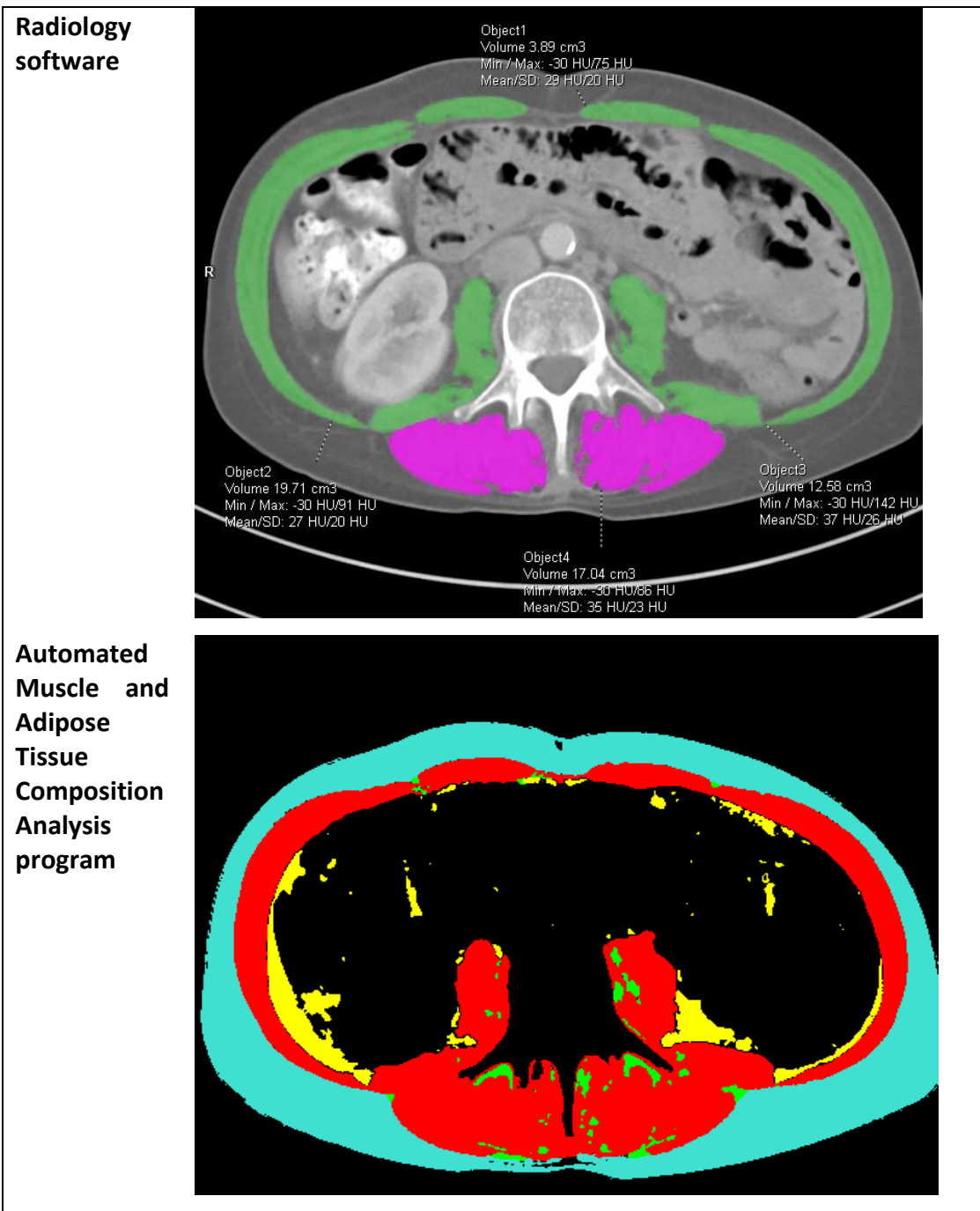


Figure 4-2. Comparison between the radiology software with radiologist assessment and the Automated analysis program

* CT slice images are within the same subject at the same time point.

4.5.5 Statistical analysis and sample size

The sample size was limited by the available data within the four-year study period. Only patients who had both a CT scan which included the L3 region and an ultrasound measurement within 72 hours of each other were included. Demographic and outcome data are reported as mean (standard deviations (SD)), medians (inter-quartile ranges [IQR]) and frequencies (n(%)) where appropriate.

To determine the primary aim, the relationship between muscle CSA (cm^2 , by CT analysis) and QMLT (cm, by ultrasound), the CSA results were explored in several linear mixed models to account for repeated measurements in some patients. All such univariate and multivariate models included a random intercept for individual patients, and were specified with robust variance estimates, which together accounted for clustering of observations within individual patients. Potential explanatory variables studied included QMLT (pressure and no pressure method), gender (female as reference), age (binary, ≥ 60 y), and BMI (reference category 25 - $< 30 \text{ kg/m}^2$) (Equation 1). The linear regression models were checked using standard diagnostics including tests of regression coefficient influence (“dfbetas”) and overall model specification (link test).

Equation 1. Linear mixed model

$$\begin{aligned} & CSA_{\text{method for assessment}} (\text{cm}^2) \\ &= \text{intercept} + \beta_1 \times QMLT_{\text{ultrasound method}} (\text{cm}) + \beta_2 \times \text{female} \\ &+ \beta_3 \times \text{age}_{>60 \text{ y}} + \beta_4 \times \text{BMI}_{<25} + \beta_5 \times \text{BMI}_{\geq 30} + u_{(\text{random effect})} \end{aligned}$$

Exploratory analysis of associations between binary outcomes, including sarcopenia and malnutrition, observed at any occasion used the Fisher exact test. Paired t-tests were used to assess the mean change in skeletal muscle CSA and QMLT in those patients who had repeat data. Independent t-tests were used to assess the mean muscle measurement differences between categorical groups of interest including gender, age (>65 years) and sarcopenia. Bias and limits of agreement between the two methods for CSA measurement

were summarised using a Bland-Altman plot, which incorporated the average of paired CSA measurements when present.

Statistical significance was set at a p value < 0.05 (two-sided) for all tests, with no adjustment for multiplicity. Data were analysed using the Statistical Package for the Social Sciences (SPSS) (IBM® SPSS® Statistics Premium Grad Pack Version 22.0) or Stata Statistical Software (Release 16.1 College Station, TX: StataCorp LLC; 2019).

4.6 Results

Between August 2015 and July 2019, 96 patients had ultrasound images of the quadriceps muscle obtained during ICU admission (Figure 3). After all exclusions and inspection of the CT images, data from 35 (64%) patients were included in the study. Only 6 (17%) had a repeat matched CT/ultrasound images, i.e. there were 35 patients and 41 CT scans that were paired to an ultrasound measurement. CT scans were completed within 24 hours of admission to ICU for 33 (80%) episodes and 8 (19%) were completed at a later time point.

4.6.1 Subject patient characteristics

The patient characteristics and outcomes are provided in table 1. The majority of the subject patients were male (n = 26, 74%) and they were most frequently admitted following emergency surgery (including trauma) (n = 25, 71%). The muscle and other nutrition related characteristics are provided in the supplementary table 1.

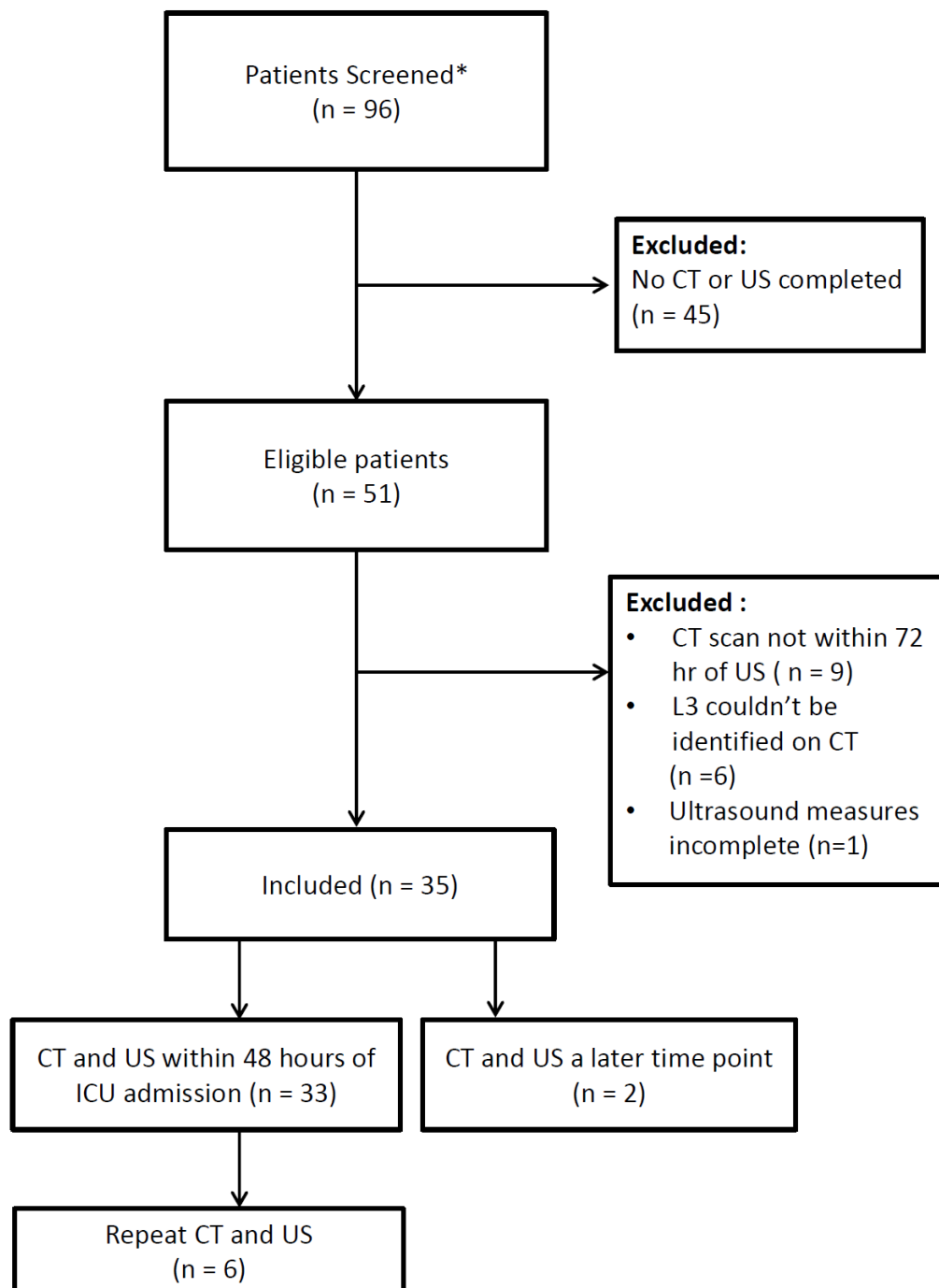


Figure 4-3. Consort Diagram

Abbreviations: CT, Computed tomography; US, Ultrasound; L3, 3rd lumbar vertebra

*patients in ultrasound data based who were enrolled in other research projects

Table 4-1. Patient characteristics and outcomes

Variables	n = 35, mean (SD) ¹
Age years	55 (16)
Gender male, n (%)	26 (74)
BMI kg/m ² , median [IQR]	27 [25 - 32]
APACHE II score	21 (6.4)
Admission category, n (%)	
Medical	8 (23)
Elective surgery	2 (6)
Emergency surgery, including trauma	25 (71)
ICU LOS, days	12 (6.4)
Hospital LOS, days	24 (14)
Length of mechanical ventilation, days	9.0 (5.2)
28-day mortality, n (%)	9 (26)
Discharge destination of survivors, n (%)	
Home	8 (23)
Rehabilitation	18 (51)
Acute hospital transfer	3 (17)

Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; LOS, length of stay.

¹All data is reported as mean (SD), unless specified

4.6.2 Measured muscle cross sectional area (cm²) using computed tomography

The mean difference between the CSA determined using automatic program analysis compared to the radiology technique was substantial [19 cm² (95%limits of agreement 11 to 28), $p < 0.001$] (supplementary figure 1). There was no proportional bias observed between the two methods (standardised coefficient of the difference -0.07, $p = 0.66$). Because the existing nutrition literature used the automatic software analysis this was selected as the reference technique for the rest of this study (Michael T. Paris et al.).

According to the automated software analysis the mean muscle CSA at baseline was 171 cm² (46) (supplementary table 1). Patients equal to or over the age of 65 years ($n = 9/29$) had a lower muscle CSA than those less than 65 years [135 cm² (28) vs. 187 cm² (43); mean difference -52.0 cm² (95% -85 to -20)]. Females (8/29) had a lower skeletal muscle CSA compared to males [134 cm² (28) vs. 184 cm² (44); mean difference -50 cm² (95%CI -16 to -85)]. Those diagnosed with sarcopenia at either time point (14/35) had lower muscle CSA than those who didn't [132 cm² (22) vs. 187cm² (44); mean difference -55 cm² (95%CI -29 to -81)].

In those patients who had a baseline and a second CT scan ($n = 6$), the muscle CSA point estimate was numerically less but there was considerable uncertainty about this estimate [mean difference -5.4 cm² (95%CI -19.0 to 8.2)]. The second scan was completed approximately 5 days after the first scan (median 4.9 [0.29 – 6.1]).

4.6.3 Measured quadriceps muscle layer thickness using ultrasound measurements

At baseline the mean QMLT (pressure, $n = 33$) was 1.8 cm (0.55) and the QMLT (minimal pressure, $n = 30$) was 3.3 cm (0.8) (supplementary table 1). There was a substantial linear association between the QMLT pressure and no pressure measurements (Pearson's correlation coefficient, $r = 0.89$, $p < 0.001$).

Females had a notably lower QMLT than males with both the pressure method [1.5 cm (0.52) vs 2.0 cm (0.52); mean difference -0.45 (95%CI -0.04 to -0.86)] and the minimal

pressure method [2.7 cm (0.67) vs. 3.5 (0.73); mean difference -0.81 (95%CI -0.18 to -1.4)] measurements. Where sarcopenia was evident based on CT analysis at either time point and the ultrasounds were matched (16/39), those with sarcopenia had lower QMLT (pressure method) compared to those who did not [1.6 (0.5) vs 2.0 (0.6); mean difference -0.39 (95% CI -0.74 to -0.35)], however this substantial difference was not observed with the minimal pressure method. Older adults compared to younger had no substantial differences in QMLT with the pressure or minimal pressure methods.

In line with the CSA finding those patients who had a baseline QMLT assessment and a second assessment (n = 6) there was a small reduction in the QMLT point estimate observed but the 95% confidence intervals included an increase in QMLT over time [QMLT (pressure method) mean difference -0.10 cm (95%CI -0.15 to 0.03) and QMLT (minimal pressure method) mean difference -0.11 cm (95%CI -0.42 to 0.18)].

4.6.4 Association between quadriceps muscle layer thickness and muscle cross sectional area

The estimated relationship between ultrasound measured QMLT and CT muscle CSA, unadjusted for any other effect, is provided in figure 4. When adjusted for sex, age and BMI, quadriceps muscle thickness using the maximum pressure technique remained a strong independent predictor of lumbar muscle cross sectional area. Mean lumbar muscle CSA was estimated to be greater by 35 cm² (95%CI 11 to 59), for each additional cm observed in quadriceps muscle layer thickness (table 2). While broadly similar associations were observed for QMLT measurements using the alternative minimal pressure method, the strength of these relationships was lower (table 3). Using the alternative radiological method for CSA assessment, similar overall unadjusted and adjusted relationships were observed with QMLT (supplementary table 2 and 3 for pressure and minimal pressure methods).

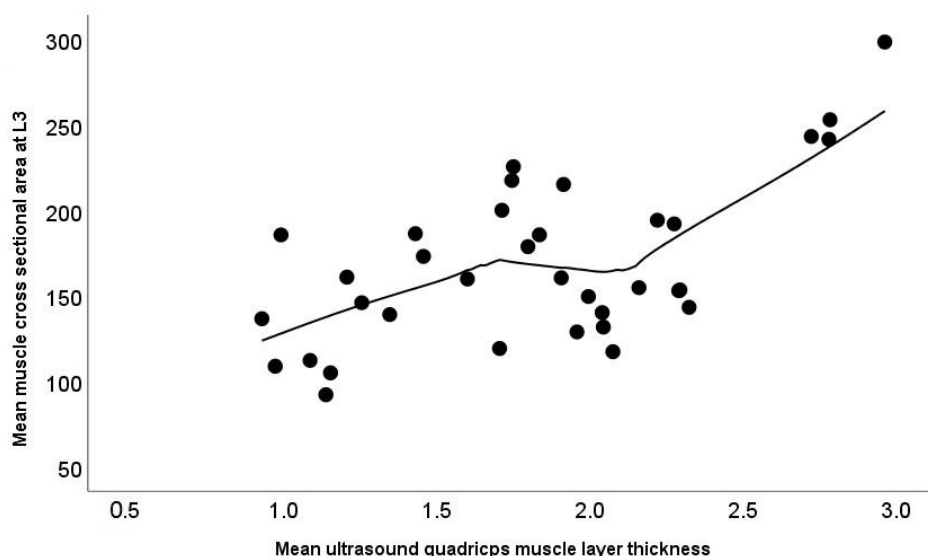


Figure 4-4. Relationship between ultrasound muscle thickness and muscle cross sectional area

¹Unadjusted relationship between observed mean quadriceps muscle layer thickness (cm) using ultrasound (pressure method) and mean muscle cross sectional area (cm²) (from computed tomography, automatic software analysis).

²The superimposed solid line is a locally estimated scatterplot smoothing (LOESS, 80% moving window).

Table 4-2. Mixed linear regression of muscle cross sectional area using the automatic method on QMLT using ultrasound pressure method

Variables	Reference	Univariate			Adjusted for all co-variants ^{1,2}		
		Effect	95% CI	p value	Effect	95% CI	P value
QMLT Pressure	per cm	57	34 to 81	<0.001	35	11 to 59	0.004
Female	Male	-48	-74 to -22	<0.001	-28	-48 to -7.2	0.008
Age							
> 60	<60 y	-18	-52 to 16	0.31	12	-35 to 11	0.31
BMI							
<25	25-30kg/m ²	5.4	-21 to 32	0.69	2.0	-19 to 23	0.85
>30		56	22 to 89	<0.001	42	16 to 68	0.002

Abbreviations: QMLT, Quadriceps muscle layer thickness; BMI, body mass index

¹Linear mixed model using a random intercept to account for correlation within individuals, multivariate effect estimates are adjusted for all covariates in the model and variance estimates accounted for clustering within individuals (n = 29).

²Model diagnostics included both the link test for overall linear model specification, and assessment of regression coefficient influence (dfbetas).

³The standard deviation of the random effect for individuals was estimated at 26 cm² (95%CI 18 to 36) and the fixed effect intercept estimate was 102 cm².

Table 4-3. Mixed linear regression of muscle cross sectional area using the automatic method on QMLT assessed using ultrasound with no pressure

Variables	Reference	Univariate Analysis			Adjusted for all co-variants ^{1,2}		
		Effect	95% CI	p value	Effect	95% CI	P value
QMLT no pressure	per cm	24	8.8 to 40	0.002	8.3	-5.4 to 22	0.24
Female	Male	-48	-74. to -22	<0.001	-25	-43 to -7.0	0.006
Age							
>60	<60 y	-18	-52 to 16	0.31	-26	-47 to -4.2	0.02
BMI							
<25	25-	5.4	-21 to 32	0.69	-4.5	-21 to 12	0.60
>30	30kg/m ²	56	23 to 89	<0.001	42	16 to 68	0.002

Abbreviations: QMLT, Quadriceps muscle layer thickness; BMI, body mass index

¹Linear mixed model using a random intercept to account for correlation within individuals, multivariate effect estimates are adjusted for all covariates in the model and for clustering within individuals (n = 30)

²Model diagnostics included both the link test for overall linear model specification, and assessment of regression coefficient influence (dfbetas).

³The standard deviation of the random effect for individuals was estimated at 22 cm² (95%CI 14 to 34) and the fixed effect intercept estimate was 144 cm².

4.6.5 Nutritional status and sarcopenia

According to BMI criteria only 2/35 (6%) patients were underweight at admission and on ICU discharge. Using the SGA classifications, 4/35 (11%) of patients on admission were malnourished, while 10/35 (29%) were malnourished on ICU discharge, including the initial four patients, who remained malnourished. Utilising the predefined cut points for sarcopenia in critically ill patients, 14/35 (40%) patients had sarcopenia (automatic and/or radiology software). Malnutrition coexisted with sarcopenia in 6/14 patients, but it was also observed in 4/21 non-sarcopenic patients.

4.6.6 Sarcopenia and other outcomes

The duration of mechanical ventilation and ICU admission was similar between those who had sarcopenia and those who did not. The point estimate for duration of hospital admission was longer in patients with sarcopenia diagnosed at any time point but there was considerable uncertainty around this estimate [mean difference 6.0 days (95%CI -3.7 to 160)]. A similar proportion of deaths occurred in patients with sarcopenia compared to those who did not have sarcopenia 4/14 (29%) compared to 5/21 (24%), p = 0.52).

4.7 Discussion

In this study QMLT assessed with ultrasound using a pressure method was a strong independent predictor of muscle CSA quantified using CT imaging. However, this signal was not present when QMLT was assessed using minimal pressure and the automatic software was used to assess CSA. Consistent with the CSA technique, point estimates for the mean QMLT were less in females and those with sarcopenia.

The relationship between ultrasound measured QMLT and CT muscle CSA was similar to previous reports, although these findings were using the QMLT measurements assessed with minimal pressure (M. T. Paris et al., 2017). The VALIDUM study included patients who had an abdominal CT scan within 24hrs before or 72 hours after ICU admission, and due to the multicentre design, various investigators completed the QMLT measurement (M. T. Paris et al., 2017). The VALIDUM study reported that the interrater reliability was reasonable with the average interclass coefficient of 0.94 (K. J. Lambell et al., 2018). In the present study greater than 85% of the measurements were completed by a single trained assessor, which may account for the increase in precision, particularly when using the pressure technique. It must be recognised that, intuitively, any measurement of the quadriceps muscle will be an imprecise estimate of abdominal muscle CSA because these two variables are separate muscle groups; however, the inference from this study is that that ultrasound measurements of the quadriceps thickness may be a useful estimate of CSA, at L3 when other variables are known. Gender and BMI were both strong independent predictors of skeletal muscle CSA, with patients with a BMI over 30, having substantially greater muscle CSA.

It has not yet been established if ultrasound is a useful tool to assess for sarcopenia, low muscle mass or nutritional status, and/or whether it is a useful tool to monitor changes in muscle mass when monitoring nutrition interventions (Bury et al.; McNelly et al.). Within the limitations of the current study and subgroup of patients with repeated measures (n=6) changes in QMLT appeared to be comparable to changes observed in CSA. Several studies have used ultrasound to measure change in muscle mass (Bury et al.; LA. S.

Chapple et al., 2017; Fetterplace et al., 2018; McNelly et al.; Parry et al., 2015; Wittholz et al., 2020) however it is unclear if there is proportional change in QMLT relative to change in total body skeletal muscle mass. In the present study it was found that those diagnosed with sarcopenia and females had substantially lower QMLT measurements compared those without sarcopenia and males respectively, and the point estimates for QMLT were less in older adults compared to younger, however there was a lack of certainty in this result due to the limited numbers. These findings were also similar to those reported in the VALIDUM study (M. T. Paris et al., 2017). Further research is required to define if ultrasound measurements can quantify sarcopenia and malnutrition (Bury et al.).

In this study the number of patients who were underweight according to BMI (5.7%) or identified as malnourished using the SGA (11%) on admission to ICU, was substantially less than the proportion of patients who met the criteria sarcopenia (34%). These results were similar to the VALIDUM study, where 2.7% were underweight but 58% were found to have sarcopenia on admission (M. T. Paris et al., 2017). Taken together these observations suggest BMI and SGA are blunt clinical tools to identify sarcopenia (Suzie Ferrie, 2020; Suzie Ferrie & Tsang, 2018; K. Lambell et al., 2016). In the VALIDUM study the mean muscle CSA was less than what was observed in the present study, which may have been due to the greater proportion of medical and female patients in the VALIDUM study. In the present study there were no substantial differences observed for duration of ICU and hospital admission, or mortality, between those diagnosed with sarcopenia compared to those not. In contrast many other studies have reported increased mortality and adverse outcomes associated with the presence of sarcopenia (Fuchs et al., 2018; L. Moisey et al., 2013; Weijs et al., 2014).

Following the validation of the Automated Muscle and Adipose Tissue Composition Analysis (AutoMATiCA) technique by Paris and colleagues, this is the first study to use subsequently make use of this method to assess muscle CSA at L3 in comparison to ultrasound measurements (Michael T. Paris et al.). This automated analysis technique has very good agreement with skeletal muscle mass assessed using previously reported

techniques, where a trained assessor manually assessed muscle area using a program such as slice-o-matic (Dice similarity coefficient (DSC) (0.983 ± 0.013)) (Michael T. Paris et al.). The AutoMATICA was relatively straight-forward to use and, once the appropriate CT image slice was identified and the DICOM image downloaded, the AutoMATiCA program rapidly quantified muscle CSA for the majority but not all of the cohort (89%). This program allows clinicians to assess muscle CSA with little additional training. However, no agreement was observed between the automatic software and the radiology assessment. The lack of agreement may have been due to the differences between the assessment of muscle volume rather than the standard area assessment, however it also may be that the radiology assessment was a more precise assessment than the current automated systems as the specific muscle groups of interest could be carefully selected and adjustments made for errors. Overall the automatic software assessed the muscle CSA to be of greater area than the radiology assessment method; where substantial differences were found between the two methods, the scans were reviewed by a radiologist who identified that the differences were possibly due to the intercostal muscles being included (which are generally not viewed at the L3 level), as well as fascia and other non-muscle soft tissue being included. This should be carefully considered when assessing skeletal muscle CSA in critical care patients using the automatic methods or other techniques.

The strengths of this study are that QMLT was examined using both pressure and no pressure methods and various methodologies to calculate L3 CSA. However, there are several limitations; this is a single centre retrospective observational study of a relatively small cohort. There were very few patients who had a repeat CT scan within 72 hours of the repeat ultrasound measurements and, therefore, it is not possible to establish whether QMLT changes over time reflected CSA changes. The study population was predominately patients presenting after traumatic injury, presumably because of the frequency of abdominal CT scanning in this group and therefore these results may not be generalizable to other patient populations. Additionally, ultrasound measurements were limited to one muscle group (QMLT), and it is unclear if an ultrasound protocol including several muscle groups has a stronger association with CSA and, thereby, more useful to identify

sarcopenia (Lambell et al.). Interpretation of effect estimated should be cautious due to the multiplicity of models and comparisons within this exploratory study.

4.7.1 Implications for clinical practice

Muscle mass has been proposed as an acute marker of subsequent muscle strength, functional capacity and quality of life after recovery (Allingstrup et al., 2012; Hurt et al., 2017; Yeh et al., 2017) and a variety of methodologies are suggested to repeatedly quantify muscle mass in critically ill patients (Price & Earthman, 2019; Weinell et al., 2019). In this study QMLT measured using ultrasound was a strong independent predictor of muscle CSA (cm²). However, the substantial variance around regression estimates reduces the current utility of QMLT alone as a non-invasive surrogate for skeletal muscle mass or sarcopenia. It remains uncertain whether ultrasound measurements of QMLT are proportional to CSA changes over time and currently cannot be recommended for routine care. Further work is required to establish if an ultrasound protocol utilising more muscle groups is a better predictor of skeletal muscle CSA so that it could be used to assess for low muscularity, and is associated with clinical outcomes. However, the AutoMATiCA program is freely available, and this program may enable clinician greater access to quantify muscle mass when CT images have been obtained.

4.8 Conclusions

While ultrasound assessment of the quadriceps muscle reasonably predicts the mean axial skeletal muscle cross sectional area of critically ill patients; substantial uncertainty within these regression estimates may reduce the utility of this technique as a non-invasive surrogate for CT assessment of skeletal muscle mass. Further research is warranted to determine if muscle ultrasound measurement is an appropriate tool to monitor nutrition therapy and assess for sarcopenia.

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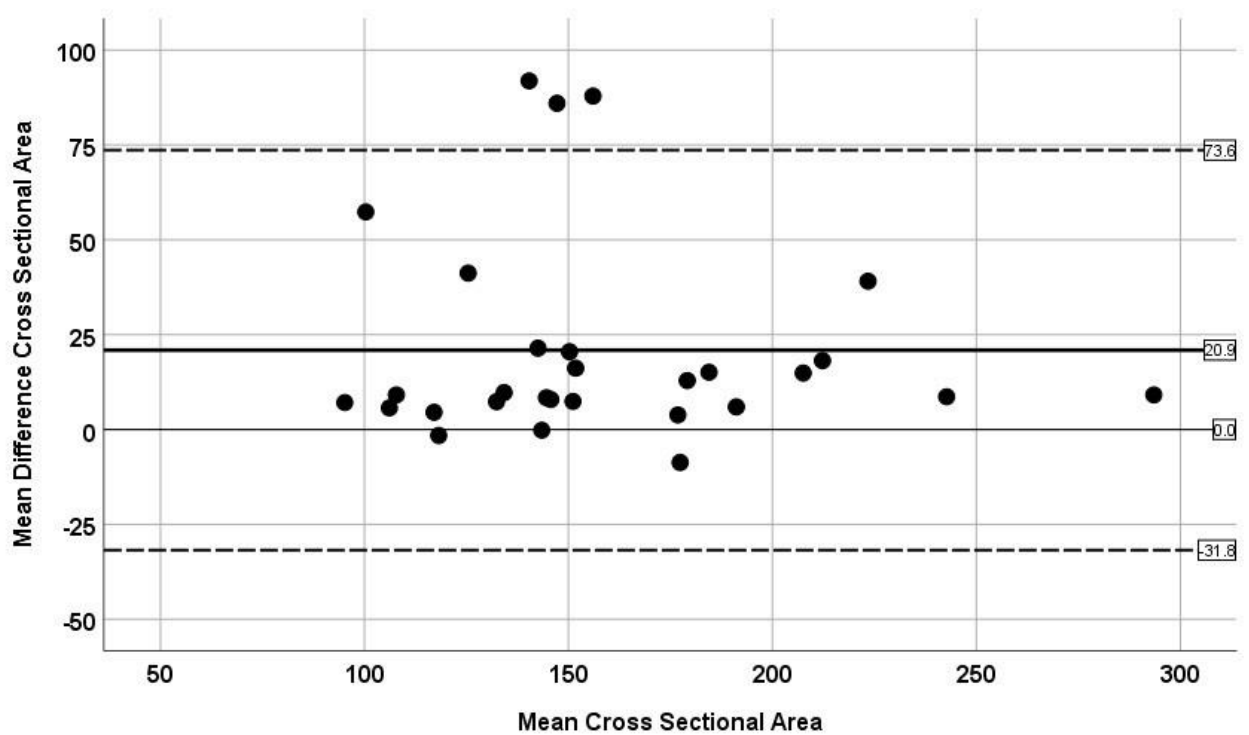
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4.10 Supplementary material for Chapter 4

Supplementary Table 4-1. Nutrition related characteristics

Variables	n	Results
Underweight (BMI < HWR for age), n (%)	35	2 (5.7)
Malnutrition diagnosis admission, n (%)	35	4 (11)
Malnutrition diagnosis discharge, n (%)	35	10 (29)
Sarcopenia diagnosis on enrolment, n (%)	32	11 (31)
Sarcopenia diagnosis at any time point, n (%)	35	14 (40)
QMLT baseline (pressure), cm, mean (SD)	33	1.8 (0.6)
QMLT second scan (pressure), cm, mean (SD)	8	1.8 (0.6)
QMLT baseline (no pressure), cm, mean (SD)	30	3.3 (0.8)
QMLT second scan (no pressure), cm, mean (SD)	7	3.2 (1.0)
Muscle CSA baseline, radiological assessment, cm ² , mean (SD)	32	148 (48)
Muscle CSA baseline, automated, cm ² , mean (SD)	29	171 (46)
Time of first CT scan in comparison to the initial ultrasound measurement, hours, median [IQR]	32	-43 [-46 – 38]
Muscle CSA second scan, automated, cm ² , mean (SD)	7	164 (52)
Muscle CSA second scan, radiology, cm ² , mean (SD)	11	136 (45)
Time of second scan in comparison to length of time from of second scan, days, median [IQR]	11	4.9 [0.29 – 6.1]
Energy requirements, kcal/day, mean (SD)	35	1929 (290)
Energy provided, kcal/day, mean (SD)	35	1643 (455)
Protein requirements, g/day, mean (SD)	35	106 (20)
Protein provided, g/day, mean (SD)	35	70 (25)

Abbreviations: BMI, body mass index; HWR, health weight range; QMLT, Quadriceps muscle layer thickness; CSA, cross sectional area.



Supplementary Figure 4-1. Bland-Altman plot comparing the mean difference in muscle cross section area (cm^2) assessed using the automatic software program compared to the radiology method

¹The solid line represents the mean difference and the dotted lines represent the 95% CIs.

²In those patients who had more than one measurement the average for the two measurements was used.

Supplementary Table 4-2. Mixed linear regression model of muscle cross sectional area at L3 using the radiology method and the relationship with QMLT using ultrasound with pressure

Variables	Reference	Univariate			Adjusted for all co-variants ^{1,2}		
		Effect	95% CI	p value	Effect	95% CI	P value
QMLT Pressure	per cm	57	36 to 79	<0.001	48	26 to 69	<0.001
Female	Male	-25	-50 to -0.19	0.05	-4.4	-27 to 19	0.71
Age							
> 60	<60 y	-27	-59 to 4.8	0.10	-17	-43 to 9.8	0.22
BMI							
<25	25-30kg/m ²	0.4	-27 to 28	0.03	1.3	-25 to 28	0.92
>30		41	5.6 to 76	0.02	27	-5.6 to 59	0.10

Abbreviations: QMLT, Quadriceps muscle layer thickness; BMI, body mass index

¹Linear mixed model using a random intercept to account for correlation within individuals, multivariate effect estimates are adjusted for all covariates in the model and for clustering within individuals (n = 33)

²Model diagnostics included both the link test for overall linear model specification, and assessment of regression coefficient influence (dfbetas).

³The standard deviation of the random effect for individuals was estimated at 32 cm² (95%CI 27 to 41) and the fixed effect intercept estimate was 57 cm².

Supplementary Table 4-3. Mixed linear regression of muscle cross sectional area assessed using the radiology method and the relationship with QMLT assessed using ultrasound with no pressure

Variables	Reference	Univariate Analysis			Adjusted for all co-variants ^{1,2}		
		Effect	95% CI	p value	Effect	95% CI	P value
QMLT no pressure	per cm	27	15 to 39	<0.001	23	13 to 32	<0.001
Female	Male	-25	-50 to -0.20	0.05	6.1	-15 to 27	0.57
Age							
>60	<60 y	-27	-59 to 4.8	0.10	-31	-56 to -7.4	0.01
BMI							
<25	25-30kg/m ²	0.40	-27 to 28	0.03	0.06	-23 to 23	0.97
>30		41	5.6 to 76	0.02	23	-10 to 55	0.17

Abbreviations: QMLT, Quadriceps muscle layer thickness; BMI, body mass index

¹Linear mixed model using a random intercept to account for correlation within individuals, multivariate effect estimates are adjusted for all covariates in the model and for clustering within individuals (n = 31)

²Model diagnostics including the link test and regression coefficient influence (dfbetas) showed satisfactory overall linear model specifications.

³The standard deviation of the random effect for individuals was estimated at 30 cm² (95%CI 23 to 40) and the fixed effect intercept estimate was 70 cm².

Chapter 5: Observed nutrition provision in critical illness and associations with patient centred outcomes

5.1 Chapter summary

This was the first study which was completed as part of this PhD program. This manuscript was published in April 2019. This study was conducted to assess nutrition provision in a critically ill patient cohort and to explore the associations with several patient centred outcomes. As described (section 1.2) this study was designed when clinicians (and researchers) had a greater focus on energy provision, which was in line with the available evidence at the time; however, the subsequent studies in this thesis shifted to focus on protein provision as new evidence emerged. The incorporation of functional and patient centred outcomes was novel when this study was undertaken.

5.2 Observational study in critical illness

Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness

Kate Fetterplace^{1,2}, Lisa J. Beach³, Christopher MacIsaac^{2,4}, Jeffrey Presneill^{2,4}, Lara Edbrooke⁵, Selina M Parry⁵, Thomas Rechner⁴, Rachel Curtis³, Sue Berney⁶, Adam M. Deane^{2,4} and Linda Denehy⁵.

1. Department of Allied Health (Clinical Nutrition), level 4 North, Royal Melbourne Hospital, Melbourne, Victoria, Australia
2. Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
3. Department of Allied Health (Physiotherapy), level 4 North, Royal Melbourne Hospital, Melbourne, Victoria, Australia

4. Intensive Care Unit, Royal Melbourne Hospital, Parkville Victoria, Australia
5. Department of Physiotherapy, The University of Melbourne, Melbourne, Victoria, Australia
6. Physiotherapy Department, Austin Health, Melbourne, Victoria, Australia

Correspondence

Kate Fetterplace,

kate.fetterplace@mh.org.au, Phone +61 9342 7440, Fax +61 93428440

Nutrition Department, level 3 Allied Health, Royal Melbourne Hospital,

Grattan Street, Parkville, Victoria, Australia 3050

Statement of authorship

K Fetterplace, LJ Beach, L Denehy, C MacIsaac, SM Parry and S Berney contributed to the conception and design of the research; K Fetterplace, L Beach, T Rechnitzer, R Curtis, J Presneill and L Edbrooke contributed to the acquisition and analysis of the data; K Fetterplace, J Presneill, L Edbrooke and AM Deane contributed to the interpretation of the data; and K. Fetterplace, LJ Beach, AM Deane and L Denehy drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of interest

K Fetterplace has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi and Nestle Health Science (not related to this study). AM Deane or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (Not related to this study). The other authors have no potential conflicts to declare.

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5.3 Abstract

Background: Patients who survive critical illness frequently develop muscle weakness that can impact quality of life; nutrition is potentially a modifiable risk factor. The purpose of this study was to explore associations between cumulative energy deficits (using indirect calorimetry and estimated requirements), nutritional and functional outcomes.

Methods: Prospective single centre observational study of 60 Intensive Care Unit (ICU) patients, who were mechanically ventilated for at least 48 hours. Cumulative energy deficit was determined from artificial nutrition delivery compared to targets. Measurements included: (i) at recruitment and ICU discharge, weight, fat free mass (bioimpedance spectroscopy) and malnutrition (Subjective Global Assessment score B/C); (ii) at awakening and ICU discharge, physical function (Physical Function in Intensive Care Test-scored) and muscle strength (Medical Research Council sum-score (MRC-SS). ICU-acquired weakness was defined as an MRC-SS < 48/60.

Results: The median [IQR] cumulative energy deficit compared with estimated targets to ICU day 12 was 3648 [2514 – 5650] kcal. Adjusting for body mass index, age and severity of illness; cumulative energy deficit (per 1000kcal) was independently associated with greater odds of ICU-acquired weakness (OR 2.1, 95%CI 1.4-3.3, p=0.001) and malnutrition (OR 1.9, 95%CI 1.1-3.2, p=0.02). In similar multivariable linear models, cumulative energy deficit was associated with reductions in fat free mass (-1.3kg, 95%CI -2.4 to -0.2, p=0.02) and physical function scores (0.6 points, 95%CI -0.9 to -0.3, p=0.001).

Conclusion: Cumulative energy deficit from artificial nutrition support was associated with reduced functional outcomes and greater loss of fat free mass in ventilated ICU patients.

Keywords: Nutrition support, indirect calorimetry, enteral nutrition, muscle strength, bioimpedance spectroscopy and critical care.

5.4 Introduction

Patients who survive critical illness frequently develop muscle weakness, which has been termed Intensive Care Unit (ICU)-acquired weakness (ICU-AW). Not only is ICU-AW associated with diminished physical function and lower health-related quality of life but it is also associated with increased ICU and hospital length of stay (LOS), health-care costs and mortality (Desai et al., 2011; D. K. Heyland et al., 2016; Kress & Hall, 2014). Optimal nutrition may attenuate ICU-AW however; there is a paucity of evidence in this area (Bear et al., 2017; Fan et al., 2014; D. K. Heyland et al., 2016).

The optimal nutrition provision for critically ill patients to improve outcomes is uncertain (Yaseen M. Arabi et al., 2011; Elke et al., 2014) and the composition of nutrition formulae is currently the subject of research (Bear et al., 2018; D. K. Heyland et al., 2016; Puthuchearry et al., 2018). Observational studies have reported energy deficits during critical illness are associated with adverse outcomes; such as increased mortality, ICU LOS and period of mechanical ventilation (Compher et al., 2017; Elke et al., 2014; Gungabissoon et al., 2015; Zusman et al., 2016). However recent randomised clinical trials comparing permissive under-, trophic-, standard- or full-feeding have not identified any link between energy deficit and mortality (Y. M. Arabi et al., 2015; Rice et al., 2012; TARGET Investigators*, 2018).

In all of these large randomised clinical trials nutrition prescriptions were based on predictive equations, which reflects standard clinical practice (Oshima et al., 2017; Zusman et al., 2016). However, predictive equations are inaccurate estimates of daily energy expenditure during critical illness when compared to 'gold-standard' measurements of energy expenditure using indirect calorimetry (Tatucu-Babet et al., 2016). Accordingly, the use of predictive equations to assess energy deficits may contribute to inconsistencies between studies regarding energy deficit and associated outcomes (Ridley, Davies, et al., 2018; Tatucu-Babet et al., 2016).

The primary objective of this study was to determine the cumulative energy deficit from artificial nutrition support using both calculated predictive equations and repeated measured energy expenditure (MEE). The secondary objectives were to explore associations between cumulative energy deficit and nutritional outcomes (change in body weight and fat free mass and the development of malnutrition) and functional outcomes (muscle strength and physical function) at ICU discharge.

5.5 Methods and materials

5.5.1 Study design and setting

This prospective single center observational cohort study was conducted in the mixed medical-surgical-trauma ICU of a tertiary-referral Australian hospital. Between 2012 and 2014 consecutive weekday admission patients were screened for eligibility. Initial written informed consent was obtained from the person responsible, with continuation of consent obtained subsequently from competent participants. Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee (project number: 2012.060) (Beach et al., 2017). Reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007).

5.5.2 Patient selection

Inclusion criteria were: age ≥ 18 years; mechanical ventilation commenced within 48 hours of ICU admission and likely to be required > 48 hours, and an estimated minimum stay in the ICU of at least five days. Exclusion criteria were: major trauma necessitating a specific period of immobilisation; new neurological insult, such as spinal cord injury or stroke; poor pre-morbid mobility, defined as inability to walk independently with or without a gait aid; inability to communicate in English; did not have medical insurance cover; ICU re-admission; or if the attending physician did not support inclusion.

5.5.3 Protocol

Standard care for all participants included nutritional assessment by a dietitian within 48 hours of admission, with estimation of their nutritional requirements (Ridley, Peake, et al., 2018). Commercially available enteral and parenteral formulas were utilised, which were prescribed based on clinical need as assessed by the dietitian or ICU physician. Enteral feeding followed the standard unit nutrition protocol, which encouraged early initiation of nutritional support within 24 hours of admission and specified prokinetic drug administration if gastric residual volumes were greater than 300ml (Reintam Blaser et al., 2017). All study participants also received respiratory and rehabilitation interventions provided by physiotherapists.

Baseline demographic data including age, gender, admission diagnosis, severity of illness (Acute Physiology And Chronic Health Evaluation (APACHE) II score) and the Nutrition Risk in Critically ill score (NUTRIC) were recorded (Rahman et al., 2016). Daily nutritional energy delivery from enteral and parenteral nutrition (not including other energy sources) and nutritional outcome data were collected on participants until ICU discharge or day 30 of the ICU admission, whichever came first.

5.5.4 Nutritional outcomes

Nutritional outcomes were collected at baseline and ICU discharge. Weight was determined via bed scales (Hill-Rom®, Indiana USA) for most patients; if the weight was not available an estimated weight was used for the nutrition prescription. Height was estimated using ulna length (Beach et al., 2017) and body mass index (BMI) in kg/m^2 was calculated. A dietitian measured the mid upper arm circumference (cm) (Ravasco et al., 2002) and assessed nutritional status using the Subjective Global Assessment (SGA) (Detsky et al., 1987; Marshall, 2008), with a score of B or C considered as malnourished. Serum albumin (g/L) and transthyretin (prealbumin) concentrations (milligram/L) were measured, with the normal ranges being 35-50 g/L and 180-360 milligram/L respectively (Marshall, 2008).

5.5.5 Estimated energy requirements

Estimated energy requirements were calculated by the dietitian at baseline using both the standard weight-based equations of 25-30kcal/kg per day (McClave et al., 2016) and the Schofield equation with appropriate stress factors, in line with standard practice in Australia (Ferrie & Ward, 2007; Schofield, 1985). For overweight participants ideal body weight (IBW) was used and for obese participants with a BMI greater than 32 kg/m², an obesity adjusted weight was used (IBW + 25% (actual body weight - IBW)) (Frankenfield et al., 2003). The nutrition prescription (prescribed energy target) was determined based on the dietitian assessment of the estimated energy requirements, using their clinical judgment of which estimation was most reflective of the participant's requirements.

5.5.6 Measured energy expenditure

Measured energy expenditure (MEE) was determined via indirect calorimetry, in patients with no contraindication, using the Deltatrac® II Metabolic Cart (Datex-Ohmeda, Helsinki, Finland) (Swinamer et al., 1990). MEE was undertaken by a trained physician and completed whilst the participant was mechanically ventilated, on the day of recruitment and on days three and five after enrolment. Standard methods were used; all expired gas was collected from the expiratory port of the ventilator, the measures were continued for 30 minutes and summary data were recorded (Petros & Engelmann, 2001). Participants were excluded from MEE if they: had an intercostal catheter with an air leak; were receiving a fraction of inspired oxygen > 0.6; were receiving extracorporeal membrane oxygenation; or were in infective isolation. Nutrition support was not stopped during MEE and there was no restriction on the participant's movement prior to MEE. Metabolic Cart outputs recorded, included oxygen consumption (VO₂) mL/min, carbon dioxide production (VCO₂) mL/min, calculated respiratory quotient (RQ) and MEE in kcal/day, using the Weir equation. The average MEE was determined from the mean of available repeated measurements.

5.5.7 Cumulative energy deficit

Each participant's cumulative energy deficit from artificial nutrition support was calculated daily for a maximum of 12 ICU days based on *a priori* determination that substantial changes to nutritional tolerance were unlikely after this time (Alberda et al., 2009; Chapple et al., 2017). Daily energy provision was measured for all participants receiving any enteral or parenteral nutrition, not including energy from other sources. Daily energy deficit was determined by deducting the energy delivered from prescribed energy target determined by the dietitian and secondly from the average MEE. The daily energy deficit was summed for the total cumulative energy deficit. The nutritional adequacy was assessed by dividing the daily energy delivery, including the day of admission and the day of discharge if it was greater than eight hours, by the prescribed requirements or the average MEE and expressing as a percentage.

5.5.8 Fat free mass change

Fat free mass was measured using the tetra-polar-configured multi-frequency SFB7 bioimpedance device (AU/NZ; ImpediMed™ Limited, Pinkenba, Australia)(Earthman, 2015). This device uses bioimpedance spectroscopy to determine total body water, extracellular fluid and intracellular fluid and subsequently calculates fat free mass and fat mass (Earthman, 2015). Use of this device has been validated in the critically ill (Baldwin et al., 2012; Kuchnia et al., 2017). Measurements were taken when the participants were supine in bed, after single use gel electrodes were placed on one ipsilateral foot and hand (Baldwin et al., 2012; Earthman, 2015). Fat free mass was determined immediately after enrolment and at ICU discharge.

5.5.9 Muscle strength and physical function

Muscle strength was assessed using the Medical Research Council sum-score (MRC-SS) with a score of less than 48/60 considered indicative of ICU-AW (Hough et al., 2011; Parry et al., 2015). Physical function was measured using the Physical Function in Intensive Care Test-scored (PFIT-s) (Denehy et al., 2013). Muscle strength and physical function testing were all conducted by physiotherapy staff and assessments were performed at ICU awakening (De Jonghe et al., 2002) and ICU discharge (see Appendix 1).

5.5.10 Participant outcomes

Twenty-eight day mortality, ICU LOS, hospital LOS, length of mechanical ventilation, days of sedation (defined as greater than eight hours on any sedative drug), duration of sepsis determined using the American College of Chest Physicians Criteria (Levy et al., 2003) and discharge destination were collected, censored at day 60.

5.5.11 Statistical analyses

Participant demographics, cumulative energy deficit, nutritional and functional outcomes are reported as mean (standard deviation) (SD) or median [inter-quartile range] [IQR] as appropriate. Comparisons between outcome measures from baseline to ICU discharge used paired t-tests or Wilcoxon signed-rank tests as appropriate. Multivariable generalised linear regression analyses explored associations between cumulative energy deficit (prescribed energy targets) and continuous outcomes, including weight, fat free mass and physical function scores at discharge. The confounding variables which were adjusted for in these models included age, APACHE II score, BMI and baseline measures where applicable. Logistic regression was performed for the binary outcomes of ICU-AW and malnutrition, adjusted for the same confounding variables, with effect estimates reported as odds ratios with 95% confidence intervals. Sensitivity analyses was performed for the outcome of ICU-AW missing values, were imputed as first having ICU-AW and then not having

ICU-AW. Energy deficits calculated from prescribed energy targets were used in the full analyses in preference to energy deficits calculated from MEE, to minimise the risk of bias as this was the most complete data set. The generalised linear regression models that were finally applied were checked using standard diagnostics, including tests of influence and specification of included variables. Protein provision was collected and reported however not analysed in relation to outcomes as this was not planned at the time of designing the study and therefore analysing these data post-hoc would risk incorrect inferences.

A two-sided p value of <0.05 was set for statistical significance for all tests, with no adjustment for multiplicity. SPSS (IBM® SPSS® Statistics Premium Grad Pack Version 22.0) and Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, 2017) were used to perform the data analyses.

At the time of designing this study no data were known which assessed muscle strength in relation to energy deficit in a critically-ill population. This observational study selected a pragmatic sample size of 60 participants.

5.6 Results

5.6.1 Participants

Five hundred and forty-three participants were eligible (Figure 1) after exclusions, 140 (26%) met inclusion criteria and 60 of these (43%) agreed to participate and were enrolled. Of the enrolled participants 57 (95%) remained in ICU until day five, 43 (72%) had at least one MEE measurement and 48 (80%) had a muscle strength assessment at ICU discharge.

5.6.2 Participant characteristics

Demographic and clinical characteristics are provided in Table 1. The participants had a mean (SD) age of 58 (16) years, median [IQR] BMI of 28 [24-31] kg/m², mean APACHE II score of 23 (7.5) and mean NUTRIC score of 4.6 (2.1).

5.6.3 Nutrition provision

Nutrition provision is summarised in Table 2. The majority of participants were enterally fed (n = 58, 97%), for a median of 5 [3.0 – 8.8] days and had a mean energy delivery of 1182 (443) kcal per day from artificial nutrition support.

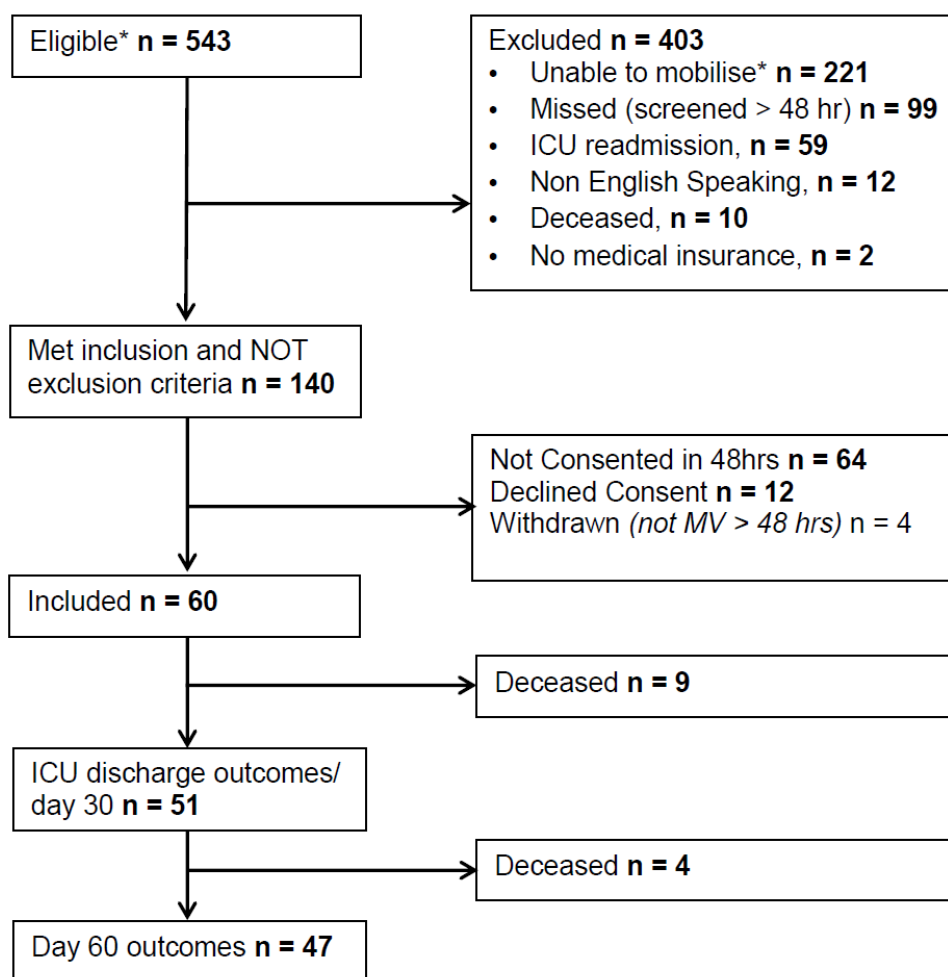


Figure 5-1. Consort diagram

Abbreviations: Eligible – patients who met all inclusion criteria at the time of screening, exclusion criteria = unable to mobilise - included major trauma necessitating a period of immobilisation; new neurological insults; and poor pre-morbid mobility (unable to mobilise independently with or without a gait aid). ICU – intensive care unit, not an Australian citizen –non citizens were excluded as they are ineligible for Medicare should their participation in the study result in the need for additional medical care. MEE – measured energy expenditure.

Table 5-1. Participant demographic and clinical characteristics

Demographics and medical data	n = 60
Age years, mean (SD)	58 (16)
Gender male, n (%)	33 (55)
BMI kg/m ² , median [IQR]	28 [24-31]
APACHE II score, mean (SD)	23 (7.5)
NUTRIC Score, (n=49), mean (SD)	4.6 (2.1)
Admission category, n (%)	Medical: 34 (57) Emergency Surgery: 21 (35) Elective Surgery: 5 (8)
Admission Diagnosis, n (%)	Cardiac arrest: 14 (23) Respiratory failure: 8 (13) Trauma: 7 (12) Cardiovascular surgery: 7 (12) Gastrointestinal surgery: 7 (12) Gastrointestinal non-surgery: 6 (10) Sepsis: 4 (7) Endocarditis: 2 (3) Other: 5 (8)
ICU-AW diagnosis (awakening), n (%)	23 (38)
ICU LOS, days	7.0 [4.0-12.0]
Hospital LOS, days	19.0 [13.0-30.8]
Length of MV, days	4.0 [3.0-8.0]
Sedation duration, days	3.5 [2-7.0]
Sepsis duration, days	3.0 [0-6.8]
28-day mortality, n (%)	13 (22)
Discharge destination of survivors, n (%)	
Home	29 (48)
Rehabilitation	14 (23)
Other (including residential care)	4 (7)

Abbreviations: BMI; Body Mass Index, Kg; kilograms, m²; meters squared, APACHE II; Acute Physiology And Chronic Health Evaluation II, NUTRIC Score; The Nutrition Risk in Critically ill, IQR; interquartile range, SD; Standard deviation, ICU-AW; Intensive care acquired weakness, LOS; Length of stay and MV; Mechanical ventilation. Values are presented as median [interquartile range] unless stated.

Table 5-2. Nutrition Provision

Variable	n = 60
EN provided, n (%)	58 (97)
PN provided n (%)	11 (18)
Days of EN	5.0 [3.0 - 8.8]
Days of PN (when provided)	6.0 [5.0-9.3]
Days NBM	1 [0-1]
Days on oral intake	2 [0-3]
Time from admission to initiating NS, hours, mean (SD)	20 (13)
Duration of NS interruption, hours	16 [6.0 - 31]
Duration of NS interruption, days	2 [1-3]
Prescribed estimated energy, kcal/day	1950 [1763 – 2160]
Energy delivered, kcal/day	1182 (443)
Energy delivered, kcal/kg/day	16 (6.1)
Energy adequacy, % of prescribed, mean (SD)	64 (22)
Estimated protein requirements, g/kg/day	1.3 [1.2-1.3]
Protein provided, g/kg/day, mean (SD)	0.58 (0.25)
Protein adequacy, % of estimate, median [IQR]	61 [44-69]

Abbreviations: EN; Enteral Nutrition, PN; Parenteral Nutrition, NBM; Nil by Mouth, NS; nutrition support, SD; standard deviation, values are presented as median [interquartile range] unless stated.

5.6.4 Energy requirements

The median [IQR] estimated energy requirements were 1800 kcal/day [1675 – 2025] (weight-based equation) and 1952 kcal/day [1733 – 2240] (Schofield equation, with a median stress factor of 1.3 [1.2-1.3]). The median prescribed energy targets, based on the estimated requirements, were 1950 kcal/day [1763 – 2160].

Measured energy expenditure (MEE) was performed in 43 (72%) participants. At baseline (n=36) the median [IQR] MEE was 1695 [1377 – 1882] kcal and the average of up to 3 time points (n=43) was 1690 [1400 – 1895] kcal. There was moderate overall agreement between the MEE and the prescribed daily energy targets, with the former showing a mean bias of -219 kcal (95% CI -307 to -132) compared to the prescribed daily energy targets ($r = 0.536$, $p < 0.0050$) (Bland & Altman, 1999).

(Supplementary Figure 1. Bland Altman plot of agreement between prescribed energy targets and measured energy expenditure).

5.6.5 Cumulative energy deficit

When energy delivery from nutrition support was compared to estimated prescribed energy targets (n=60), the median [IQR] daily nutritional energy deficit was 281 [193 – 435] kcal/day (Figure 2) and the cumulative energy deficit was 3648 [2514 – 5650] kcal. The mean nutritional energy adequacy using the prescribed energy targets over the 12 days was 64% (22).

Comparing energy delivery from artificial nutrition support with MEE the median [IQR] daily nutritional energy deficit was 172 [42 – 362] kcal and the cumulative energy deficit to ICU day 12 was 2234 [541 – 4710] kcal. The mean nutritional energy adequacy using MEE over the 12 days was 74% (26).

5.6.6 Nutritional outcomes

From baseline to ICU discharge there were significant reductions in weight, fat free mass and mid upper arm circumference (Table 3). Serum transthyretin concentrations increased significantly over the ICU stay, however albumin concentrations were similar between time points (Table 3). Where malnutrition was assessed at baseline and discharge (n = 50) there was an observed increase in the proportion of participants who were malnourished at discharge compared to admission (baseline 12 (24%), discharge 18 (36%), (McNemar's exact p = 0.03).

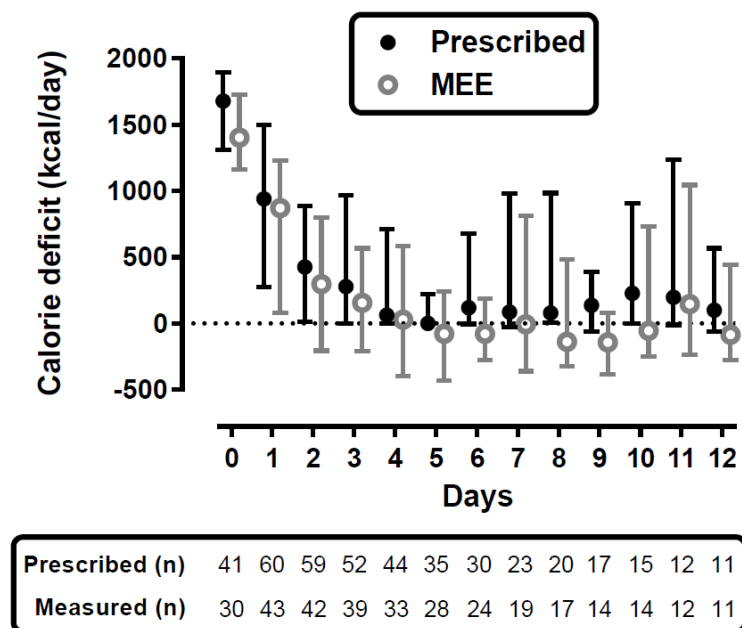


Figure 5-2. Daily energy deficit from nutrition support versus estimated prescribed energy targets and MEE

Abbreviations: MEE; Measured energy expenditure, error bars indicate interquartile range.

Table 5-3. Nutritional outcomes

Variable	n	Baseline Mean (SD)	Discharge Mean (SD)	Mean difference (95%CI)	p value
Weight, kg	45	85 (22)	82 (19)	-3.0 (-5.2 to -0.7)	0.01
BIS FFM, kg	45	69 (19)	62 (19)	-7.7 (-10 to -5.0)	<0.001
MUAC, cm	49	34 (5.3)	32 (5.3)	-1.9 (-2.3 to -1.4)	<0.005
Transthyretin millig/L	32	108 (35)	153 (17)	46 (11 to 81)	0.01
Albumin g/L	50	27 (5.2)	26 (4.6)	-0.73 (-2.3 to 0.7)	0.31

Abbreviations: Kg; Kilograms, BIS; Bioimpedance spectroscopy, FFM; Fat Free Mass, MUAC; Mid Upper Arm Circumference, g/L; grams per litre. The mean difference was determined using a paired t-test.

5.6.7 Muscle strength and physical function

Muscle strength at discharge was measured in 48 (80%) participants. Of the 12 participants who did not have this measured nine died prior to discharge and the others were unable to complete the test due to inability to follow commands. The prevalence of weakness at awakening was 23 (38%) and at ICU discharge amongst

survivors was 10 (21%). Physical function at ICU discharge was measured in 49 (82%) survivors, with a mean (SD) PFIT-s interval score of 6.5 (2.1) out of 10.

5.6.8 Associations between cumulative energy deficit and outcomes

Participants with energy deficits from artificial nutrition support below prescribed targets, were observed to have a greater risk of ICU-AW and malnutrition. Per 1000kcal cumulative energy deficit, there was approximately a two-fold increased risk of both ICU-AW [OR 2.1 (95%CI 1.4-3.3), $p=0.001$] and malnutrition [OR 1.9 adjusted for baseline malnutrition (95%CI 1.1-3.2), $p=0.02$] at ICU discharge. Likewise, adjusted for baseline, subjects were observed to lose on average 1.3kg (95%CI 0.2-3.4, $p=0.02$) fat free mass per 1000kcal cumulative deficit. A moderate association was observed between reduced physical function at ICU discharge and cumulative energy deficit, with mean physical function score decreasing by 0.6 points (95%CI 0.3 – 0.9, $p=0.001$) per 1000kcal deficit. There was no strong evidence of an association between weight loss and nutritional energy deficit. When MEE was used to calculate energy deficit a similar result was found for the development of ICU-AW ($n=31$) [OR 1.9 (95%CI 1.1-3.4), $p=0.021$] (Supplemental Table 1).

There was no strong association observed between cumulative energy deficit from artificial nutrition support and length of stay, length of mechanical ventilation or mortality (Table 1. includes medical outcome data).

Table 5-4. Cumulative nutritional energy deficit and associated outcomes

ICU acquired weakness at ICU discharge						
Variable	Univariate analysis			Multivariable Sensitivity analysis		
	OR	95% CI	P value	OR	95% CI	P value
Calorie deficit (per 1000kcal)	2.2	1.3- 3.7	<0.01	2.1	1.4-3.3	0.001
BMI ($\geq 30\text{kg/m}^2$)	6.2	1.1- 35	0.04	3.6	0.9- 5.2	0.08
Age (> 60 years)	1.0	0.2- 4.6	1.0	2.0	0.5- 8.2	0.35
APACHE II (> 25)	0.62	0.1 -3.5	0.59	5.0	1.1- 23	0.04
Malnutrition at discharge adjusted for baseline						
Variable	Univariate analysis adjusted for baseline malnutrition diagnosis			Multivariable analysis adjusted for all variables		
	OR	95% CI	P value	OR	95% CI	P value
Calorie deficit (per 1000kcal)	1.6	1.1-2.4	0.01	1.9	1.1- 3.2	0.02
BMI ($\geq 30\text{kg/m}^2$)	0.55	0.10 - 2.9	0.48	0.31	0.03 - 3.4	0.34
Age (> 60 years)	2.	0.50- 17	0.23	2.4	0.32- 18	0.40
APACHE II (> 25)	1.1	0.21-5.8	0.10	2.9	0.34- 26	0.33
Fat Free mass at discharge adjusted for baseline						
Variable	Univariate analysis adjusted for Baseline FFM			Multivariable analysis adjusted for all variables		
	effect	95% CI	P value	effect	95% CI	P value
FFM (Baseline), kg	0.93	0.80 to 1.1	<0.001	0.91	0.8 to 1.1	<0.001
Calorie deficit (per 1000kcal)	-1.1	-2.2 to -0.08	0.04	-1.3	-2.4 to -0.21	0.02
BMI ($\geq 30\text{kg/m}^2$)	2.2	-4.1 to 8.5	0.49	2.1	-4.1 to 8.1	0.51
Age (> 60 years)	-0.71	-6.2 to 4.7	0.80	0.24	-5.1 to 5.5	0.91
APACHE II (> 25)	-2.5	-11 to 9.8	0.38	-4.0	-9.5 to 1.6	0.15
Physical function at ICU discharge						
Variable	Univariate analysis			Multivariable analysis adjusted for all variables		
	effect	95% CI	P value	effect	95% CI	P value
Calorie deficit (per 1000kcal)	-0.6	-0.9 to -0.2	0.002	-0.59	-0.92 to -0.26	0.001
BMI ($\geq 30\text{kg/m}^2$)	-1.9	-3.7 to -0.15	0.03	-2.0	-3.5 to -0.38	0.02
Age (> 60 years)	-1.1	-2.9 to 0.71	0.23	-1.2	-2.7 to 0.38	0.14
APACHE II (> 25)	-0.31	-2.2 to 1.6	0.75	-1.1	-2.8 to 0.54	0.18

Abbreviations: BMI; Body Mass Index centered at 30 kg/m², Age centered at 60 years, APACHE II; Acute Physiology And Chronic Health Evaluation II, centred at 25, FFM; Fat free Mass. Logistic regression analysis models were used for ICU-Acquired weakness and Malnutrition. Linear regression analysis models were used for fat free mass and physical function.

5.7 Discussion

In a critically ill population this study evaluated energy deficit from artificial nutrition support compared to measured energy expenditure and estimated energy requirements and concurrently assessed fat free mass, muscle strength and physical function. In this mechanically ventilated cohort, the mean cumulative energy deficit was approximately 200 kcal smaller per day when measured energy expenditure was used compared to estimated prescribed energy targets. Cumulative energy deficit from artificial nutrition support was found to be associated with an increased prevalence of ICU-AW and malnutrition, reduced physical function scores at ICU discharge and greater loss of fat free mass over the ICU stay.

The observed energy deficit in this cohort appeared to be slightly lower than some previously reported multi-center studies, where critically ill patients meet a mean of 60 percent of their prescribed energy targets (Elke et al., 2014; D.K. Heyland et al., 2011; Peake et al., 2014). In this study the mean amount of energy provided from nutrition support compared to estimated energy targets was 64% however when MEE was used it improved to 74%. Cumulative energy deficit has been previously reported to be associated with poorer outcomes, such as lower rates of discharge to home, increased infection rates, reduced ventilator free days and higher mortality rates (Elke et al., 2014; Villet et al., 2005; Yeh et al., 2016). These were not observed in the present study however direct comparisons cannot be made due differences in accounting for non-nutritional energy provision.

Indirect calorimetry is infrequently used as part of routine clinical practice to determine energy targets, due to the high cost, time and expertise required (De Waele et al., 2018; Zusman et al., 2016). Predictive equations are reported to be inaccurate, with weight-based equations being the least accurate (Tatucu-Babet et al., 2016). Our finding again showed there was only moderate agreement between prescribed estimated energy requirements and measured energy expenditure. This

difference in energy deficit may support the use of indirect calorimetry to more accurately assess nutritional adequacy and its impact on outcomes.

Data evaluating the relationships between energy deficits and muscle mass are sparse and somewhat conflicting (Lambell et al., 2018). In this study, it was observed that there was substantial change in fat free mass over the ICU stay, and when adjusted for baseline fat free mass, greater energy deficit from artificial nutrition support was associated with greater fat free mass loss. Few previous studies have used BIS to assess change in fat free mass and associations with energy deficits (Lambell et al., 2018), and therefore comparisons with other studies are difficult. Using subjective measures, the administration of early parenteral nutrition, which improved energy delivery appeared to reduce muscle wasting (Doig et al., 2013). However in contrast, in a small sub-analysis of a large randomised clinical trial (EPaNIC) greater energy delivery via early parenteral nutrition did not lead to any difference in muscle loss, when assessed using qualitative computed tomography (CT) analysis (Michael P. Casaer et al., 2011). There was however, deterioration in muscle quality observed, with increased intramuscular water and lipid content in the group who received early parenteral nutrition, over a seven-day period in the ICU (M.P. Casaer et al., 2013). Observational studies have also reported conflicting results; similar to the present study one found that nutritional adequacy based on estimated energy targets was the only predictor of muscle loss, assessed using CT analysis (Braunschweig et al., 2014) and in contrast the other found that energy balance made no difference to the rate of muscle loss, assessed using ultrasound (Reid et al., 2004).

The impact of acute energy deficit on muscle strength and physical function in the critically ill is uncertain (Bear et al., 2017). In the present study 21% of survivors had ICU-AW and the mean PFITs was 6.5 (2.1) out of 10 at ICU discharge; Greater energy deficit was associated with an increasing risk of developing ICU-AW and lower physical function scores at ICU discharge. Additionally, multivariable analysis

suggested that participants with higher BMIs and APACHE II scores had a higher risk of developing ICU-AW. This is in contrast to another sub-analysis of EPaNIC which reported that lower calorie deficit was associated with greater ICU-AW at awakening (107 (34%) late PN group versus 127 (43%) early PN group, $p = 0.03$) and slower rates of recovery, however there was no difference in the rates of ICU-AW at ICU discharge (78 (26%) late PN group versus 91 (31%) in the early PN group, $p = 0.15$) (Hermans et al., 2013). However, in a nested cohort study within the EDEN trial, trophic feeding for the first five days of ICU admission when compared to standard care increased early calorie deficit but did not affect physical function scores using the SF-36 at 12-months but did result in a greater proportion of patients admitted to a physical rehabilitation facility (57 (23%) trophic feeding group versus 30 (14%) standard care, $p = 0.01$) (Needham et al., 2013).

The differences in the findings between observational studies and recent interventional trials for both muscle mass changes and functional outcomes may be explained by the timing of nutrition support, the route of delivery and the composition of the nutrition provided (Bear et al., 2018; Puthuchearry et al., 2018), as well as the methodology and timing of the outcome measures. Further research is required to explore the effect of different methods of nutrition delivery and substrates to minimise muscle wastage as well as standardising the methods to assess muscle mass and functional outcomes.

The strengths of this study include that both measured energy expenditure and estimated prescribed energy targets were used to calculate energy deficit and that simultaneously several other nutrition-associated and patient-centered outcomes were assessed, including fat free mass, muscle strength and physical function. Additionally, muscle strength was measured in 80 percent of the cohort. Study limitations included that this was a single centre observational study with a relatively small sample size of 60 participants; therefore, there is the potential for bias and many of the outcome variables are subjective, including the functional outcome

measures and the diagnosis of malnutrition. Also, importantly, the calculation of energy deficits did not include non-nutritional calories or energy provided from oral intake. In addition, measured energy expenditure was only completed in a subset of participants, and as such only 43 participants were included in the MEE cumulative energy deficit analysis and given the missing MEE data, associations between calorie deficit calculated from MEE and outcomes were not performed. The use of clinical measures to assess muscle strength, the diagnoses of ICU-AW and physical function limits findings to a cohort of patients who survived critical illness and who were able to obey commands. However, we attempted to control for this by undertaking sensitivity analysis for the outcome of ICU-AW, and when all missing results were imputed as participants being 'weak' the overall conclusion remained unchanged. This study was not powered to determine important effects on patient-centered outcomes, such as mortality, and it did not explore associations between protein deficits and outcomes. Finally, due to the observational design of this study only associations and not causality, could be reported.

5.8 Conclusion

Cumulative energy deficit from artificial nutrition support was lower when measured energy expenditure was used compared to prescribed energy targets. Cumulative energy deficit from artificial nutrition support was observed to be associated with the development of ICU acquired weakness, malnutrition, reduced physical function at ICU discharge and greater loss of fat free mass. Large well-designed randomised controlled trials, exploring the role of protein and absolute energy delivery, that include muscle mass and functional outcomes are warranted and required to confirm these results.

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5.10 Supplementary material for Chapter 5

Methods for muscle strength and physical function assessment

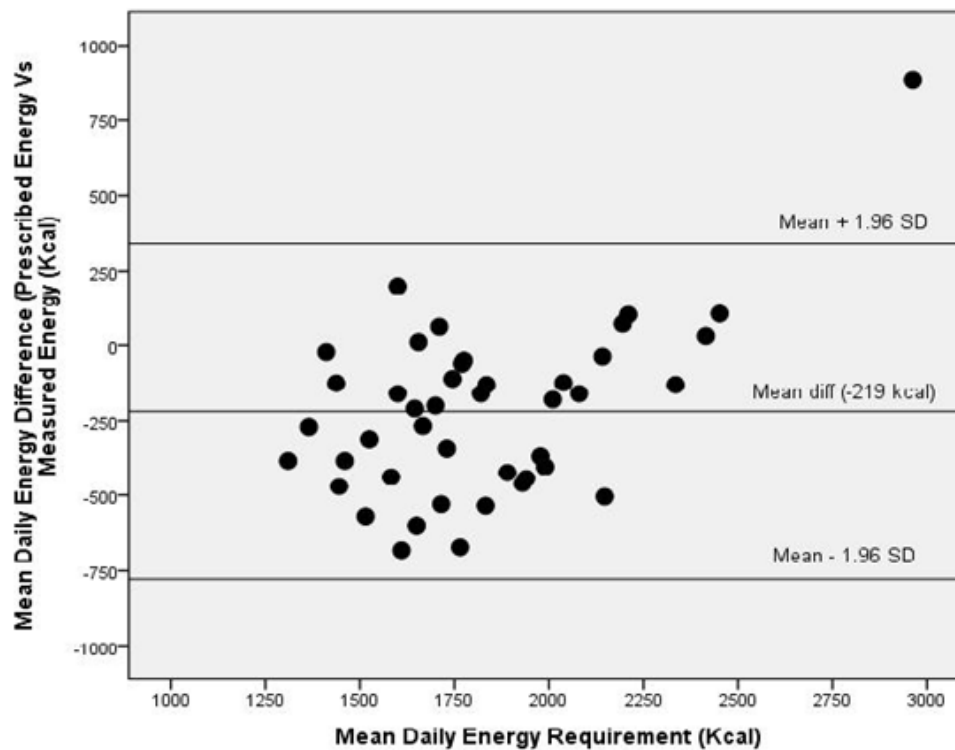
Muscle strength and physical function tests were performed at awakening and discharge from the ICU. Awakening was defined as a score of $\geq 3/5$ on the De Jonghe comprehension criteria on two consecutive occasions within a six-hour period (De Jonghe, 2002).

Muscle strength

Muscle strength was assessed using the Medical Research Council sum score (MRC-SS); this scale is recommended for the clinical diagnosis of ICU-AW (E. Fan et al., 2014; Hough et al., 2011; Parry, 2015). MRC-SS has been shown to be a reliable test when performed by an experienced operator (E. Fan et al., 2010), with good inter-observer agreement for identifying ICU-AW and excellent agreement for identifying severe weakness ($< 36/60$) (Hermans et al., 2012). Strength assessments were conducted throughout muscle range of movement in this study, consistent with current Australian practice at the time of the study. "Through-range testing means that the assessor provides resistance to the muscle whilst the joint is moving" (S. Parry et al., 2015).

Physical function

Physical function was measured using the Physical Function in Intensive care Test-scored (PFIT-s) (Denehy et al., 2013). This test has four components that examine endurance, function and strength. The PFIT-s comprises: sit to stand (graded assistance), marching on the spot (steps and cadence), and muscle strength (knee extension and shoulder flexion assessed by Oxford Grading). The PFIT-s is scored between zero to 10 on an interval scale, with higher scores indicating improved physical function. The PFIT-s has been shown to be reliable, valid, responsive to change and predictive of outcomes (Denehy et al., 2013; Nordon-Craft et al., 2014; S. M. Parry et al., 2015).



Supplementary Figure 5-1. Bland Altman plot of agreement between prescribed energy targets and measured energy expenditure

Supplementary Table 5-1. Associations between cumulative energy deficit using measured energy expenditure and ICU AW at ICU discharge

ICU acquired weakness at ICU discharge (n = 31)			
Variable	Multivariable analysis		
	OR	95% CI	P value
Calorie deficit verse MEE (per 1000kcal)	1.9	1.1 – 3.4	0.02
BMI ($\geq 30\text{kg/m}^2$)	95	0.93 – 9882	0.05
Age (> 60 years)	0.82	0.05 – 13	0.89
APACHE II (> 25)	0.01	0.0 – 2.4	0.10

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Chapter 6: Observed nutrition provision following critical illness and associations with patient-centred outcomes

6.1 Chapter summary

This study was completed in collaboration with Kym Wittholz, who was lead author on the published manuscript, which was published in May 2020 (print) in the Journal of Human Nutrition and Dietetics. This study explored the feasibility of repeatedly assessing nutrition provision and nutrition-related patient-centred outcomes in a cohort of trauma patients through their ICU admission and after discharge to the general hospital ward. This was a logical extension of the work presented in Chapter 5 that included various precipitating illness or injuries but was limited to ICU admission. The trauma cohort was selected because these patients are at high nutritional risk (Yeh et al., 2016), and it was hypothesised that they would benefit the most from nutrition support interventions throughout their hospital admission. This project was important because data on nutrition provision following ICU discharge is sparse. It was crucial to determine whether collecting data during the post-ICU period was feasible; this will inform the design of future trials of nutritional intervention in this group.

6.2 Observational study following critical illness

Measuring nutrition related outcomes in multi-trauma patients following intensive care unit discharge

Kym Wittholz¹, Kate Fetterplace^{1,2}, Melanie Clode³, Elena S. George³, Christopher M. MacIsaac^{2,4}, Rodney Judson⁵, Jeffrey J. Presneill^{2,4}, Adam M. Deane^{2,4}.

1. Department of Allied Health (Clinical Nutrition), The Royal Melbourne Hospital, Melbourne, Australia
2. The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, VIC 3050, Australia

3. Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Science, Deakin University, Geelong, Australia
4. Department of Intensive Care, The Royal Melbourne Hospital, Melbourne, Australia
5. Department of Trauma, The Royal Melbourne Hospital, Melbourne, Australia

Corresponding author

Ms Kate Fetterplace^{1,2} BNutDiet, APD

Senior Dietitian, Allied Health Royal Melbourne Hospital

Grattan St Parkville, Victoria, Australia 3050

Phone: +61 3 9342 7440 Fax +61 3 9342 8440

Email: Kate.Fetterplace@mh.org.au

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE (Vandenbroucke et al., 2014) guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. This project was approved by the Melbourne Health Human Research Ethics Committee (QA2018048).

Authorship declaration

K Wittholz, K Fetterplace, AM Deane contributed equally to the conception and design of the research; ES George, R Judson and CM MacIsaac contributed to the design of the research; K Wittholz, M Clode, K Fetterplace contributed to the acquisition of the data; K Wittholz, K Fetterplace and JJ Presneill contributed to the analysis and the interpretation of the data; K Wittholz, K Fetterplace and AM Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Conflicts of interest

No funding was received for this study. K Fetterplace has received conference, travel grants and/or honoraria from Baxter, Abbott, Fresenius Kabi, Nutrica and Nestle Health Science (not related to this study). AM Deane or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study). The other authors have no potential conflicts to declare.

6.3 Abstract

Background: Functional recovery is an important outcome for those that survive critical illness. The aim of this study was to assess nutrition provision and nutrition related outcomes in a multi-trauma cohort following intensive care unit (ICU) discharge.

Methods: A prospective cohort study of patients discharged from the ICU alive who had been admitted because of major trauma and required mechanical ventilation for at least 48 hours. Nutrition-related outcomes including body weight, quadriceps muscle layer thickness (QMLT), handgrip strength and subjective global assessment were recorded on ICU discharge, day 5-7 post ICU discharge and then weekly until hospital discharge. Nutrition intake was recorded for 5 days post ICU discharge. Unless otherwise stated, data are presented as mean (SD).

Results: Twenty-eight patients [75% males, 55 (22.5) years] were included. Intake met 64% (28%) of estimated energy and 72% (32%) of protein requirements over the 5 days post ICU discharge, which was similar to over the ICU admission. From ICU admission to hospital discharge the mean reduction in weight was 4.2 kg (95% CI 2.2 to 6.3, $p < 0.001$) and after ICU discharge, the mean reduction in weight and QMLT were 2.6 kg (95% CI 1.0 to 4.2, $p = 0.004$) and 0.23 cm (95% CI 0.06 to 0.4, $p = 0.01$) respectively.

Conclusion: Patients received less energy and protein than estimated requirements after ICU discharge. Weight loss and reduction in QMLT also occurred during this period.

Key words: nutrition, multi-trauma, intensive care unit, muscle mass and feasibility

6.4 Introduction

Functional ability and health-related quality of life are important outcomes for those that survive critical illness (Desai et al., 2011; Kean et al., 2017). An intensive care unit (ICU) admission can lead to rapid reductions in muscle mass and substantial muscle weakness (Desai et al., 2011; Fan et al., 2014; Puthucheariy et al., 2013) and changes in body composition have been associated with prolonged hospital admissions, reductions in post-hospital discharge functional recovery and diminished health-related quality of life (QOL) (Desai et al., 2011; Fan et al., 2014; Fetterplace et al., 2018; Puthucheariy et al., 2013; Wei et al., 2015).

Nutrition has been identified as a potential modifiable factor which may aid in the preservation of skeletal muscle during critical illness and help to restore muscle lost in the recovery phase (Bear et al., 2017; Heyland et al., 2016; Puthucheariy et al., 2018). However, the amount, type and phase of critical illness, or recovery which nutrition support will have greatest impact, remain unknown (Bear et al., 2017; Heyland et al., 2016; Puthucheariy et al., 2018). Various nutritional interventions have been administered within the ICU with the objective of attenuating muscle loss and functional weakness but the impact has been inconsistent (Casaer et al., 2013; S. Ferrie et al., 2016; Fetterplace et al., 2018). This may be because the interventions chosen are of limited or no benefit, the period that the nutrition intervention is provide is not ideal for the substrate to be utilised, the period of the ICU admission is too brief to obtain benefit or that the studies to date have not been sufficiently powered to detect a difference (Bear et al., 2017). It has been suggested that nutritional interventions administered after the acute phase of critical illness may have greater impact (Bear, Parry, et al., 2018; Bear et al., 2017; Walsh et al., 2015; Wischmeyer & San-Millan, 2015). However quantifying nutritional intake and nutrition-related outcomes after ICU discharge is likely to be more challenging due to a variety of factors including equipment and personnel availability, challenges in accurately quantifying volitional ingested nutrient intake, and less predictable timing of discharge from hospital (Chapple et al., 2016; Chapple et al., 2017; Ridley et al., 2019).

One cohort of patients that may benefit from a nutritional intervention post-ICU discharge are those admitted because of severe traumatic injuries. After a traumatic injury, patients can have elevated energy expenditure and increased protein catabolism (Genton & Pichard, 2011; Monk et al., 1996), which is likely to continue post ICU and throughout recovery (Monk et al., 1996; Wade et al., 2015). Despite patients with traumatic injury frequently being prescribed more energy and protein than non-trauma patients in ICU (Plank & Hill, 2000), substantial cumulative nutritional deficits have been observed during ICU for this cohort (Chapple et al., 2017; Plank & Hill, 2000).

There are limited data reporting nutrition intake and nutrition-related outcomes after ICU discharge. The primary aim of this study was to determine the feasibility of repeatedly assessing nutrition intake and measuring nutrition-related outcomes (weight, nutritional status, muscle mass and strength) in a cohort of patients with traumatic injury following ICU discharge. Secondary aims were to i) compare nutrition intake post ICU discharge to nutrition intake whilst in the ICU, ii) to determine whether post ICU discharge there were any differences between those receiving only oral intake compared to any artificial nutrition support and iii) to explore the relationships between nutritional intake and nutrition-related outcomes.

6.5 Materials and methods

This cohort study was conducted in one of the two trauma referral centres that receive all major adult trauma for the state of Victoria (population approximately 6.3 million). Between July to September 2018, all patients admitted to the ICU due to a traumatic injury who were ≥ 18 years old and mechanically ventilated for at least 48 hours were screened for eligibility. Recruitment occurred on the day of discharge from the ICU. Patients were excluded if on discharge to the ward they had impaired neurology (defined as best motor score of abnormal flexion or worse), bilateral upper arm injury, or the goal of treatment was altered to include a focus on palliative care. Reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2014). This project was approved by the Melbourne Health Human

Research Ethics Committee (QA2018048). Eligible patients, or their person responsible (if they were unable to comprehend written information), were provided with written information regarding the study and they were given the opportunity to opt out from inclusion in the study.

Data were collected from ICU discharge and censored 26 days after ICU discharge or on hospital discharge, whichever came first (figure 1). Baseline demographic data and patient characteristics were collected from the ICU admission. Routine care in this ICU includes that all patients who are mechanically ventilated for ≥ 48 hours and are receiving nutritional therapy are assessed by an ICU dietitian. Protein and energy requirements were based on the dietitians' assessment in the ICU and post ICU discharge. Estimated nutritional requirements were calculated using actual body weight for patients below or within the ideal body weight (IBW) range (Body mass index (BMI) $18.5 - 25\text{kg/m}^2$ and for those aged ≥ 65 years BMI $22 - 27\text{kg/m}^2$) (Suzie Ferrie & Ward, 2007). For overweight participants IBW was used and for obese participants with a BMI greater than 30kg/m^2 , an obesity adjusted weight was used ($\text{IBW} + 25\% (\text{actual body weight} - \text{IBW})$) (Suzie Ferrie & Ward, 2007).

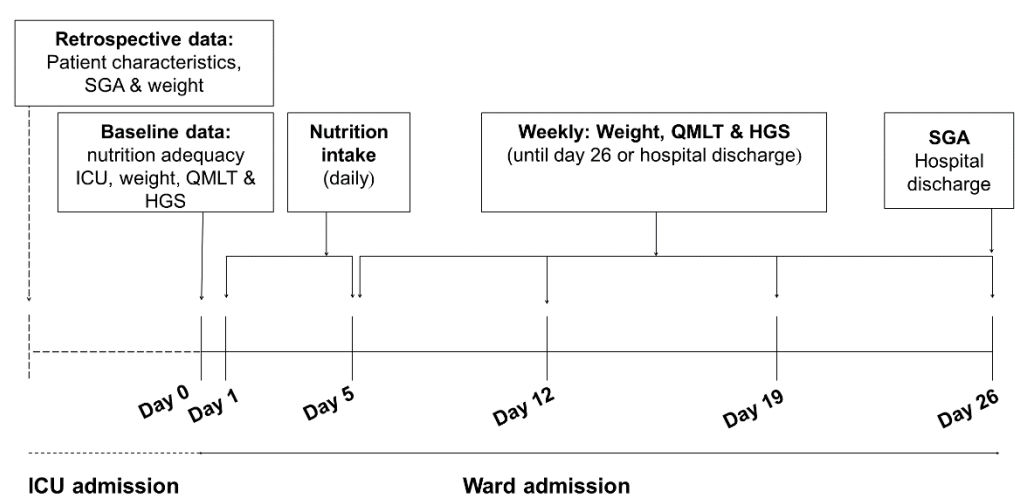


Figure 6-1. Outcome Measurement Procedure

Abbreviations: HGS; handgrip strength, QMLT; Quadriceps muscle layer thickness, SGA; subjective global assessment

6.5.1 Nutrition-related outcomes

Nutrition intake over the ICU admission was retrospectively determined from fluid balance charts, through daily analysis of enteral and parenteral nutrition delivery. Energy provided from other sources (e.g. intravenous propofol and glucose as part of fluid therapy) were not included and discarded gastric residual volumes were not subtracted from energy provision.

Ward nutrition intake was collected for five days post ICU discharge. Diet orders, nutrition consumed and mode of nutrition delivery were recorded daily. For patients receiving artificial nutrition, fluid balance charts were reviewed to determine protein and energy intakes. For patients with volitional intake, the proportion of each component of the meal consumed (using visual estimates of 0%, 25%, 50%, 75% or 100%) was recorded in the Mobile Intake™ data application in the hospitals electronic menu management system (CBORD™, The CBORD group, New York). If a meal period was not able to be assessed by a dietitian, food record charts, completed by nursing staff including visual estimates of meals consumed, or patient reported intake, were used to estimate the food intake. The hospital menu management system CBORD™ was used to analyse protein and energy intake using the 2011-2013 AUStralian Food and NUTrient (AUSNUT) database.

The ward (5 days) and ICU energy and protein adequacy were calculated in the same way, daily intake was compared to dietitian estimated requirements, and averaged over the study period; the ICU adequacy excluding the day of ICU admission and discharge if it was less than 12 hours.

Nutrition-related outcomes including weight and muscle mass and strength were recorded at baseline (within 48 hours of discharge from the ICU), day 5-7 post ICU discharge and then weekly thereafter.

Weight on admission to ICU was recorded using bed scales (Hill-Rom[®], Indiana USA) for the majority of patients. If it was not physically possible to weigh the patient on admission, family reports were used for the admission weight. Post ICU weight was measured using standing scales (Seca 876, Hamburg, Germany), chair (Colonial BW1122, Melbourne, Australia) or hoist scales (Ajour Maxi Move L8038, Malmö, Sweden) depending on the patient's injury type and mobility. Weight change was calculated as the difference in weight from ICU admission to ICU discharge and to hospital discharge.

Muscle mass was assessed using an ultrasound to measure quadriceps muscle layer thickness (QMLT). QMLT measurements were performed using a portable ultrasound machine (Sonosite S-ICU) with a multiple-frequency transducer (13-6 MHz, 6 cm) using the technique initially described by Tillquist and colleagues (Chapple et al., 2017; Fetterplace et al., 2018; Tillquist et al., 2014). Measurements were taken with the patient lying supine with leg relaxed and in extension and the bedhead elevated at approximately 30 degrees. QMLT was measured unilaterally (on the right side unless contraindicated due to injury or impairment) at two points; the midpoint between the anterior superior iliac spine and the upper pole of the patella and at the point two thirds between the anterior superior iliac spine and the top of the patella. A still image was taken with minimal pressure and then again with maximal pressure applied. The measurements were taken twice for each point and then the four measurements were averaged to obtain the final QMLT measurement. A third measure was taken if there was a difference of >10% between the first two measurements, and the measurement with greater than a 10% difference was discarded.

A trained dietitian used handgrip dynamometry (JTECH Medical Commander Echo Dynamometer) to assess upper limb muscle strength bilaterally (Vanpee et al., 2011). Patients were assessed in a seated position, in a chair where possible or sitting at least at 45 degrees in bed, with their forearm in flexion at 90 degrees and wrist in extension, supported by the arm of the chair or a pillow. Patients were asked to perform a maximal voluntary isometric contraction and maintain the contraction for 3–5 seconds. Three

consecutive isometric contractions with 30-60 second of rest in between test were completed and the highest measurement was recorded.

The Subjective Global Assessment (SGA), was used to assess nutritional status (Detsky et al., 1987). Patients were categorised as well nourished (Score A), mild to moderately malnutrition (Score B) or severely malnourished (Score C). As part of usual care at the study institution, the SGA is completed by ICU dietitians on initial assessment (within 48hrs of admission). This score was then retrospectively extracted from the notes of eligible patients. The SGA was subsequently repeated at hospital discharge by the trained research dietitian.

6.5.2 Feasibility

Feasibility was determined through retention of study participants for at least 5 days post ICU. Feasibility was predefined as >75% of eligible participants completing 5 days of intake data and having ≥ 1 repeat measure recorded.

6.5.3 Statistical analysis

Continuous and interval data were reported as means (standard deviations, SD) and/ or medians [inter-quartile ranges, IQR] as appropriate. Proportions were used to summarise ratios, and malnutrition was compared over time with McNemar's test accompanied by a 95% confidence interval. Initial univariable exploration of differences in continuous measures over time used the construction of trajectory plots, followed by paired t-tests. Changes in QMLT over time were explored using a population-averaged multivariable linear model with a generalised estimating equation (GEE) approach, an exchangeable working correlation structure and robust standard error estimates accounting for clustering within individual subjects. Independent variables included baseline QMLT, protein adequacy, BMI, presence of traumatic brain injury, age at or above 65 years, and the patient's ICU admission APACHE II severity of illness score. A two-sided p value of <0.05 was set for statistical significance for all tests, with no adjustment for multiple

testing. Data analysis was carried out using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics Premium Grad Pack Version 23.0) and Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LP).

6.6 Results

During the 4-month study period 67 patients were screened for inclusion, 32 (47%) met all inclusion and no exclusion criteria, and 28 (42%) patients agreed to participate (figure 2). Study participant characteristics are described (table 1).

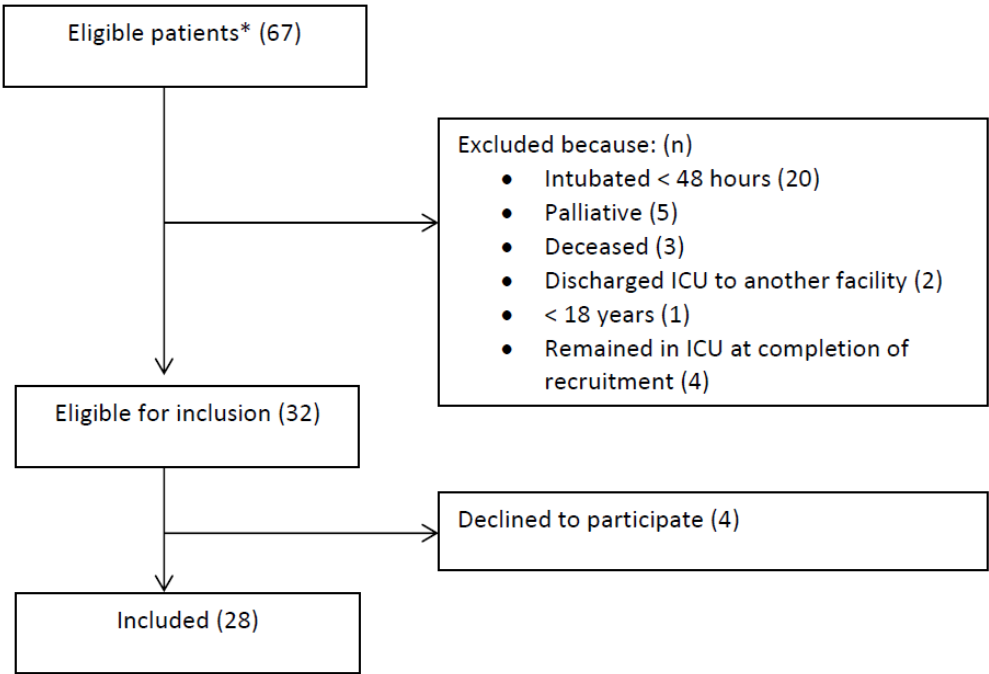


Figure 6-2. Consort diagram

*Eligible patients were those admitted to the ICU due to a traumatic injury

Table 6-1. Patient characteristics

Patient Characteristics (n = 28)	Value
Age – year, mean (SD)	50 (22.5)
Males – n (%)	21 (75)
Length of Stay, mean (SD)	
ICU	10.6 (6.7)
Ward	10.9 (9.2)
Total hospital	21.6 (11.8)
Mechanical Ventilation – days, median [IQR]	6.0 [3.0-9.5]
Injury – n (%)	
Multi-trauma	16 (57)
Multi-trauma with TBI	12 (43)
APACHE II score, mean (SD)	15 (6)
APACHE III score, mean (SD)	111 (55)
Body Mass Index – kg/m ² , median [IQR]	26 [25-32]
Body weight ICU admission – kg, mean (SD)	86 (23)
Malnourished – SGA B/C, n (%)	3 (11)

Abbreviations: APACHE; acute physiology and chronic health evaluation, ICU; Intensive Care Unit, IQR; Inter Quartile Range, Kg; kilogram, SD; Standard deviation; TBI, Traumatic Brain Injury, SGA; Subjective global assessment.

During ICU admission participants received 62 (17) % and 63 (19) % of estimated energy and protein requirements. At ICU discharge 19 (68%) of participants were receiving exclusive oral intake, five (18%) participants were on a combination of oral diet and enteral nutrition (EN) via a feeding tube, three (11%) participants were receiving exclusive EN via a feeding tube, and one (4%) patient was receiving a combination of EN and parenteral nutrition (PN).

Over the 5 days post ICU discharge that nutritional intake was observed, there were a total of 120 days (85% of all days) of data available, with all missing data due to patient discharge from hospital (table 2). Daily energy and protein intake were 1478 (651) kcal and 75 (37) grams, which equated to 64 (28) % and 72 (32) % of estimated energy and protein requirements (Figure 3). There were no statistical group differences in either energy [-3 % (95%CI -15 to 10), p = 0.66] or protein adequacy [-10 % (95% CI -25 to 5), p = 0.19] between ICU admission and post ICU periods.

Patients receiving solely oral intake consumed less energy and protein compared to patients receiving any artificial nutrition support (oral diet plus EN, EN alone or EN plus

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PN); the mean energy and protein intakes were 1298 (640) kcal and 68 (39) grams and 1857 (524) kcal and 89 (30) grams respectively. The between group difference was statistically significant for daily energy [mean difference 558 kcal (95% CI 53 to 1062), $p = 0.03$] but not protein [mean difference 22 g (95% CI -8 to 51), $p = 0.15$]. Compared with dietitian prescriptions, patients on any artificial nutrition received a mean adequacy of 87 (14) % of energy and 87 (17) % of protein compared to those on oral diets who consumed a mean adequacy of 54 (26) % of energy and 65 (36) % of protein.

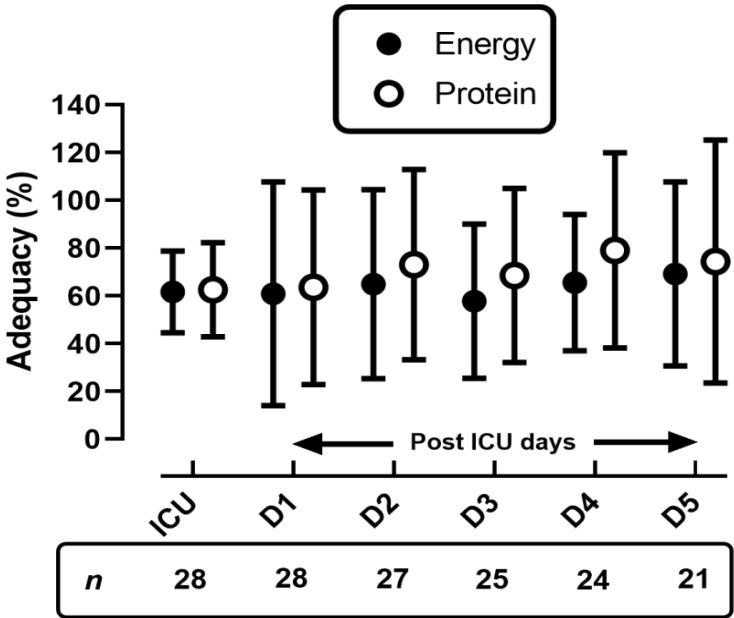


Figure 6-3. Mean daily energy and protein adequacy for the ICU admission and the first 5 days post ICU discharge

*Error bars represent mean and standard deviation; (n) represents the number of participants included at each time point.

Nutritional intake data and the measurement of nutritional status using the SGA were both found to be feasible outcomes measures, however the other nutrition-related outcome measures (weight, QMLT and handgrip strength) were not found to be feasible in this cohort (table 2).

Table 6-2. Feasibility of outcome measures

Variable	Baseline ⁺ n (%)	Day 5 post ICU discharge n (%)	At least ≥ 1 time point	Met feasibility criteria (Y/N)
Weight	25 (89)	13 (46)	15 (54)	N
QMLT	27 (97)	18 (64)	18 (64)	N
Handgrip Strength	17 (61)	12 (43)	14 (50)	N
Subjective Global Assessment	28 (100)	NA	28 (100)	Y
Intake -days [†]	NA	120 (85)	NA	Y

Abbreviations: ICU; intensive care unit, QMLT; quadriceps

⁺Baseline: within 48 hours of ICU discharge

⁺⁺SGA completed at baseline and hospital discharge.

[†]Intake days: number of days intake data was recorded for the first 5 days post ICU discharge.

The proportion of participants observed to be malnourished increased from ICU admission to hospital discharge, however this was not found to be statistically significant [3/28 (11%) versus 7/28 (25%), change 14% (95%CI -2 to 31), p = 0.13]. Of the participants who had weight measured at ICU admission and ICU discharge (n = 25), there was a significant reduction in weight [mean reduction 2.3 kg (95% CI (0.5 to 4.2), p = 0.02], with the mean percentage loss of weight over this period of 3.9 (4.6) %. From ICU admission to hospital discharge the mean reduction in weight was 4.2 kg (95% CI (2.2 to 6.3, p < 0.001), with a significant loss of weight also observed over the first five days post ICU (table 3).

Table 6-3. Change in nutrition related outcomes from ICU discharge to day 5 post ICU discharge

Variable	n	Baseline ⁺ Mean (SD)	Day 5 post ICU discharge, mean (SD)	Mean difference (95% CI)	P-Value
Body weight – kg	13	83.6 (16.1)	81.0 (16.2)	-2.6 (-0.98 to -4.2)	0.004*
Handgrip strength – kg	10	27.9 (9.5)	30.1 (11.1)	2.3 (0.22 to 4.3)	0.034
QMLT no pressure – cm	18	2.8 (0.8)	2.6 (0.8)	-0.23 (-0.06 to -0.40)	0.01*

Abbreviations: cm; centimetres, kg; kilograms, ICU; intensive care unit, QMLT; quadriceps muscle layer thickness.

⁺Baseline: within 48 hours of ICU discharge

Quadriceps muscle layer thickness (QMLT) was measured on more than one occasion post ICU discharge in 18/28 patients (64%) (table 2). There was a significant reduction in mean QMLT (no pressure) over ward admission by 0.23 cm (95% CI (0.06 to 0.40), p = 0.01) (table 3) and the mean percentage reduction was 7.2 (13) %. Change in QMLT (no pressure) for individuals over time is shown in supplementary figure 1. Mean change in QMLT over time was associated with greater baseline QMLT and a greater number of days post ICU discharge (table 4). There was no significant association found between change in QMLT and age, BMI, severity of illness on admission to the ICU, presence of a traumatic brain injury or ICU or ward protein adequacy. There was a significant improvement in handgrip strength from baseline to day five post ICU discharge in the group of participants (n =10) who had two measurements completed (table 3).

Table 6-4. Effect estimates from multivariable linear model assessing change in QMLT from baseline to hospital discharge

Variable	Coefficient of effect ⁺	95% CI	P value
QMLT Baseline, cm	0.88	0.79 to 0.96	<0.001
ICU protein adequacy, per 10%	-0.04	-0.07 to 0.002	0.06
Number of days post-ICU discharge	-0.04	-0.05 to -0.02	<0.001
BMI ≥ 30kg/m ²	0.07	-0.08 to 0.2	0.37
Presence of a traumatic brain injury	0.05	-0.05 to 0.15	0.31
Age ≥ 65 years	-0.02	-0.13 to 0.09	0.69
APACHE II score on admission, per 5 points	0.02	-0.04 to 0.07	0.59

Abbreviations: QMLT; quadriceps muscle layer thickness, ICU; Intensive Care Unit, BMI; Body Mass Index, APACHE; acute physiology and chronic health evaluation.

⁺All reported effect estimates are adjusted for all other variables in the table within a multivariable linear model, using a generalised estimating equation approach (refer to statistical analysis methods for details)

6.7 Discussion

In this single-centre cohort study of patients with a traumatic injury who were discharged from ICU, patients received less energy and protein than it was estimated that they required. Energy and protein provision and nutritional adequacy on the ward were similar to what was provided during the ICU admission; however, patients receiving artificial nutrition support post ICU discharge had improvements in energy and protein provision. It was also observed that after ICU discharge a significant reduction in weight and QMLT occurred. According to the pre-defined criteria, missing data limited feasibility for several nutrition-related outcomes.

The results observed in the present study are similar to several studies conducted in the ICU, with patients receiving approximately 60% of their nutritional targets (Cahill et al., 2010; Elke et al., 2014; Reid, 2006; Ridley et al., 2018). Whilst few studies have reported nutritional adequacy after ICU discharge, in a single-centre study of 37 patients with

traumatic brain injury by Chapple and colleagues, patients received similar nutritional adequacy in ICU and after ICU discharge (Chapple et al., 2016). However, they observed greater energy and protein provision in both settings than the present study, with patients receiving 81% (35) of energy and 77 % (35) of protein requirements after ICU discharge. These differences could be related to the different patient cohorts and the proportion of patients with traumatic brain injury who require artificial nutrition after ICU discharge rather than consuming oral intake. In the present study it was observed that patients who received any artificial nutrition had significant increases in energy but not protein adequacy in the post ICU period compared to those receiving oral intake alone. These results are similar to that observed by Chapple and colleagues who described less intake in those reliant solely on oral diet (Chapple et al., 2016). Additionally, Peterson and colleagues examined oral nutrition intake via multi-pass 24 hour food recall for 7 days post extubation in a single centre cohort of 50 critically ill patients (Peterson et al., 2010); they observed that mean energy and protein intake never exceeded 55% of daily requirements (Peterson et al., 2010). These results highlight that nutritional inadequacy persists in the cohort of patients after traumatic injury, and patients receiving oral intake alone are possibly at greatest risk of nutritional inadequacy in ICU and the post ICU period. This may be due to early withdrawal of artificial nutrition support or that hospital systems do not support achieving nutritional adequacy during periods of volitional oral intake (Merriweather et al., 2014). Further research is warranted to understand why nutritional inadequacy persists after ICU discharge and how to improve nutritional adequacy throughout the entire hospital admission (Ridley et al., 2015).

In the present study nutrition-related outcome data for weight, QMLT and handgrip strength were not recorded in sufficient numbers to meet the pre-defined feasibility criteria. Patient factors, including delirium, agitation, and post-traumatic amnesia; hospital factors, including appropriate equipment availability, multiple procedures and scans; early discharge; and research resource allocation all contributed to missing data. It has been reported that the prevalence of cognitive impairment after a traumatic brain injury is up to 70% (Vaishnavi et al., 2009), and this may affect capacity to complete some of the outcome measures. Therefore, outcome measures, which do not require participation,

volitional movements and cooperation such as QMLT are probably more feasible in this population, rather than handgrip strength and functional capacity and quality of life (Bear, Griffith, et al., 2018). Although the frequency of QMLT measurements did not achieve the predefined feasibility criteria, it was successfully measured in 64% of participants and, of the missing data, five (14%) participants were discharged prior to the first repeat measure time point (day 5 post ICU). These results are similar to that reported by Chapple and colleagues, who measured QMLT weekly post ICU in 79% of their TBI cohort (Chapple et al., 2017; Tillquist et al., 2014). Evidence from these two centres therefore supports the concept that QMLT is perhaps the most feasible variable to repeatedly measure in this population when attempting to evaluate the impact of nutritional therapies on body composition.

It remains unclear what, if any, impact energy and protein provision in the ICU or following ICU admission has on patient-centred and nutrition-related outcomes (Bear et al., 2017). In the present study it was observed that there was a significant reduction in weight and QMLT over the study period, however there was no evidence found to suggest that greater protein provision was associated attenuation of QMLT loss. Similarly in a previous multi-centre observational study (UK MUSCLE), they reported that greater loss of quadriceps muscle was associated with greater protein delivery in ICU (Puthuchearry et al., 2013). However in contrast to this observed association, other cohort studies (Allingstrup et al., 2012; Nicolo et al., 2016), and a recent randomised control trial by our group, report that greater protein delivery is associated with attenuation of muscle loss in ICU (Fetterplace et al., 2018). These conflicting results highlight the issues with interpreting associations in observational studies of critically ill cohorts, particularly as severity of illness is a confounder that may not be adequately accounted for. Whilst muscle thickness and body composition outcomes are only surrogate physiological outcomes for outcomes that are important to patients, Chapple and colleagues reported that greater QMLT at hospital discharge was associated with significant improvements in self-related quality of life three months after hospital discharge (Chapple et al., 2017). Further research is required to evaluate the impact of nutritional therapies on functional outcomes post discharge from hospital (Bear et al., 2017; Ridley et al., 2015).

This is the first study to evaluate the feasibility of measuring nutrition-related outcomes and nutritional intake in patients with multiple injuries following trauma after ICU discharge. Nutritional intake was measured using meal observations and an electronic menu management system and nutritional outcomes such as muscle mass, muscle strength and nutritional status were recorded. However, there are several limitations, including that this was a single centre study and a relatively small number of patients were studied. Moreover, the size of the cohort was not sufficient to determine whether nutrition-related outcomes were affected by nutritional adequacy, and due to the observational nature, causality cannot be established for any associations observed. Data collection was limited to weekdays and the acute hospital admission. Increasing the resource allocation and study timeframes in future interventional studies may increase sample size and data completeness and consideration should be given to include outcome data from admissions to rehabilitation facilities. It was also not within the scope of this study to examine the feasibility of measuring nutrition-related outcomes post hospital discharge. With recovery from acute illness, patient participation in outcome measures may increase and therefore increase their utility.

6.8 Conclusions

Mean energy and protein intake were below the estimated requirements, and were similar during the ICU admission and after ICU discharge; however, patients receiving artificial nutrition support received greater amounts of energy. Within the limitation of missing data, weight loss and reductions in QMLT were observed after ICU discharge. Greater change in QMLT was associated with greater baseline QMLT and the length of ward admission. The most appropriate outcome measures to investigate associations between nutrition provision and recovery remains unclear and warrants further investigation. Well-designed and adequately powered randomised clinical trials are required to determine the effect of greater nutrition provision on nutrition-related outcomes in patients discharged from ICU after major trauma.

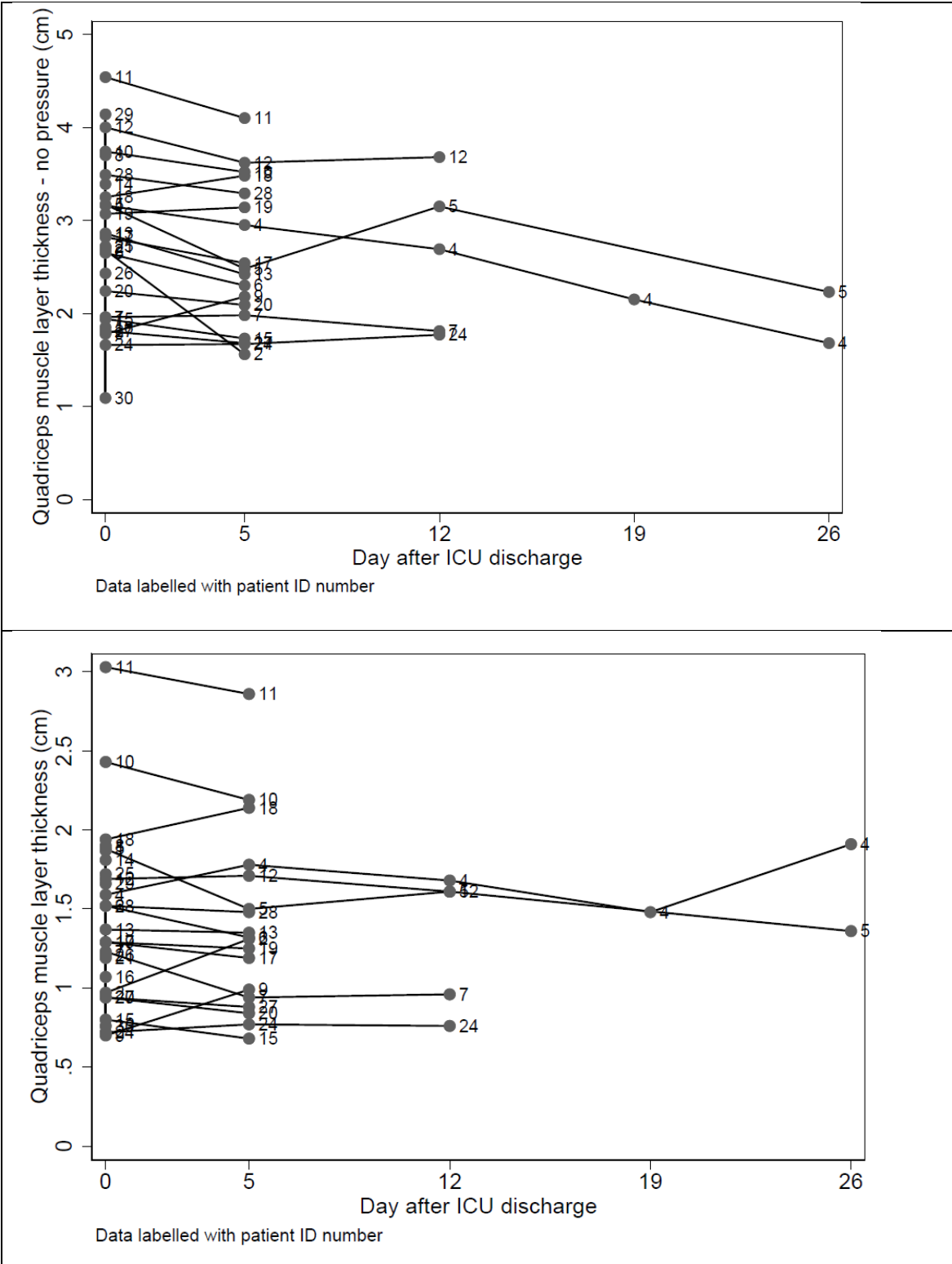
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6.10 Supplementary material for Chapter 6



Supplementary Figure 6-1. Quadriceps muscle layer thickness measurements over time post ICU discharge

Chapter 7: Methodology for a pilot randomised control trial assessing the feasibility of delivering greater protein and energy via enteral nutrition to critically ill patients

7.1 Chapter summary

This chapter provides the methodologies and design of the pilot RCT (Chapter 8). The RCT was the most substantial study completed as part of this PhD program. The protocol manuscript was published in 2018 prior to the completion of the trial. This chapter also provides a more detailed literature review than is allowed in a results manuscript, and summarises the methodology and the statistical analysis plan for the subsequent trial.

7.2 Methods for a pilot randomised control trial

Targeted full energy and protein delivery in critically ill patients: A study protocol for a pilot randomised control trial (FEED Trial)

Kate Fetterplace^{1,2}, Adam M. Deane^{3,4}, Audrey Tierney², Lisa Beach⁵, Laura D Knight⁵, Thomas Rechnitzer³, Adrienne Forsyth², Marina Mourtzakis⁶, Jeffrey Presneill^{3,4} and Christopher MacIsaac^{3,4}

1. Department of Clinical Nutrition, Allied Health, Royal Melbourne Hospital, Melbourne, Australia
2. Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne Australia
3. Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne Australia
4. Department of Medicine, The University of Melbourne, Melbourne, Australia
5. Department of Physiotherapy, Allied Health, Royal Melbourne Hospital, Melbourne Australia
6. Department of Kinesiology, Faculty of Applied Health Sciences, University of Waterloo, Ontario, Canada

Corresponding author

Ms Kate Fetterplace^{1,2}

Royal Melbourne Hospital

Phone: +61 3 9342 7440

Fax +61 93428440

Email: Kate.Fetterplace@mh.org.au

7.3 Abstract

Background: Current guidelines for the provision of protein for critically ill patients are based on incomplete evidence, due to limited data from randomised controlled trials. The present pilot randomised controlled trial is part of a program of work to expand knowledge about the clinical effects of protein delivery to critically ill patients. The primary aim of this pilot study is to determine whether an enteral feeding protocol using a volume target, with additional protein supplementation, delivers a greater amount of protein and energy to mechanically ventilated critically ill patients than a standard nutrition protocol. Secondary aims are to evaluate the effects of this feeding strategy on muscle mass and other patient-centred outcomes.

Methods: This prospective, single centre, pilot, randomised control trial will include 60 participants who are mechanically ventilated and can be enterally-fed. Following informed consent, participants receiving enteral nutrition in the intensive care unit (ICU) will be allocated using a randomisation algorithm in a 1:1 ratio to the intervention (high protein daily volume-based feeding protocol, providing 25kcal/kg and 1.5g/kg protein), or standard care (hourly rate-based feeding protocol providing 25kcal/kg and 1g/kg protein). The co-primary outcomes are the average daily protein and energy delivered to the end of day 15 following randomisation. Secondary outcomes include change in quadriceps muscle layer thickness (QMLT) from baseline (prior to randomisation) to ICU discharge and other nutritional and patient-centred outcomes.

Discussion: This trial aims to examine whether a volume-based feeding protocol with supplemental protein increases protein and energy delivery. The potential effect of such increases on muscle mass loss will be explored. These outcomes will assist in formulating larger randomised control trials to assess mortality and morbidity.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.ANZCTR.org.au/> Registration number U1111-1172-8563

Key words: nutritional support, enteral nutrition, nutritional requirements, dietary protein, amino acids, critical illness, critical care, Intensive care

7.4 Background

Nutritional therapy, preferably via the enteral route, is part of standard care for critically ill patients (McClave et al., 2016). Prominent critical care nutrition guidelines recommend that protein should be provided at a level of 1.2-2.0 g/kg/day, with possibly higher amounts for patients with multi-trauma, obesity and burns and greater than 80% of energy targets should be met (McClave et al., 2016); however, there is a lack of high-quality evidence to support these guidelines (Plank, 2013). Despite these and similar guidelines, nutritional delivery in the intensive care unit (ICU) is frequently less than these targets; observational data from a large international dataset suggests that critically ill patients only receive, mean SD, 43g $\pm$ 27 of protein and 1054kcal $\pm$ 717 of energy per day, which equates to approximately 50% and 60% of their protein and energy targets respectively (Heyland et al., 2011). More recent observational data from this dataset suggests that increasing protein delivery by 30g, or meeting greater than 80 percent of prescribed protein targets, is associated with greater survival, an increase in ventilator-free days and a shorter time to discharge alive from the ICU (Elke et al., 2014; Nicolo et al., 2016). In addition data from a prospective observational cohort study from a single centre suggested that the provision of more protein (greater than 1.5 g/kg/day) was associated with a reduction in mortality when adjusted for severity of illness and age (Allingstrup et al., 2012). Finally, observational study and preliminary trial data supporting the concept that increasing calorie delivery will improve outcomes (Alberda et al., 2009; Heidegger et al., 2013; Singer et al., 2011).

Standard enteral feeding regimens are generally based on an hourly target rate of administration of a selected formulation, calculated according to daily energy and protein targets (Reintam Blaser et al., 2017). Therefore, if interruptions to feed delivery occur, protein and energy targets are not met (Heyland et al., 2013). Furthermore, protein delivery is generally restricted by the composition of the enteral formula available because overall energy requirements mostly determine the volume of the formula prescribed. In a cluster randomised control trial, Heyland and colleagues reported that with a novel approach to feeding, including a volume based feeding protocol, delivery of protein increased by 14% (95% CI, 5–23%) and calories by 12% (95% CI, 5–20%)(Heyland et al.,

2013). However, theoretically volume based feeding protocols with protein supplementation may not achieve greater delivery of protein and energy to patients due to issues with feeding intolerance, as increased nutrient delivery, particularly protein, to the small intestine, stimulates the feedback loop to slow gastric emptying (Kar et al., 2016; Karamanlis et al., 2007). Therefore this approach may inadvertently decrease protein and energy delivery.

Beyond mortality, patient-centred functional outcomes in survivors of critical illness are increasingly being recognised as important variables that may be influenced by nutrition (Iwashyna & Deane, 2016; Summers et al., 2016). This includes muscle weakness, which is often described as Intensive Care Unit Acquired Weakness (ICUAW) (Poulson et al., 2009). Lower health-related quality of life (HRQoL) scores are associated with ICUAW, emphasising that weakness is important to patients (ANZICS, 2012; Cuthbertson B. H et al., 2010; Herridge, 2009). The loss of skeletal muscle has been identified as a crucial contributing factor to the development of ICUAW (Moisey et al., 2013; Wandrag et al., 2015), with ultrasound being a potentially useful and minimally-invasive modality to quantify muscle mass and muscle loss in the critically ill (Chapple et al., 2017; Paris et al., 2017; Tillquist et al., 2014).

Augmenting nutrient delivery, particularly increased protein delivery, has been proposed as an approach that may attenuate muscle loss associated with critical illness. At present, there is an absence of robust data to support this approach (Heyland et al., 2016) and recent studies have reported conflicting conclusions. (Allingstrup et al., 2012). Most recently, Ferrie and colleagues (S. Ferrie et al., 2016) performed a randomised controlled trial in parenterally fed patients. Amongst other outcomes they measured muscle mass and strength (S. Ferrie et al., 2016). This study of 119 critically ill patients, who were randomised to receive a target of either 0.8g/kg or 1.2g/kg protein per day with isocaloric parenteral nutrition, did not find strong evidence of a difference in the primary outcome of handgrip strength at day 7, but the observed point estimate was in the direction of benefit for those receiving greater protein delivery. Moreover, the augmented protein

intervention may have been associated with reduced fatigue and greater forearm muscle thickness using ultrasound (S. Ferrie et al., 2016). A retrospective observational study of 106 critically ill patients, by Ishibashi and colleagues, reported that protein intake above 1.5g/kg/day substantially reduced total body protein loss when compared to those who receive less than 1.1g/kg/day (Ishibashi et al., 1998). In contrast, Casaer and colleagues reported that greater calorie and protein administration, particularly when delivered via the parenteral route, reduced the quantity and quality of muscle and was associated with greater muscle weakness (Casaer et al., 2013). This negative signal was also described by Puthucherry and colleagues, who reported greater muscle wasting associated with increased protein delivery (Puthucherry et al., 2013).

At present there is conflicting evidence around the optimal protein provision to critically ill patients, including a lack of high-quality evidence, which includes patient-centred functional outcomes. This single centre pilot trial in mechanically ventilated critically ill patients, is part of a program to explore the influence of protein prescription on outcomes; aims to determine whether a volume-based enteral feeding protocol with additional protein supplementation delivers a greater amount of protein and energy than a standard nutrition protocol.

7.4.1 Study objectives

Co-primary

To determine whether a volume-based feeding protocol with supplemental protein effects the average daily protein and energy delivery, when compared to standard care in mechanically ventilated critically ill patients.

Secondary

To evaluate whether a volume-based feeding protocol with supplemental protein when compared to standard care:

- I. Improves overall protein and energy adequacy without increasing feeding intolerance or diarrhoea.
- II. Improves nutritional related outcomes including the incidence of malnutrition at ICU discharge or mid upper arm circumference change from baseline to discharge.
- III. Decreases the change in quadriceps muscle layer thickness (QMLT) from baseline to ICU discharge.
- IV. Decreases the incidence of ICUAW or alters muscle strength or physical function scores at ICU discharge.
- V. Alters the duration of the ICU admission, number of deaths and the requirement for discharge to a rehabilitation facility.

7.5 Methods and design

This pilot, single centre, single-blinded, parallel group, prospective randomised controlled trial has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) (Chan et al., 2013) and the Consolidated Standards for Reporting of Trials CONSORT guidelines (Schulz et al., 2010) (Fig. 1, study flow diagram. The study will be undertaken at the Royal Melbourne Hospital ICU, which is a university affiliated, tertiary referral, mixed medical-surgical-trauma ICU with 32-beds that has > 2,500 patients admitted per year.

7.5.1 Study participants

Sixty patients will be recruited within 48 hours of their index ICU admission. Screening commenced on 10th of August 2015 and is performed only on weekdays. Patients who meet the study criteria (Table 1.) will be eligible to participate. As all eligible patients are mechanically ventilated and unable to consent to participation, informed consent will be obtained from the person responsible as per local laws. Consent to continue in the trial will be obtained from the participant if they recover adequately and they are deemed competent. The protocol and consent process has been approved by the Royal Melbourne Hospital Human Research Ethics Committee (2015.048). The protocol is registered with Australian New Zealand Clinical Trials Registry (ANZCTR; U1111-1172-85630).

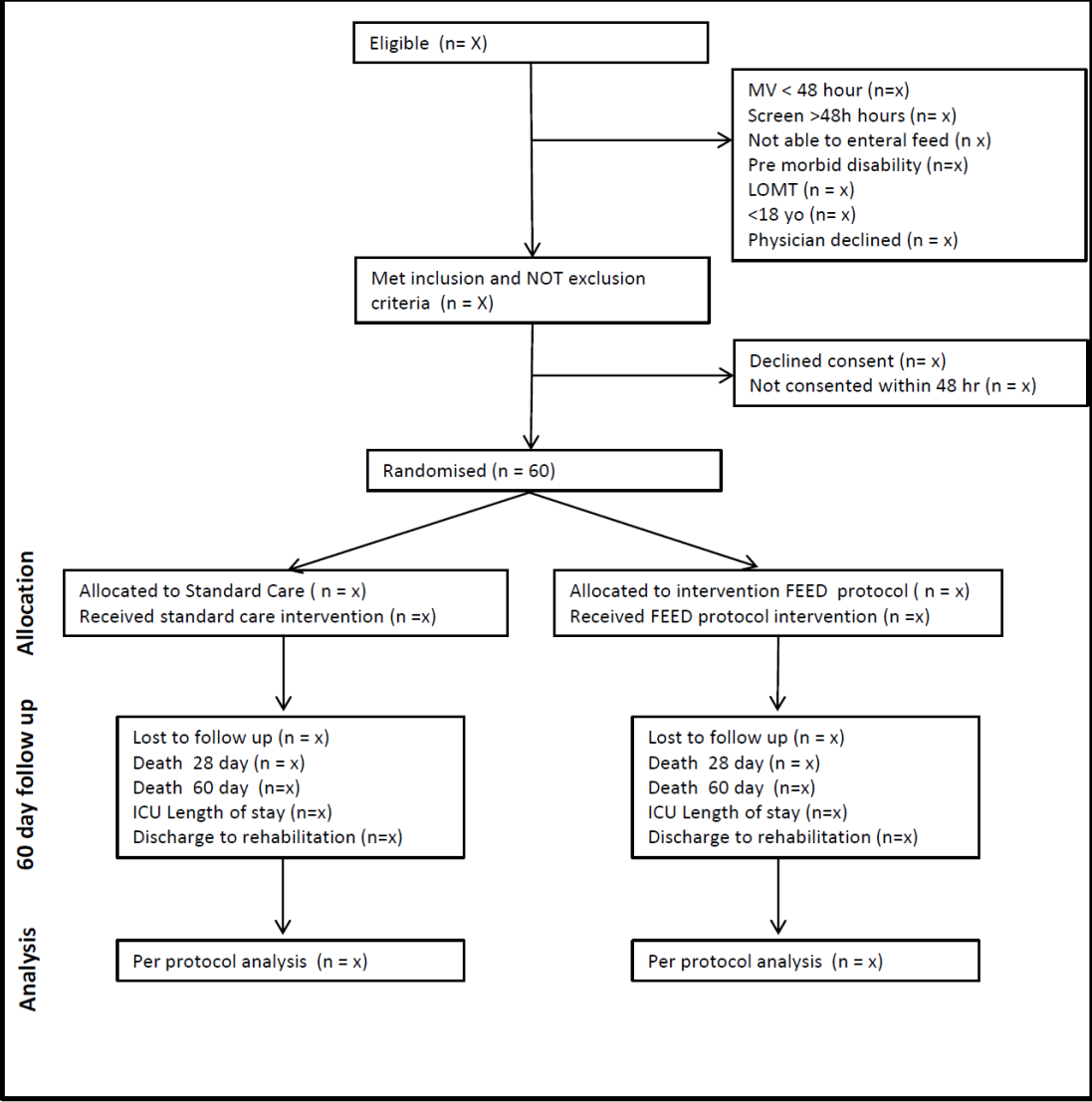


Figure 7-1. Study flow diagram; Flow diagram of patients recruited and study conduct

Abbreviations: MV; Mechanically ventilated, LOMT; Limit of medical treatment, yo; years old, FEED Protocol; intervention

Table 7-1. Inclusion and exclusion criteria

Inclusion	• Adults, ≥ 18 years of age • Mechanically ventilated (MV) for ≥ 48 hours with no immediate plans to extubate in the next 24 hours
Exclusion	• Patients who have a contraindication to enteral feeding • Limit of medical treatment order in place or imminent death • Pre-morbid disability causing inability to ambulate > 10m independently (+/- gait aid) • Pregnancy • The treating clinician considers the intervention not in the patient’s best interest or too burdensome

7.5.2 Baseline data collection

Baseline measurements will reflect the status of patients at or prior to randomisation. Demographic data includes admission diagnosis, comorbid illness including quantification using the Charlson Comorbidity Index (Charlson et al., 1987), Katz Activities of Daily Living (ADL) index (Katz et al., 1970) (prior to the ICU admission), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and admission Sequential Organ Failure Assessment (SOFA) Score. Baseline measures, collected by the study Dietitian, include height (using ulna length (Beach et al., 2017)) weight (from bed scales), Body Mass Index (BMI), mid upper arm circumference, nutritional status using the subjective global assessment (SGA) (Detsky et al., 1987; Marshall, 2008), plasma albumin, highest and lowest blood glucose in the first 24hours of ICU admission, independent dietitian estimation of energy (weight based or Schofield equation (S. Ferrie, Ward, M. , 2007)) and protein requirements and the first quadriceps muscle layer thickness measure (Tillquist et al., 2014). See table 3 for details of data collection.

7.5.3 Randomisation and blinding

We will use a simple randomisation system to assign participants [1:1] to receive either standard care or the intervention. Allocation will be concealed using sequentially numbered opaque sealed envelopes, held by research personal not involved with the study. If the participant or the person responsible wishes to withdraw consent at any time,

all study procedures will cease and the participant will receive standard ICU care as directed by the clinical team. Due to the nature of the intervention the study is single-blinded. However, outcomes of muscle strength and physical function will be measured by an investigator blinded to the group allocation. Data analysis will be performed using a binary treatment code to maintain group allocation of blinding until results are finalised.

7.5.4 Trial intervention and comparator

The intervention or standard care will be delivered following randomisation until ICU discharge; the patient no longer requires enteral tube feeding, or the end of day 15, with the day of randomisation being day 1. Tolerance of enteral nutrition will be assessed and managed similarly for both groups, with prokinetic drugs (metoclopramide 10 mg q.i.d. and erythromycin 200 mg b.d.) administered if gastric residue volumes at any time equal or exceed 300ml (Deane et al., 2009). The need for parenteral nutrition will be determined by treating clinical staff that are not investigators and are not aware of group allocations.

7.5.5 Standard care group

The comparator group will receive standard nutrition care (Peake et al., 2012), which includes commencing a standard commercially available 1.0kcal/ml enteral formula (Nutrison® 1.0kcal, Nutricia, Wuxi, China), providing 40g protein and 1000kcal per litre. Liquid nutrient will be commenced using our ICU nutrition protocol (Appendix 1), and the target rate will be set at 25 kcal/kg ideal body weight (IBW) (McClave et al., 2016). This strategy is designed to prescribe 1.0g/kg protein and 25 kcal/kg of energy per day, however it is anticipated participants will receive less than this due to interruptions to nutrition therapy (Peake et al., 2012). For participants below or within the IBW range (defined as a BMI between 18.5-25kg/m² for 18-65 years and 22-27kg/m² for ≥ 65 years ("National Health and Medical Research Council, *Australian Dietary Guidelines*," 2013) actual body weight will be used. For participants with BMI ≥ 32kg/m² an adjusted IBW will be used (IBW + 25% (Actual weight – IBW) (S. Ferrie & Ward, 2007).

7.5.6 Intervention group

The intervention group will receive their nutrition care based on the FEED protocol (Fig 2. FEED protocol). It is anticipated that this will provide 1.5g/kg protein and 25 kcal/kg of energy per day. The enteral formula will be a 1.25kcal/ml formula (Nutrison® Protein plus, Nutricia, Zoetermeer, The Netherlands), providing 1250kcal and 63g protein per litre. The target formula volume will be determined based on 25kcal/kg IBW and the difference between the protein provided from the enteral formula and the target protein requirement of 1.5g/kg IBW, will be calculated. This difference will be met using protein powder (Beneprotein®, Nestle Health Sciences, Switzerland), provided in 6g protein boluses (1 scoop of powder (7g), provides 6g of protein) over the day. Beneprotein® is a commercially available product that contains 100% whey protein isolate. To ensure that the target volume of formula is delivered, at 16:00 each day the ICU bedside nurse will calculate the volume of formula provided, compared to the target volume and then adjust the feed rate to aim to deliver the remaining feed volume over the eight hour period to midnight, with a maximum feeding rate of 150ml/hr (Heyland et al., 2013) Data on compliance to the feeding protocol will be collected.

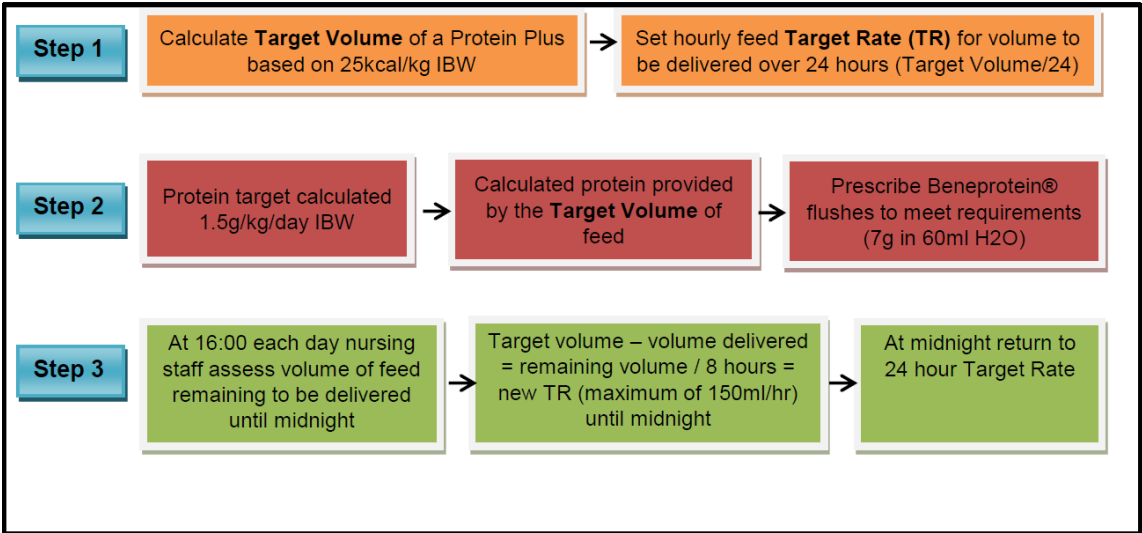


Figure 7-2. FEED protocol; how nutrition will be delivered in the intervention group

Abbreviations: kg; kilogram, IBW; Ideal body weight, g; gram, ml; millilitre, H2O; water.

7.5.7 Management of fluid overload

For both groups, if the attending intensivist wishes to reduce the volume of feed provided, the feed will be changed to Nutrison® Concentrate 2.0kcal/ml, (Nutricia, Zoetermeer, The Netherlands) with a goal to provide 25kcal/kg of energy. For the standard care group this will mean they will receive comparable protein delivery to the 1.0kcal formula. For the intervention group the protein supplementation will be increased in an attempt to achieve 1.5g/kg/day. These changes will be recorded.

7.5.8 Management of withdrawal

Stopping criteria are provided (Table 2) and any withdrawals will be recorded. Data will be retained and reported for all withdrawals where allowed by patient consent. Any adverse events will be recorded and reported.

Table 7-2. Criteria for withdrawal

Criteria	Measure
Feed intolerance	Tolerating < 40% of requirements via the enteral route for ≥ 3 days
Renal Failure	If eGFR is < 25% and the patient is not commenced on continuous renal replacement therapy within 2 days
Severe oedema	> 5 L positive fluid balance, without alternative way to manage fluid balance and attending physician assesses the feed volume and additional protein to be impacting on the patient’s treatment after the above volume considerations have been implemented
Diarrhoea	≥ 500ml per day or 5 bowel actions
Intensivist or attending Physician request	No parameter
Participant/person responsible request to withdraw	No parameter

7.5.9 Management of adverse events

It is not expected that any adverse events will occur in relation to the study protocol. However, each participant will be monitored regularly by study personnel for adverse events occurring throughout the study. If any adverse events do present, the nature, severity, causality and course of the adverse event will be recorded. Adverse events such as death, ischaemic bowel, renal failure, and diarrhoea will be recorded from the time of consent, if these events occur this will be discussed with the attending ICU consultant to determine if they may be related to the study. Any severe adverse events related to the study will be reported to the Melbourne Health Human Research and Ethics Committee within 24 hours of personnel becoming aware of it.

7.6 Outcome measures

Data collection and the outcome measures are summarised in Figure 3.

7.6.1 Primary outcomes

The co-primary outcomes are mean daily protein and energy provided over the 15-day study period. The provision of protein and energy will be calculated on a daily basis and will be determined taking into account all sources; this includes nutrition therapy (enteral formula, protein supplements and parenteral formula), dextrose and propofol. The mean protein and energy provided will be determined, by adding the daily provision over the 15-day study period (the 14 complete calendar days). The provision of any nutrition prior to commencing the study protocol will be collected and reported but not included in the primary outcome analysis.

7.6.2 Secondary outcomes

The first secondary outcome measurement is the change in muscle mass, determined as the change in QMLT using ultrasound from baseline to day 15 or ICU discharge if earlier. A portable ultrasound device (Sonosite S-ICU™) with a multiple frequency transducer (13-6MHz, 6cm) will be used to obtain muscle mass images. The method to obtain the images will be carried out as described by Tillquist and colleagues (Tillquist et al., 2014), with measurements completed using both minimal and maximal pressures. The first measure will be taken before randomisation, then on day 5, day 10 and at discharge or day 15 of ICU. A single trained operator will complete all QMLT measures, this technique has very good intrarater reliability in both healthy populations (Tillquist et al., 2014) and critically ill patients (Seger et al., 2015). The measurement will be completed on all participants, with bilateral measurements at two points; the midpoint between the Anterior Superior Iliac Spine (ASIS) and the upper pole of the patella and at the point two thirds between the ASIS and the top of the patella (Chapple et al., 2017; Paris et al., 2017; Tillquist et al., 2014), the landmarks will be marked using a permanent pen. A linear measure will be taken for each point twice, with minimal pressure and maximal pressure applied and the measures will be recorded (Paris et al., 2017). The device settings will be standardised for each measure, and bony landmarks will be used to determine if the transducer is oriented perpendicular to the muscle (Tillquist et al., 2014). Each image will be stored to the hard drive of the ultrasound device and then transferred for further blinded analysis at a later date. The change in QMLT from baseline to day 5 and discharge or day 15 will be calculated for each patient for the measurements taken with minimal pressure and maximal pressure separately.

The other secondary outcomes are: total calorie and protein provision, calorie deficit and protein adequacy, incidence of feed intolerance, number of days of feed intolerance, incidence of diarrhoea defined as more than 3 bowel actions or greater than 300ml per day (S. Ferrie & East, 2007), length of ICU stay, hospital mortality at 28 and 60 days, discharge destination, muscle strength, the incidence of ICU AW and physical function at ICU discharge and the change in nutritional markers over the study period. Nutritional markers include assessment of malnutrition using the Subjective Globe Assessment (SGA)

(Detsky et al., 1987), mid upper arm circumference (MUAC), and body weight. These measures will be carried out at baseline, day 5 and at discharge from ICU; the change from baseline to discharge or day 15 will be calculated. The presence of acute renal failure defined by the RIFLE criteria (Bellomo et al., 2004) and plasma urea and creatinine levels will be assessed on a daily basis.

Protein adequacy will be determined over the ICU admission or until day 15 by adding the daily protein provision and comparing this to the estimated protein requirements determined by the dietitian. The protein adequacy will then be explored in relation to the other outcome measures.

Calorie deficit will be determined using both predicted weight-based energy requirements (25kcal/kg). In eligible patients, calorie deficit will also be calculated using measured energy expenditure (MEE) (K. Fetterplace et al., 2019). Cumulative calorie deficit will be calculated over the ICU admission or until day 15 of the study. MEE will be assessed with indirect calorimetry using E-sCOVX (GE, Helsinki, Finland) (Sundstrom et al., 2013). The first MEE will be within 24 hours of enrolment into the study and repeated on day 3, day 5 and day 7 of the ICU stay. The measurements will be carried out with the patient in a fed state lying supine. The measure will be taken over a two-hour period and the summary data of respiratory quotient (RQ) and MEE will be recorded. The feeding rates will not be adjusted in relation to the MEE (Petros & Engelmann, 2001). Contraindications to carrying out a metabolic measurement will include if the patient is on continuous renal replacement therapy or extracorporeal membrane oxygenation (ECMO) or if the patient has an intercostal catheter with an air leak or is on a fraction of inspired oxygen greater than 0.6 (Petros & Engelmann, 2001). Feed intolerance will be determined as a single gastric residual volume > 300ml (Blaser et al., 2014).

Muscle strength will be determined in suitable participants using handgrip dynamometry and the Medical Research Council (MRC) scale (Baldwin et al., 2013; Hermans et al., 2012). The first muscle strength test will be performed at awakening (Hermans et al., 2012) and

then again at discharge or day 15, whichever comes first. Patients will be screened for attention and comprehension on the basis of their ability to follow commands, they will be considered awake if they score at least three out of five using the De Jonghe comprehension criteria on at least two occasions within a six hour period (De Jonghe et al., 2002) and have a Riker sedation-agitation scale score of three to five (Fraser & Riker, 2001). Handgrip dynamometry (Commander Echo™ Wireless Grip Dynamometer, USA) will be measured in both limbs with the participant in a chair or sitting at least at 45 degrees in bed, with the patients elbow at 90 degrees supported by a pillow or the arm of the chair. The Medical Research Council sum score (MRC-SS) will be measured as previously described (Beach et al., 2017; Ciesla et al., 2011; De Jonghe et al., 2002) with ICUAW defined as an MRC-SS of < 48/60 (Hough et al., 2011).

Physical function will also be assessed using the physical function in Intensive Care Test – scored (PFIT-s) (Denehy et al., 2013; Skinner et al., 2009). Patients may only be able to perform part of the test, but are still able to obtain a score.

7.6.3 Sample size

A sample size of 60 is based on observational data (K Fetterplace et al., 2014), where daily protein intake, mean (SD), was 50.8 g (20.1 g) protein per day, therefore 29 participants per group will provide 80% power (two-sided α 0.05) to detect a minimum difference of 15 g protein between groups. While there is limited data on change in muscle mass using ultrasound, using data from the VALIDUM study, mean (SD) QMLT of 1.3 (0.6) cm (Paris et al., 2017) a sample size of 28 participants in each group will also provide over 80% power to detect a mean difference of 0.5cm in QMLT.

7.6.4 Statistical analysis

All analyses will use an intention-to-treat approach. Baseline patient demographics, severity of illness, ICU length of stay, mortality and nutritional markers will be tabulated according to treatment group. Initial exploratory data analysis will involve calculation of

summary statistics, and comparison between treatment groups using non-parametric (Wilcoxon), parametric (t-test) and Fisher exact tests as appropriate, as well as construction of trajectory plots according to treatment group. The co-primary outcomes of average daily energy and protein delivery will be compared between treatment and control groups with two-sample unpaired t tests, with statistical significance for each set conservatively at two-sided values of 0.025 to limit the family-wise type 1 error for the two co-primary outcomes to less than 0.05 overall.

All secondary outcomes will be regarded as exploratory and hypothesis-generating, with no multiple comparison adjustment to conventional 5% type 1 error thresholds. Group differences for change from baseline at selected time points in continuous outcome variables, including QMLT, will be compared after adjustment for initial values using analysis of covariance (ANCOVA) regression models, initially unadjusted, and subsequently adjusted as described below for other regression models. Natural logarithmic transformations may be applied to stabilise variance within these or other linear models if appropriate. The relationships between calorie deficits using both prescribed calories (25kcal/kg) and MEE and protein adequacy and the outcome measures (QMLT change, muscle strength, diagnosis of ICUAW and physical function at ICU discharge) will be explored using linear or logistic regression analyses, with adjustment for likely confounders and any baseline variable found to show substantial imbalance between treatment groups. Finally, a population-averaged generalised linear model using a generalised estimating equation (GEE) approach with an unstructured working correlation matrix and robust standard error estimates adjusted for clustering within individual subjects will be applied to these longitudinal data to evaluate the overall associations of the vector of (untransformed or log transformed) outcome variables with treatment group across multiple time points. Multiple imputations for missing data may be used to support conclusions from other generalised linear models constructed without imputation of missing data. Data analysis will be carried out using the Statistical Package for the Social Sciences (SPSS) (IBM® SPSS® Statistics Premium Grad Pack Version 22.0) or Stata Corporation (Stata Statistical Software: Release 15. College Station, TX: StataCorp LP; 2017).

7.7 Discussion

It has been hypothesised that protein provision may be more important than energy provision for critically ill patients (Heyland et al., 2016). Optimal protein delivery may also influence functional outcomes via attenuation of muscle loss. However, the optimal amount of enteral protein required in critical illness is relatively unknown and has not been rigorously studied. Moreover, attempts to augment enteral protein delivery may result in slower gastric emptying, greater feeding intolerance and, thereby, paradoxically less protein and calorie delivery.

The strengths of this study include randomisation, comparing two different protein amounts using enteral nutrition, and assessment of the impact of nutrition provision on muscle mass and functional outcomes that is essential for planning a larger multicentre study.

This pilot study aims to clarify whether an enteral feeding protocol with a volume target and supplemental protein has potential to increase protein and energy delivery in mechanically-ventilated critically ill patients, and will provide preliminary estimates as to whether this intervention has the capacity to affect muscle mass or other patient-centred outcomes.

7.8 Declarations

7.8.1 Ethical approval and consent to participate

This study is being conducted in full accordance with the National Statement on Ethical Conduct in Human Research (2007), the Guidelines for Good Clinical Research Practice and Melbourne Health Research Policies and Guidelines. This study was approved by the Melbourne Health human research ethics committee (project number, 2015.048), on the 11th of May 2015 and was also approved by the La Trobe University Human Ethics

Committee on the 3rd of June 2015 under the same project number. As outlined above all eligible patients will be mechanically ventilated and unable to consent to participation, informed consent will be obtained from the person responsible as per local laws.

7.8.2 Availability of data and material

All data obtained during the study will be coded, de-identified and stored in a secure area of the Intensive Care Department at the RMH. Only the investigator and staff of the department will have access to the records

7.8.3 Funding

This project is supported by the Mary Elizabeth Watson Early Career in Allied Health Research Fellowship provided by Melbourne Health, which provides \$30,000 per year over two years.

7.8.4 Trial status

The trial commenced on the 10th of August 2015. Final recruitment is expected to be achieved by September 2017.

7.9 References

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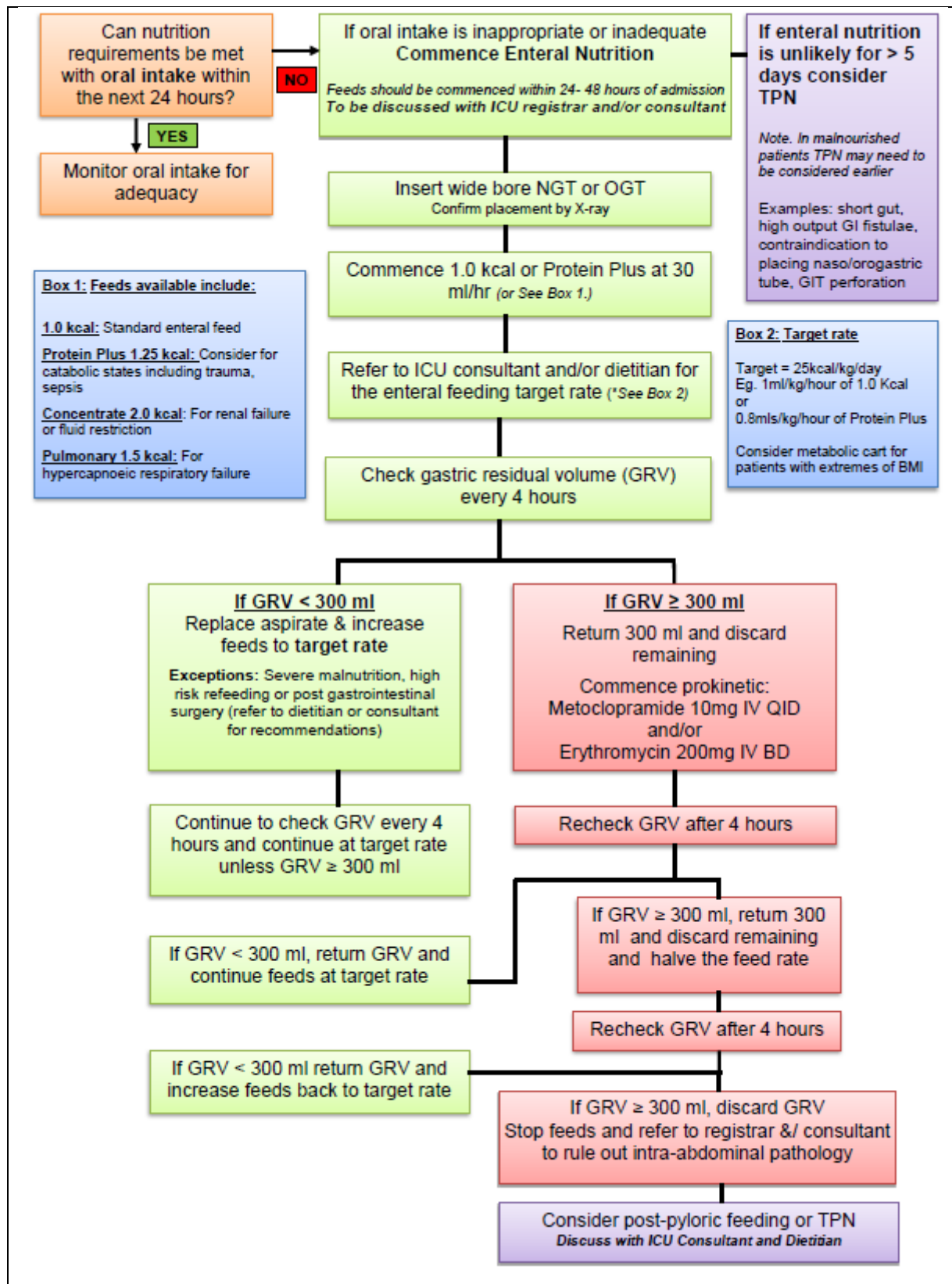
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7.10 Supplemental material for Chapter 7

Appendix 1: RMH enteral feeding protocol



Supplementary appendix 2: Nutrition study products

Nutrison

Nutrition Information		Per 100ml	Per 1000ml
Energy	kcal	100	1000
	kJ	420	4200
Protein	g	4 (16%E)	40
Casein	g	1	10
Whey	g	1.4	14
Soy	g	0.8	8
Pea	g	0.8	8
Carbohydrate	g	12.3 (49%E)	123
Sugars	g	0.7	7
as Lactose	g	<0.025	<0.25
Fat	g	3.9 (35%E)	39
Saturates	g	1	10
- of which MCT	g	0.6	6
Monounsaturates	g	2.2	22
Polyunsaturates	g	0.7	7
DHA	mg	14	140
EPA	mg	19.5	195
$\omega 6 / \omega 3$ ratio		2.9:1	2.9:1
Fibre	g	<0.1	<1
Water	ml	85	850

Minerals		Per 100ml	Per 1000ml
Sodium	mg	100	1000
	mmol	4.3	43
Potassium	mg	150	1500
	mmol	3.8	38
Calcium	mg	80	800
Phosphorus	mg	72	720
Magnesium	mg	23	230
Chloride	mg	125	1250
Ca:P ratio		1.1:1	1.1:1

Vitamins		Per 100ml	Per 1000ml
Vitamin A	$\mu\text{g-RE}$	82	820
Vitamin D ₃	μg	1	10
Vitamin E	mg- α -T.E.	1.3	13
Vitamin K	μg	5.3	53
Vitamin C	mg	10	100
Thiamin	mg	0.15	1.5
Riboflavin	mg	0.16	1.6
Niacin	mg NE	1.8	18
Vitamin B6	mg	0.17	1.7
Vitamin B12	μg	0.21	2.1
Folic Acid	μg	27	270
Pantothenic Acid	mg	0.53	5.3
Biotin	μg	4	40

Trace Elements		Per 100ml	Per 1000ml
Iron	mg	1.6	16
Zinc	mg	1.2	12
Manganese	mg	0.33	3.3
Copper	μg	180	1800
Iodine	μg	13	130
Molybdenum	μg	10	100
Selenium	μg	5.7	57
Chromium	μg	6.7	67
Fluoride	mg	0.1	1

Other		Per 100ml	Per 1000ml
 Carotenoids	mg	0.2	2
Choline	mg	37	370
Osmolality	mOsmol/kgH ₂ O	305	305

Nutrison Protein Plus

Nutrition Information		Per 100ml	Per 1000ml
Energy	kcal	125	1250
	kJ	525	5250
Protein	g	6.3 (20%E)	63
Casein	g	1.6	16
Whey	g	2.2	22
Soy	g	1.3	13
Pea	g	1.3	13
Carbohydrate	g	14.2 (45%E)	142
Sugars	g	0.9	9
as Lactose	g	<0.025	<0.25
Fat	g	4.9 (35%E)	49
Saturates	g	1.3	13
- of which MCT	g	0.8	8
Monounsaturates	g	2.7	27
Polyunsaturates	g	0.9	9
DHA	mg	21.2	212
EPA	mg	29.6	296
ω6 / ω3 ratio		2.7:1	2.7:1
Fibre	g	<0.1	<1
Water	ml	81	810

Minerals		Per 100ml	Per 1000ml
Sodium	mg	111	1110
	mmol	4.8	48
Potassium	mg	168	1680
	mmol	4.3	43
Calcium	mg	90	900
Phosphorus	mg	90	900
Magnesium	mg	28	280
Chloride	mg	80	800
Ca:P ratio		1:1	1:1

Vitamins		Per 100ml	Per 1000ml
Vitamin A	µg RE	102	1020
Vitamin D	µg	1.7	17
Vitamin E	mg α-T.E	1.6	16
Vitamin K	µg	6.6	66
Vitamin C	mg	13	130
Thiamin	mg	0.19	1.9
Riboflavin	mg	0.2	2
Niacin	mg NE	2.3	23
Vitamin B6	mg	0.21	2.1
Vitamin B12	µg	0.26	2.6
Folic Acid	µg	33	330
Pantothenic Acid	mg	0.66	6.6
Biotin	µg	5	50

Trace Elements		Per 100ml	Per 1000ml
Iron	mg	2	20
Zinc	mg	1.5	15
Manganese	mg	0.41	4.1
Copper	µg	225	2250
Iodine	µg	17	170
Molybdenum	µg	13	130
Selenium	µg	7.1	71
Chromium	µg	8.3	83
Fluoride	mg	0.13	1.3

Other		Per 100ml	Per 1000ml
 Carotenoids	mg	0.25	2.5
Choline	mg	46	460
Osmolality	mOsmol/kgH ₂ O	340	340

Protein Powder Supplementation:

Beneprotein®

Ingredients (unflavored): whey protein isolate (milk), soy lecithin

Nutrition Information (Unflavored)		1 Scoop Serving* (7 g)
Calories	kcal	25
Total Fat	g	0
Sodium	mg (mEq)	15 (0.65)
Potassium	mg (mEq)	30 (0.8)
Total Carbohydrate	g	0
Protein**	g	6
Calcium	mg	20

**One serving = 1 unpacked level scoop = 7 g = 1½ tablespoons of powder*
***PDCAAS = 100 (Protein Digestibility Corrected Amino Acid Score)*

Chapter 8: Results of a pilot randomised control trial delivering greater protein and energy in critically ill patients and the impact on patient centred outcomes

8.1 Chapter summary

This chapter provides the results of the pilot RCT which was conducted as described in Chapter 7. This trial was undertaken to assess whether a volume-based enteral feeding protocol with supplemental protein, when compared to usual care, delivered greater protein and energy to critically ill adult patients. This trial also explored the impact of this intervention on patient-centred outcomes. This is the first RCT that has delivered enteral protein within the current guidelines and observed an improvement in muscle mass. This paper was published in 2018.

8.2 Pilot randomised control trial

Targeted full energy and protein delivery in critically ill patients: A pilot randomized controlled trial (FEED Trial)

Kate Fetterplace^{1,2,4} APD BNutrDiet, Adam M. Deane^{3,4} MBBS PhD, Audrey Tierney^{2,5} APD PhD, Lisa J Beach⁶ PT MPhty, Laura D Knight⁶ PT BPhty MHSM, Jeffrey Presneill^{3,4} MBBS PhD, Thomas Rechnitzer³ MBBS FCICM, Adrienne Forsyth² APD AEP PhD, Benjamin MT Gill^{1,4} APD MDiet, Marina Mourtzakis⁶ PhD and Christopher MacIsaac^{3,4} MBBS PhD.

1. Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia
2. Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne Australia
3. Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne Australia

4. Department of Medicine, The University of Melbourne, Melbourne, Australia
5. Department of Clinical Therapies, University of Limerick, Ireland
6. Allied Health (Physiotherapy), Royal Melbourne Hospital, Melbourne Australia
7. Department of Kinesiology, Faculty of Applied Health Sciences, University of Waterloo, Ontario, Canada

Corresponding author

Ms Kate Fetterplace^{1,2} BNutDiet, APD
Senior Dietitian, Royal Melbourne Hospital
Allied Health, Royal Melbourne Hospital
Grattan St Parkville, Victoria, Australia 3050
Phone: +61 3 9342 7440
Fax +61 93428440
Email: Kate.Fetterplace@mh.org.au

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Statement of Authorship

K Fetterplace, C MacIsaac, LJ Beach and A Tierney equally contributed to the conception and design of the research; AM Deane, M Mourtzakis and A Forsyth contributed to the design of the research; K Fetterplace, BMT Gill, T Rechnitzer, L Beach and LD Knight contributed to the acquisition of the data; K Fetterplace and J Presneill contributed to the analysis and the interpretation of the data; and K Fetterplace and AM Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of interests

K Fetterplace has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi and Nestle Health Science (not related to this study). AM Deane or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (Not related to this study). The other authors have no potential conflicts to declare.

8.3 Abstract

Background: International guidelines recommend greater protein delivery to critically ill patients than they currently receive. This pilot randomized clinical trial aimed to determine whether a volume-target enteral protocol with supplemental protein delivered greater amounts of protein and energy to critically ill patients compared to standard care.

Methods: Sixty participants received either the intervention (volume-based protocol, with protein supplementation) or standard nutrition care (hourly rate-based protocol, without protein supplementation) in the intensive care unit (ICU). Co-primary outcomes were average daily protein and energy delivery. Secondary outcomes included change in quadriceps muscle layer thickness (QMLT, ultrasound) and malnutrition (Subjective Global Assessment) at ICU discharge.

Results: Mean (SD) protein and energy delivery per day from nutrition therapy for the intervention were 1.2 (0.30) g/kg and 21 (5.2) kcal/kg compared to 0.75 (0.11) g/kg and 18 (2.7) kcal/kg for standard care. The mean difference between groups in protein and energy delivery per day was 0.45 g/kg (95%CI 0.33 – 0.56, $p < 0.001$) and 2.8 kcal/kg (95%CI 0.67 – 4.9, $p = 0.01$). Muscle loss (QMLT) at discharge was attenuated by 0.22 cm (95%CI 0.06 – 0.38, $p = 0.01$) in patients receiving the intervention compared to standard care. The number of malnourished patients was fewer in the intervention (2 (7%) vs. 8 (28%), $p = 0.04$). Mortality and duration of admission were similar between groups.

Conclusion: A high protein volume-based protocol with protein supplementation delivered greater amounts of protein and energy. This intervention was associated with attenuation of QMLT loss and reduced prevalence of malnutrition at ICU discharge.

Trial registration: This trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.ANZCTR.org.au/> ACTRN:12615000876594, UTM: U1111-1172-8563.

Key words: Critical illness, dietary proteins, enteral nutrition, enteral formulas, nutritional support, ultrasound, muscle mass and functional outcomes.

8.4 Clinically relevant statement

Current international guidelines recommend that critically ill patients should receive at least 1.2-2.0 g/kg per day of protein. In clinical practice patients often receive considerably less protein due, in part, to healthcare factors (interruption to nutrition therapy for other medical therapy) and patient factors (feeding intolerance). The aim of this pilot randomized clinical trial was to determine whether a high protein enteral feeding protocol using a volume target and protein supplementation delivered greater amounts of protein and energy to critically ill patients when compared to standard care. In this single center, open label, parallel group trial of critically ill mechanically ventilated patients the intervention was associated with greater delivery of protein and energy, attenuation of muscle loss and a lower prevalence of malnutrition at ICU discharge. Further research using this intervention is warranted given the achievement of recommended protein delivery and observed point estimates favouring beneficial effect in key secondary outcomes.

8.5 Introduction

The current Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition guidelines recommend that protein should be provided at a level of 1.2-2.0 g/kg/day, with possibly greater amounts for patients who are obese or present with multi-trauma or burns (McClave et al., 2016) and other guidelines have similar recommendations (Singer et al., 2018). However, there is a lack of high-quality randomized controlled trials to support these protein recommendations (Heyland et al., 2017; Hurt et al., 2017).

Observational data suggest that greater protein provision may be associated with improvements in survival, ventilator free days and time to discharge alive from the Intensive Care Unit (ICU) (Allingstrup et al., 2012; Compher et al., 2017; Elke et al., 2014; Nicolo et al., 2016; P. J. Weijs et al., 2014). Higher levels of protein provision may not only reduce mortality but also stimulate the synthesis of new proteins and preserve muscle

mass (Hurt et al., 2017). Skeletal muscle preservation has been identified as an important surrogate outcome of ICU patients given of the association between muscle loss and the development of ICU-acquired weakness (Moisey et al., 2013; Wandrag et al., 2015). Optimal nutrition, particularly with adequate protein provision may have the capacity to attenuate muscle loss (Iwashyna & Deane, 2016; Summers et al., 2016) but randomized controlled trial data to substantiate this are limited (Ferrie et al., 2016).

Despite current guidelines, the delivery of nutrition in the ICU is substantially less than recommended (Heyland et al., 2011). The provision of nutrition via the enteral route is considered preferable (McClave et al., 2016), however adequate delivery of protein and energy to critically ill patients via this route remains a challenge (Gungabissoon et al., 2015). Standard enteral feeding regimens are based on energy targets and as a result protein delivery is more often restricted by the formula composition; this may result in protein prescriptions that are less than the current guidelines (Hurt et al., 2017). Several methods to increase protein delivery via the enteral route have been proposed, these include the use of high protein formulas, volume based feeding protocols and additional protein supplementation (Heyland et al., 2013). However in practice, these methods may not result in more protein and energy being administered as protein is a potent stimulant of the small intestine feedback loop which slows gastric emptying (Karamanlis et al., 2007) and can cause feed-intolerance (Blaser et al., 2014) thereby possibly reducing protein and energy provision. The combination of these methods has not previously been studied.

The primary aim of this single center pilot randomized controlled trial was to determine whether a high protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly rate-based nutrition protocol without protein supplementation to mechanically ventilated critically ill patients. The secondary aims were to evaluate if this intervention increased feed-intolerance or the development of diarrhea, whether the intervention attenuated muscle or weight loss or the prevalence of malnutrition at ICU discharge, and to estimate the impact of the intervention on patient-centered outcomes.

8.6 Materials and methods

The study protocol was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.ANZCTR.org.au/> Registration number UTN: U1111-1172-8563). A protocol and statistical analysis plan manuscript was submitted during the enrolment period, prior to analysis of data (Kate Fetterplace et al., 2018)

8.6.1 Patients

This trial was conducted between August 2015 and August 2017 at the Royal Melbourne Hospital ICU. This ICU is a 32-bed University affiliated, tertiary referral, mixed medical-surgical-trauma ICU. Screening was only performed on weekdays. Patients were eligible if they were greater than 18 years of age, mechanically ventilated for < 48 hours, and were anticipated to remain ventilated for at least 72 hours. Patients were excluded if they had a contraindication to enteral feeding, if there was futility of care or death was imminent, if they had a pre-morbid disability resulting in an inability to ambulate greater than 10 meters, if they were pregnant or the treating clinician considered the intervention was not in the patient's best interest. The trial was conducted in accordance with the declaration of Helsinki and prior informed consent was obtained from the surrogate decision maker. Continuation of participation was obtained if the participant recovered adequately to provide consent. The protocol and consent process was approved by the Royal Melbourne Hospital Human Research Ethics Committee (2015.048).

The overall sample size of 60 patients (two groups of 30 patients) was calculated using a two-sided α level of 0.05 and a power ($1-\beta$) of 80% to detect a minimum difference of 15 g protein delivered per day between groups based on data from an observational study undertaken within the trial ICU (K Fetterplace et al., 2014), which showed a baseline protein intake [mean (SD)] of 50.8 (20.1) g/day. Using data from the VALIDUM study (Paris et al., 2017), mean (SD) quadriceps muscle layer thickness (QMLT) was 1.3 (0.6) cm (Paris et al., 2017), suggesting that a sample size of 27 participants in each group, accounting for 10 percent missing data, was sufficient to also provide more than 80% power to detect a mean difference of 0.5 cm in QMLT between groups.

8.6.2 Study design

Participants were randomly assigned using a simple 1:1 randomization system to receive either the intervention or standard care. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes that were held in a secure location by research personnel not involved with the trial. Due to the nature of the intervention clinicians were not blinded; however blinded assessors undertook the outcome measurements of muscle strength and physical function.

The intervention or standard care was delivered following randomization until ICU discharge; or until the patient no longer required enteral tube feeding, or the end of study day 15, whichever came first. Feeding intolerance was managed for both groups according to standard unit protocols, which included the use of gastrokinetic drugs, without ceasing enteral nutrition, and the consideration of post pyloric feeding tubes or supplemental parenteral nutrition if severe feeding intolerance occurred. The need for parenteral nutrition was determined by treating physicians who were not study investigators. The intervention group receive a volume based nutrition protocol (Heyland et al., 2013) using a high protein enteral formula (Nutrison® Protein Plus, Nutricia, Zoetermeer, The Netherlands; 63g protein and 1250 kcal per liter). Nursing staff were provided with a detailed regimen, which included a volume target and an hourly rate target with instructions to deliver the volume target over a 24-hour period based on 25 kcal/kg/day. Nursing staff assessed the volume of feed that had been delivered at 16:00 each day and calculated the volume required for the remaining 8 hours in order to achieve goal volume and adjusted the rate accordingly. A maximum rate of 150 ml/hr was set to minimize the risk of aspiration (Heyland et al., 2013). Protein supplements (Beneprotein®, Nestle Health Sciences, Switzerland, 6g of protein per scoop) were prescribed by the study dietitian in an attempt to achieve delivery of 1.5 g/kg/day protein (liquid formula plus protein supplement). The standard care group received standard nutrition care (Peake et al., 2012), which included commencing a standard commercially available 1.0 kcal/ml enteral formula (Nutrison® 1.0kcal, Nutricia, Wuxi, China), which provides 40 g protein and 1000 kcal per liter. Enteral nutrition was commenced as per the standard facility protocol, aiming to provide 1.0 g/kg/day protein and 25 kcal/day (McClave et al., 2016). For both groups the weight used to calculate the nutrition provision was based on actual body weight or ideal body weight if above the healthy weight range. Weight was obtained using

the bed scales and height was calculated using the estimate provided by measuring ulna length ("Malnutrition Advisory Group, Malnutrition Universal Screening Tool," 2008). Ideal body weight for participants aged < 65 years is defined as a Body Mass Index (BMI) between 18.5 and 25kg/m² and for those aged ≥ 65 years, a BMI between 22 and 27kg/m² ("National Health and Medical Research Council, *Australian Dietary Guidelines*," 2013). For participants with a BMI ≥ 32kg/m² an adjusted ideal body weight was used (ideal body weight + 25% (actual body weight – ideal body weight) (Ferrie & Ward, 2007).

At baseline, data was collected including admission diagnosis, Charlson Comorbidity Index, Katz Activities of Daily Living (ADL) index, Acute Physiology and Chronic Health Evaluation II and III (APACHE II and III) score, and admission Sequential Organ Failure Assessment (SOFA) Score. Duration of ICU and hospital admission, discharge destination and survival at days 28 and 60 were recorded.

8.6.3 Protein and energy provision

The co-primary outcomes were the mean daily protein and energy delivered over the 15-day study period. Administration of nutrition prior to commencing the study protocol was not included. The provision of protein and energy was calculated on a daily basis from enteral and/or parenteral formula and/or protein supplements but separate from all other sources. Total energy delivery included nutrition therapy as well as calories from dextrose and propofol. Day 1 (day of randomization) and day of discharge were included even if they were partial days.

8.6.4 Feeding intolerance

The proportion of patients who developed feeding intolerance was determined by the number of patients in the group who had at least one gastric residual volume > 300 ml (Blaser et al., 2014) over the study period. The cumulative incidence of feeding intolerance was determined by the number of days a patient had gastric residual volumes > 300 ml. The proportion of patients who developed diarrhea was determined by the number of

patients who had more than 3 bowel actions or greater than 300 ml of stool output in a 24 hour period on at least one occasion (Ferrie & East, 2007) and the cumulative incidence was determined by the number of days the patient met the above criteria.

8.6.5 Muscle mass

Muscle mass was assessed with ultrasound, measuring QMLT using the technique described by Tillquist and colleagues (Tillquist et al., 2014). The QMLT measurements were performed by a single trained operator (KF) using a portable ultrasound machine (Sonosite S-ICU™) with a multiple frequency transducer (13-6MHz, 6cm). The device settings were standardized and the measurements were taken with the patient lying in a supine position with legs relaxed and extended. QMLT was completed on bilateral lower limbs; measurements were obtained at two different landmarks; the midpoint and two thirds between the Anterior Superior Iliac Spine and the upper pole of the patella (Chapple et al., 2017; Paris et al., 2017; Tillquist et al., 2014). A still image was taken with the transducer held perpendicular to the skin; the muscle thickness was quantified by using the onscreen callipers to measure the distance between the upper margin of the femoral bone and the lower boundary of the deep fascia of the rectus femoris muscle (Paris et al., 2017). Duplicate measurements were taken at each landmark and the mean of the four linear thicknesses were calculated for each leg separately (Chapple et al., 2017). The first measurement was taken before randomization and then at discharge from ICU or day 15 (whichever came first).

8.6.6 Nutritional assessment and outcomes

Prior to randomization baseline measures were undertaken including height (cm) (using ulna length ("Malnutrition Advisory Group, Malnutrition Universal Screening Tool," 2008)), body weight (kg) (from bed scales), BMI (kg/m^2), mid upper arm circumference (cm), nutritional status using the subjective global assessment (SGA) (Marshall, 2008), plasma albumin (g/L) and an estimate of energy and protein requirements obtained by an independent dietician. Body weight, nutritional status, mid upper arm circumference and plasma albumin levels were repeated at discharge from ICU or day 15, whichever came

first. Additionally measured energy expenditure (MEE) was assessed by indirect calorimetry using the E-sCOVX (GE, Helsinki, Finland) monitor (Sundstrom et al., 2016; Sundstrom et al., 2013). The measurements were carried out within the first 5 days following enrolment, if a trained operator was available, patients were excluded if they were on continuous renal replacement therapy, attached to extracorporeal circulation, had an intercostal catheter with an air leak or were receiving a fraction of inspired oxygen greater than 0.6 (Petros & Engelmann, 2001). The measurement was completed with the patient in a fed state lying supine. The mean respiratory quotient (RQ) and MEE (kcal/day) were recorded.

8.6.7 Functional outcomes

Muscle strength was assessed in suitable participants using handgrip dynamometry and the Medical Research Council (MRC) scale (Baldwin et al., 2013; Hermans et al., 2012). The first muscle strength test was performed at awakening (Hermans et al., 2012) and then again at discharge or day 15, whichever came first. Patients were screened for attention and comprehension on the basis of their ability to follow commands, they were considered awake if they scored at least three out of five using the De Jonghe comprehension criteria on at least two occasions within a six-hour period and had a Riker sedation-agitation scale score of three to five. Handgrip dynamometry (Commander Echo™ Wireless Grip Dynamometer, USA) was measured in both limbs with the participant in a chair or sitting at least at 45 degrees in bed, with the patient's elbow at 90 degrees supported by a pillow or the arm of the chair. The Medical Research Council sum score (MRC-SS) was measured as previously described (Ciesla et al., 2011) with ICUAW defined as an MRC-SS of < 48/60 (Beach et al., 2017; Hermans et al., 2014; Hough et al., 2011). Physical function was assessed using the physical function in Intensive Care Test –scored (PFIT-s) (Denehy et al., 2013)

8.6.8 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM® SPSS® Statistics Premium Grad Pack Version 23.0) and Stata (Stata Statistical Software: Release 15. College Station,

TX: StataCorp LP; 2017). All analyses were conducted using the intention-to-treat patient sample. Baseline patient demographics, severity of illness, ICU length of stay, mortality and nutritional markers were tabulated according to treatment group and summarized as mean (standard deviation) (SD) or median and [Interquartile range] [IQR], as appropriate. Initial exploratory data analysis included the calculation of summary statistics, and comparison between treatment groups using non-parametric (Wilcoxon), parametric (t-test) and Fisher exact tests as appropriate, as well as construction of trajectory plots according to treatment group. The co-primary outcomes of average daily energy and protein delivery were compared between the two groups using two-sample unpaired t-tests, with statistical significance for each set conservatively at two-sided values of 0.025, to control the family-wise type 1 error to less than 0.05 overall.

All secondary outcomes were regarded as exploratory and hypothesis-generating with, as a consequence, no adjustment for multiple comparisons to their conventional 5% type 1 error thresholds. Group differences for each patient's discharge QMLT were compared after adjustment for initial baseline values and other selected covariables using linear regression (analysis of covariance, ANCOVA). Robust standard errors were specified to allow for within subject correlation of the repeated muscle mass observations from left and right sides and across time. No imputation of missing data was performed. Standard model diagnostics of linearity and influence were performed.

8.7 Results

A total of 885 mechanically ventilated patients were screened, with 160 patients found to meet the eligibility criteria (Figure 1). Consent was obtained for 60 patients, who were randomized to receive either the intervention (n = 30) or standard care (n = 30). The goals of medical treatment were changed to 'comfort care' for one patient (intervention group) soon after randomization but prior to commencement of the intervention nutritional regimen. One patient from each group was liberated from the ventilator prior to 48 hours.

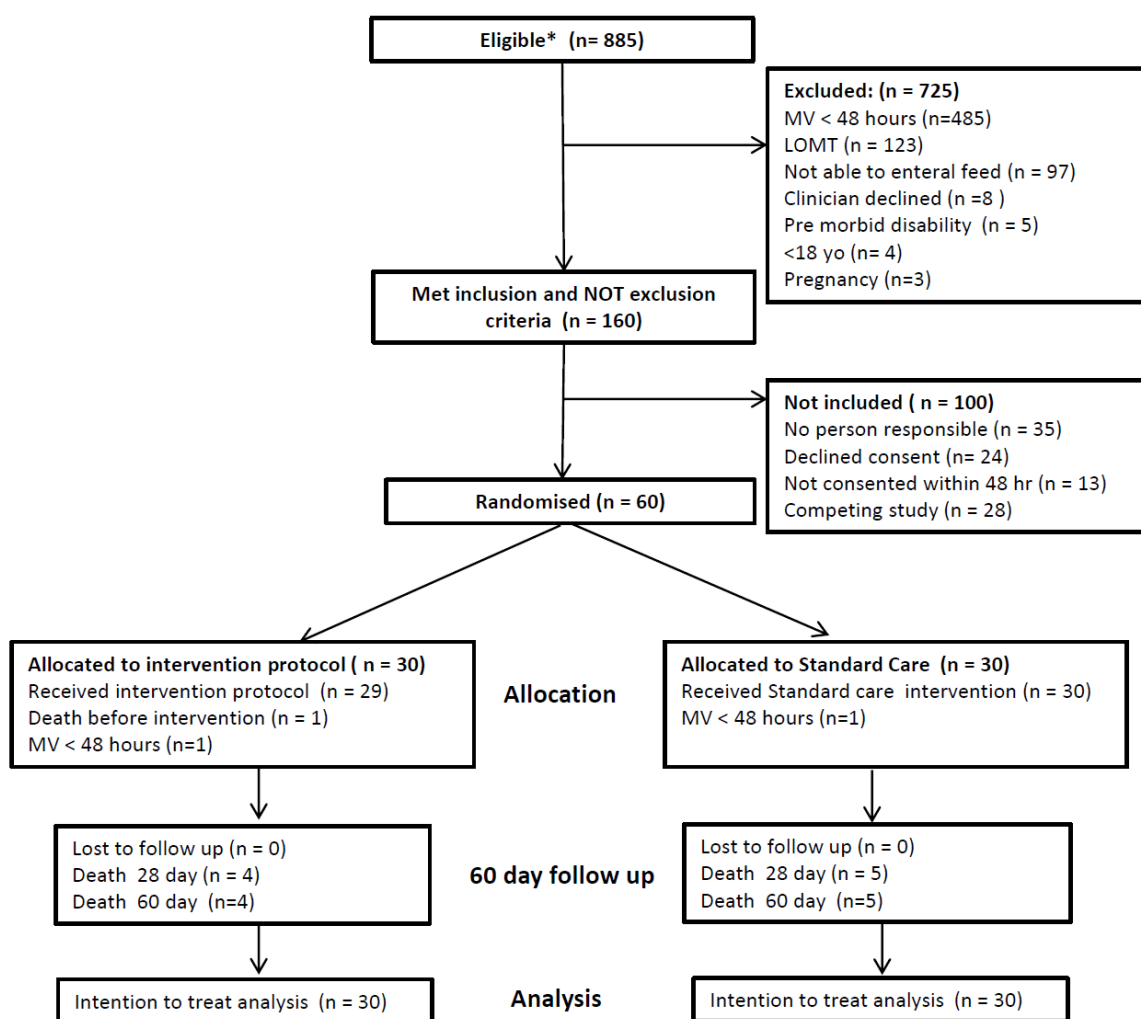


Figure 8-1. Patient flowchart, flow diagram of patient eligibility and study conduct

Abbreviations: LOMT, Limit of medical treatment; n, number of participants; MV, mechanically ventilated; yo, years old

*Eligible patients - patients mechanically ventilated and admitted to the ICU <48 hours at time of screening

At baseline, participants in both groups were similar with regards to age, sex, APACHE II and III scores, BMI, admission weight and co morbidity index (Table 1). The majority of the patients in both groups were classified with medical rather than surgical diagnoses.

Table 8-1. Baseline demographics and comparisons of study groups^a

Demographics	Intervention (n= 30)	Standard (n = 30)
Age, years	55 (13)	57 (16)
Sex, Male, n (%)	23 (77)	21 (70)
BMI, kg/m ²	30 (7.1)	29 (5.3)
APACHE II Score	22 (6.2)	20 (5.9)
APACHE III Score	77 (25)	71 (22)
Comorbidity Index	3 [1 – 5]	3 [2 – 4]
Katz ADLs index	6 [6 – 6]	6 [6-6]
Admission Category, n (%)		
Medical	21 (70)	16 (53)
Elective Surgery	1 (3.3)	1 (3.3)
Emergency Surgery	8 (27)	13 (43)
Admission Diagnosis, n (%)		
Neurological conditions	13 (43)	7 (23)
Multi-trauma/head-trauma	7 (23)	11 (37)
Respiratory	1 (3.3)	5 (17)
Cardiac arrest	3 (10)	1 (3.3)
Sepsis	3 (10)	1 (3.3)
Cardiac surgery	0	2 (6.7)
Other	3 (10)	3 (10)
Chronic Renal Failure, n (%)	1 (3.3)	0 (0)

Abbreviations: ADL, Activities of Daily Living; APACHE - Acute Physiology and Chronic Health Evaluation; BMI, Body mass index; kg, kilograms, m, meters; n, number of participants

^aValues are represented as mean (SD), median [IQR] or n (%) if list in table

8.7.1 Co-primary outcomes

The intervention was associated with an increased total protein delivery over the study period [mean increased protein delivery of 37 g/day (95%CI 26 to 47, $p < 0.001$)], equivalent to a mean overall protein advantage of 0.45 g/kg/day (95%CI 0.33 to 0.56, $p < 0.001$) (Table 2). A difference was observed over multiple days, with significantly more protein delivered to the intervention group compared to control group on 13 of the 15 study days (Figure 2A and Table 2).

The intervention was also associated with increased energy delivery from enteral nutrition per day [mean increase of 2.8 kcal/kg (95%CI 0.7 to 4.9, $p = 0.01$)] (Table 2). There was increased energy delivery from nutrition on 5 of the 15 study days (Figure 2B) and total energy delivered was greater in the intervention group [mean difference of 237 kcal/day (95%CI 10 – 464, $p = 0.04$)] (Table 2).

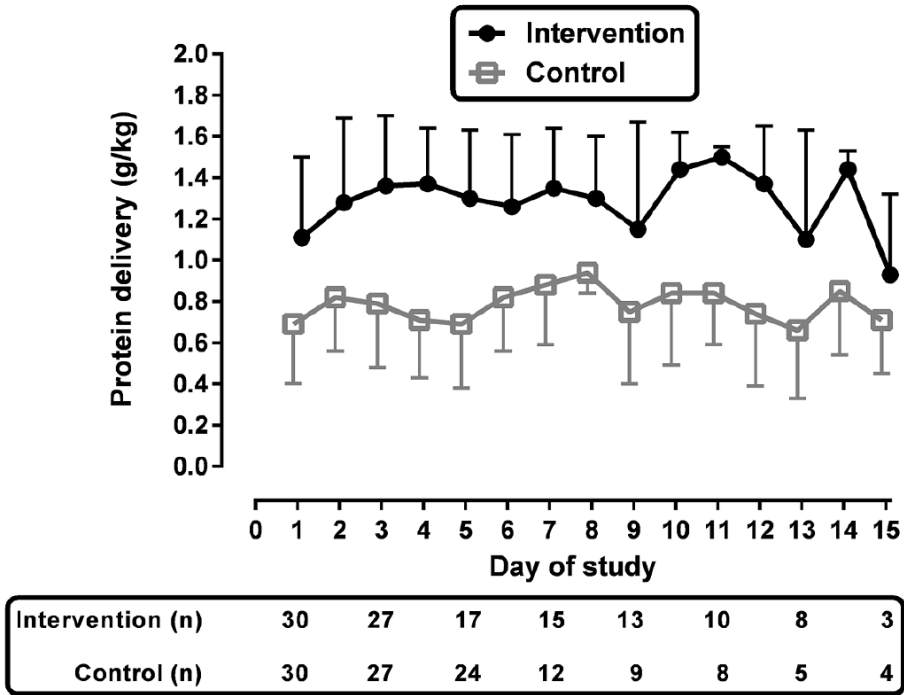


Figure 2A.

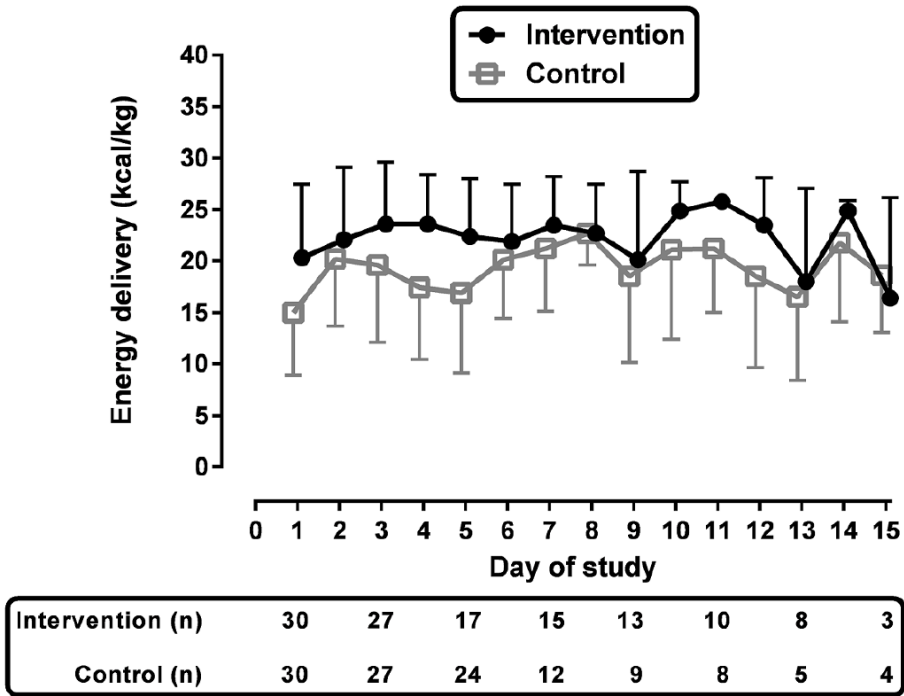


Figure 2B.

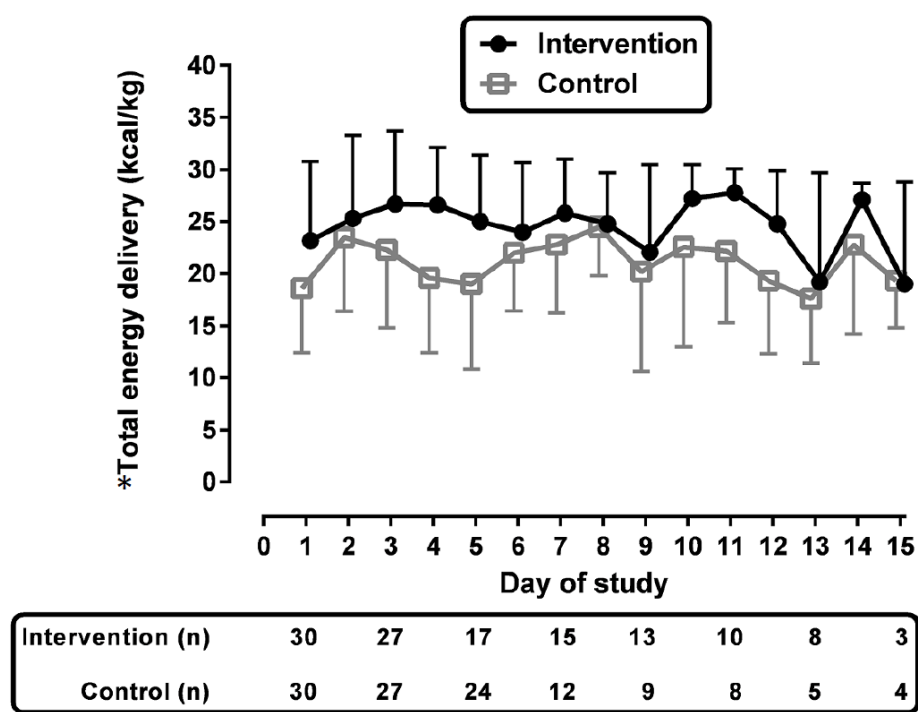


Figure 2C.

Figure 8-2. Daily protein (2A) and energy (2B) delivery from nutrition and total energy delivery (2C) over the study period

Abbreviations: g, grams; kcal, kilocalories; kg, kilograms

Mean daily protein (2A), Energy (2B) and total energy (2C) delivery according to research group, with error bars representing one standard deviation

*Total energy delivery includes energy from nutrition therapy plus calories from dextrose and propofol

Table 8-2. Primary outcomes and nutritional provision

Outcomes	Intervention (n =30)	Standard (n =30)	Mean Difference (95%CI)	p value
Protein provided, g/day	94 (27)	58 (12)	37 (26 – 47)	<0.001
	101 [85 – 113]	56 [49 – 64]		
Protein provided, g/kg/day	1.2 (0.30)	0.75 (0.11)	0.45 (0.33 – 0.56)	<0.001
	1.3 [1.1 – 1.5]	0.73 [0.68 – 0.82]		
Protein adequacy, % of estimated requirements	90 (25)	57 (8.0)	33 (24 – 43)	<0.001
	96 [81 – 108]	56 [52 – 63]		
Energy provided from nutrition, kcal/day	1646 (447)	1398 (308)	248 (50 – 447)	0.02
	1754 [1508 - 1971]	1372 [1215-1582]		0.001
Energy provided from nutrition, kcal/kg/day	21 (5.2)	18 (2.7)	2.8 (0.7 – 4.9)	0.01
	22 [20 – 24]	18 [16 – 20]		<0.001
Total energy provided ^b , kcal/day	1835 (340)	1598 (340)	237 (10 – 464)	0.04
	1955 [1639 – 2177]	1545 [1399 – 1858]		<0.01
Total energy provided ^b , kcal/kg/day	23 (5.7)	21 (3.3)	2.5 (0.05 – 4.9)	0.05
	25 [22 – 26]	21 [18 – 23]		<0.001
Energy adequacy, % of prescribed energy	84 (21)	73 (11)	11 (-2.7 – 20)	0.01
	89 [80 – 96]	71 [63 – 81]		<0.001
Estimated protein requirement, g/kg/day	1.3 (0.1)	1.3 (0.1)	0 (-0.05 – 0.05)	1.0
	1.3 [1.3 – 1.4]	1.3 [1.3 – 1.3]		0.85
Estimated protein requirement, g/day	105 (19)	101 (17)	3.6 (-5.7 – 13)	0.44
	104 [92 – 113]	98 [92 – 102]		0.46
Estimated energy requirement, kcal/day	1969 (277)	1918 (255)	51 (-87 – 189)	0.46
Measured energy expenditure, kcal/day (n = 15 per group)	2440 (435)	2194 (718)	246 (-196 – 688)	0.26
Time spent fasting, hours	19 (19)	20 (31)	-0.4 (-14 – 13)	0.94
	12 [3.8 – 34]	7.0 [0 – 19]		0.39
Time to commence enteral nutrition, hours	13 (8)	20 (10)	6.3 (1.6 – 11)	0.01
	13 [7.0 – 18]	17 [12 – 25]		0.01

Abbreviations: g, gram; kcal, kilocalorie; kg, kilogram.

^aNormally distributed values are represented as mean (SD) 95% CI with p values, non-normally distributed values are represented as mean (SD) 95% CI and median [IQR] with p values.

^bTotal energy included nutrition therapy plus energy from propofol and dextrose

8.7.2 Nutritional provision and outcomes

The participants required enteral nutrition following randomization for a mean of 8.0 days (4.4) in the intervention and 7.0 days (4.5) in the standard care group [mean difference 1.0 day (95%CI (-1.3 – 2.3), $p = 0.87$]. Estimated energy and protein requirements were similar between groups (Table 2). Energy expenditure was measured in a convenience sample of 15 patients from each group (50%) and the daily energy expenditure was similar between groups (Table 2). Nutritional adequacy was greater in the intervention group (Table 2). Enteral nutrition was commenced earlier in the intervention group and the period of time fasting was similar between groups (Table 2). Two patients in the standard care group and no patients in the intervention group received parenteral nutrition for a mean of 4.5 days in combination with enteral nutrition due to feeding intolerance. The proportion of patients who developed feeding intolerance or diarrhea and the cumulative incidence of these were similar between groups (Table 3). There were fewer patients in the intervention group classified as malnourished (SGA assessment) at ICU discharge but all other assessed nutritional outcomes, including weight loss, were similar between groups (Table 3).

Table 8-3. Nutrition outcomes

Outcomes variables	Intervention ^a	n	Standard	n	Risk Ratio (95%CI)	p value
Patients with feeding intolerance	9 (30)	30	8 (27)	30	1.1 (0.5-2.5)	0.77
Patient who developed Diarrhea	16 (53)	30	16 (53)	30	1.0 (0.58 – 1.7)	1.0
Malnourished ^d at ICU discharge	2 (6.9)	29	8 (27.6)	29	0.25 (0.06 – 1.1)	0.04
Outcomes variables	Intervention ^b	n	Standard	n	Mean Difference (95%CI)	p value
Cumulative incidence of feeding intolerance, days	0.3 (0.5)	30	0.7 (1.5)	30	-0.4 (-1.0 – 0.2)	0.18
	0 [0 – 1]		0 [0 – 1]			0.86
Cumulative incidence of diarrhea, days	1.9 (2.2)	30	1.3 (1.6)	30	0.7 (-0.4 – 1.8)	0.23
	1 [0 – 3.5]		1 [0 – 2]			0.57
Weight change admission to discharge, kg	-1.3 (8.5)	22	-2.6 (4.7)	19	1.3 (-3.2 – 5.7)	0.57
Mid upper arm circumference change admission to discharge, cm	-1.7 (1.5)	18	-2.0 (1.2)	20	0.3 (-0.6 – 1.2)	0.50
Plasma albumin at discharge, g/L	24 (4.3)	27	24 (5.4)	30	0.5 (-2.6 – 3.7)	0.76

Abbreviations: g, grams, kg – kilograms; L, liter.

^aProportion values represented as n (%)

^bNormally distributed values are represented as mean (SD), non-normally distributed data represented as mean SD (95%CI) with p values and median [IQR] with p values.

^cPearson Chi-squared p values

^dMalnutrition defined by Subjective Global Assessment category B or C

8.7.3 Muscle mass outcomes

QMLT measurements were not available at baseline and discharge in 6 (23%) participants in the intervention group and 7 (27%) participants in the standard care group. These missed observations were primarily due to participant unavailability, a change of focus to comfort care, death, other medical issues or discharge from intensive care when the primary investigator was not available. Adjusted for baseline QMLT, the intervention was associated with less QMLT loss at discharge, with a mean attenuated loss of 0.22 cm (95%CI 0.06 to 0.38, p = 0.01), controlling for patient age, severity of illness (APACHE III

score), BMI and admission category (Table 4.). Greater baseline QMLT was associated with a greater absolute QMLT at discharge, and surgical patients appeared to lose more QMLT compared to medical patients [-0.28 cm (95% CI -0.44 to -0.01, p = 0.01)].

Table 8-4. Effect estimate of variables on QMLT (cm) at ICU discharge adjusted for baseline QMLT (cm)^a

Variables	Effect estimate adjusted for baseline QMLT				Effect estimate adjusted for all co-variants			
	Effect	Robust Std.Err or	95% CI	P value	Effect	Robust Std. error	95% CI	P value
Baseline QMLT, cm	0.61	0.11	0.38 – 0.83	<0.001	0.56	0.11	0.33 – 0.79	<0.001
Intervention	0.22	0.08	0.05 – 0.39	0.01	0.22	0.08	0.06 – 0.38	0.01
APACHE III ^b	0.02	0.02	-0.02 – 0.06	0.44	0.01	0.02	-0.03 – 0.05	0.70
Age ^c , years	0.02	0.03	-0.03 – 0.08	0.44	-0.00	0.02	-0.05 – 0.05	0.92
BMI ^d kg/m ²	0.02	0.09	-0.17 – 0.21	0.82	0.03	0.08	-0.14 – 0.19	0.73
Admission ^e category								
Elective	-0.44	0.07	-0.58 – -0.30	<0.001	-0.57	0.08	-0.73 – -0.41	<0.001
Surgical	-0.28	0.08	-0.44 – -0.11	<0.01	-0.24	0.09	-0.41 – -0.06	0.01

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; cm, centimetre; QMLT, Quadriceps muscle layer thickness.

^aQMLT at discharge, mean right and left side measurement have been paired within individuals and adjusted for baseline mean right and left side measurements (n=92)

^bAPACHE III was centered at 75

^cAge was centered at 60 (per 10 years)

^dBMI was centered at 30kg/m²

^eAdmission category compared to medical admissions

8.7.4 Physical assessment outcomes

Only 6 (20%) participants in the intervention and 16 (53%) participants in the standard care group completed handgrip strength, 7 (23%) and 14 (47%) participants completed MRC-s muscle strength measurements and 8 (27%) and 14 (47%) participants completed physical function tests respectively. The missed observations were primarily due to participants’ inability to complete these assessments based on the de Jonge criteria or participant unavailability as above. In this small patient subgroup, the intervention and

control groups showed similar muscle strength, physical function and clinical outcomes (Table 5).

Table 8-5. Functional and other secondary outcomes^a

Outcome variables	Intervention ^a	n	Standard	n	Mean Difference (95%CI)	p value ^c
Handgrip strength (best), kg	20 (6.1)	6	21 (9.3)	16	-0.34 (-9.0 – 8.3)	0.94
Muscle strength (MRC score)	55 (5.9)	7	52 (9.6)	14	2.6 (-5.8 – 11.0)	0.53
Physical Function ^e	6.8 (3.8)	8	7.9 (3.4)	14	-1.1 (-4.4 – 2.2)	0.49
ICU LOS, days	10.6 (8.3)	30	9.1 (5.5)	30	1.5 (-2.2 – 5.1)	0.42
	7.8 [5.9 – 13.4]		7.5 [4.9 – 12.7]			0.52
Hospital LOS, days	27.4 (19.0)	30	18.8 (10.9)	30	8.6 (0.6 – 16.6)	0.04
	22 [9.9 – 43]		15 [9.9 – 25]			0.14
Length of MV, days	8.7 (7.5)	30	7.0 (5.0)	30	1.7 (-1.6 – 5.0)	0.30
	6.2 [4.5 – 10.8]		5.1 [3.6 – 8.5]			0.32
Outcome variables	Intervention ^b	n	Standard	n	Risk Ratio (95%CI)	p value
ICU acquired weakness ^d	1 (14)	7	4 (28)	14	0.5 (0.07 – 3.7)	0.47
Renal failure ^f	3 (10)	30	3 (10)	30	1.0 (0.22 – 4.6)	1.0
Mortality 28 days	4 (13)	30	5 (17)	30	0.8 (0.24 – 2.7)	0.72
Mortality 60 days	4 (13)	30	5 (17)	30	0.8 (0.24 – 2.7)	0.72
Discharge to a rehabilitation facility	12 (40)	30	13 (43)	30	0.9 (0.51 – 1.7)	0.77

Abbreviations: Kg, kilogram; LOS, length of stay; MRC, Medical research council score; MV, Mechanical ventilation

^aNormally distributed values are represented as mean (SD) 95% CI with p values, non-normally distributed values are represented as mean (SD) 95% CI with p values and median [IQR] with p values.

^bPortions are listed as n (%)

^cPearson Chi-squared p values

^dICU Acquired weakness defined as MRC score < 48

^ePhysical function, measured using Physical function in ICU Test –Score

^fRenal Failure defined using the RIFLE criteria

8.8 Discussion

This trial prospectively randomized participants to receive an enteral feeding intervention that resulted in delivery of considerably more protein and energy delivery via nutrition therapy compared with standard care. Importantly, the intervention did not appear to increase adverse events, such as feed-intolerance or diarrhea and the proportion of patients who developed these issues was consistent with observational literature (Gungabissoon et al., 2015; Yagmurdur & Leblebici, 2016). Moreover, the intervention was associated with attenuation of QMLT loss and a reduced proportion of malnourished patients on discharge from ICU, without other signals of harm in terms of other patient-centered outcomes.

In this trial, the intervention resulted in greater protein and energy delivery, which is consistent with previous studies of volume-based feeding (Heyland et al., 2010; Heyland et al., 2013). Heyland and colleagues described a novel multi-modal approach termed the “PEP uP protocol”, which incorporated a volume-based enteral feeding regimen (Heyland et al., 2010; Heyland et al., 2013). In a single center sequential period feasibility study the point estimates of enteral protein and energy delivery were augmented by approximately 10 percent, with nutritional adequacy improving from, mean (SD), 74 (29) percent (Heyland et al., 2010). In a subsequent prospective cluster randomized trial of 18 ICUs, those sites that were allocated to the PEP uP protocol delivered 14 percent more protein and 12 percent more calories than the control sites, however the overall nutritional adequacy with the intervention was, mean (SD) 48 (33) percent (Heyland et al., 2013). Subsequently, a single center randomized control trial utilized a similar PEP uP style protocol and reported that a volume based feeding protocol delivered more energy (mean (SD), 93 % (17)) compared to a rate based feeding protocol (81 % (19)) in critically ill patients, however protein delivery was not reported (McClave et al., 2015). Moreover, none of the previous mentioned trials of volume-based regimens incorporated functional effects of nutrition such as muscle mass or strength measures. This current trial also differs from previous trials in that prophylactic gastrokinetic drugs and semi-elemental formulae were not prescribed. In addition, the strategy to aid adherence to the volume target implemented included requesting staff to assess nutrition delivery at a set time point in

the day (1600 h) rather than at the time of the interruption. Lastly, additional protein was supplemented throughout the study period.

While there is considerable enthusiasm for, and face-validity underlying, greater protein delivery to improve patient-centered outcomes (Hurt et al., 2017), there is limited evidence to support this intervention. In a systemic review of all relevant randomized controlled trials (Davies ML et al., 2017), increasing protein delivery did not improve patient-centered outcomes, although the authors noted that none of the included studies compared standard protein provision with the current guideline recommendations. Ferrie and colleagues recently reported the impact of delivering different intravenous protein doses (Ferrie et al., 2016). In this study of 119 critically ill patients the augmented protein intervention was associated with improvements in surrogate outcomes including handgrip strength, reduced fatigue and greater forearm muscle thickness (Ferrie et al., 2016). Collectively, the results of Ferrie (Ferrie et al., 2016) and the current trial provide preliminary single-centre trial evidence that early protein delivery within the guideline range may attenuate muscle loss in critically ill patients. This concept is also supported by a number of observational studies (Alberda et al., 2009; Allingstrup et al., 2012; Compher et al., 2017; Nicolo et al., 2016; Song et al., 2017; P. J. M. Weijs et al., 2012), however conflicting data have been reported. In the multi-center UK MUSCLE study greater loss of quadriceps muscle was associated with more protein delivery (Puthuchear et al., 2013). Furthermore, in rabbits studied after burn injury administration of amino acids was associated with an increase in muscle vacuolization (Derde et al., 2012) and in a pediatric population increasing doses of intravenous protein were associated with inferior patient-centered outcomes (Vanhorebeek et al., 2017). Accordingly, the point estimates in the current trial favoring improvement in surrogate outcomes (QMLT and SGA) should be interpreted with caution.

8.8.1 Clinical significance

The intervention achieved treatment separation between the groups, with the increase in protein delivery to be at least 0.33 g/kg/day and as much as 0.56 g/kg/day. Particularly in those patients admitted and exposed to the intervention for longer periods, it is possible that this magnitude of protein supplementation could limit the muscle mass losses,

commonly observed in critical care patients, or otherwise improve patient-centered outcomes.

8.8.2 Strengths and limitations

The strengths of this trial include allocation concealment and randomization to limit selection bias, as well as submission of protocol and planned statistical analysis prior to completion of the trial (Kate Fetterplace et al., 2018). The study aimed to provide two different protein targets using enteral nutrition. The intervention delivered protein within the current guideline recommendations and the control group received care (protein and energy delivery) representative of routine care in Australia and New Zealand (Peake et al., 2012).

The limitations of this trial include conduct at a single center without a practical method of blinding the intervention, making further validation in other settings desirable. As a pilot trial with a relatively small cohort the point estimates for important surrogate outcomes, such as QMLT, must be interpreted with considerable caution and may not represent effects at a population level. Also, the intervention was a volume-based protocol with protein supplementation meaning energy delivery was also increased, which may confound the observed impact of protein on outcomes. Missing data for some of the secondary and tertiary outcomes, particularly for the functional measurements, makes any estimates of effect provisional (Walsh et al., 2014). Lastly, only mechanically ventilated enterally fed critically ill patients were enrolled and of the participants the majority fell into broad medical or trauma classifications. Accordingly, the present data may not be generalizable to patients requiring parenteral nutrition or those with primary gastrointestinal disease.

8.9 Conclusion

A high protein volume-based enteral feeding protocol with supplemental protein delivered greater amounts of protein and energy to critically ill mechanically ventilated patients. This

intervention was associated with attenuation of muscle loss and reduced prevalence of malnutrition at ICU discharge. These data support the feasibility and clinical relevance of further investigations using this intervention.

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Chapter 9: Conclusions

9.1 Chapter summary

This chapter summarises the key research finding of this PhD program. It also details the strengths and limitations of the studies, and provides recommendations for future research in this area.

9.2 Summary of key research findings

This thesis describes the conduct and outcomes of several defined studies within a coordinated research program, which included a systematic literature review and meta-analysis of protein provision and the impact on patient-centred outcomes (Chapter 2), a narrative review of methods to quantify the response to nutrition therapy (Chapter 3), a retrospective study of muscle mass assessment techniques (Chapter 4), two observational studies of nutrition provision during and after ICU admission, and associations with nutrition delivery and patient-centred outcomes (Chapters 5 and 6), and a pilot RCT of the impact of a bundled intervention to optimise protein provision to the critically ill (Chapters 7 and 8).

The greatest impact this program of research has had on the existing understanding of nutritional therapy in the critically ill derives from the pilot RCT. This single-centre parallel group trial of 60 critically ill patients evaluated whether a volume-target enteral feeding protocol with supplemental protein delivered greater amounts of protein and energy to critically ill patients than usual care (Chapters 7 and 8). It was observed that this intervention achieved protein provision within the current international guidelines, with adequate energy provision, and was associated with attenuation of muscle loss as measured by ultrasound (Chapter 8). This trial was novel at the time it was designed, and it was the first trial to report that providing enteral protein within the current guidelines had a positive impact on an outcome.

The systematic literature review and meta-analysis conducted to assess the effect of enteral protein provision within the current guideline recommendations compared to usual care also provided valuable insights into the evidence in this research area (Chapter 2). Previous reviews on this topic had looked at different protein doses; this was the first systematic review to assess protein provision in relation to the dose recommended by the international guidelines and the effect on patient-centred outcomes. This systematic review highlights the significant lack of research in this field, with only 511 patients included in RCTs to date. With such a small combined sample, it is not surprising that previous researchers were unable to show that greater protein provision reduced mortality or length of stay in ICU or hospital. The mean protein provision for the intervention group across the studies was 1.3 (0.1) g/kg/day, with no studies providing protein at the upper end of the guideline recommendations. From the available evidence, it was concluded that there was insufficient trial data to assess whether enteral protein provision according to the current international guideline recommendations has any effect on patient-centred outcomes.

The three observational studies completed during candidature also represent important contributions to the field of nutrition therapy in critical care. The study of 60 critically ill patients (Chapter 5), which was undertaken to assess the associations between nutritional deficits and several nutrition-related and functional patient-centred outcomes, reported that it was feasible to collect these patient-centred outcome measures from a heterogeneous cohort of critically ill patients – a novel finding. It was also observed that there were strong associations between cumulative nutrition deficits and several patient-centred outcomes, including ICU-acquired weakness, malnutrition, reduced physical function at ICU discharge and greater loss of fat-free mass. Due to the study design, however, causality could not be determined. The second observational study evaluated the feasibility of measuring nutritional and patient-centred outcomes following ICU discharge in those admitted with traumatic injuries (Chapter 6). This study highlighted the challenges of measuring functional outcomes that require volitional movement after ICU discharge. This was one of only a small number of studies which have assessed nutrition

provision following ICU discharge. It was observed that patients receiving oral intake alone consume significantly less than those patients receiving any artificial nutrition support.

The narrative review also contributed to the field by summarising the many different patient-centred outcomes that have been used in critical care nutrition research, and explored which outcomes may be of greatest use to quantify the effect of nutrition therapy (Chapter 3). It was identified that patient-centred and surrogate outcomes are increasingly being used in the critical care nutrition field, but there is a lack of consistency in the tools used and many have substantial limitations. Additionally, patient-centred outcomes, which require volitional measurements, may not be feasible in all critically ill patient cohorts. The measurement of muscle mass using ultrasound seems promising; however, protocols need further evaluation before the optimal technique is identified. The retrospective observations study identified that quadriceps muscle layer thickness measured with ultrasound is a strong independent predictor of a more precise measurement of skeletal muscle mass, but it may lack sufficient precision for use as a surrogate assessment for total body muscle mass or the presence of sarcopenia (Chapter 4).

9.3 Strengths and limitations of the research

The work undertaken for this PhD program provides insight into several important questions relating to nutrition therapy in critically ill patients. The clinical trial which was undertaken to explore protein provision in critically ill people was novel and highly relevant to the increasing focus on the effect of protein on preservation of lean muscle mass and subsequent outcomes (Heyland et al., 2017; Hurt et al., 2017). However, there is still a paucity of research in this area and the findings from this research need to be confirmed with larger (preferably blinded) multi-centre randomised trials. The focus on patient-centred outcomes throughout all the studies undertaken during candidature is a very important strength of this research program. It is increasingly being recognised that as more people survive critical illness, the quality of survivorship – not just quantity – is of great importance to patients (Bear et al., 2017; Iwashyna & Netzer, 2012). Additionally, this research program incorporated several rigorous methodologies, including a systematic

literature review with meta-analysis, observational studies including key outcomes and a pilot RCT.

The most significant limitation to this research is that it was conducted in a single centre within Australia, and therefore the findings may not be generalisable to other locations and regions. The sample sizes of the studies were also small relative to some previous work and, at times, hampered by missing data, which is particularly relevant given the studies were not powered to find a difference in key secondary outcomes of interest. The inferences drawn from the systematic review and meta-analysis with regard to the effect of enteral protein provision on patient-centred outcomes were limited by the available data, and a meta-analysis could not be completed for the primary outcome measure. A further limitation of the literature to date on protein provision is that in most cases energy provision has not been adequately controlled or standardised, which could confound these results.

9.4 Future directions and recommendations

Large multi-centre and methodologically rigorous RCTs evaluating protein provision within the international guideline recommendations, whilst controlling for energy provision, are required to assess its impact on patient-centred outcomes. Researchers should consider providing protein at the upper end of the guideline recommendations, because patients on average receive only 60–80% of prescribed targets.

Future trials evaluating the impact of protein provision to critically ill patients should also explore the type of protein provided, the mode of delivery, if particular amino acids have specific benefits or harms, and the composition of enteral formulas with respect to other macronutrients and overall energy provision (Heyland et al., 2017; Heyland et al., 2018; Puthuchearry et al., 2018). Nutrition therapy trials in the critically ill should consider the duration of the nutrition intervention, with a particular focus on nutrition provision following ICU discharge, because there is increasing evidence that this period contributes to significant nutritional deficits (Ridley et al., 2020). Furthermore, the combination of

optimal nutrition provision and physical therapy has theoretical benefits and should be explored to assess its impacts on muscle mass and functional recovery (Heyland et al., 2016).

Finally, within critical care nutrition research, standardisation of outcome assessments, so-called core-outcome sets, may be beneficial (Arabi & Preiser, 2017). However, the use of core-outcome sets should not stifle innovation in this field. Better tools to measure the effect of nutrition therapy are required; ideally, these would not require significant patient participation and would be simple to administer. The measurement of muscle mass using ultrasound does show some promise, but further research is warranted to determine if muscle ultrasound measurement is an appropriate way to monitor the effect of nutrition therapy (Weinel et al., 2019). Moreover, before muscle mass can be considered a useful surrogate outcome of improved quality of life, a causal relationship between muscle mass and outcomes that are important to patients must be proven.

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Appendices

Appendix 1 (page 223): **Fetterplace K**, Gill BMT, Chapple LS, Presneill JJ, MacIsaac CM, Deane AM. 'Systematic review with meta-analysis of patient-centered outcomes, comparing international guideline recommended enteral protein delivery to usual care'. Journal of Parenteral and Enteral Nutrition 2020; 44(4):610-620. DOI: 10.1002/jpen.725. PMID: 31617220

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Appendix 2 (page 234): **Fetterplace K**, Beach LJ, MacIsaac CM, Presneill JJ, Edbrooke L, Parry SM, Rechnitzer T, Curtis R, Berney S, Deane AM, Denehy L. 'Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness'. Journal of Human Nutrition and Dietetics 2019; 32(6):702-12.

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Appendix 3 (page 245): Wittholz K, **Fetterplace K**, Clode M, George ES, MacIsaac CM, Judson R, Presneill JJ, Deane AM. 'Measuring nutrition related outcomes in a cohort of multi-trauma patients follow intensive care unit discharge'. Journal of Human Nutrition and Dietetics 2020; 33(3):414-422. DOI: 10.1111/jhn.12719 PMID: 31788891

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Appendix 4 (Page 254) **Fetterplace K**, Deane AM, Tierney A, Beach L, Knight LD, Rechnitzer T, Forsyth A, Mourtzakis M, Presneill J, MacIsaac C. 'Targeted full energy and protein delivery in critically ill patients: A study protocol for a pilot randomised control trial (FEED Trial)'. Pilot and Feasibility Studies 2018; 4:52. DOI: doi.org/10.1186/s40814-018-0249-9 PMID: 2948196

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Appendix 5 (page 265): **Fetterplace K**, Deane AM, Tierney A, Beach LJ, Knight LD, Presneill JJ, Rechnitzer T, Forsyth A, Gill BMT, Mourtzakis M, MacIsaac C. 'Targeted full energy and protein delivery in critically ill patients: A pilot randomized controlled trial (FEED Trial)'. *Journal of Parenteral and Enteral Nutrition* 2018; 42(8):1252-1262. DOI: 10.1002/jpen.1166.

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Appendix 1

Review



Systematic Review With Meta-Analysis of Patient-Centered Outcomes, Comparing International Guideline-Recommended Enteral Protein Delivery With Usual Care

Kate Fetterplace, APD, BNutDiet^{1,2} ; Benjamin M. T. Gill, APD, MDiet¹; Lee-anne S. Chapple, APD, PhD^{3,4} ; Jeffrey J. Presneill, MBBS, PhD^{2,5}; Christopher MacIsaac, MBBS, PhD^{2,5}; and Adam M. Deane, MBBS, PhD^{2,5}

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Abstract

Background: International guidelines recommend that protein be administered enterally to critically ill patients at doses between 1.2 and 2 g/kg per day. Observational data indicate that patients frequently receive less protein. The aim of this systematic review was to evaluate patient-centered outcomes with guideline-recommended enteral protein compared with usual care. **Methods:** A systematic review was performed of randomized controlled trials including critically ill adult patients provided predominately enteral nutrition with mean protein at ≥ 1.2 g/kg per day (intervention) and < 1.2 g/kg per day (comparator). Random-effects models were applied for outcomes reported in ≥ 3 trials. **Results:** Of 1375 abstracts, 69 full-text articles were reviewed, and 6 trials met the inclusion criteria, including 511 patients. The intervention group received a mean (SD) of 1.3 (0.08) g/kg per day, and the comparator group received 0.75 (0.15) g/kg per day protein. Insufficient data were available for meta-analyses on the primary outcome (muscle mass or strength). According to our meta-analyses, mortality at 28 days (5 studies) (risk ratio 0.92 [95% CI 0.63–1.35], $P = .66$) and the durations of intensive care unit (6 studies) and hospital admission (4 studies) were similar between the intervention and comparator, with some uncertainty due to sample sizes and heterogeneity. **Conclusion:** There are insufficient data to conclude whether protein provision within the current international guideline recommendations improves outcomes. In a limited dataset, enteral protein intakes near the lower level of current recommendations do not appear to reduce admission duration or mortality when compared with usual care in critically ill. (*JPEN J Parenter Enteral Nutr.* 2020;44:610–620)

Keywords

critical care; enteral nutrition; muscle mass; outcomes research/quality; protein

Introduction

Recommendations from international critical care guidelines suggest that critically ill patients should receive at least 1.2 g/kg body weight per day of protein via the enteral

route.^{1–4} These guidelines were developed on the assumption that protein delivery > 1.2 g/kg body weight per day may reduce morbidity and mortality.³ However, observational data suggest that many patients do not meet these recommended

From ¹Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia; ²Department of Medicine, The University of Melbourne, Parkville, Australia; ³Discipline of Acute Care Medicine, School of Medicine, University of Adelaide, Adelaide, South Australia, Australia; ⁴Intensive Care Research, Royal Adelaide Hospital, Adelaide, South Australia, Australia; and the ⁵Intensive Care Unit, Royal Melbourne Hospital, Parkville, Australia.

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Corresponding Author:

Kate Fetterplace, APD, BNutDiet, Senior Dietitian, Allied Health, Royal Melbourne Hospital, Grattan St Parkville, Victoria, 3050, Australia.
Email: kate.fetterplace@mh.org.au

protein targets, with several studies reporting that during usual critical care management, patients only receive a mean of 0.6–0.8 g/kg per day protein, presumably because of interruptions to feeding, intolerance, and limited availability of higher-protein formulas.^{5–9}

During critical illness, the frequent occurrence of muscle loss is associated with inferior patient-centered outcomes.³ Inflammatory mediators, coupled with inactivity, may drive an imbalance between protein breakdown and synthesis,^{10,11} with rapid muscle loss of up to 1%–2% of lean body mass per day.^{11,12} It remains unclear whether increased delivery of protein may stimulate protein synthesis and attenuate this muscle loss¹¹ or otherwise favorably influence important patient-centered outcomes, including acute illness duration and mortality, or functional capacity and quality of life in survivors.^{3,13,14}

The aim of this systematic literature review was to evaluate data from all eligible randomized clinical trials to estimate the effect of enteral protein delivered according to international guideline recommendations (ie, ≥ 1.2 g/kg per day) when compared with the care usually administered (ie, <1.2 g/kg per day). The outcomes of interest were muscle mass and strength, duration of intensive care unit (ICU) and hospital admission, requirement for transfer to a rehabilitation facility, physical function, quality of life, and mortality.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹⁵ and methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁶ and Centre for Research and Dissemination guidance.¹⁷ The protocol was registered on PROSPERO (registration CRD42018109924).

The research question was “In critically ill adult patients (population), does protein delivery ≥ 1.2 g/kg per day of ideal body weight (IBW) via enteral nutrition (EN) (intervention), when compared with <1.2 g/kg per day of IBW (comparator), influence patient-centered outcomes (outcome)?” All of the study procedures were undertaken by the lead author (KF), with a second reviewer (BG) independently completing title and abstract screening, full-text review, quality assessment, and data extraction and with a third and fourth reviewer (AMD and LC) resolving any conflicts and discrepancies between the first and second reviewers. Endnote reference manager software program (version X7.8, USA: Thomas Reuters, 2014), Covidence 2018 (www.covidence.org), and Review Manager (version 5.3) were used to undertake the review and track processes.

Inclusion and Exclusion Criteria

Studies were included if

- They were randomized clinical trials;
- They included only adult patients (≥ 18 years old);
- The participants were admitted to an ICU with the majority receiving mechanical ventilation;
- One group received ≥ 1.2 g/kg IBW per day of protein via predominately EN (more protein cohort), whereas the other group received <1.2 g/kg IBW per day of protein (less protein cohort);
- The difference in protein delivery between the 2 groups was statistically different (significance set at the 0.05 level); and
- At least 1 of the predefined outcomes was reported as a primary or secondary outcome.

Studies were excluded if

- Protein provided was exclusively parenteral nutrition (PN);
- Protein provision was due to glutamine supplementation or other immune-enhancing amino acids such as arginine; and
- The original article could not be located or was not available in English.

“Predominately enteral” protein was a definition used for this systematic review to identify studies that clearly provided nutrition therapy via the enteral route in preference to PN. Although PN, either as total or supplemental nutrition support, was not an exclusion criterion, studies were only included if PN was administered when the enteral route was not possible or was insufficient. This approach to use “predominately enteral” was taken because it is in line with current international guidelines and local practice.^{1,6} This is in contrast to the use of PN as part of initial therapy, which does not represent usual care, and the route of protein administration (ie, intravenous) may be a potential confounding variable.¹⁸ The threshold protein provision of ≥ 1.2 g/kg was based on IBW to try to account for studies that included participants with body mass indices (BMIs) greater than the healthy weight range. IBW was selected because there is uncertainty about what weight (actual or ideal) should be used to dose protein.¹⁹

Search Strategy

A systematic search of the literature was conducted using 4 databases, MEDLINE (Ovid SP, from 1948 to current), EMBASE (OVID SP, from 1948 to current), the current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL, EBSCOhost, from 1948 to current), including studies published up until November 9, 2018. The search strategy was refined to exclude infant and pediatric patients and animals. No other restrictions or limits were placed on the search strategy. The

search terms used included all variations of critical ill, intensive care, critical care, nutrition support, EN, nasogastric, nasojejunal, dietary protein, protein, and amino acids. A full sample of the MEDLINE search strategy is included in supplementary Appendix 1. Additionally, reference lists from relevant reviews and guidelines were checked, and the MEDLINE search was repeated on March 15, 2019, for any additional studies for inclusion.^{1,2,20-22}

Outcome Measures

The major outcomes of interest were muscle mass at ICU or hospital discharge (assessed using ultrasonography of any muscle, such as quadriceps muscle layer thickness as described by Tillquist et al.²³ or any other validated technique such as computed tomography and bioimpedance)²⁴ or muscle strength at ICU or hospital discharge (assessed using handgrip dynamometry or any other validated technique).²⁵ The secondary outcomes were physical function at ICU discharge, quality of life at any time point, the requirement for transfer to a rehabilitation facility, mortality at any time point, duration of ICU and hospital admission, and incidence of diarrhea. Following the systematic review and extraction of trials, it became apparent that only the outcomes of mortality, duration of ICU and hospital admission, and incidence of diarrhea provided sufficient data to be included in the meta-analysis.

Data Extraction and Risk of Bias

Data extraction was completed independently by 2 reviewers (KF and BG). Data collection included study characteristics (author, year of publication, patient inclusion criteria, trial objectives, intervention and control methods, protein and energy targets, characteristics of participants, protein and energy provision, and all reported outcomes of interest). The corresponding authors of relevant publications were contacted to clarify missing data and protein provision if they were not documented in g/kg IBW per day and the mean BMI was above the healthy weight range. Each included study was assessed independently by the first and second reviewer for risk of bias in random sequencing generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other sources of bias using the Cochrane Risk of Bias Tool,¹⁶ with AMD providing assessment when required for consensus.

Data Handling and Statistical Analysis

Binary data are presented as proportions or percentages. If original studies reported mortality at different time points, all were noted; however, 28-day mortality was selected for analysis as the most complete outcome data. For continuous variables, mean and SD were directly recorded, and

median with interquartile range data were converted prior to analysis to approximate mean (SD) data as described by Wan et al.²⁶ All included studies reported protein and energy provision in g/kg per day and kcal/kg per day; when actual weight was reported and the mean BMI was within the healthy weight range (BMI 18.5–25 kg/m² if ≤65 years old, 22–27 kg/m² if >65 years old), the reported mean (SD) protein dose was used in data analyses; if actual weight was reported and the mean BMI was above the healthy weight range, then calculations were done to assess the protein provision based on IBW (defined as the upper end of the healthy weight range); if studies reported IBW or an adjusted IBW for the protein dose, this was used in the data analyses. One author was contacted²⁷ to further assess their data to confirm that protein was provided at a level of 1.2 g/kg IBW per day in the intervention.

Random-effects meta-analyses were applied to the outcomes of mortality and length of admission using the package “metan” in Stata statistical software (version 15.1, College Station, TX, USA). Effect estimates for mortality are presented as risk ratios (RRs) with 95% CIs, and the effect estimates of length of stay are reported as standardized mean differences (SMDs) with 95% CI. Variation in RR and SMD attributable to heterogeneity was summarized for each of these outcomes using the I² statistic.

Results

There were 2215 records identified from the database searching and no additional papers from other sources. After duplicates and irrelevant papers were excluded based on titles and abstracts alone, 69 papers underwent full-text review. Six trials were eligible for inclusion, which included 511 patients (Figure 1, PRISMA diagram).²⁷⁻³²

Study and Patient Characteristics

The included trials were conducted over a range of years and in various regions (3 from Europe and 1 each from the United States of America, South America, and Australia) from 1993 to 2018.²⁷⁻³² The study objectives and interventions varied; however, all studies except that of Eyer et al.²⁹ aimed to deliver protein within the guidelines’ range from the outset in the intervention group and below the guidelines’ range in the comparator group. In order to meet the higher protein requirements, all studies incorporated the use of a higher-protein enteral formula, with 2 studies also using supplemental protein powder.^{30,31} Three studies aimed to deliver standardized amounts of energy between groups.^{27,30,32} Two studies used supplemental PN to meet energy and protein needs.^{27,28} The full details of the included study methodologies are provided in Table 1. All studies, except Van Zanten et al.,³² were single center and all studied relatively small cohorts, enrolling between 38 and 199 participants. The mean (SD)

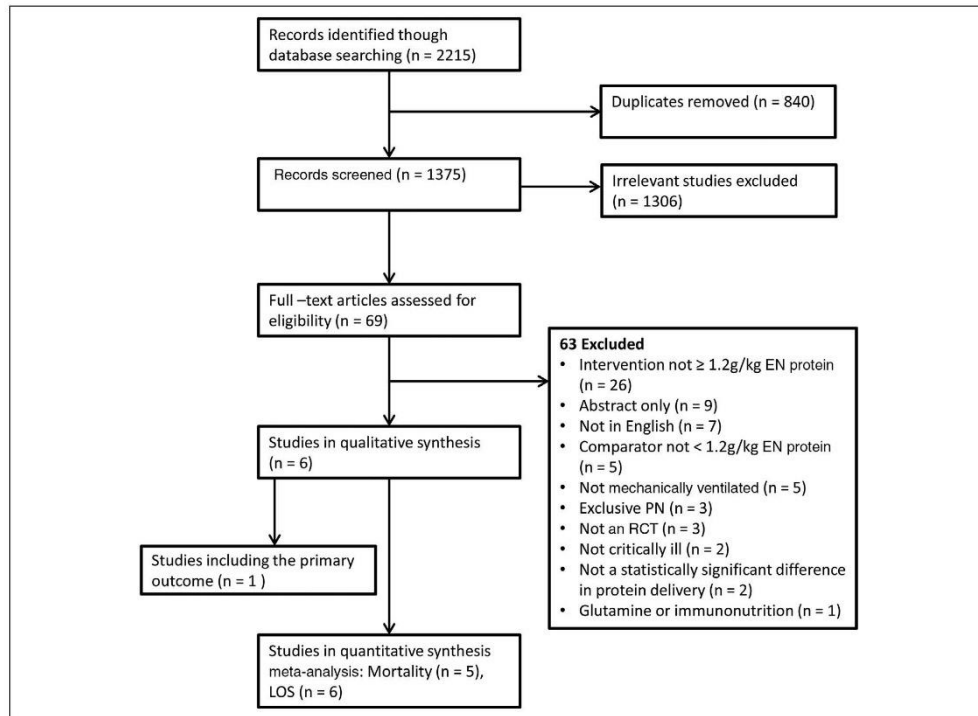


Figure 1. PRISMA diagram. EN, enteral nutrition; LOS, length of stay; PN, parenteral nutrition; RCT, randomized controlled trial.

ages for the intervention and control groups were 57 (7.9) and 57 (8.3) years. The mean (SD) BMIs for the intervention and control group were 27 (3.7) and 27 (3.4) kg/m^2 , respectively, and the mean (SD) Acute Physiology and Chronic Health Evaluation II scores were 22 (6) and 22 (5.4), respectively. Details of the participant characteristics in the included studies are provided in Table 2.

Protein and Energy Provision

The mean duration of the interventions ranged from 7 to 18 days, with an unweighted pooled mean of 11 (3.8) days. All studies included an intervention group that delivered a greater amount of protein (Table 3). The intervention group received a mean (SD) protein delivery of 1.3 (0.08) g/kg per day, and the control group received a mean protein delivery of 0.75 (0.15) g/kg per day, with an unweighted pooled mean difference of 0.55 (95% CI 0.40–0.71) g/kg per day. Energy provision was variable within the 2 groups, with 2 studies delivering substantially more energy in the intervention group

(Table 3). The intervention group received an unweighted pooled mean of 21 (6.3) kcal/kg per day, and the control group received a mean of 17 (3.8) kcal/kg per day, with the mean difference in energy delivery being 3.5 (95% CI 3.3–10.2) kcal/kg per day.

Assessment for Risk of Bias

The risk-of-bias assessment for each of the included studies can be visualized (Figures 2a and 2b). Four studies were considered of high quality,^{27,28,30,32} and 2 studies were of low quality.^{29,30} Only 1 study had unequivocally adequate blinding,³² and although a second study reported using double-blind methodology,²⁷ it was unclear how this was achieved.

Outcomes

Functional outcomes. Muscle mass, muscle strength, quality of life, and physical function outcomes were reported in only 1 study. Our group (Fetterplace et al) reported that

Table 1. Summary of Methods for Included Studies.

Author, Year, Country	Number of Centers	Study Objective	Methods		Protein Target Per Day		Energy Target Per Day	
			Study Intervention	Study Control	Intervention	Control	Intervention	Control
Allingsstrup, 2017, ²⁶ Denmark	1	To assess the effects of individualized energy and protein nutrition optimized by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance) on physical quality of life at 6 mo in acutely admitted, adult ICU patients	Standard high-protein formula (1.5 kcal/mL, 75 g protein/1000 mL), with addition of supplemental PN, if required to reach the goals, up to 90 d or discharge	Standard formula (1 kcal/mL, 38 g protein/1000 mL); if calculated goal rate was not met by 7 d, supplemental PN was commenced	At least 1.5 g/kg actual weight, assessed with urinary nitrogen	Approximately 0.95 g/kg actual weight	Measured energy expenditure	25 kcal/kg
Eyer, 1993, ²⁹ USA	1	To assess whether early enteral nutrition will attenuate the metabolic response after blunt trauma	Early nutrition support (day 0), peptide-based formula (1.33 kcal/mL, 58 g protein/1000 mL), up to discharge	Late nutrition support (72 h, IV fluid), peptide-based formula (1.33 kcal/mL, 58 g protein/1000 mL)	1.5 g/kg actual weight	1.5 g/kg actual weight (once feeds commenced)	Approximately 34 kcal/kg	Approximately 34 kcal/kg (once feeds commenced)
Fetterplace, 2018, ³⁰ Australia	1	To determine whether a high-protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly rate-based nutrition protocol for critically ill patients without protein supplementation to mechanically ventilated	Standard high-protein formula (1.25 kcal/mL, 63 g protein/1000 mL) with a volume-based feeding protocol, plus supplemental protein powder in 3–4 bolus/d, for up to 15 d or discharge	Standard formula (1 kcal/mL, 40 g protein/1000 mL)	1.5 g/kg IBW Based on BMI for age For BMI > 32 Adjusted IBW was used = IBW + (25% actual – IBW)	Approximately 1 g/kg IBW	25 kcal/kg IBW Based on BMI for age For BMI > 32, adjusted IBW was used = IBW + (25% actual – IBW)	25 kcal/kg IBW Based on BMI for age For BMI > 32, adjusted IBW was used = IBW + (25% actual – IBW)
Jacob, 2017, ²⁷ Switzerland	1	To test the effect of a new enteral formula on the frequency of diarrhea and gastrointestinal tolerance and on all diarrhea-related costs in ICU long-stayers	High-protein enteral ICU-specific formula (1.5 kcal/mL, 94 g protein/1000 mL), for up to 10 d or discharge	Standard formula (1.57 kcal/mL, 61 g protein/1000 mL)	Approximately 1.55 g/kg actual weight	Approximately 0.97 g/kg actual weight	25 kcal/kg actual weight	25 kcal/kg actual weight
Rugeles, 2013, ³¹ Colombia	1	To compare 2 enteral nutrition regimens in the critically ill patient and their impact in the development of severe organic failure, as measured with SOFA	Standard enteral feed (1.3 kcal/mL, 66.6 g protein/1000 mL), plus supplemental soy protein powder in 2 bolus/d, for up to 7 d or discharge	Standard enteral feed (1.3 kcal/mL, 66.6 g protein/1000 mL)	1.5 g/kg actual weight	Approximately 1 g/kg actual weight	15 kcal/kg actual weight	25 kcal/kg actual weight
Van Zanten, 2018, ³² Netherlands	4	To investigate protein and energy intake, gastrointestinal tolerance, and safety of this new polymeric very high-protein formula	Very high-protein formula (1.25 kcal/mL enteral, 100 g protein/1000 mL), up to 28 d or discharge	Standard high-protein formula (1.25 kcal/mL, 63 g protein/1000 mL)	Approximately 2 g/kg IBW	Approximately 1.25 g/kg IBW	25 kcal/kg IBW For BMI > 30 IBW = 30x(Ht m ²)	25 kcal/kg IBW For BMI > 30 IBW = 30x(Ht m ²)

BMI, body mass index; Ht, height; IBW, ideal body weight; ICU, intensive care unit; IV, intravenous fluid; PN, parenteral nutrition; SOFA, sequential organ failure assessment.

Table 2. Participant Characteristics of Included Studies.

Author, Year	No. Randomized		Age, Year, Mean (SD)		Sex, n % Males		BMI, kg/m ² , Mean (SD)		Proportion of Medical Admission, n (%)		APACHE II Score, Mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Allingstrup, 2017 ²⁸	100	99	62 (15.8)	65 (17)	65 (65)	59 (60)	22.7 (4.5)	22 (3.8)	52(52)	43 (43)	N/A	N/A
Eyer, 1993 ²⁹	19	19	44 (22)	41 (18)	14 (73)	8 (42)	N/A	N/A	0 (0)	0 (0)	N/A	N/A
Fetterplace, 2018 ³⁰	30	30	55 (13)	57 (16)	23 (77)	21 (70)	30 (7.1)	29 (5.3)	21 (70)	16 (53)	22 (6.2)	20 (5.9)
Jakob, 2017 ²⁷	46	44	64 (17)	61 (17)	33 (72)	28 (64)	29 (7)	28 (6.1)	N/A	N/A	28 (8)	28 (8.7)
Rugeles, 2013 ³¹	40	40	53 (20)	56 (20)	22 (55)	24 (60)	24 (3.3)	24 (4.4)	40 (100)	40 (100)	14 (4.8)	15 (6.2)
Van Zanten, 2018 ³²	22	22	64 (13)	61 (15)	9 (41)	13 (59)	30 (4.1)	31 (8.4)	8 (36)	9 (41)	25 (5.6)	23 (7.1)

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index.

muscle mass loss, measured using quadriceps muscle layer thickness, was attenuated with greater protein delivery.³⁰ There was no difference in muscle strength and physical function; however, inferences were limited by significant amounts of missing data (up to 80% of participants). Allingstrup et al attempted to assess muscle strength, but this was abandoned mid-study because of methodological difficulties.²⁸ The latter study was the only one to assess quality of life; they found there was no difference between the high- and low-protein groups at 6 months post hospital discharge²⁸; however, outcome data were missing in 18% of survivors. The requirement for transfer to a rehabilitation facility was only reported by a single study, in which greater protein administration did not impact the proportion of patients who required rehabilitation.³⁰

Mortality. The provision of ≥ 1.2 g/kg per day protein did not reduce 28-day mortality (Figure 3, 5 studies, 431 participants)^{27-30,32} (RR 0.92, 95% CI 0.63–1.35, $P = .66$, $I^2 = 0\%$ $P = .99$).

Length of stay. Greater protein delivery did not reduce length of ICU or hospital admission. The SMD for length of ICU admission (Figure 4) (6 studies, 511 participants)²⁷⁻³² was 0.01 days (95% CI 0.39–0.38, $P = .98$, $I^2 = 76\%$, $P = .001$), and for hospital length of admission (4 studies, 393 participants)^{27,28,30,32} the SMD was 0.09 days (95% CI 0.29–0.11, $P = .38$, $I^2 = 76\%$, $P = .01$).

Diarrhea. Three studies reported the incidence of diarrhea.^{27,30,32} Diarrhea was not significantly different between the 2 groups (RR 0.90, 95% CI 0.71–1.1, $P = .37$, $I^2 = 0\%$).

Discussion

This systematic literature review and meta-analysis did not detect any effect on mortality or length of admission with protein provision at the level of international guidelines (≥ 1.2 g/kg IBW per day) when compared with what the majority of patients receive as usual care (< 1.2 g/kg IBW per day). However, confidence in these results is low because of both the small number of participants that have been included in trials ($n = 511$) and the heterogeneity of study methodology. Importantly, many of the outcomes of interest, including the major primary outcomes muscle mass and strength, as well as quality of life and the requirement for transfer to a rehabilitation facility, were not sufficiently reported in the original studies to enable meta-analyses. Accordingly, this review highlights the lack of trial data available to evaluate current guideline recommendations regarding optimal enteral protein administration to the critically ill.

Mean protein provision was consistent across the included studies, with the intervention group receiving a mean

Table 3. Energy and Protein Provision of Included Studies.

Author, Year	Duration of Intervention Mean (SD), days	Delivered Protein, Mean (SD), g/kg per day		Delivered Energy, Mean (SD), kcal/kg per day	
		Intervention	Control	Intervention	Control
Allingstrup, 2017	11.3 (12.8)	1.4 (0.42)	0.49 (0.30)	24 (6.6)	14 (6.8)
Eyer, 1993	11.8 (7.9)	1.3 (0.30)	0.9 (0.2)	30 (6)	19 (5)
Fetterplace, 2018	10.6 (8.3)	1.2 (0.30)	0.75 (0.11)	23 (5.7)	21 (3.3)
Jakob, 2017	7 (2.6)	1.2 (0.47)	0.90 (0.20)	20 (7.4)	22 (4.9)
Rugeles, 2013 ^a	9.5 (5.5)	1.4	0.76	12	14
Van Zanten, 2018	18.4 (13.4)	1.3 (0.95)	0.70 (0.32)	16 (11)	15 (6.3)

^aOnly mean figures for protein and energy delivery were reported in the original paper. The author was contacted for clarification of the variance; however, this was not provided.

of 1.3 (0.08) g/kg per day of protein, inferring that approximately two-thirds of the patients in this group received the minimum recommended amount of protein (≥ 1.2 g/kg per day). Protein delivery was less consistent in the comparator group, with the mean protein delivery ranging from 0.5 to 0.9 g/kg per day (mean 0.75 (1.5) g/kg per day); this is reflective of variation in clinical practice.⁶ This review highlights that to date, all studies aiming to achieve higher protein provision with predominately EN have only managed to deliver mean protein at the lower end of the current international guidelines’ recommendations, and therefore, a proportion of patients in the intervention group of this systematic review received less protein than recommended. No randomized controlled trial has successfully delivered protein at the upper end of the international guidelines (ie, 1.6–2 g/kg per day) to all patients using predominately EN, and therefore, it is unknown whether outcomes would be better or worse if this occurred. It is also uncertain as to whether it is the protein dose per se that is important or whether the route of delivery or type of protein is relevant and what effect energy intake has on protein utilization or whether protein should be delivered as a “package” of care in combination with exercise.^{33–36} Furthermore, it remains unclear whether enteral protein digestion and absorption is impaired during critical illness and how any abnormality impacts delivery of protein and outcome.³⁷

It should be recognized that energy delivery varied between trials. Energy provision across the high-protein group and the comparator group was not standardized, and in most of the studies, the energy delivery was not in line with the current guideline recommendations.¹ Although the amount of energy delivered may confound the impact of protein delivery,^{7,8,38} a recent large blinded randomized controlled trial reported that augmented energy delivery (ie, consistent with international guidelines) when compared with standard care had no impact on mortality or other patient-centered outcomes when similar amounts of protein

were administered.^{39–41} However, functional outcomes for this trial are yet to be published.

The novelty of this systematic review is that only randomized clinical trials that provided predominately enteral protein, within the guidelines range in the intervention group, were included. Accordingly, the intervention group approached what current international guidelines recommend, and the comparator group represents “usual” clinical care, as established in numerous observational trials in various regions. Three systematic reviews have previously evaluated the impact of protein provision in the critically ill.^{20,22,42} The most recent of these was by Davies et al,²⁰ who evaluated the effect of 2 different protein doses on mortality, length of stay, incidence of pneumonia, and length of mechanical ventilation. Similar to the current review, they reported that greater protein provision did not appear to influence mortality or any of the other secondary outcomes.²⁰ However, this review included studies that administered EN or PN, as well as including studies that administered specific amino acids such as glutamine. This is important because guidelines recommend that PN is reserved for specific cases, and trial data suggest outcomes from exogenous glutamine supplementation are worse than with standard care.⁴³ Hence, including studies using specific amino acids is unlikely to be representative of mixed protein administration. Davies et al also included all studies that delivered 2 different amounts of protein, irrespective of whether this was within the current guideline recommendations. Of the 8 studies included by Davies et al that delivered predominately EN,^{44–51} none of these achieved ≥ 1.2 g/kg per day protein in the intervention group (ie, international guideline recommendations) and <1.2 g/kg per day in the comparator group. Furthermore, there have been trials recently published in this field, with 4 out of the 6 studies included in the current systematic review published after the review by Davies et al.²⁰ The 2 systematic reviews conducted prior to Davies et al^{22,42} also incorporated both EN and PN and multiple study methodologies. In addition,

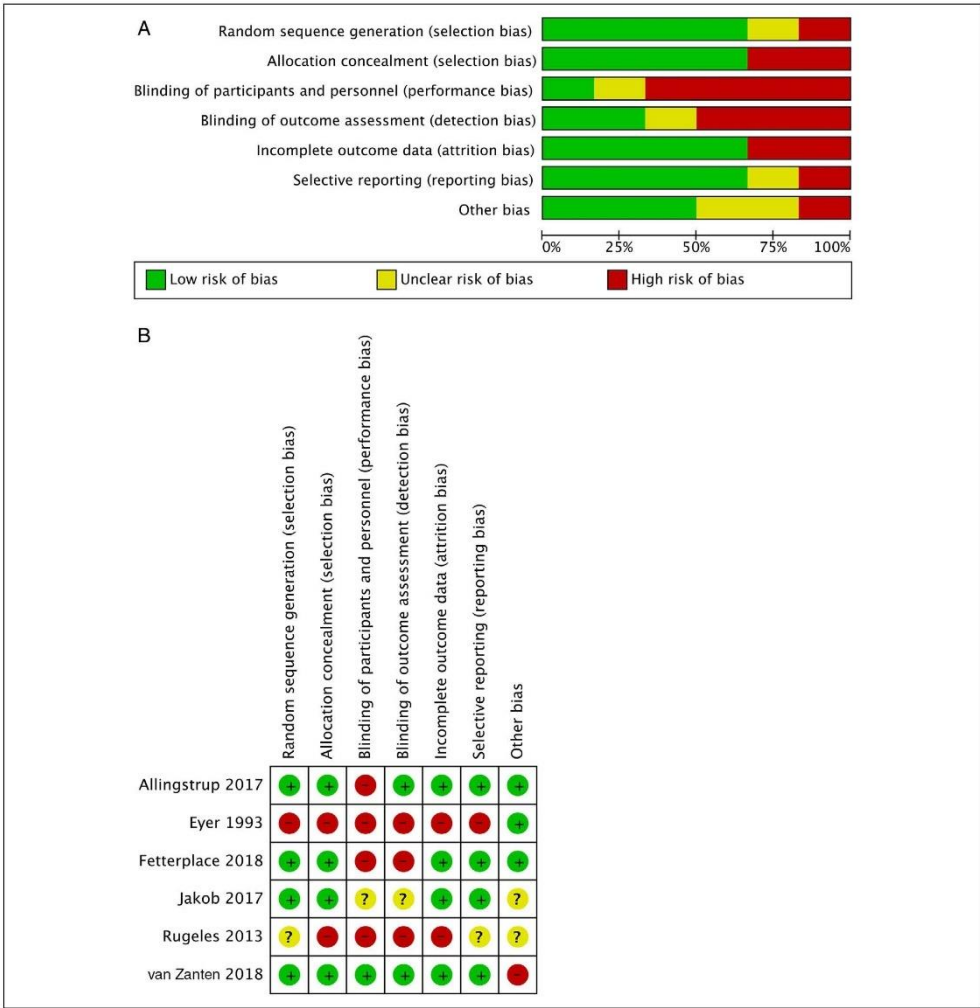


Figure 2. Summary of risk-of-bias assessment. (A) Risk-of-bias summary for each included study. (B) Summary of domains for risk of bias for included studies.

Ferrie et al included studies that were not conducted in the ICU.²²

Strength and Limitations

The main strength of this systematic review is that randomized clinical trials that provided predominately EN, with mean protein provision within the current guidelines

range in the intervention and similar to usual care in the comparator, were included. This removed potential confounders of PN and immune-modulating amino acids such as glutamine.

There are several limitations to this review. The most substantial limitation is the lack of data available to facilitate analyses for the primary outcomes. Likewise, many of the other secondary outcomes of interest were not able to

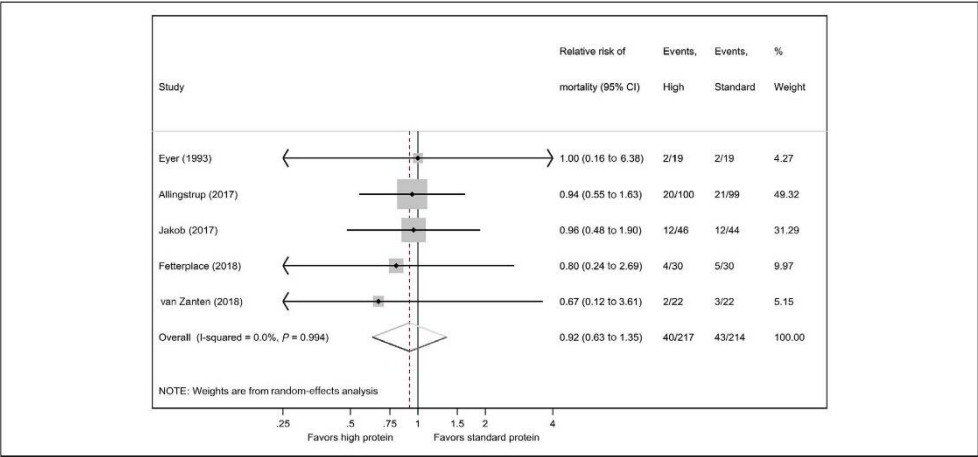


Figure 3. Random-effects meta-analysis of mortality, sorted by ascending year of publication. Random-effects model using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Analysis using Stata command “metan” in Stata version 15.1, College Station, TX, USA. High, higher protein (intervention group); SMD, standardized mean difference; Standard, usual protein group (Comparator).

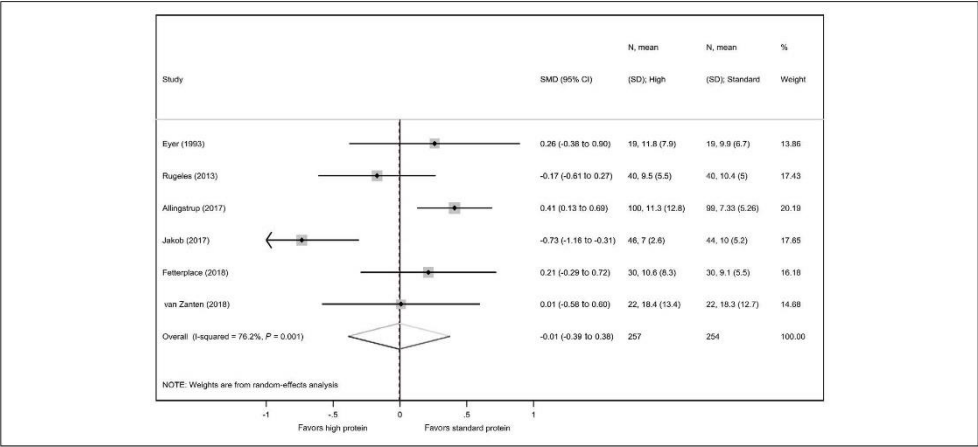


Figure 4. Random-effects analysis of length of admission, sorted by ascending year of publication. Random-effects model returned by using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the from the Mantel-Haenszel model. Analysis using Stata command “metan” in Stata version 15.1, College Station, TX, USA. High, higher protein (intervention group); SMD, standardized mean difference; Standard, usual protein group (Comparator).

be included in meta-analyses because of insufficient data; these outcomes included physical function, requirement for rehabilitation, and quality of life. Even when there were sufficient data to conduct meta-analyses, such as with mortality, point estimates were limited by an inadequate number of patients, particularly for such a ubiquitous intervention as nutrition therapy,⁵² leading to wide CIs. The duration of ICU- and hospital-admission point estimates was also limited by small sample sizes as well as significant heterogeneity, resulting in considerable uncertainty in these results. A limitation of meta-analyses includes clinical heterogeneity⁵³; clinical heterogeneity that may have affected the results

of this study includes patient factors, premorbid nutrition state, and duration of intervention. Lack of data and heterogeneity within existing data may explain why the current international guidelines acknowledge that there is some uncertainty regarding the optimal protein dose.¹

Conclusion

There are insufficient data to conclude whether enteral protein provision within the current international guideline recommendations improves patient-centered outcomes for critically ill patients. In a limited dataset of critically ill patients, mean enteral protein intake at approximately the lower end of the range recommended by international guidelines did not appear to reduce acute admission duration or mortality when compared with usual care. Large, methodologically rigorous, randomized clinical trials evaluating protein provision within the guideline recommendations, possibly combined with physical therapy interventions, are required to assess the impact on patient-centered outcomes such as functional capacity and muscle mass and strength and, thereby, inform clinical practice.

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Statement of Authorship

K. Fetterplace and A. M. Deane equally contributed to the conception and design of the research; L. S. Chapple and C. MacIsaac contributed to the design of the research; K. Fetterplace, B. M. T. Gill, L. S. Chapple, A. M. Deane, and J. J. Presneill contributed to the acquisition and analysis of the data; K. Fetterplace, J. J. Presneill, and A. M. Deane contributed to the interpretation of the data; and K. Fetterplace and A. M. Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix 2



RESEARCH PAPER

Associations between nutritional energy delivery, bioimpedance spectroscopy and functional outcomes in survivors of critical illness

K. Fetterplace,^{1,2} L. J. Beach,³ C. MacIsaac,^{2,4} J. Presneill,^{2,4} L. Edbrooke,⁵ S. M. Parry,⁵ T. Rehnitz,⁴ R. Curtis,³ S. Berney,⁶ A. M. Deane^{2,4} & L. Denhehy⁵

¹Department of Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, VIC, Australia

²Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia

³Department of Allied Health (Physiotherapy), Royal Melbourne Hospital, Melbourne, VIC, Australia

⁴Intensive Care Unit, Royal Melbourne Hospital, Parkville, VIC, Australia

⁵Department of Physiotherapy, The University of Melbourne, Melbourne, VIC, Australia

⁶Department of Physiotherapy, Austin Health, Melbourne, VIC, Australia

Keywords

bioimpedance spectroscopy, critical care, enteral nutrition, indirect calorimetry, muscle strength, nutrition support.

Correspondence

K. Fetterplace, Nutrition Department, Level 3 Allied Health, Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3050, Australia.
Tel.: +61 9342 7440
Fax: +61 93428440
E-mail: kate.fetterplace@mh.org.au

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Abstract

Background: Patients who survive critical illness frequently develop muscle weakness that can impact on quality of life; nutrition is potentially a modifiable risk factor. The present study aimed to explore the associations between cumulative energy deficits (using indirect calorimetry and estimated requirements), nutritional and functional outcomes.

Methods: A prospective single-centre observational study of 60 intensive care unit (ICU) patients, who were mechanically ventilated for at least 48 h, was conducted. Cumulative energy deficit was determined from artificial nutrition delivery compared to targets. Measurements included: (i) at recruitment and ICU discharge, weight, fat-free mass (bioimpedance spectroscopy) and malnutrition (Subjective Global Assessment score B/C); (ii) at awakening and ICU discharge, physical function (Physical Function in Intensive Care Test-scored) and muscle strength (Medical Research Council sum-score (MRC-SS)). ICU-acquired weakness was defined as a MRC-SS score of less than 48/60.

Results: The median (interquartile range) cumulative energy deficit compared to the estimated targets up to ICU day 12 was 3648 (2514–5650) kcal. Adjusting for body mass index, age and severity of illness, cumulative energy deficit (per 1000 kcal) was independently associated with greater odds of ICU-acquired weakness [odds ratio (OR) = 2.1, 95% confidence interval (CI) = 1.4–3.3, $P = 0.001$] and malnutrition (OR = 1.9, 95% CI = 1.1–3.2, $P = 0.02$). In similar multivariable linear models, cumulative energy deficit was associated with reductions in fat-free mass (–1.3 kg; 95% CI = –2.4 to –0.2, $P = 0.02$) and physical function scores (–0.6 points; 95% CI = –0.9 to –0.3, $P = 0.001$).

Conclusions: Cumulative energy deficit from artificial nutrition support was associated with reduced functional outcomes and greater loss of fat-free mass in ventilated ICU patients.

Introduction

Patients who survive critical illness frequently develop muscle weakness, which has been termed intensive care unit (ICU)-acquired weakness (ICU-AW). ICU-AW is associated with diminished physical function and lower health-related quality of life, as well as increased ICU and hospital length of stay (LOS), healthcare costs and mortality⁽¹⁻³⁾. Optimal nutrition may attenuate ICU-AW; however, there is a paucity of evidence in this area^(1,4,5).

The optimal nutrition provision for critically ill patients to improve outcomes is uncertain^(6,7) and the composition of nutrition formulae is currently the subject of research^(1,8-10). Observational studies have reported that energy deficits during critical illness are associated with adverse outcomes; such as increased mortality, ICU LOS and period of mechanical ventilation⁽¹¹⁻¹⁴⁾. However, recent randomised clinical trials comparing permissive under-, trophic-, standard- or full-feeding have not identified any link between energy deficit and mortality⁽¹⁵⁻¹⁷⁾.

In all of these large randomised clinical trials, nutrition prescriptions were based on predictive equations, which reflects standard clinical practice^(13,18). However, predictive equations are inaccurate estimates of daily energy expenditure during critical illness compared to 'gold-standard' measurements of energy expenditure using indirect calorimetry⁽¹⁹⁾. Accordingly, the use of predictive equations to assess energy deficits may contribute to inconsistencies between studies regarding energy deficit and associated outcomes^(19,20).

The primary objective of the present study was to determine the cumulative energy deficit from artificial nutrition support using both calculated predictive equations and repeated measured energy expenditure (MEE). The secondary objectives were to explore associations between cumulative energy deficit and nutritional outcomes (change in body weight and fat-free mass and the development of malnutrition) and functional outcomes (muscle strength and physical function) at ICU discharge.

Materials and methods

Study design and setting

This prospective single-centre observational cohort study was conducted in the mixed medical-surgical-trauma ICU of a tertiary-referral Australian hospital. Between 2012 and 2014, consecutive weekday admission patients were screened for eligibility. Initial written informed consent was obtained from the person responsible, with continuation of consent obtained subsequently from competent participants. Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee

(project number: 2012.060)⁽²¹⁾. Reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines⁽²²⁾.

Patient selection

Inclusion criteria were: age ≥ 18 years; mechanical ventilation commenced within 48 h of ICU admission and likely to be required >48 h and an estimated minimum stay in the ICU of at least 5 days. Exclusion criteria were: major trauma necessitating a specific period of immobilisation; new neurological insult, such as spinal cord injury or stroke; poor pre-morbid mobility, defined as inability to walk independently with or without a gait aid; inability to communicate in English; did not have medical insurance cover; ICU re-admission; or if the attending physician did not support inclusion.

Protocol

Standard care for all participants included nutritional assessment by a dietitian within 48 h of admission, with estimation of their nutritional requirements⁽²³⁾. Commercially available enteral and parenteral formulas were utilised, which were prescribed based on clinical need as assessed by the dietitian or ICU physician. Enteral feeding followed the standard unit nutrition protocol, which encouraged the early initiation of nutritional support within 24 h of admission and specified prokinetic drug administration if gastric residual volumes were greater than 300 mL⁽²⁴⁾. All study participants also received respiratory and rehabilitation interventions provided by physiotherapists.

Baseline demographic data including age, gender, admission diagnosis, severity of illness [Acute Physiology and Chronic Health Evaluation (APACHE) II score] and the Nutrition Risk in Critically ill score (NUTRIC) were recorded⁽²⁵⁾. Daily nutritional energy delivery from enteral and parenteral nutrition (not including other energy sources) and nutritional outcome data were collected on participants until ICU discharge or day 30 of the ICU admission, whichever came first.

Nutritional outcomes

Nutritional outcomes were collected at baseline and ICU discharge. Weight was determined via bed scales (Hill-Rom®; Batesville, Indiana, USA) for most patients; if the weight was not available, an estimated weight was used for the nutrition prescription. Height was estimated using ulna length⁽²⁰⁾ and body mass index (BMI) in kg m^{-2} was calculated. A dietitian measured the mid upper arm circumference (cm)⁽²⁶⁾ and assessed nutritional status

using the Subjective Global Assessment (SGA) ^(27,28), with a score of B or C considered as malnourished. Serum albumin (g L^{-1}) and transthyretin (prealbumin) concentrations (mg L^{-1}) were measured, with the normal ranges being 35–50 g L^{-1} and 180–360 mg L^{-1} , respectively ⁽²⁸⁾.

Estimated energy requirements

Estimated energy requirements were calculated by the dietitian at baseline using both the standard weight-based equations of 25–30 $\text{kcal kg}^{-1} \text{day}^{-1}$ ⁽²⁹⁾ and the Schofield equation with appropriate stress factors, in line with standard practice in Australia ^(30,31). For overweight participants ideal body weight (IBW) was used and, for obese participants with a BMI greater than 32 kg m^{-2} , an obesity adjusted weight was used $[\text{IBW} + 25\% (\text{actual body weight} - \text{IBW})]$ ⁽³²⁾. The nutrition prescription (prescribed energy target) was determined based on the dietitian assessment of the estimated energy requirements, using their clinical judgment of which estimation was most reflective of the participant's requirements.

Measured energy expenditure

MEE was determined via indirect calorimetry, in patients with no contraindication, using the Deltatrac[®] II Metabolic Cart (Datex-Ohmeda, Helsinki, Finland) ⁽³³⁾. MEE was undertaken by a trained physician and completed when the participant was mechanically ventilated, on the day of recruitment and on days 3 and 5 after enrolment. Standard methods were used; all expired gas was collected from the expiratory port of the ventilator, the measures were continued for 30 min and summary data were recorded ⁽³⁴⁾. Participants were excluded from MEE if they: had an intercostal catheter with an air leak; were receiving extracorporeal membrane oxygenation; or were in infective isolation. Nutrition support was not stopped during MEE and there was no restriction on the participant's movement prior to MEE. The Metabolic Cart outputs recorded included oxygen consumption (mL min^{-1}), carbon dioxide production (mL min^{-1}), calculated respiratory quotient and MEE (kcal day^{-1}), using the Weir equation. The average MEE was determined from the mean of available repeated measurements.

Cumulative energy deficit

Each participant's cumulative energy deficit from artificial nutrition support was calculated daily for a maximum of 12 ICU days based on *a priori* determination that substantial changes to nutritional tolerance were unlikely

after this time ^(35,36). Daily energy provision was measured for all participants receiving any enteral or parenteral nutrition, not including energy from other sources. Daily energy deficit was determined by deducting the energy delivered from prescribed energy target determined by the dietitian and, secondly, from the average MEE. The daily energy deficit was summed for the total cumulative energy deficit. The nutritional adequacy was assessed by dividing the daily energy delivery, including the day of admission and the day of discharge if it was >8 h, by the prescribed requirements or the average MEE and expressing as a percentage.

Fat-free mass change

Fat-free mass was measured using the tetra-polar-configured multifrequency SFB7 bioimpedance device (AU/NZ; ImpediMed[™] Limited, Pinkenba, QLD, Australia) ⁽³⁷⁾. This device uses bioimpedance spectroscopy to determine total body water, extracellular fluid and intracellular fluid and subsequently calculates fat-free mass and fat mass ⁽³⁷⁾. The use of this device has been validated in the critically ill ^(38,39). Measurements were taken when the participants were supine in bed, after single use gel electrodes were placed on one ipsilateral foot and hand ^(37,39). Fat-free mass was determined immediately after enrolment and at ICU discharge.

Muscle strength and physical function

Muscle strength was assessed using the Medical Research Council sum-score (MRC-SS) with a score of less than 48/60 considered indicative of ICU-AW ^(40,41). Physical function was measured using the Physical Function in Intensive Care Test-scored (PFIT-s) ⁽⁴²⁾. Muscle strength and physical function testing were all conducted by physiotherapy staff and assessments were performed at ICU awakening ⁽⁴³⁾ and ICU discharge (see Appendix S1).

Participant outcomes

Twenty-eight day mortality, ICU LOS, hospital LOS, length of mechanical ventilation, days of sedation (defined as >8 h on any sedative drug), duration of sepsis determined using the American College of Chest Physicians Criteria ⁽⁴⁴⁾ and discharge destination were collected, censored at day 60.

Statistical analysis

Participant demographics, cumulative energy deficit, nutritional and functional outcomes are reported as the mean (SD) or median [interquartile range (IQR)] as

appropriate. Comparisons between outcome measures from baseline to ICU discharge used paired *t*-tests or Wilcoxon signed-rank tests as appropriate. Multivariable generalised linear regression analyses explored associations between cumulative energy deficit (prescribed energy targets) and continuous outcomes, including weight, fat-free mass and physical function scores at discharge. The confounding variables that were adjusted for in these models included age, APACHE II score, BMI and baseline measures where applicable. Logistic regression was performed for the binary outcomes of ICU-AW and malnutrition, adjusted for the same confounding variables, with effect estimates reported as odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analyses were performed for the outcome of ICU-AW, missing values were imputed as first having ICU-AW and then not having ICU-AW. Energy deficits calculated from prescribed energy targets were used in the full analyses in preference to energy deficits calculated from MEE, aiming to minimise the risk of bias because this was the most complete data set. The generalised linear regression models that were finally applied were checked using standard diagnostics, including tests of influence and specification of included variables. Protein provision was collected and reported; however, this was not analysed in relation to outcomes because this was not planned at the time of designing the study and therefore analysing these data post-hoc would risk incorrect inferences.

$P < 0.05$ (two-sided) was considered statistically significant for all tests, with no adjustment for multiplicity. SPSS, version 22.0 (IBM Corp., Armonk, NY, USA) and STATA, version 15 (StataCorp, College Station, TX, USA) were used to perform the data analyses.

At the time of designing the study, no data were known that assessed muscle strength in relation to energy deficit in a critically-ill population. This observational study selected a pragmatic sample size of 60 participants.

Results

Participants

Five hundred and forty-three participants were eligible (Figure 1). After exclusions, 140 (26%) met the inclusion criteria and 60 of these (43%) agreed to participate and were enrolled. Of the enrolled participants, 57 (95%) remained in ICU until day 5, 43 (72%) had at least one MEE measurement and 48 (80%) had a muscle strength assessment at ICU discharge.

Participant characteristics

Demographic and clinical characteristics are provided in Table 1. The participants had a mean (SD) age of 58 (16)

years, median (IQR) BMI of 28 (24–31) kg m^{-2} , mean APACHE II score of 23 (7.5) and mean NUTRIC score of 4.6 (2.1).

Nutrition provision

Nutrition provision is summarised in Table 2. The majority of participants were enterally fed ($n = 58$; 97%), for a median of 5 (3.0–8.8) days and had a mean energy delivery of 1182 (443) kcal day^{-1} from artificial nutrition support.

Energy requirements

The median (IQR) estimated energy requirements were 1800 (1675–2025) kcal day^{-1} (weight-based equation) and 1952 (1733–2240) kcal day^{-1} [Schofield equation, with a median stress factor of 1.3 (1.2–1.3)]. The median prescribed energy targets, based on the estimated requirements, were 1950 (1763–2160) kcal day^{-1} .

Measured energy expenditure was performed in 43 (72%) participants. At baseline ($n = 36$), the median (IQR) MEE was 1695 (1377–1882) kcal and the average of up to 3 time points ($n = 43$) was 1690 (1400–1895) kcal . There was moderate overall agreement between the MEE and the prescribed daily energy targets, with the former showing a mean bias of -219 (95% CI = -307 to -132) kcal compared to the prescribed daily energy targets ($r = 0.536$, $P < 0.005$)⁽⁴⁵⁾ (see Supporting information, Figure S1).

Cumulative energy deficit

When energy delivery from nutrition support was compared with estimated prescribed energy targets ($n = 60$), the median (IQR) daily nutritional energy deficit was 281 (193–435) kcal day^{-1} (Figure 2) and the cumulative energy deficit was 3648 (2514–5650) kcal . The mean nutritional energy adequacy using the prescribed energy targets over the 12 days was 64% (22%).

Comparing energy delivery from artificial nutrition support with MEE, the median (IQR) daily nutritional energy deficit was 172 (42–362) kcal and the cumulative energy deficit to ICU day 12 was 2234 (541–4710) kcal . The mean nutritional energy adequacy using MEE over the 12 days was 74% (26%).

Nutritional outcomes

From baseline to ICU discharge, there were significant reductions in weight, fat-free mass and mid upper arm circumference (Table 3). Serum transthyretin concentrations increased significantly over the ICU stay; however, albumin concentrations were similar between time points (Table 3). Where malnutrition was assessed at baseline

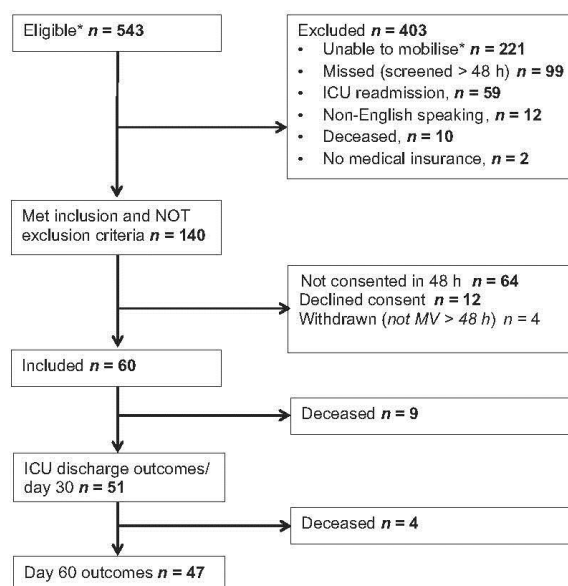


Figure 1 Consort diagram. Eligible – patients who met all inclusion criteria at the time of screening, exclusion criteria – unable to mobilise included major trauma necessitating a period of immobilisation; new neurological insults; and poor premorbid mobility (unable to mobilise independently with or without a gait aid). ICU – intensive care unit, not an Australian citizen – noncitizens were excluded because they are ineligible for Medicare should their participation in the study result in the need for additional medical care. MV, mechanical ventilation.

and discharge ($n = 50$), there was an observed increase in the proportion of participants who were malnourished at discharge compared to admission (baseline 12 (24%), discharge 18 (36%) (McNemar’s exact $P = 0.03$).

Muscle strength and physical function

Muscle strength at discharge was measured in 48 (80%) participants. Of the 12 participants who did not have this measured, nine died prior to discharge and the others were unable to complete the test as a result of an inability to follow commands. The prevalence of weakness at awakening was 23 (38%) and at ICU discharge amongst survivors was 10 (21%). Physical function at ICU discharge was measured in 49 (82%) survivors, with a mean (SD) PFIT-s interval score of 6.5 (2.1) out of 10.

Associations between cumulative energy deficit and outcomes

Participants with energy deficits from artificial nutrition support below prescribed targets were observed to have a

greater risk of ICU-AW and malnutrition. Per 1000 kcal cumulative energy deficit, there was approximately a two-fold increased risk of both ICU-AW (OR = 2.1; 95% CI = 1.4–3.3; $P = 0.001$) (Table 4) and malnutrition (OR = 1.9 adjusted for baseline malnutrition; 95% CI = 1.1–3.2; $P = 0.02$) at ICU discharge (Table 5). Likewise, adjusted for baseline, subjects were observed to lose on average 1.3 kg (95% CI = 0.2–2.4 kg; $P = 0.02$) fat-free mass per 1000 kcal cumulative deficit (Table 6). A moderate association was observed between reduced physical function at ICU discharge and cumulative energy deficit, with mean physical function score decreasing by 0.6 points (95% CI = 0.3–0.9 points; $P = 0.001$) per 1000 kcal deficit (Table 7). There was no strong evidence of an association between weight loss and nutritional energy deficit. When MEE was used to calculate energy deficit, a similar result was found for the development of ICU-AW ($n = 31$) (OR = 1.9; 95% CI = 1.1–3.4; $P = 0.021$) (see Supporting information, Table S1).

There was no strong association observed between cumulative energy deficit from artificial nutrition support and LOS, length of mechanical ventilation or mortality (medical outcome data are provided in Table 1).

Table 1 Participant demographic and clinical characteristics

Demographics and medical data	n = 60
Age years, mean (SD)	58 (16)
Gender male, n (%)	33 (55)
BMI (kg m ⁻²)	28 (24 31)
APACHE II score, mean (SD)	23 (7.5)
NUTRIC score (n = 49), mean (SD)	4.6 (2.1)
Admission category, n (%)	Medical: 34 (57) Emergency surgery: 21 (35) Elective surgery: 5 (8)
Admission diagnosis, n (%)	Cardiac arrest: 14 (23) Respiratory failure: 8 (13) Trauma: 7 (12) Cardiovascular surgery: 7 (12) Gastrointestinal surgery: 7 (12) Gastrointestinal nonsurgery: 6 (10) Sepsis: 4 (7) Endocarditis: 2 (3) Other: 5 (8)
ICU-AW diagnosis (awakening), n (%)	23 (38)
ICU LOS, days	7.0 (4.0 12.0)
Hospital LOS, days	19.0 (13.0 30.8)
Length of MV, days	4.0 (3.0 8.0)
Sedation duration, days	3.5 (2 7.0)
Sepsis duration, days	3.0 (0 6.8)
28-day mortality, n (%)	13 (22)
Discharge destination of survivors, n (%)	Home: 29 (48) Rehabilitation: 14 (23) Other (including residential care): 4 (7)

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ICU-AW, intensive care acquired weakness; IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation; NUTRIC Score, The Nutrition Risk in Critically Ill. Values are presented as the median (interquartile range) unless stated otherwise.

Discussion

In a critically ill population, the present study evaluated the energy deficit from artificial nutrition support compared to MEE and estimated energy requirements and concurrently assessed fat-free mass, muscle strength and physical function. In this mechanically ventilated cohort, the mean cumulative energy deficit was approximately 200 kcal day⁻¹ smaller when MEE was used compared to the estimated prescribed energy targets. Cumulative energy deficit from artificial nutrition support was found to be associated with an increased prevalence of ICU-AW and malnutrition, reduced physical function scores at ICU discharge and greater loss of fat-free mass over the ICU stay. The observed energy deficit in this cohort appeared to be slightly lower than some previously reported

Table 2 Nutrition provision

	n = 60
EN provided, n (%)	58 (97)
PN provided n (%)	11 (18)
Days of EN	5.0 (3.0 8.8)
Days of PN (when provided)	6.0 (5.0 9.3)
Days NBM	1 (0 1)
Days on oral intake	2 (0 3)
Time from admission to initiating NS (h), mean (SD)	20 (13)
Duration of NS interruption (h)	16 (6.0 31)
Duration of NS interruption (days)	2 (1 3)
Prescribed estimated energy (kcal day ⁻¹)	1950 (1763 2160)
Energy delivered (kcal day ⁻¹)	1182 (443)
Energy delivered (kcal kg ⁻¹ day ⁻¹)	16 (6.1)
Energy adequacy (% of prescribed), mean (SD)	64 (22)
Estimated protein requirements (g kg ⁻¹ day ⁻¹)	1.3 (1.2 1.3)
Protein provided (g kg ⁻¹ day ⁻¹), mean (SD)	0.58 (0.25)
Protein adequacy (% of estimate), median (IQR)	61 (44 69)

EN, enteral nutrition; NBM, nil by mouth; NS, nutrition support; PN, parenteral nutrition. Values are presented as the median (interquartile range) unless stated otherwise.

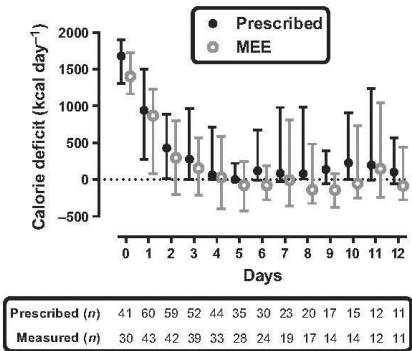


Figure 2 Daily energy deficit from nutrition support using estimated prescribed energy targets and measured energy expenditure (MEE). Error bars indicate interquartile range.

multicentre studies, where critically ill patients meet a mean of 60% of their prescribed energy targets^(6,46,47). In the present study, the mean amount of energy provided from nutrition support compared to estimated energy targets was 64%; however, when MEE was used, this improved to 74%. Cumulative energy deficit has been previously reported to be associated with poorer outcomes, such as lower rates of discharge to home, increased infection rates, reduced ventilator-free days and higher mortality rates^(11,48,49). These were not observed

Table 3 Nutritional outcomes

	<i>n</i>	Baseline, mean (SD)	Discharge, mean (SD)	Mean difference (95% CI)	<i>P</i> value
Weight (kg)	45	85 (22)	82 (19)	−3.0 (−5.2 to −0.7)	0.01
BIS FFM (kg)	45	69 (19)	62 (19)	−7.7 (−10 to −5.0)	<0.001
MUAC (cm)	49	34 (5.3)	32 (5.3)	−1.9 (−2.3 to −1.4)	<0.005
Transthyretin (mg L ^{−1})	32	108 (35)	153 (17)	46 (11 to 81)	0.01
Albumin (g L ^{−1})	50	27 (5.2)	26 (4.6)	−0.73 (−2.3 to 0.7)	0.31

BIS, bioimpedance spectroscopy; CI, confidence interval; FFM, fat-free mass; MUAC, mid upper arm circumference.
 The mean difference was determined using a paired *t*-test.

Table 4 Cumulative energy deficit and associations with ICU acquired weakness at ICU discharge

Variable	Univariate analysis			Multivariable sensitivity analysis		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Calorie deficit (per 1000 kcal)	2.2	1.3 3.7	<0.01	2.1	1.4 3.3	0.001
BMI (≥30 kg m ^{−2})	6.2	1.1 35	0.04	3.6	0.9 5.2	0.08
Age (>60 years)	1.0	0.2 4.6	1.0	2.0	0.5 8.2	0.35
APACHE II (>25)	0.62	0.1 3.5	0.59	5.0	1.1 23	0.04

Analyses were completed using a logistic regression model.
 APACHE II; Acute Physiology and Chronic Health Evaluation II, centred at 25; BMI, body mass index centered at 30 kg m^{−2}, age centered at 60 years; FFM, fat free mass.

Table 5 Cumulative energy deficit and associations with malnutrition at ICU discharge

Variable	Univariate analysis adjusted for baseline malnutrition diagnosis			Multivariable analysis adjusted for all variables		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Calorie deficit (per 1000 kcal)	1.6	1.1 2.4	0.01	1.9	1.1 3.2	0.02
BMI (≥30 kg m ^{−2})	0.55	0.10 2.9	0.48	0.31	0.03 3.4	0.34
Age (> 60 years)	2.	0.50 17	0.23	2.4	0.32 18	0.40
APACHE II (>25)	1.1	0.21 5.8	0.10	2.9	0.34 26	0.33

Analyses were completed using a logistic regression model adjusted for baseline malnutrition assessment.
 APACHE II; Acute Physiology and Chronic Health Evaluation II, centred at 25; BMI; body mass index centered at 30 kg m^{−2}, age centered at 60 years; FFM; fat free mass.

Table 6 Cumulative energy deficit and associations with fat free mass at ICU discharge

Variable	Univariate analysis adjusted for Baseline FFM			Multivariable analysis adjusted for all variables		
	Effect	95% CI	<i>P</i> value	effect	95% CI	<i>P</i> value
FFM (Baseline), kg	0.93	0.80 to 1.1	<0.001	0.91	0.8 to 1.1	<0.001
Calorie deficit (per 1000 kcal)	−1.1	−2.2 to −0.08	0.04	−1.3	−2.4 to −0.21	0.02
BMI (≥30 kg m ^{−2})	2.2	−4.1 to 8.5	0.49	2.1	−4.1 to 8.1	0.51
Age (>60 years)	−0.71	−6.2 to 4.7	0.80	0.24	−5.1 to 5.5	0.91
APACHE II (>25)	−2.5	−11 to 9.8	0.38	−4.0	−9.5 to 1.6	0.15

Analyses were completed using a linear regression model adjusted for baseline fat-free mass measurements.
 APACHE II; Acute Physiology and Chronic Health Evaluation II, centred at 25; BMI, body mass index centered at 30 kg m^{−2}, age centered at 60 years; FFM, fat free mass.

Table 7 Cumulative energy deficit and associations with physical function score at ICU Discharge

Variable	Univariate analysis			Multivariable analysis adjusted for all variables		
	Effect	95% CI	P value	Effect	95% CI	P value
Calorie deficit (per 1000 kcal)	−0.6	−0.9 to −0.2	0.002	−0.59	−0.92 to −0.26	0.001
BMI (≥30 kg m ^{−2})	−1.9	−3.7 to −0.15	0.03	−2.0	−3.5 to −0.38	0.02
Age (>60 years)	−1.1	−2.9 to 0.71	0.23	−1.2	−2.7 to 0.38	0.14
APACHE II (>25)	−0.31	−2.2 to 1.6	0.75	−1.1	−2.8 to 0.54	0.18

Analyses were completed using a linear regression model.
APACHE II, Acute Physiology and Chronic Health Evaluation II, centred at 25; BMI, body mass index centered at 30 kg m^{−2}, age centered at 60 years; FFM, fat free mass.

in the present study; however, direct comparisons cannot be made as a result of differences with respect to accounting for non-nutritional energy provision.

Indirect calorimetry is infrequently used as part of routine clinical practice to determine energy targets as a result of the high cost, time and expertise required^(13,50). Predictive equations are reported to be inaccurate, with weight-based equations being the least accurate⁽¹⁹⁾. Our finding again showed that there was only moderate agreement between prescribed estimated energy requirements and MEE. This difference in energy deficit may support the use of indirect calorimetry to more accurately assess nutritional adequacy and its impact on outcomes.

Data evaluating the relationships between energy deficits and muscle mass are sparse and somewhat conflicting⁽⁵¹⁾. In the present study, there was substantial change in fat-free mass over the ICU stay and, when adjusted for baseline fat-free mass, greater energy deficit from artificial nutrition support was associated with greater fat-free mass loss. Few previous studies have used BIS to assess change in fat-free mass and associations with energy deficits⁽⁵¹⁾ and therefore comparisons with other studies are difficult. Using subjective measures, the administration of early parenteral nutrition, which improved energy delivery, appeared to reduce muscle wasting⁽⁵²⁾. However, in contrast, in a small sub-analysis of a large randomised clinical trial (EPaNIC), greater energy delivery via early parenteral nutrition did not lead to any difference in muscle loss when assessed using qualitative computed tomography (CT) analysis⁽⁵³⁾. However, deterioration in muscle quality was observed, with increased intramuscular water and lipid content in the group who received early parenteral nutrition, over a 7-day period in the ICU⁽⁵⁴⁾. Observational studies have also reported conflicting results; similar to the present study, a previous study found that nutritional adequacy based on estimated energy targets was the only predictor of muscle loss, as assessed using CT analysis⁽⁵⁵⁾ and, in contrast, another found that energy balance made no difference to the rate of muscle loss, assessed using ultrasound⁽⁵⁶⁾.

The impact of acute energy deficit on muscle strength and physical function in the critically ill is uncertain⁽⁵⁾. In the present study, 21% of survivors had ICU-AW and the mean PFITs was 6.5 (2.1) out of 10 at ICU discharge; Greater energy deficit was associated with an increasing risk of developing ICU-AW and lower physical function scores at ICU discharge. Additionally, multivariable analysis suggested that participants with higher BMIs and APACHE II scores had a higher risk of developing ICU-AW. This is in contrast to another sub-analysis of EPaNIC reporting that lower calorie deficit was associated with greater ICU-AW at awakening [107 (34%) late PN group versus 127 (43%) early PN group, *P* = 0.03] and slower rates of recovery; however, there was no difference in the rates of ICU-AW at ICU discharge [78 (26%) late PN group versus 91 (31%) in the early PN group, *P* = 0.15]⁽⁵⁷⁾. In a nested cohort study within the EDEN trial, trophic feeding for the first 5 days of ICU admission compared to standard care increased early calorie deficit but did not affect physical function scores using the 36-Item Short Form Health Survey at 12-months, although it did result in a greater proportion of patients being admitted to a physical rehabilitation facility [57 (23%) trophic feeding group versus 30 (14%) standard care, *P* = 0.01]⁽⁵⁸⁾.

The differences in the findings between observational studies and recent interventional trials for both muscle mass changes and functional outcomes may be explained by the timing of nutrition support, the route of delivery and the composition of the nutrition provided^(8,9), as well as the methodology and timing of the outcome measures. Further research is required to explore the effects of different methods of nutrition delivery and substrates with the aim of minimising muscle wastage, as well as standardising the methods for assessing muscle mass and functional outcomes.

The strengths of the present study include that both MEE and estimated prescribed energy targets were used to calculate energy deficit and that several other nutrition-associated and patient-centred outcomes were assessed simultaneously, including fat-free mass, muscle

strength and physical function. Additionally, muscle strength was measured in 80% of the cohort. The study limitations included that this was a single-centre observational study with a relatively small sample size of 60 participants; therefore, there is potential for bias and many of the outcome variables are subjective, including the functional outcome measures and the diagnosis of malnutrition. Also, importantly, the calculation of energy deficits did not include non-nutritional calories or energy provided from oral intake. In addition, MEE was only completed in a subset of participants and, as such, only 43 participants were included in the MEE cumulative energy deficit analysis and, given the missing MEE data, associations between calorie deficit calculated from MEE and outcomes were not performed. The use of clinical measures to assess muscle strength, the diagnoses of ICU-AW and physical function limits the findings to a cohort of patients who survived critical illness and who were also able to obey commands. However, we attempted to control for this by undertaking sensitivity analysis for the outcome of ICU-AW and, when all of the missing results were imputed as participants being 'weak', the overall conclusion remained unchanged. The present study was not powered to determine important effects on patient-centred outcomes, such as mortality, and it did not explore associations between protein deficits and outcomes. Finally, as a result of the observational design of this study, only associations, and not causality, could be reported.

Conclusions

Cumulative energy deficit from artificial nutrition support was lower when MEE was used compared to prescribed energy targets. Cumulative energy deficit from artificial nutrition support was observed to be associated with the development of ICU acquired weakness, malnutrition, reduced physical function at ICU discharge and greater loss of fat-free mass. Large well-designed randomised controlled trials exploring the role of protein and absolute energy delivery, including muscle mass and functional outcomes, are warranted to confirm these results.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned, which was approved by the Melbourne Health Human Research

Ethics Committee (project number: 2012.060), have been explained.

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Conflict of interests, source of funding and authorship

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KF, LJB, LD, CM and SMP and SB contributed to the conception and design of the research. KF, LB, TR, RC, JP and LE contributed to the acquisition and analysis of the data. KF, JP, LE and AMD contributed to the interpretation of the data. KF, LJB, AMD and LD drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final version of the manuscript submitted for publication.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Bland–Altman plot of agreement between prescribed energy targets and measured energy expenditure.

Appendix S1. Methods for muscle strength and physical function assessment.

Table S1. Associations between cumulative energy deficit using measured energy expenditure and intensive care unit (ICU)-acquired weakness at ICU discharge.

CLINICAL NUTRITION

Measuring nutrition-related outcomes in a cohort of multi-trauma patients following intensive care unit discharge

K. Wittholz,¹ K. Fetterplace,^{1,2} M. Clode,³ E. S. George,³ C. M. Madsaas,^{2,4} R. Judson,⁵ J. J. Presnell^{2,4} & A. M. Deane^{2,4}

¹Department of Allied Health (Clinical Nutrition), The Royal Melbourne Hospital, Melbourne, VIC, Australia

²Department of Medicine and Radiology, Royal Melbourne Hospital, The University of Melbourne, Melbourne Medical School, Parkville, VIC, Australia

³Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Science, Deakin University, Geelong, VIC, Australia

⁴Department of Intensive Care, The Royal Melbourne Hospital, Melbourne, VIC, Australia

⁵Department of Trauma, The Royal Melbourne Hospital, Melbourne, VIC, Australia

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feasibility, intensive care unit, multi-trauma, muscle mass, nutrition.

Correspondence

K. Fetterplace, Allied Health Royal Melbourne Hospital, Grattan St Parkville, Melbourne, VIC 3050, Australia.
 Tel.: +61 3 9342 7440
 Fax: +61 3 9342 8440
 E-mail: katie.fetterplace@rnh.org.au

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Abstract

Background: Functional recovery is an important outcome for those who survive critical illness. The present study aimed to assess nutrition provision and nutrition-related outcomes in a multi-trauma cohort following intensive care unit (ICU) discharge.

Methods: The present study investigated a prospective cohort of patients discharged from an ICU, who had been admitted because of major trauma and required mechanical ventilation for at least 48 h. Nutrition-related outcomes, including body weight, quadriceps muscle layer thickness (QMLT), handgrip strength and subjective global assessment, were recorded on ICU discharge, days 5–7 post-ICU discharge and then weekly until hospital discharge. Nutrition intake was recorded for 5 days post-ICU discharge. Unless otherwise stated, data are presented as the mean (SD).

Results: Twenty-eight patients (75% males, 55 (22.5) years) were included. Intake met 64% (28%) of estimated energy and 72% (32%) of protein requirements over the 5 days post-ICU discharge, which was similar to over the ICU admission. From ICU admission to hospital discharge, the mean reduction in weight was 4.2 kg (95% confidence interval – 2.2–6.3, $P < 0.001$) and after ICU discharge, the mean reduction in weight and QMLT was 2.6 kg (95% confidence interval – 1.0–4.2, $P = 0.004$) and 0.23 cm (95% confidence interval – 0.06–0.4, $P = 0.01$), respectively.

Conclusions: Patients received less energy and protein than estimated requirements after ICU discharge. Weight loss and reduction in QMLT also occurred during this period.

Introduction

Functional ability and health-related quality of life are important outcomes for those who survive critical illness (1–3). An intensive care unit (ICU) admission can lead to rapid reductions in muscle mass and substantial muscle weakness (4,5) and changes in body composition have been associated with prolonged hospital admissions, reductions in post-hospital discharge functional recovery and diminished health-related quality of life (4,6–7).

Nutrition has been identified as a potential modifiable factor that may aid in the preservation of skeletal muscle during critical illness and help restore muscle lost in the recovery phase (8–10). However, the amount, type and phase of critical illness or recovery on which nutrition support will have greatest impact all remain unknown (8–10). Various nutritional interventions have been administered within the ICU with the objective of attenuating muscle loss and functional weakness, although the impact has been inconsistent (7,11,12). This may be a result of the

interventions chosen being of limited or no benefit, the duration of period provided by the nutrition intervention not being ideal for the substrate to be utilised, the period of the ICU admission being too brief to obtain a benefit, or the studies conducted to date not having been sufficiently powered to detect a difference⁽⁸⁾. It has been suggested that nutritional interventions administered after the acute phase of critical illness may have greater impact^(8,13–15). However, quantifying nutritional intake and nutrition-related outcomes after ICU discharge is likely to be more challenging because of a variety of factors, including equipment and personnel availability, challenges in accurately quantifying volitional ingested nutrient intake, and less predictable timing of discharge from hospital^(16–18).

One cohort of patients that may benefit from a nutritional intervention post-ICU discharge comprises those admitted as a result of severe traumatic injuries. After a traumatic injury, patients can have elevated energy expenditure and increased protein catabolism^(19,20), which is likely to continue post-ICU and throughout recovery^(20,21). Despite patients with traumatic injury frequently being prescribed more energy and protein than non-trauma patients in ICU⁽²²⁾, substantial cumulative nutritional deficits have been observed during ICU for this cohort^(16,22).

There are limited data available reporting nutrition intake and nutrition-related outcomes after ICU discharge. The primary aim of the present study was to determine the feasibility of repeatedly assessing nutrition intake and measuring nutrition-related outcomes (weight, nutritional status, muscle mass and strength) in a cohort of patients with traumatic injury following ICU discharge. The secondary aims were to (i) compare nutrition intake post-ICU discharge to nutrition intake when in the ICU; (ii) to determine whether post-ICU discharge there were

any differences between those receiving only oral intake compared to any artificial nutrition support; and (iii) to explore the relationships between nutritional intake and nutrition-related outcomes.

Materials and methods

This cohort study was conducted in one of the two trauma referral centres that receive all major adult trauma for the state of Victoria (population approximately 6.3 million). Between July to September 2018, all patients admitted to the ICU as a result of a traumatic injury and who were ≥ 18 years old and mechanically ventilated for at least 48 h were screened for eligibility. Recruitment occurred on the day of discharge from the ICU. Patients were excluded if, on discharge to the ward, they had impaired neurology (defined as the best motor score of abnormal flexion or worse) or bilateral upper arm injury, or the goal of treatment was altered to include a focus on palliative care. Reporting of the present study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines⁽²³⁾. This project was approved by the Melbourne Health Human Research Ethics Committee (QA2018048). Eligible patients, or their responsible person (if they were unable to comprehend written information), were provided with written information regarding the study and they were given the opportunity to opt out from inclusion in the study.

Data were collected from ICU discharge and censored 26 days after ICU discharge or on hospital discharge, whichever came first (Figure 1). Baseline demographic data and patient characteristics were collected from the ICU admission. Routine care in this ICU includes assessment by an ICU dietitian for all patients who are mechanically ventilated for ≥ 48 h and are receiving nutritional therapy. Protein and energy requirements were

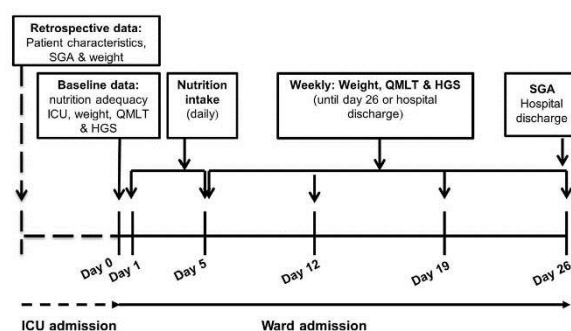


Figure 1 Outcome measurement procedure. HGS, handgrip strength; QMLT, quadriceps muscle layer thickness; SGA, Subjective Global Assessment.

based on the dietitians' assessment in the ICU and post-ICU discharge. Estimated nutritional requirements were calculated using actual body weight for patients below or within the ideal body weight (IBW) range [body mass index (BMI) 18.5–25 kg m⁻² and for those aged ≥ 65 years BMI 22–27 kg m⁻²] ⁽²⁴⁾. For overweight participants, IBW was used and, for obese participants with a BMI greater than 30 kg m⁻², an obesity adjusted weight was used [IBW + 25% (actual body weight – IBW)] ⁽²⁴⁾.

Nutrition intake over the ICU admission was retrospectively determined from fluid balance charts through daily analysis of enteral and parenteral nutrition delivery. Energy provided from other sources (e.g. intravenous propofol and glucose as part of fluid therapy) was not included and discarded gastric residual volumes were not subtracted from energy provision.

Ward nutrition intake was collected for 5 days post-ICU discharge. Diet orders, nutrition consumed and mode of nutrition delivery were recorded daily. For patients receiving artificial nutrition, fluid balance charts were reviewed to determine protein and energy intakes. For patients with volitional intake, the proportion of each component of the meal consumed (using visual estimates of 0%, 25%, 50%, 75% or 100%) was recorded in the MOBILE INTAKE™ data application in the hospitals electronic menu management system (CBORD™; The CBORD group, New York, NY, USA). If a meal period could not be assessed by a dietitian, food record charts, completed by nursing staff and including visual estimates of meals consumed, or patient-reported intake were used to estimate the food intake. The hospital menu management system CBORD™ was used to analyse protein and energy intake using the 2011–2013 AUStralian Food and NUTrient (AUSNUT) database (<https://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/ausnutdatafiles/Pages/foodnutrient.aspx>).

The ward (5 days) and ICU energy and protein adequacy was calculated in the same way. Daily intake was compared with dietitian estimated requirements, and averaged over the study period. The ICU adequacy excluded the day of ICU admission and discharge if it was less than 12 h.

Nutrition-related outcomes including weight and muscle mass and strength were recorded at baseline (within 48 h of discharge from the ICU), days 5–7 post-ICU discharge and then weekly thereafter.

Weight on admission to ICU was recorded using bed scales (Hill-Rom®; Hill-Rom, Inc., Indiana, USA) for the majority of patients. If it was not physically possible to weigh the patient on admission, family reports were used for the admission weight. Post-ICU weight was measured using standing scales (model 876; Seca, Hamburg,

Germany), chair scales (BW1122; Colonial, Melbourne, Australia) or hoist scales (Maxi Move L8038; Ajor, Malmö, Sweden), depending on the patient's injury type and mobility. Weight change was calculated as the difference in weight from ICU admission to ICU discharge and to hospital discharge.

Muscle mass was assessed using an ultrasound to measure quadriceps muscle layer thickness (QMLT). QMLT measurements were performed using a portable ultrasound machine (S-ICU; Sonosite, Bothell, WA, USA) with a multiple-frequency transducer (13–6 MHz, 6 cm) using the technique described previously ^(7,16,25). Measurements were taken with the patient lying supine with leg relaxed and in extension and the bedhead elevated at approximately 30°. QMLT was measured unilaterally (on the right side unless contraindicated as a result of injury or impairment) at two points: the midpoint between the anterior superior iliac spine and the upper pole of the patella and at the point two thirds between the anterior superior iliac spine and the top of the patella. A still image was taken with minimal pressure and then again with maximal pressure applied. The measurements were taken twice for each point and then the four measurements were averaged to obtain the final QMLT measurement. A third measurement was taken if there was a difference of >10% between the first two measurements, and the measurement with greater than a 10% difference was discarded.

A trained dietitian used handgrip dynamometry (Commander Echo Dynamometer; JTECH Medical, Midvale, UT, USA) to assess upper limb muscle strength bilaterally ⁽²⁶⁾. Patients were assessed in a seated position, in a chair where possible or sitting at least at 45° in bed, with their forearm in flexion at 90° and wrist in extension, supported by the arm of the chair or a pillow. Patients were asked to perform a maximal voluntary isometric contraction and maintain the contraction for 3–5 s. Three consecutive isometric contractions with 30–60 s of rest in between test were completed and the highest measurement was recorded.

The Subjective Global Assessment (SGA), was used to assess nutritional status ⁽²⁷⁾. Patients were categorised as well nourished (Score A), with mild to moderately malnutrition (Score B) or severely malnourished (Score C). As part of usual care at the study institution, the SGA is completed by ICU dietitians on initial assessment (within 48 h of admission). This score was then retrospectively extracted from the notes of eligible patients. The SGA was subsequently repeated at hospital discharge by the trained research dietitian.

Feasibility was determined through retention of study participants for at least 5 days post-ICU. Feasibility was predefined as >75% of eligible participants completing 5 days of intake data and having ≥1 repeat measure recorded.

Statistical analysis

Continuous and interval data were reported as the mean (SD) and/or median interquartile range as appropriate. Proportions were used to summarise ratios, and malnutrition was compared over time with McNemar’s test accompanied by a 95% confidence interval (CI). Initial univariable exploration of differences in continuous measures over time used the construction of trajectory plots, followed by paired *t*-tests. Changes in QMLT over time were explored using a population-averaged multivariable linear model with a generalised estimating equation approach, an exchangeable working correlation structure and robust standard error estimates accounting for clustering within individual subjects. Independent variables included baseline QMLT, protein adequacy, BMI, presence of traumatic brain injury, age ≥65 years and the patient’s ICU admission. *P* < 0.05 (two-sided) was considered statistically significant, with no adjustment for multiple testing. Data analysis was carried out using the SPSS, version 23.0 (IBM Corp., Armonk, NY, USA) and STATA, version 15.1 (StataCorp, College Station, TX, USA).

Results

During the 4-month study period, 67 patients were screened for inclusion, 32 (47%) met all inclusion and no exclusion criteria, and 28 (42%) patients agreed to participate (Figure 2). Study participant characteristics are described (Table 1).

During ICU admission, participants received a mean of 62% (17%) and 63% (19%) of estimated energy and protein requirements. At ICU discharge 19 (68%)

participants were receiving exclusive oral intake, five (18%) participants were on a combination of oral diet and enteral nutrition (EN) via a feeding tube, three (11%) participants were receiving exclusive EN via a feeding tube, and one (4%) patient was receiving a combination of EN and parenteral nutrition (PN).

Over the 5 days post-ICU discharge that nutritional intake was observed, there was a total of 120 days (85% of all days) of data available, with all missing data being a result of patient discharge from hospital (Table 2). Daily mean energy and protein intake was 1478 (651) kcal and 75 (37) g, which equated to 64% (28%) and 72% (32%) of estimated energy and protein requirements (Figure 3). There were no statistical group differences in either energy (−3%; 95% CI = −15 to 10; *P* = 0.66) or protein adequacy (−10%; 95% CI = −25 to 5; *P* = 0.19) between ICU admission and post-ICU periods.

Patients receiving solely oral intake consumed less energy and protein compared to patients receiving any artificial nutrition support (oral diet plus EN, EN alone or EN plus PN); the mean energy and protein intakes were 1298 (640) kcal and 68 (39) g and 1857 (524) kcal and 89 (30) g, respectively. The between group difference was statistically significant for daily energy (mean difference 558 kcal; 95% CI = 53–1062; *P* = 0.03) but not protein (mean difference 22 g; 95% CI = −8 to 51; *P* = 0.15). Compared with dietitian prescriptions, patients on any artificial nutrition received a mean adequacy of 87% (14%) of energy and 87% (17%) of protein compared to those on oral diets who consumed a mean adequacy of 54% (26%) of energy and 65% (36%) of protein.

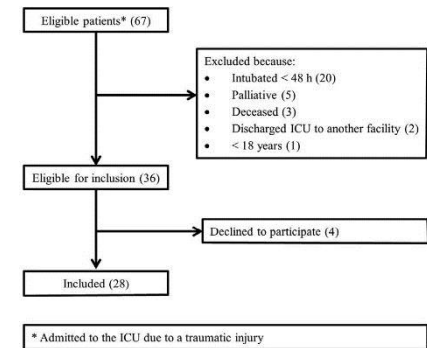


Figure 2 Consort diagram. *Eligible patients, were those admitted to the intensive care unit as a result of a traumatic injury. ICU, intensive care unit.

Table 1 Patient characteristics

Patient characteristics (n = 28)	Value
Age (years), mean (SD)	50 (22.5)
Males, n (%)	21 (75)
Length of stay, mean (SD)	
ICU	10.6 (6.7)
Ward	10.9 (9.2)
Total hospital	21.6 (11.8)
Mechanical ventilation (days), median (IQR)	6.0 (3.0–9.5)
Injury, n (%)	
Multi-trauma	16 (57)
Multi-trauma with TBI	12 (43)
APACHE II score, mean (SD)	15 (6)
APACHE III score, mean (SD)	111 (55)
Body mass index (kg m ^{−2}), median (IQR)	26 (25–32)
Body weight ICU admission (kg), mean (SD)	86 (23)
Malnourished – SGA B/C, n (%)	3 (11)

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; IQR, interquartile range; SGA, Subjective Global Assessment; TBI, traumatic brain injury.

Table 2 Feasibility of outcome measures

	Baseline* n (%)	Day 5 post-ICU discharge n (%)	At least ≥ 1 time point	Met feasibility criteria (Yes/No)
Weight	25 (89)	13 (46)	15 (54)	No
QMLT	27 (97)	18 (64)	18 (64)	No
Handgrip Strength	17 (61)	12 (43)	14 (50)	No
Subjective Global Assessment†	28 (100)	NA	28 (100)	Yes
Intake (days)‡	NA	120 (85)	NA	Yes

ICU, intensive care unit; NA, not available; QMLT, quadriceps muscle layer thickness.
 *Baseline: within 48 h of ICU discharge.
 †Subjective Global Assessment completed at baseline and hospital discharge.
 ‡Intake days: number of days intake data was recorded for the first 5 days post-ICU discharge.

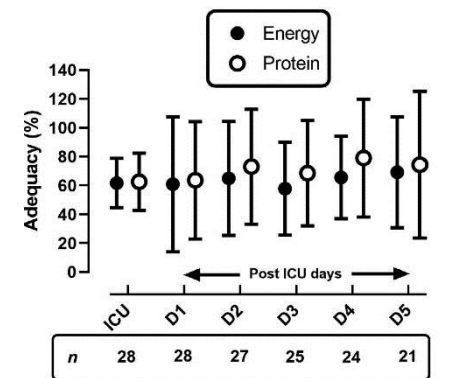


Figure 3 Mean daily energy and protein adequacy for intensive care unit (ICU) admission and the first 5 days post-ICU discharge. *Error bars indicate the mean (SD); n, number of participants included at each time point.

Nutritional intake data and the measurement of nutritional status using the SGA were both found to be feasible outcomes measures; however, the other nutrition-related outcome measures (weight, QMLT and handgrip strength) were not found to be feasible in this cohort (Table 2).

The proportion of participants observed to be malnourished increased from ICU admission to hospital discharge; however, this was not found to be statistically significant [3/28 (11%) versus 7/28 (25%), change 14%; 95% CI = −2 to 31; *P* = 0.13]. Of the participants who had weight measured at ICU admission and ICU discharge (*n* = 25), there was a significant reduction in weight [mean reduction 2.3 kg (95% CI = 0.5–4.2; *P* = 0.02), with a mean percentage loss of weight over this period of 3.9% (4.6%). From ICU admission to hospital discharge, the mean reduction in weight was 4.2 kg (95% CI = 2.2–6.3; *P* < 0.001), with a significant loss of weight also observed over the first 5 days post-ICU (Table 3).

QMLT was measured on more than one occasion post-ICU discharge in 18/28 patients (64%) (Table 2). There was a significant reduction in mean QMLT (no pressure) over ward admission by 0.23 cm (95% CI = 0.06–0.40; *P* = 0.01) (Table 3) and the mean percentage reduction was 7.2% (13%). The change in QMLT (no pressure) for individuals over time is shown in the Supporting information (Figure S1). Mean change in QMLT over time was associated with greater baseline QMLT and a greater number of days post-ICU discharge (Table 4). There was no significant association found between change in QMLT and age, BMI, severity of illness on admission to the ICU, presence of a traumatic brain injury or ward protein adequacy. There was a significant improvement in handgrip strength from baseline to day 5 post-ICU discharge in the group of participants (*n* = 10) who had two measurements completed (Table 3).

Discussion

In this single-centre cohort study of patients with a traumatic injury who were discharged from an ICU, patients received less energy and protein than it was estimated that they required. Energy and protein provision and nutritional adequacy on the ward were similar to that provided during the ICU admission; however, patients receiving artificial nutrition support post-ICU discharge had improvements in energy and protein provision. It was also observed that, after ICU discharge, a significant reduction in weight and QMLT occurred. According to the predefined criteria, missing data limited feasibility for several nutrition-related outcomes.

The results obtained in the present study are similar to those of several studies conducted in the ICU, with patients receiving approximately 60% of their nutritional targets^(28–31). Although few studies have reported nutritional adequacy after ICU discharge, in a single-centre study of 37 patients with traumatic brain injury by Chapelle *et al.*⁽¹⁸⁾, patients received similar nutritional adequacy in ICU and after ICU discharge. However, greater

Table 3 Change in nutrition-related outcomes from ICU discharge to day 5 post-ICU discharge

	<i>n</i>	Baseline* Mean (SD)	Day 5 post-ICU discharge, mean (SD)	Mean difference (95% CI)	<i>P</i> -value
Body weight (kg)	13	83.6 (16.1)	81.0 (16.2)	−2.6 (−0.98 to −4.2)	0.004
Handgrip strength (kg)	10	27.9 (9.5)	30.1 (11.1)	2.3 (0.22 to 4.3)	0.034
QMLT no pressure (cm)	18	2.8 (0.8)	2.6 (0.8)	−0.23 (−0.06 to −0.40)	0.01

CI, confidence interval; ICU, intensive care unit; QMLT, quadriceps muscle layer thickness.
*Baseline: within 48 hours of ICU discharge.

Table 4 Effect estimates from multivariable linear model assessing change in QMLT from baseline to hospital discharge

Variable	Coefficient of effect*	95% CI	<i>P</i> -value
QMLT Baseline (cm)	0.88	0.79 to 0.96	<0.001
ICU protein adequacy, per 10%	−0.04	−0.07 to 0.002	0.06
Number of days post-ICU discharge	−0.04	−0.05 to −0.02	<0.001
BMI ≥ 30 kg m ^{−2}	0.07	−0.08 to 0.2	0.37
Presence of a traumatic brain injury	0.05	−0.05 to 0.15	0.31
Age ≥65 years	−0.02	−0.13 to 0.0.9	0.69
APACHE II score on admission, per 5 points	0.02	−0.04 to 0.07	0.59

APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; QMLT, quadriceps muscle layer thickness.
*All reported effect estimates are adjusted for all other variables within a multivariable linear model, using a generalised estimating equation approach (refer to statistical analysis methods for details).

energy and protein provision were observed in both settings than in the present study, with patient receiving a mean of 81% (35%) of energy and 77% (35%) of protein requirements after ICU discharge. These differences could be related to the different patient cohorts and the proportion of patients with traumatic brain injury who require artificial nutrition after ICU discharge rather than consuming oral intake. In the present study, patients who received any artificial nutrition had significant increases in energy but not protein adequacy in the post-ICU period compared to those receiving oral intake alone. These results are similar to those observed by Chapple *et al.* (18) who described less intake in patients who were reliant solely on oral diet. Additionally, Peterson *et al.* (32) examined oral nutrition intake via multi-pass 24 h food recall for 7 days post-extubation in a single-centre cohort of 50 critically ill patients; it was observed that mean energy and protein intake never exceeded 55% of daily requirements (32). These results demonstrate that nutritional inadequacy persists in the cohort of patients after traumatic injury, and that patients receiving oral intake alone are possibly at greatest risk of nutritional inadequacy in the ICU and the post-ICU period. This may be a result of the early withdrawal of artificial nutrition support or because hospital systems do not support achieving nutritional adequacy during periods of volitional oral intake (33). Further research is warranted to understand why nutritional inadequacy persists after ICU discharge and

how to improve nutritional adequacy throughout the entire hospital admission (34).
In the present study, nutrition-related outcome data for weight, QMLT and handgrip strength were not recorded in sufficient numbers to meet the predefined feasibility criteria. Patient factors, including delirium, agitation and post-traumatic amnesia; hospital factors, including appropriate equipment availability, multiple procedures and scans; early discharge; and research resource allocation all contributed to missing data. It has been reported that the prevalence of cognitive impairment after a traumatic brain injury is up to 70% (35), and this may affect capacity to complete some of the outcome measures. Therefore, outcome measures that do not require participation, volitional movements and cooperation, such as QMLT, are probably more feasible in this population, rather than handgrip strength and functional capacity and quality of life (36). Although the frequency of QMLT measurements did not achieve the predefined feasibility criteria, it was successfully measured in 64% of participants and, of the missing data, five (14%) participants were discharged prior to the first repeat measure time point (day 5 post-ICU). These results are similar to those reported previously by Chapple *et al.* (16,25) in studies measuring QMLT weekly post-ICU in 79% of a traumatic brain injury cohort. The evidence from these two centres therefore supports the concept that QMLT is perhaps the most feasible variable for repeated measurement

in this population when attempting to evaluate the impact of nutritional therapies on body composition.

It remains unclear what, if any, impact energy and protein provision in the ICU or following ICU admission have on patient-centred and nutrition-related outcomes⁽⁸⁾. In the present study, there was a significant reduction in weight and QMLT over the study period; however, there was no evidence to suggest that greater protein provision was associated with attenuation of QMLT loss. Similarly, a previous multi-centre observational study (UK MUSCLE) reported that greater loss of quadriceps muscle was associated with greater protein delivery in ICU⁽⁵⁾. However, in contrast to this observed association, other cohort studies^(37,38), as well as a recent randomised control trial by our group, report that greater protein delivery is associated with attenuation of muscle loss in ICU⁽⁷⁾. These conflicting results highlight the issues involved when interpreting associations in observational studies of critically ill cohorts, particularly because the severity of illness is a confounder that may not be adequately accounted for. Although muscle thickness and body composition outcomes are only surrogate physiological outcomes for outcomes that are important to patients, Chapple *et al.*⁽¹⁶⁾ reported that greater QMLT at hospital discharge was associated with significant improvements in self-related quality of life 3 months after hospital discharge. Further research is required to evaluate the impact of nutritional therapies on functional outcomes post-discharge from hospital^(8,34).

This is the first study to evaluate the feasibility of measuring nutrition-related outcomes and nutritional intake in patients with multiple injuries following trauma after ICU discharge. Nutritional intake was measured using meal observations and an electronic menu management system and nutritional outcomes such as muscle mass, muscle strength and nutritional status were recorded. However, there are several limitations, including the study comprising a single-centre study, with a relatively small number of patients being investigated. Moreover, the size of the cohort was not sufficient to determine whether nutrition-related outcomes were affected by nutritional adequacy and, as a result of the observational nature, causality cannot be established for any associations observed. Data collection was limited to weekdays and acute hospital admission. Increasing the resource allocation and study timeframes in future interventional studies may increase the sample size and data completeness and consideration should be given to include outcome data from admissions to rehabilitation facilities. It was also not within the scope of the present study to examine the feasibility of measuring nutrition-related outcomes post-hospital discharge. With recovery from acute illness, patient participation in outcome measures may increase and therefore increase their utility.

Conclusions

Mean energy and protein intake were below the estimated requirements and were similar during the ICU admission and after ICU discharge; however, patients receiving artificial nutrition support received greater amounts of energy. Within the limitation of missing data, weight loss and reductions in QMLT were observed after ICU discharge. A greater change in QMLT was associated with a greater baseline QMLT and length of ward admission. The most appropriate outcome measures for investigating associations between nutrition provision and recovery remain unclear and warrant further investigation. Well-designed and adequately powered randomised clinical trials are required to determine the effect of greater nutrition provision on nutrition-related outcomes in patients discharged from an ICU after major trauma.

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Conflict of interests, source of funding and authorship

K. Fetterplace has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi, Nutricia and Nestle Health Science (not related to this study). A. M. Deane and his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study). The other authors declare that they have no conflicts of interest.

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KW, KF and AMD contributed equally to the conception and design of the research. ESG, RJ and CMM contributed to the design of the research. KW, MC and KF contributed to the acquisition of the data. KW, KF and JJP contributed to the analysis and the interpretation of the data. KW, KF and AMD drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript submitted for publication.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being

reported. The reporting of this work is compliant with STROBE⁽¹⁾ guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. This project was approved by the Melbourne Health Human Research Ethics Committee (QA2018048).

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Quadriceps muscle layer thickness measurements over time post-ICU discharge.

Appendix 4

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Pilot and Feasibility Studies

STUDY PROTOCOL

Open Access



Targeted full energy and protein delivery in critically ill patients: a study protocol for a pilot randomised control trial (FEED Trial)

Kate Fetterplace^{1,2,3,4*}, Adam M. Deane^{3,4}, Audrey Tierney², Lisa Beach⁵, Laura D. Knight⁵, Thomas Rechnitzer³, Adrienne Forsyth², Marina Mourtzakis⁶, Jeffrey Presneill^{3,4} and Christopher Madsaas^{3,4}

Abstract

Background: Current guidelines for the provision of protein for critically ill patients are based on incomplete evidence, due to limited data from randomised controlled trials. The present pilot randomised controlled trial is part of a program of work to expand knowledge about the clinical effects of protein delivery to critically ill patients. The primary aim of this pilot study is to determine whether an enteral feeding protocol using a volume target, with additional protein supplementation, delivers a greater amount of protein and energy to mechanically ventilated critically ill patients than a standard nutrition protocol. The secondary aims are to evaluate the potential effects of this feeding strategy on muscle mass and other patient-centred outcomes.

Methods: This prospective, single-centred, pilot, randomised control trial will include 60 participants who are mechanically ventilated and can be enterally fed. Following informed consent, the participants receiving enteral nutrition in the intensive care unit (ICU) will be allocated using a randomisation algorithm in a 1:1 ratio to the intervention (high-protein daily volume-based feeding protocol, providing 25 kcal/kg and 1.5 g/kg protein) or standard care (hourly rate-based feeding protocol providing 25 kcal/kg and 1 g/kg protein). The co-primary outcomes are the average daily protein and energy delivered to the end of day 15 following randomisation. The secondary outcomes include change in quadriceps muscle layer thickness (QMLT) from baseline (prior to randomisation) to ICU discharge and other nutritional and patient-centred outcomes.

Discussion: This trial aims to examine whether a volume-based feeding protocol with supplemental protein increases protein and energy delivery. The potential effect of such increases on muscle mass loss will be explored. These outcomes will assist in formulating larger randomised control trials to assess mortality and morbidity.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN: 12615000876594 UTM: U1111-1172-8563.

Keywords: Nutritional support, Enteral nutrition, Nutritional requirements, Dietary protein, Critical illness, Critical care, Intensive care

* Correspondence: Kate.Fetterplace@mh.org.au

¹Department of Clinical Nutrition, Allied Health, Royal Melbourne Hospital, Melbourne, Australia

²Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Australia

Full list of author information is available at the end of the article



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Background

Nutritional therapy, preferably via the enteral route, is part of the standard care for critically ill patients [1]. Prominent critical care nutrition guidelines recommend that protein should be provided at a level of 1.2–2.0 g/kg/day, with possibly higher amounts for patients with multi-trauma, obesity and burns and greater than 80% of energy targets should be met [1]; however, there is a lack of high-quality evidence to support these guidelines [2]. Despite these and similar guidelines, nutritional delivery in the intensive care unit (ICU) is frequently less than these targets; observational data from a large international dataset suggests that critically ill patients only receive, mean SD, 43 g $\pm$ 27 of protein and 1054 kcal $\pm$ 717 of energy per day, which equates to approximately 50 and 60% of their protein and energy targets, respectively [3]. More recent observational data from this dataset suggests that increasing protein delivery by 30 g, or meeting greater than 80% of prescribed protein targets, is associated with greater survival, an increase in ventilator-free days and a shorter time to discharge alive from the ICU [4, 5]. In addition, data from a prospective observational cohort study from a single centre suggested that the provision of more protein (greater than 1.5 g/kg/day) was associated with a reduction in mortality when adjusted for severity of illness and age [6]. Finally, observational study and preliminary trial data supporting the concept that increasing calorie delivery will improve outcomes [7–9].

Standard enteral feeding regimens are generally based on an hourly target rate of administration of a selected formulation, calculated according to daily energy and protein targets [10]. Therefore, if interruptions to feed delivery occur, protein and energy targets are not met [11]. Furthermore, protein delivery is generally restricted by the composition of the enteral formula available because overall energy requirements mostly determine the volume of the formula prescribed. In a cluster randomised control trial, Heyland and colleagues reported that with a novel approach to feeding, including a volume-based feeding protocol, delivery of protein increased by 14% (95% CI, 5–23%) and calories by 12% (95% CI, 5–20%) [11]. However, theoretically, volume-based feeding protocols with protein supplementation may not achieve greater delivery of protein and energy to patients due to issues with feeding intolerance, as increased nutrient delivery, particularly protein, to the small intestine, stimulates the feedback loop to slow gastric emptying [12, 13]. Therefore, this approach may inadvertently decrease protein and energy delivery.

Beyond mortality, patient-centred functional outcomes in survivors of critical illness are increasingly being recognised as important variables that may be influenced by nutrition [14, 15]. This includes muscle weakness, which is often described as Intensive Care Unit Acquired Weakness (ICUAW) [16]. Lower health-related quality of life (HRQoL) scores are associated with ICUAW, emphasising that weakness is important to patients [17–19]. The loss of skeletal muscle has been identified as a crucial contributing factor to the development of ICUAW [20, 21], with ultrasound being a potentially useful and minimally invasive modality to quantify muscle mass and muscle loss in the critically ill [22–24].

Augmenting nutrient delivery, particularly increased protein delivery, has been proposed as an approach that may attenuate muscle loss associated with critical illness. At present, there is an absence of robust data to support this approach [25] and recent studies have reported conflicting conclusions [6]. Most recently, Ferrie and colleagues [26] performed a randomised controlled trial in parenterally fed patients. Amongst other outcomes, they measured muscle mass and strength [26]. This study of 119 critically ill patients, who were randomised to receive a target of either 0.8 or 1.2 g/kg protein per day with isocaloric parenteral nutrition, did not find strong evidence of a difference in the primary outcome of handgrip strength at day 7, but the observed point estimate was in the direction of benefit for those receiving greater protein delivery. Moreover, the augmented protein intervention may have been associated with reduced fatigue and greater forearm muscle thickness using ultrasound [26]. A retrospective observational study of 106 critically ill patients, by Ishibashi and colleagues, reported that protein intake above 1.5 g/kg/day substantially reduced total body protein loss when compared to those who receive less than 1.1 g/kg/day [27]. In contrast, Casaer and colleagues reported that greater calorie and protein administration, particularly when delivered via the parenteral route, reduced the quantity and quality of muscle and was associated with greater muscle weakness [28]. This negative signal was also described by Puthucherry and colleagues, who reported greater muscle wasting associated with increased protein delivery [29].

At present, there is conflicting evidence around the optimal protein provision to critically ill patients including a lack of high-quality evidence which includes patient-centred functional outcomes. This single-centre pilot trial in mechanically ventilated critically ill patients is part of a program to explore the influence of protein prescription on outcomes;

aims to determine whether a volume-based enteral feeding protocol with additional protein supplementation delivers a greater amount of protein and energy than a standard nutrition protocol.

Study objectives

Co-primary

The primary aim of this pilot study is to determine whether a volume-based feeding protocol with supplemental protein potentially improves the average daily protein and energy delivery, when compared to standard care in mechanically ventilated critically ill patients.

Secondary

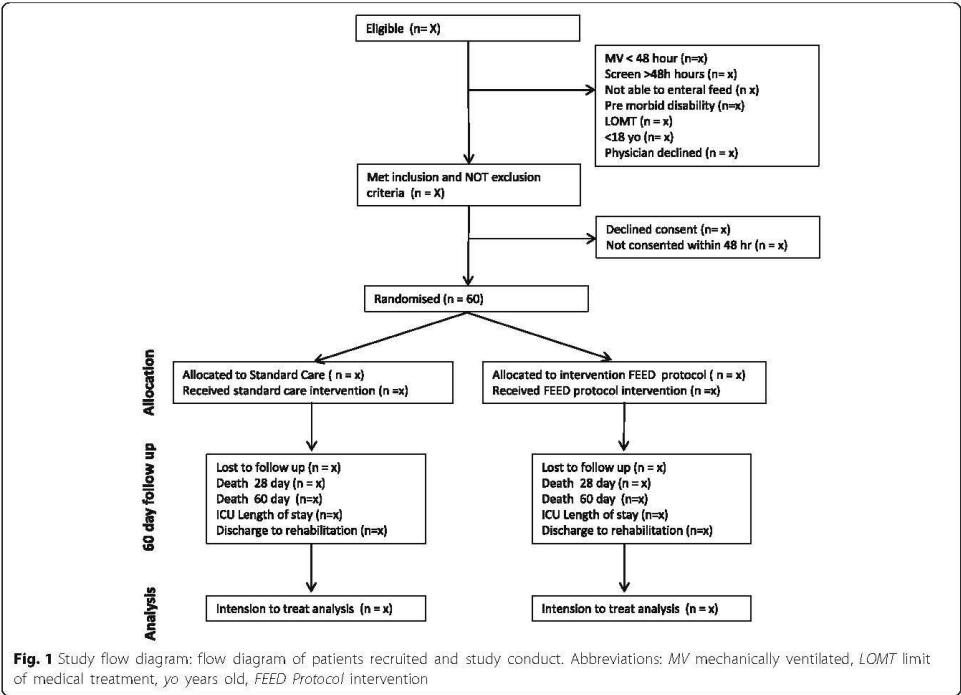
The secondary aims are to evaluate whether a volume-based feeding protocol with supplemental protein when compared to standard care:

- I. Improves overall protein and energy adequacy without increasing feeding intolerance or diarrhoea.
- II. Improves nutritional-related outcomes including the incidence of malnutrition at ICU discharge

- or mid upper arm circumference change from baseline to discharge.
- III. Decreases the change in quadriceps muscle layer thickness (QMLT) from baseline to ICU discharge.
- IV. Decreases the incidence of ICUAW or alters muscle strength or physical function scores at ICU discharge.
- V. Alters the duration of the ICU admission, number of deaths, and the requirement for discharge to a rehabilitation facility.

Methods/design

This pilot, single-centred, single-blinded, parallel group, prospective randomised controlled trial has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) [30] and the Consolidated Standards for Reporting of Trials CONSORT guidelines [31] (Fig. 1, study flow diagram. The study will be undertaken at the Royal Melbourne Hospital ICU, which is a university-affiliated, tertiary referral,



mixed medical-surgical-trauma ICU with 32-beds that has >2500 patients admitted per year.

Study participants

Sixty patients will be recruited within 48 h of their index ICU admission. Screening commenced on 10th of August 2015 and is performed only on weekdays. Patients who meet the study criteria (Table 1.) will be eligible to participate. As all eligible patients are mechanically ventilated and unable to consent to participation, informed consent will be obtained from the person responsible as per local laws. Consent to continue in the trial will be obtained from the participant if they recover adequately and they are deemed competent. The protocol and consent process has been approved by the Royal Melbourne Hospital Human Research Ethics Committee (2015.048). The protocol is registered with Australian New Zealand Clinical Trials Registry (ANZCTR; U1111-1172-85630).

Baseline data collection

Baseline measurements will reflect the status of patients at or prior to randomisation. Demographic data includes admission diagnosis, comorbid illness including quantification using the Charlson Comorbidity Index [32], Katz Activities of Daily Living (ADL) index [33] (prior to the ICU admission), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and admission Sequential Organ Failure Assessment (SOFA) Score. Baseline measures, collected by the study Dietitian, include height (using ulna length [34]), weight (from bed scales), body mass index (BMI), mid upper arm circumference, nutritional status using the subjective global assessment (SGA) [35, 36], plasma albumin, highest and lowest blood glucose in the first 24 h of ICU admission, independent dietitian estimation of energy (weight-based or Schofield equation [37]) and protein requirements and the first quadriceps muscle layer thickness measure [24], see Table 3 for details of data collection.

Randomisation and blinding

We will use a simple randomisation system to assign participants [1:1] to receive either standard care or

the intervention. Allocation will be concealed using sequentially numbered opaque sealed envelopes, held by research personal not involved with the study. If the participant or the person responsible wishes to withdraw consent at any time, all study procedures will cease and the participant will receive standard ICU care as directed by the clinical team. Due to the nature of the intervention, the study is single-blinded. However, outcomes of muscle strength and physical function will be measured by an investigator blinded to the group allocation. Data analysis will be performed using a binary treatment code to maintain group allocation of blinding until the results are finalised.

Trial intervention and comparator

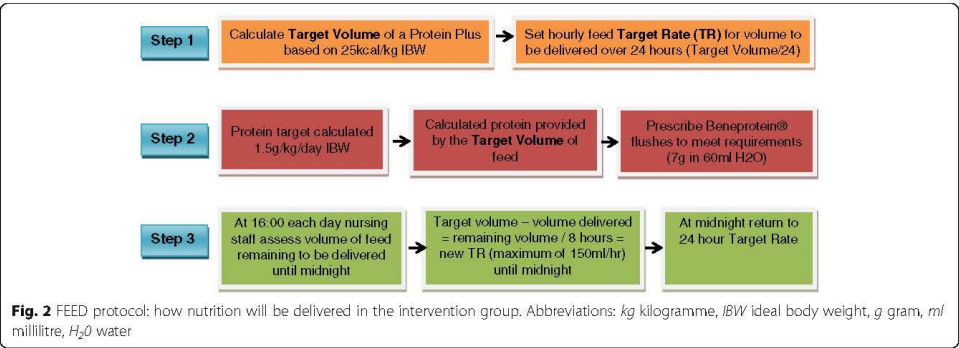
The intervention or standard care will be delivered following randomisation until ICU discharge; the patient no longer requires enteral tube feeding, or at the end of day 15, with the day of randomisation being day 1. Tolerance of enteral nutrition will be assessed and managed similarly for both groups, with prokinetic drugs (metoclopramide 10 mg q.i.d. and erythromycin 200 mg b.d.) administered if gastric residue volumes at any time equal or exceed 300 ml [38]. The need for parenteral nutrition will be determined by treating clinical staff that are not investigators and are not aware of group allocations.

Standard care group

The comparator group will receive standard nutrition care [39], which includes commencing a standard commercially available 1.0 kcal/ml enteral formula (Nutrison® 1.0 kcal, Nutricia, Wuxi, China), providing 40 g protein and 1000 kcal per litre. Liquid nutrient will be commenced using our ICU nutrition protocol (Appendix), and the target rate will be set at 25 kcal/kg ideal body weight (IBW) [1]. This strategy is designed to prescribe 1.0 g/kg protein and 25 kcal/kg of energy per day, however it is anticipated participants will receive less than this due to interruptions to nutrition therapy [39]. For participants below or within the IBW range (defined as a BMI between 18.5–25 kg/m² for 18–65 years

Table 1 Inclusion and exclusion criteria

Inclusion	• Adults, ≥ 18 years of age • Mechanically ventilated (MV) for ≥ 48 h with no immediate plans to extubate in the next 24 h
Exclusion	• Patients who have a contraindication to enteral feeding • Limit of medical treatment order in place or imminent death • Pre-morbid disability causing inability to ambulate > 10 m independently (+/- gait aid) • Pregnancy • The treating clinician considers the intervention not in the patients best interest or too burdensome



and 22–27 kg/m² for ≥ 65 years [40]), actual body weight will be used. For participants with BMI ≥ 32 kg/m², an adjusted IBW will be used (IBW + 25% (actual weight – IBW)) [41].

compared to the target volume, and then adjust the feed rate to aim to deliver the remaining feed volume over the 8-h period to midnight, with a maximum feeding rate of 150 ml/h [11]. The data on compliance to the feeding protocol will be collected.

Intervention group

The intervention group will receive their nutrition care based on the FEED protocol (Fig. 2, FEED protocol). It is anticipated that this will provide 1.5 g/kg protein and 25 kcal/kg of energy per day. The enteral formula will be a 1.25 kcal/ml formula (Nutrison® Protein plus, Nutricia, Zoetermeer, The Netherlands), providing 1250 kcal and 63 g protein per litre. The target formula volume will be determined based on 25 kcal/kg IBW, and the difference between the protein provided from the enteral formula and the target protein requirement of 1.5 g/kg IBW will be calculated. This difference will be met using protein powder (Beneprotein®, Nestle Health Sciences, Switzerland), provided in 6 g protein boluses (1 scoop of powder (7 g), provides 6 g of protein) over the day. Beneprotein® is a commercially available product that contains 100% whey protein isolate. To ensure that the target volume of formula is delivered, at 16:00 each day, the ICU bedside nurse will calculate the volume of formula provided,

Management of fluid overload

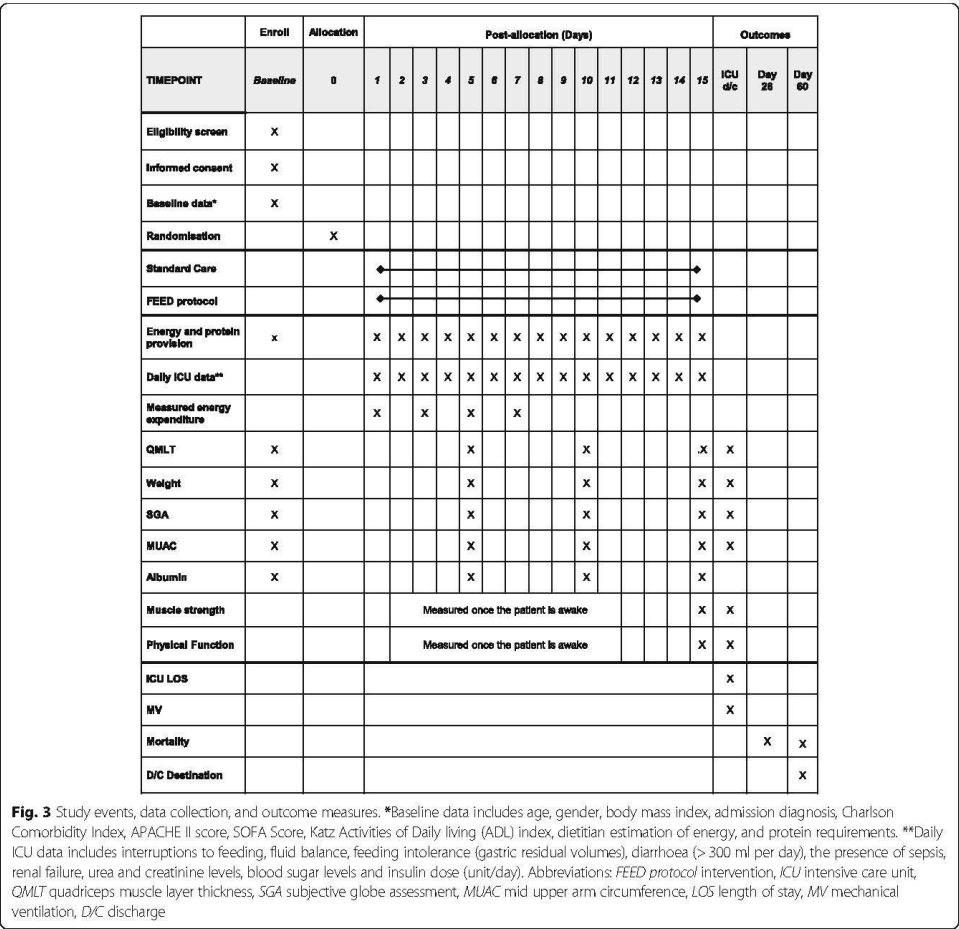
For both groups, if the attending intensivist wishes to reduce the volume of feed provided, the feed will be changed to Nutrison® Concentrate 2.0 kcal/ml, (Nutricia, Zoetermeer, The Netherlands) with a goal to provide 25 kcal/kg of energy. For the standard care group, this will mean they will receive comparable protein delivery to the 1.0 kcal formula. For the intervention group, the protein supplementation will be increased in an attempt to achieve 1.5 g/kg/day. These changes will be recorded.

Management of withdrawal

Stopping criteria are provided (Table 2), and any withdrawals will be recorded. The data will be retained and reported for all withdrawals where allowed by patient consent. Any adverse events will be recorded and reported.

Table 2 Criteria for withdrawal

Criteria	Measure
Feed intolerance	Tolerating < 40% of requirements via the enteral route for ≥ 3 days
Renal failure	If eGFR is < 25% and the patient is not commenced on continuous renal replacement therapy within 2 days
Severe oedema	> 5 L positive fluid balance, without alternative way to manage fluid balance and attending physician assesses the feed volume and additional protein to be impacting on the patients treatment after the above volume considerations have been implemented
Diarrhoea	≥ 500 ml per day or five bowel actions
Intensivist or attending physician request	No parameter
Participant/person responsible request to withdraw	No parameter



Management of adverse events
It is not expected that any adverse events will occur in relation to the study protocol. However, each participant will be monitored regularly by study personnel for adverse events occurring throughout the study. If any adverse events do present the nature, severity, causality, and course of the adverse event will be recorded. Adverse events such as death, ischaemic bowel, renal failure, and diarrhoea will be recorded from the time of consent; if these events occur, this will be discussed with the attending ICU consultant to determine if they may be related to the study. Any severe adverse events related to the study will be reported to the Melbourne

Health Human Research and Ethics Committee within 24 h of personnel becoming aware of it.

Outcome measures
The data collection and the outcome measures are summarised in Fig. 3.

Primary outcomes
The co-primary outcomes are mean daily protein and energy provided over the 15-day study period. The provision of protein and energy will be calculated on a daily basis and will be determined taking into account all sources; this includes nutrition therapy (enteral formula, protein supplements, and

parenteral formula), dextrose, and propofol. The mean protein and energy provided will be determined, by adding the daily provision over the 15-day study period (the 14 complete calendar days). The provision of any nutrition prior to commencing the study protocol will be collected and reported but not included in the primary outcome analysis.

Secondary outcomes

The first secondary outcome measurement is the change in muscle mass, determined as the change in QMLT using ultrasound from baseline to day 15 or ICU discharge if earlier. A portable ultrasound device (Sonosite S-ICU™) with a multiple frequency transducer (13–6 MHz, 6 cm) will be used to obtain muscle mass images. The method to obtain the images will be carried out as described by Tillquist and colleagues [24], with measurements completed using both minimal and maximal pressures. The first measure will be taken before randomisation, then on day 5, day 10, and at discharge or day 15 of ICU. A single-trained operator will complete all QMLT measures, and this technique has a very good intrarater reliability in both healthy populations [24] and critically ill patients [42]. The measurement will be completed on all participants, with bilateral measurements at two points; the midpoint between the Anterior Superior Iliac Spine (ASIS) and the upper pole of the patella and at the point two thirds between the ASIS and the top of the patella [22–24], the landmarks will be marked using a permanent pen. A linear measure will be taken for each point twice, with minimal pressure and maximal pressure applied and the measures will be recorded [22]. The device settings will be standardised for each measure, and bony landmarks will be used to determine if the transducer is oriented perpendicular to the muscle [24]. Each image will be stored to the hard drive of the ultrasound device and then transferred for further blinded analysis at a later date. The change in QMLT from baseline to day 5 and discharge or day 15 will be calculated for each patient for the measurements taken with minimal pressure and maximal pressure separately.

The other secondary outcomes are total calorie and protein provision, calorie deficit and protein adequacy, incidence of feed intolerance, number of days of feed intolerance, incidence of diarrhoea defined as more than three bowel actions or greater than 300 ml per day [43], length of ICU stay, hospital mortality at 28 and 60 days, discharge destination, muscle strength, the incidence of ICU AW and physical function at ICU discharge, and the change in nutritional markers over the study period. Nutritional markers include assessment of

malnutrition using the Subjective Globe Assessment (SGA) [35], mid upper arm circumference (MUAC), and body weight. These measures will be carried out at baseline, day 5, and at discharge from ICU; the change from baseline to discharge or day 15 will be calculated. The presence of acute renal failure defined by the RIFLE criteria [44] and plasma urea and creatinine levels will be assessed on a daily basis.

Protein adequacy will be determined over the ICU admission or until day 15 by adding the daily protein provision and comparing this to the estimated protein requirements determined by the dietitian. The protein adequacy will then be explored in relation to the other outcome measures.

Calorie deficit will be determined using both predicted weight-based energy requirements (25 kcal/kg). In eligible patients, calorie deficit will also be calculated using measured energy expenditure (MEE) [45]. Cumulative calorie deficit will be calculated over the ICU admission or until day 15 of the study. MEE will be assessed with indirect calorimetry using E-sCOVX (GE, Helsinki, Finland) [46]. The first MEE will be within 24 h of enrolment into the study and repeated on day 3, day 5, and day 7 of the ICU stay. The measurements will be carried out with the patient in a fed state lying supine. The measure will be taken over a 2-h period, and the summary data of respiratory quotient (RQ) and MEE will be recorded. The feeding rates will not be adjusted in relation to the MEE [47]. Contraindications to carrying out a metabolic measurement will include if the patient is on continuous renal replacement therapy or extracorporeal membrane oxygenation (ECMO) or if the patient has an intercostal catheter with an air leak or is on a fraction of inspired oxygen greater than 0.6 [47].

Feed intolerance will be determined as a single gastric residual volume > 300 ml [48].

Muscle strength will be determined in suitable participants using handgrip dynamometry and the Medical Research Council (MRC) scale [49, 50]. The first muscle strength test will be performed at awakening [50] and then again at discharge or day 15, whichever comes first. Patients will be screened for attention and comprehension on the basis of their ability to follow commands, they will be considered awake if they score at least three out of five using the De Jonghe comprehension criteria on at least two occasions within a 6-h period [51] and have a Riker sedation-agitation scale score of three to five [52]. Handgrip dynamometry (Commander Echo™ Wireless Grip Dynamometer, USA) will be measured in both limbs with the participant in a chair or sitting at least at 45° in bed, with the patients elbow at 90°

supported by a pillow or the arm of the chair. The Medical Research Council sum score (MRC-SS) will be measured as previously described [51, 53, 54] with ICUAW defined as an MRC-SS of $<48/60$ [55].

Physical function will also be assessed using the physical function in Intensive Care Test-scored (PFIT-s) [56, 57]. Patients may only be able to perform part of the test, but are still able to obtain a score.

Sample size

A sample size of 60 is based on observational data [45], where daily protein intake, mean (SD), was 50.8 g (20.1 g) protein per day; therefore, 29 participants per group will provide 80% power (two-sided α 0.05) to detect a minimum difference of a 15-g protein between groups. While there is limited data on change in muscle mass using ultrasound, using the data from the VALIDUM study, mean (SD) QMLT of 1.3 (0.6) cm [22], a sample size of 28 participants in each group will also provide over 80% power to detect a mean difference of 0.5 cm in QMLT.

Statistical analysis

All analyses will use an intention-to-treat approach. Baseline patient demographics, severity of illness, ICU length of stay, mortality, and nutritional markers will be tabulated according to the treatment group. Initial exploratory data analysis will involve calculation of summary statistics and comparison between treatment groups using non-parametric (Wilcoxon), parametric (t test), and Fisher's exact tests as appropriate, as well as construction of trajectory plots according to the treatment group. The co-primary outcomes of average daily energy and protein delivery will be compared between treatment and control groups with two-sample unpaired t tests, with statistical significance for each set conservatively at two-sided values of 0.025 to limit the family-wise type 1 error for the two co-primary outcomes to less than 0.05 overall.

All secondary outcomes will be regarded as exploratory and hypothesis-generating, with no multiple comparison adjustment to conventional 5% type 1 error thresholds. Group differences for change from baseline at selected time points in continuous outcome variables, including QMLT, will be compared after adjustment for initial values using analysis of covariance (ANCOVA) regression models, initially unadjusted, and subsequently adjusted as described below for other regression models. Natural logarithmic transformations may be applied to stabilise variance within these or other linear models if appropriate. The relationships between calorie

deficits using both prescribed calories (25 kcal/kg) and MEE and protein adequacy and the outcome measures (QMLT change, muscle strength, diagnosis of ICUAW, and physical function at ICU discharge) will be explored using linear or logistic regression analyses, with adjustment for likely confounders and any baseline variable found to show substantial imbalance between treatment groups. Finally, a population-averaged generalised linear model using a generalised estimating equation (GEE) approach with an unstructured working correlation matrix and robust standard error estimates adjusted for clustering within individual subjects will be applied to these longitudinal data to evaluate the overall associations of the vector of (untransformed or log transformed) outcome variables with treatment group across multiple time points. Multiple imputations for missing data may be used to support conclusions from other generalised linear models constructed without imputation of missing data. Data analysis will be carried out using the Statistical Package for the Social Sciences (SPSS) (IBM® SPSS® Statistics Premium Grad Pack Version 22.0) or Stata Corporation (Stata Statistical Software: Release 15. College Station, TX: StataCorp LP; 2017).

Discussion

It has been hypothesised that protein provision may be more important than energy provision for critically ill patients [25]. Optimal protein delivery may also influence functional outcomes via attenuation of muscle loss. However, the optimal amount of enteral protein required in critical illness is relatively unknown and has not been rigorously studied. Moreover, attempts to augment enteral protein delivery may result in slower gastric emptying, greater feeding intolerance, and, thereby, paradoxically less protein and calorie delivery.

The strengths of this study include randomisation, comparing two different protein amounts using enteral nutrition, and assessment of the impact of nutrition provision on muscle mass and functional outcomes that is essential for planning a larger multicentre study.

This pilot study aims to clarify whether an enteral feeding protocol with a volume target and supplemental protein has potential to increase protein and energy delivery in mechanically ventilated critically ill patients and will provide preliminary estimates as to whether this intervention has the capacity to affect muscle mass or other patient-centred outcomes.

Appendix

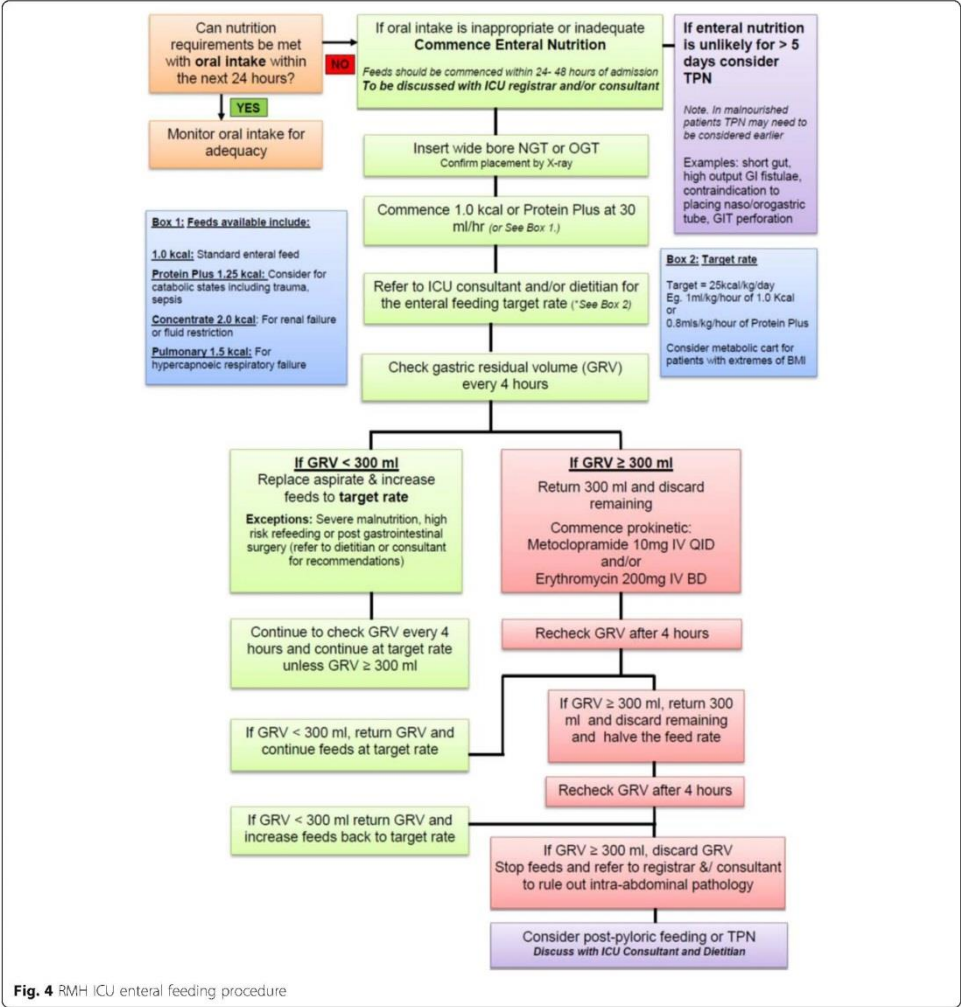


Fig. 4 RMH ICU enteral feeding procedure

Abbreviations

ADL: Activities of daily living; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index; CONSORT: Consolidated Standards for Reporting of Trials; ECMO: Extracorporeal membrane oxygenation; GEE: Generalized estimating equation; HRQoL: Health-related quality of life; IBW: Ideal body weight; ICU: Intensive care unit; ICUAW: Intensive care unit acquired weakness; MEE: Measured using energy expenditure; MRC: Medical Research Council; MRC-SS: Medical Research Council sum score; MUAC: Mid Upper Arm Circumference; MV: Mechanically ventilated; PFET-s: Physical Function in Intensive Care Test – scored; QMLT: Quadriceps muscle layer

thickness; RQ: Respiratory quotient; SD: Standard deviation; SGA: Subjective global assessment; SOFA: Sequential Organ Failure Assessment

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Trial status

The trial commenced on the 10th of August 2015. Final recruitment is expected to be achieved in September 2017.

Dissemination

It is intended that the results of this study will be presented at national and international conferences and also submitted for publication in a peer reviewed journal.

Funding

This project is supported by the Mary Elizabeth Watson Early Career in Allied Health Research Fellowship provided by Melbourne Health, which provides \$30,000 per year over 2 years.

Availability of data and materials

All data obtained during the study will be coded, de-identified, and stored in a secure area of the Intensive Care Department at the RMH. Only the investigator and staff of the department will have access to the records.

Authors' contributions

All authors contributed to the study design. KF and AD drafted the manuscript, and all authors reviewed the final manuscript and agreed to be accountable for the accuracy and integrity of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study is being conducted in full accordance with the National Statement on Ethical Conduct in Human Research (2007), the Guidelines for Good Clinical Research Practice and Melbourne Health Research Policies and Guidelines. This study was approved by the Melbourne Health human research ethics committee (project number 2015.048), on the 11th of May 2015 and was also approved by the La Trobe University Human Ethics Committee on the 3rd of June 2015 under the same project number. As outlined above, all eligible patients will be mechanically ventilated and unable to consent to participation; informed consent will be obtained from the person responsible as per local laws.

Consent for publication

Not applicable.

Competing interests

KF has received conference/travel grants from Baxter, Fresenius Kabi, and Nestle Health Science (not related to this study). AMD or his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic, and Takeda.

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Author details

¹Department of Clinical Nutrition, Allied Health, Royal Melbourne Hospital, Melbourne, Australia. ²Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Australia. ³Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne, Australia. ⁴Department of Medicine, The University of Melbourne, Melbourne, Australia. ⁵Department of Physiotherapy, Allied Health, Royal Melbourne Hospital, Melbourne, Australia. ⁶Department of Kinesiology, Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Canada.

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Appendix 5

2018 Promising Investigator Award



Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial)

Kate Fetterplace, APD, BNutrDiet^{1,2,3}; Adam M. Deane, MBBS, PhD^{3,4}; Audrey Tierney, APD, PhD^{2,5}; Lisa J. Beach, PT, MPhy⁶; Laura D. Knight, PT, BPhy, MHSM⁶; Jeffrey Presneill, MBBS, PhD^{3,4}; Thomas Rechnitzer, MBBS, FCICM⁴; Adrienne Forsyth, APD, AEP, PhD² ; Benjamin M. T. Gill, APD, MDiet^{1,3}; Marina Mourtzakis, PhD⁷; and Christopher MacIsaac, MBBS, PhD^{3,4}

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Abstract

Background: International guidelines recommend greater protein delivery to critically ill patients than they currently receive. This pilot randomized clinical trial aimed to determine whether a volume-target enteral protocol with supplemental protein delivered greater amounts of protein and energy to critically ill patients compared with standard care. **Methods:** Sixty participants received either the intervention (volume-based protocol, with protein supplementation) or standard nutrition care (hourly-rate-based protocol, without protein supplementation) in the intensive care unit (ICU). Coprimary outcomes were average daily protein and energy delivery. Secondary outcomes included change in quadriceps muscle layer thickness (QMLT, ultrasound) and malnutrition (subjective global assessment) at ICU discharge. **Results:** Mean (SD) protein and energy delivery per day from nutrition therapy for the intervention were 1.2 (0.30) g/kg and 21 (5.2) kcal/kg compared with 0.75 (0.11) g/kg and 18 (2.7) kcal/kg for standard care. The mean difference between groups in protein and energy delivery per day was 0.45 g/kg (95% CI, 0.33–0.56; $P < .001$) and 2.8 kcal/kg (95% CI, 0.67–4.9, $P = .01$). Muscle loss (QMLT) at discharge was attenuated by 0.22 cm (95% CI, 0.06–0.38, $P = .01$) in patients receiving the intervention compared with standard care. The number of malnourished patients was fewer in the intervention [2 (7%) vs 8 (28%); $P = .04$]. Mortality and duration of admission were similar between groups. **Conclusions:** A high-protein volume-based protocol with protein supplementation delivered greater amounts of protein and energy. This intervention was associated with attenuation of QMLT loss and reduced prevalence of malnutrition at ICU discharge. (*JPEN J Parenter Enteral Nutr.* 2018;42:1252–1262)

Keywords

critical illness; dietary proteins; enteral nutrition; enteral formulas; functional outcomes; muscle mass; nutrition support; ultrasound

Clinically Relevancy Statement

Current international guidelines recommend that critically ill patients should receive at least 1.2–2.0 g/kg/day of

protein. In clinical practice, patients often receive considerably less protein due, in part, to healthcare factors (interruption to nutrition therapy for other medical therapy) and patient factors (feeding intolerance). The aim of this

From the ¹Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia; ²Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Australia; ³Department of Medicine, The University of Melbourne, Melbourne, Australia; ⁴Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne, Australia; ⁵Department of Clinical Therapies, University of Limerick, Limerick, Ireland; ⁶Allied Health (Physiotherapy), Royal Melbourne Hospital, Melbourne, Australia; and the ⁷Department of Kinesiology, Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Ontario, Canada.

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Conflicts of interests: K. Fetterplace has received conference, travel grants, and/or honoraria from Baxter, Fresenius Kabi, and Nestlé Health Science (not related to this study). A. M. Deane or his institution has received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic, and Takeda (not related to this study). The other authors have no potential conflicts to declare.

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Corresponding Author:

Kate Fetterplace, APD, BNutrDiet, Senior Dietitian, Royal Melbourne Hospital, Allied Health, Royal Melbourne Hospital, Grattan St, Parkville, Victoria, Australia 3050.
Email: kate.fetterplace@mh.org.au

pilot randomized clinical trial was to determine whether a high-protein enteral feeding protocol using a volume target and protein supplementation delivered greater amounts of protein and energy to critically ill patients when compared with standard care. In this single-center, open-label, parallel group trial of critically ill mechanically ventilated patients, the intervention was associated with greater delivery of protein and energy, attenuation of muscle loss, and a lower prevalence of malnutrition at ICU discharge. Further research using this intervention is warranted given the achievement of recommended protein delivery and observed point estimates favoring beneficial effect in key secondary outcomes.

Introduction

The current Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition guidelines recommend that protein should be provided at a level of 1.2–2.0 g/kg/d, with possibly greater amounts for patients who are obese or present with multitrauma or burns,¹ and other guidelines have similar recommendations (eg, European Society of Parenteral and Enteral Nutrition). However, there is a lack of high-quality randomized controlled trials to support these protein recommendations.^{2,3}

Observational data suggest that greater protein provision may be associated with improvements in survival, ventilator-free days, and time to discharge alive from the intensive care unit (ICU).^{4–8} Higher levels of protein provision may not only reduce mortality, but also stimulate the synthesis of new proteins and preserve muscle mass.³ Skeletal muscle preservation has been identified as an important surrogate outcome of ICU patients given the association between muscle loss and the development of ICU-acquired weakness (ICUAW).^{9,10} Optimal nutrition, particularly with adequate protein provision, may have the capacity to attenuate muscle loss,^{11,12} but randomized controlled trial data to substantiate this are limited.¹³

Despite current guidelines, the delivery of nutrition in the ICU is substantially less than recommended.¹⁴ The provision of nutrition via the enteral route is considered preferable¹; however, adequate delivery of protein and energy to critically ill patients via this route remains a challenge.¹⁵ Standard enteral feeding regimens are based on energy targets, and as a result protein delivery is more often restricted by the formula composition; this may result in protein prescriptions that are less than the current guidelines.³ Several methods to increase protein delivery via the enteral route have been proposed; these include the use of high-protein formulas, volume-based feeding protocols, and additional protein supplementation.¹⁶ However, in practice, these methods may not result in more protein and energy being administered because protein is a potent stimulant of the small intestine feedback loop, which slows

gastric emptying¹⁷ and can cause feed intolerance,¹⁸ thereby possibly reducing protein and energy provision. The combination of these methods has not previously been studied.

The primary aim of this single-center pilot randomized controlled trial was to determine whether a high-protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly-rate-based nutrition protocol without protein supplementation to mechanically ventilated critically ill patients. The secondary aims were to evaluate whether this intervention increased feed intolerance or the development of diarrhea, whether the intervention attenuated muscle or weight loss or the prevalence of malnutrition at ICU discharge, and to estimate the impact of the intervention on patient-centered outcomes.

Materials and Methods

The study protocol was registered with the Australian New Zealand Clinical Trials Registry (<http://www.ANZCTR.org.au/>; ACTRN: 12615000876594, UTM: U1111-1172-8563). A protocol and statistical analysis plan manuscript was submitted during the enrollment period, before analysis of data.¹⁹

Patients

This trial was conducted between August 2015 and August 2017 at the Royal Melbourne Hospital ICU. This ICU is a 32-bed university-affiliated, tertiary referral, mixed medical-surgical-trauma ICU. Screening was performed only on weekdays. Patients were eligible if they were >18 years of age, mechanically ventilated for <48 hours, and were anticipated to remain ventilated for at least 72 hours. Patients were excluded if they had a contraindication to enteral feeding, if there was futility of care or death was imminent, if they had a premorbid disability resulting in an inability to ambulate >10 m, if they were pregnant, or the treating clinician considered the intervention was not in the patient's best interest. The trial was conducted in accordance with the Declaration of Helsinki, and prior informed consent was obtained from the surrogate decision maker. Continuation of participation was obtained if the participant recovered adequately to provide consent. The protocol and consent process was approved by the Royal Melbourne Hospital Human Research Ethics Committee (2015.048).

The overall sample size of 60 patients (2 groups of 30 patients) was calculated using a 2-sided α level of .05 and a power ($1-\beta$) of 80% to detect a minimum difference of 15 g protein delivered per day between groups based on data from an observational study undertaken within the trial ICU,²⁰ which showed a baseline protein intake [mean (SD)] of 50.8 (20.1) g/d. Using data from the Validation of Bedside Ultrasound of Muscle Layer Thickness of the Quadriceps in the Critically Ill Patient study,²¹ mean (SD)

quadriceps muscle layer thickness (QMLT) was 1.3 (0.6) cm,²¹ suggesting that a sample size of 27 participants in each group, accounting for 10% missing data, was sufficient to also provide >80% power to detect a mean difference of 0.5 cm in QMLT between groups.

Study Design

Participants were randomly assigned using a simple 1:1 randomization system to receive either the intervention or standard care. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes that were held in a secure location by research personnel not involved with the trial. Due to the nature of the intervention clinicians were not blinded; however, blinded assessors undertook the outcome measurements of muscle strength and physical function.

The intervention or standard care was delivered after randomization until ICU discharge, until the patient no longer required enteral tube feeding, or until the end of study day 15, whichever came first. Feeding intolerance was managed for both groups according to standard unit protocols, which included the use of gastrokinetic drugs, without ceasing enteral nutrition (EN), and the consideration of postpyloric feeding tubes or supplemental parenteral nutrition (PN) if severe feeding intolerance occurred. The need for PN was determined by treating physicians who were not study investigators. The intervention group received a volume-based nutrition protocol¹⁶ using a high-protein enteral formula (Nutrison Protein Plus [Nutricia, Zoetermeer, the Netherlands]; 63 g of protein and 1250 kcal/L). Nursing staff was provided with a detailed regimen, which included a volume target and an hourly rate target with instructions to deliver the volume target over a 24-hour period based on 25 kcal/kg/d. Nursing staff assessed the volume of feed that had been delivered at 4:00 pm each day and calculated the volume required for the remaining 8 hours to achieve goal volume and adjusted the rate accordingly. A maximum rate of 150 mL/h was set to minimize the risk for aspiration.¹⁶ Protein supplements (Beneprotein [Nestlé Health Sciences, Lausanne, Switzerland]; 6 g of protein per scoop) were prescribed by the study dietitian in an attempt to achieve delivery of 1.5 g/kg/d protein (liquid formula plus protein supplement). The standard care group received standard nutrition care,²² which included commencing a standard commercially available 1.0 kcal/mL enteral formula (1.0 kcal Nutrison [Nutricia, Wuxi, China]), which provides 40 g of protein and 1000 kcal/L. EN was commenced as per the standard facility protocol, aiming to provide 1.0 g/kg/d protein and 25 kcal/d.¹ For both groups, the weight used to calculate the nutrition provision was based on actual body weight or ideal body weight if above the healthy weight range. Weight was obtained using the bed scales, and height was calculated using the estimate provided by measuring

ulna length.²³ Ideal body weight for participants aged <65 years is defined as a body mass index (BMI) between 18.5 and 25 kg/m², and for those aged ≥65 years, a BMI between 22 and 27 kg/m².²⁴ For participants with a BMI ≥32 kg/m², an adjusted ideal body weight was used (ideal body weight + 25% [actual body weight – ideal body weight]).²⁵

At baseline, data were collected including admission diagnosis, Charlson Comorbidity Index, Katz activities of daily living index, Acute Physiology and Chronic Health Evaluation II and III (APACHE II and III) score, and admission Sequential Organ Failure Assessment (SOFA) score. Duration of ICU and hospital admission, discharge destination, and survival at days 28 and 60 were recorded.

Protein and Energy Provision

The coprimary outcomes were the mean daily protein and energy delivered over the 15-day study period. Administration of nutrition before commencing the study protocol was not included. The provision of protein and energy was calculated on a daily basis from enteral and/or parenteral formula and/or protein supplements, but separate from all other sources. Total energy delivery included nutrition therapy, as well as calories from dextrose and propofol. Day 1 (day of randomization) and day of discharge were included even if they were partial days.

Feeding Intolerance

The proportion of patients who experienced development of feeding intolerance was determined by the number of patients in the group who had at least 1 gastric residual volume >300 mL¹⁸ over the study period. The cumulative incidence of feeding intolerance was determined by the number of days a patient had gastric residual volumes >300 mL. The proportion of patients who had diarrhea was determined by the number of patients who had >3 bowel actions or >300 mL of stool output in a 24-hour period on at least 1 occasion,²⁶ and the cumulative incidence was determined by the number of days the patient met the earlier criteria.

Muscle Mass

Muscle mass was assessed with ultrasound, measuring QMLT using the technique described by Tillquist and colleagues.²⁷ The QMLT measurements were performed by a single trained operator (K.F.) using a portable ultrasound machine (Sonosite S-ICU) with a multiple-frequency transducer (13–6 MHz, 6 cm). The device settings were standardized, and the measurements were taken with the patient lying in a supine position with legs relaxed and extended. QMLT was completed on bilateral lower limbs; measurements were obtained at 2 different landmarks, the midpoint and two-thirds between the anterior superior iliac

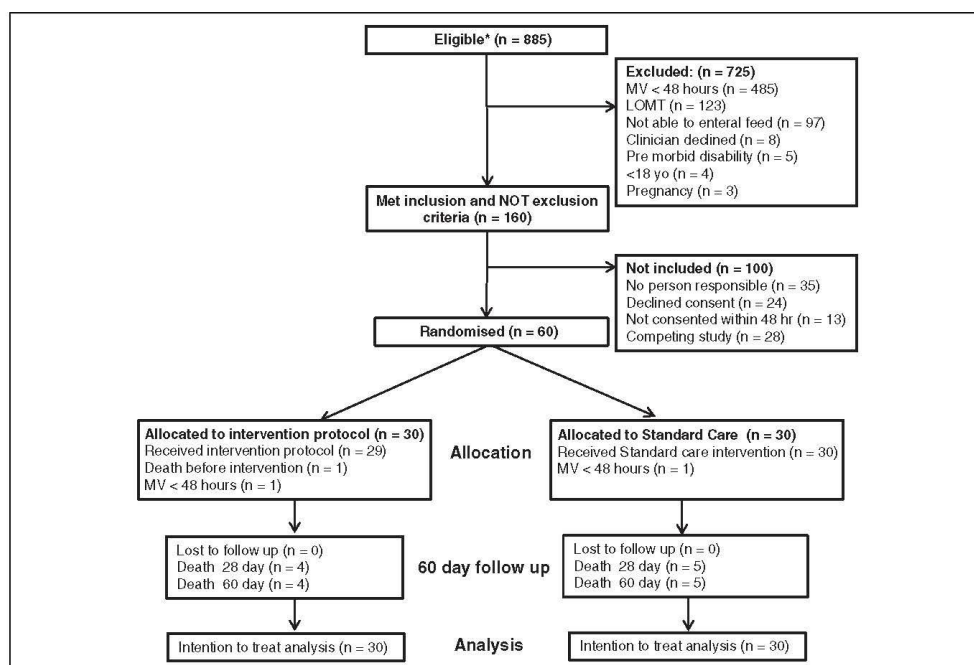


Figure 1. Patient flowchart and flow diagram of patient eligibility and study conduct. *Eligible patients: patients mechanically ventilated and admitted to the intensive care unit <48 hours at time of screening. LOMT, limit of medical treatment; MV, mechanically ventilated; yo, years old.

spine and the upper pole of the patella.^{21,27,28} A still image was taken with the transducer held perpendicular to the skin; the muscle thickness was quantified by using the onscreen calipers to measure the distance between the upper margin of the femoral bone and the lower boundary of the deep fascia of the rectus femoris muscle.²¹ Duplicate measurements were taken at each landmark, and the mean of the 4 linear thicknesses was calculated for each leg separately.²⁸ The first measurement was taken before randomization and then at discharge from ICU or day 15 (whichever came first).

Nutrition Assessment and Outcomes

Before randomization, baseline measures were undertaken including height (cm; using ulna length²³), body weight (kg; from bed scales), BMI (kg/m²), mid upper arm circumference (cm), nutrition status using the subjective global assessment (SGA),²⁹ plasma albumin level (g/L), and an estimate of energy and protein requirements obtained by an independent dietitian. Body weight, nutrition status, mid upper arm circumference and plasma albumin levels were

repeated at discharge from ICU or day 15, whichever came first. In addition, measured energy expenditure (MEE) was assessed by indirect calorimetry using the E-sCOVX (GE, Helsinki, Finland) monitor.^{30,31} The measurements were carried out within the first 5 days after enrolment, if a trained operator was available, and patients were excluded if they were receiving continuous renal replacement therapy, attached to extracorporeal circulation, had an intercostal catheter with an air leak, or were receiving a fraction of inspired oxygen >0.6.³² The measurement was completed with the patient in a fed state lying supine. The mean respiratory quotient and MEE (kcal/d) were recorded.

Functional Outcomes

Muscle strength was assessed in suitable participants using handgrip dynamometry and the Medical Research Council (MRC) Scale.^{33,34} The first muscle strength test was performed at awakening³⁴ and then again at discharge or day 15, whichever came first. Patients were screened for attention and comprehension on the basis of their

Table 1. Baseline Demographics and Comparisons of Study Groups.

Demographics	Intervention (n = 30)	Standard (n = 30)
Age, y, mean (SD)	55 (13)	57 (16)
Male sex, n (%)	23 (77)	21 (70)
Body mass index, kg/m ² , mean (SD)	30 (7.1)	29 (5.3)
APACHE II score, mean (SD)	22 (6.2)	20 (5.9)
APACHE III score, mean (SD)	77 (25)	71 (22)
Comorbidity index, mean [IQR]	3 [1–5]	3 [2–4]
Katz activities of daily living index, mean [IQR]	6 [6–6]	6 [6–6]
Admission category, n (%)		
Medical	21 (70)	16 (53)
Elective surgery	1 (3.3)	1 (3.3)
Emergency surgery	8 (27)	13 (43)
Admission diagnosis, n (%)		
Neurological conditions	13 (43)	7 (23)
Multitrauma/head trauma	7 (23)	11 (37)
Respiratory	1 (3.3)	5 (17)
Cardiac arrest	3 (10)	1 (3.3)
Sepsis	3 (10)	1 (3.3)
Cardiac surgery	0	2 (6.7)
Other	3 (10)	3 (10)
Chronic renal failure, n (%)	1 (3.3)	0 (0)

APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range.

ability to follow commands; they were considered awake if they scored at least 3 out of 5 using the De Jonghe comprehension criteria on at least 2 occasions within a 6-hour period and had a Riker sedation-agitation scale score of 3–5. Handgrip dynamometry (Commander Echo Wireless Grip Dynamometer, JTECH Medical, UT, USA) was measured in both limbs with the participant in a chair or sitting at least at 45 degrees in bed, with the patient’s elbow at 90 degrees supported by a pillow or the arm of the chair. The MRC Sum Score (MRC-SS) was measured as previously described,³⁵ with ICUAW defined as an MRC-SS <48/60.^{36–38} Physical function was assessed using the scored Physical Function in Intensive Care Unit Test (PFIT-s).³⁹

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM SPSS Statistics Premium Grad Pack Version 23.0) and Stata (Stata Statistical Software: Release 15, 2017; StataCorp, College Station, TX, USA). All analyses were conducted using the intention-to-treat patient sample. Baseline patient demographics, severity of illness, ICU length of stay, mortality, and nutrition markers were tabulated according to treatment group and summarized as mean (SD) or median [interquartile range (IQR)], as appropriate. Initial exploratory data analysis included the

calculation of summary statistics and comparison between treatment groups using nonparametric (Wilcoxon), parametric (*t*-test), and Fisher exact tests as appropriate, as well as construction of trajectory plots according to treatment group. The coprimary outcomes of average daily energy and protein delivery were compared between the 2 groups using 2-sample unpaired *t*-tests, with statistical significance for each set conservatively at 2-sided values of 0.025, to control the family-wise type 1 error to <0.05 overall.

All secondary outcomes were regarded as exploratory and hypothesis generating with, as a consequence, no adjustment for multiple comparisons to their conventional 5% type 1 error thresholds. Group differences for each patient’s discharge QMLT were compared after adjustment for initial baseline values and other selected covariables using linear regression (analysis of covariance). Robust standard errors were specified to allow for within-subject correlation of the repeated muscle mass observations from left and right sides and across time. No imputation of missing data was performed. Standard model diagnostics of linearity and influence were performed.

Results

A total of 885 mechanically ventilated patients were screened, with 160 patients found to meet the eligibility criteria (Figure 1). Consent was obtained for 60 patients, who were randomized to receive either the intervention (n = 30) or standard care (n = 30). The goals of medical treatment were changed to “comfort care” for 1 patient (intervention group) soon after randomization but before commencement of the intervention nutrition regimen. One patient from each group was liberated from the ventilator before 48 hours.

At baseline, participants in both groups were similar with regards to age, sex, APACHE II and III scores, BMI, admission weight, and comorbidity index (Table 1). The majority of the patients in both groups were classified with medical rather than surgical diagnoses.

Coprimary Outcomes

The intervention was associated with an increased total protein delivery over the study period (mean increased protein delivery of 37 g/d [95% CI, 26–47; *P* < .001], equivalent to a mean overall protein advantage of 0.45 g/kg/d [95% CI, 0.33–0.56; *P* < .001]) (Table 2). A difference was observed over multiple days, with significantly more protein delivered to the intervention group compared with the control group on 13 of the 15 study days (Figure 2A, Table 2).

The intervention was also associated with increased energy delivery from EN per day (mean increase of 2.8 kcal/kg [95% CI, 0.7–4.9; *P* = .01]) (Table 2). There was

Table 2. Primary Outcomes and Nutrition Provision.^a

Outcomes	Intervention (n = 30)	Standard (n = 30)	Mean Difference (95% CI)	P-Value
Protein provided, g/d	94 (27)	58 (12)	37 (26–47)	<.001
	101 [85–113]	56 [49–64]		
Protein provided, g/kg/d	1.2 (0.30)	0.75 (0.11)	0.45 (0.33–0.56)	<.001
	1.3 [1.1–1.5]	0.73 [0.68–0.82]		
Protein adequacy, % of estimated requirements	90 (25)	57 (8.0)	33 (24–43)	<.001
	96 [81–108]	56 [52–63]		
Energy provided from nutrition, kcal/d	1646 (447)	1398 (308)	248 (50–447)	.02
	1754 [1508–1971]	1372 [1215–1582]		.001
Energy provided from nutrition, kcal/kg/d	21 (5.2)	18 (2.7)	2.8 (0.7–4.9)	.01
	22 [20–24]	18 [16–20]		<.001
Total energy provided, ^b kcal/d	1835 (340)	1598 (340)	237 (10–464)	.04
	1955 [1639–2177]	1545 [1399–1858]		<.01
Total energy provided, ^b kcal/kg/d	23 (5.7)	21 (3.3)	2.5 (0.05–4.9)	.05
	25 [22–26]	21 [18–23]		<.001
Energy adequacy, % of prescribed energy	84 (21)	73 (11)	11 (–2.7 to 20)	.01
	89 [80–96]	71 [63–81]		<.001
Estimated protein requirement, g/kg/d	1.3 (0.1)	1.3 (0.1)	0 (–0.05 to 0.05)	1.0
	1.3 [1.3–1.4]	1.3 [1.3–1.3]		.85
Estimated protein requirement, g/d	105 (19)	101 (17)	3.6 (–5.7 to 13)	.44
	104 [92–113]	98 [92–102]		.46
Estimated energy requirement, kcal/d	1969 (277)	1918 (255)	51 (–87 to 189)	.46
Measured energy expenditure, kcal/d (n = 15 per group)	2440 (435)	2194 (718)	246 (–196 to 688)	.26
Time spent fasting, h	19 (19)	20 (31)	–0.4 (–14 to 13)	.94
	12 [3.8–34]	7.0 [0–19]		.39
Time to commence enteral nutrition, h	13 (8)	20 (10)	6.3 (1.6–11)	.01
	13 [7.0–18]	17 [12–25]		.01

^aNormally distributed values are represented as mean (SD) 95% CI with *P*-values; nonnormally distributed values are represented as mean (SD) 95% CI and median [IQR] with *P*-values.

^bTotal energy included nutrition therapy plus energy from propofol and dextrose.

increased energy delivery from nutrition on 5 of the 15 study days (Figure 2B), and total energy delivered was greater in the intervention group (mean difference of 237 kcal/d [95% CI, 10–464; *P* = .04]) (Table 2).

Nutrition Provision and Outcomes

The participants required EN after randomization for a mean of 8.0 days (4.4) in the intervention and 7.0 days (4.5) in the standard care group (mean difference 1.0 day [95% CI, –1.3 to 2.3; *P* = .87]). Estimated energy and protein requirements were similar between groups (Table 2). Energy expenditure was measured in a convenience sample of 15 patients from each group (50%), and the daily energy expenditure was similar between groups (Table 2). Nutrition adequacy was greater in the intervention group (Table 2). EN was commenced earlier in the intervention group, and the period of time fasting was similar between groups (Table 2). Two patients in the standard care group and no patients in the intervention group received PN for a mean of 4.5 days in combination with EN because of feeding intolerance. The

proportion of patients who experienced feeding intolerance or diarrhea, and the cumulative incidence of these were similar between groups (Table 3). There were fewer patients in the intervention group classified as malnourished (SGA assessment) at ICU discharge, but all other assessed nutrition outcomes, including weight loss, were similar between groups (Table 3).

Muscle Mass Outcomes

QMLT measurements were not available at baseline and discharge in 6 (23%) participants in the intervention group and 7 (27%) participants in the standard care group. These missed observations were primarily due to participant unavailability, a change of focus to comfort care, death, other medical issues, or discharge from intensive care when the primary investigator was not available. Adjusted for baseline QMLT, the intervention was associated with less QMLT loss at discharge, with a mean attenuated loss of 0.22 cm (95% CI, 0.06–0.38; *P* = .01), controlling for patient age, severity of illness (APACHE III score), BMI, and admission

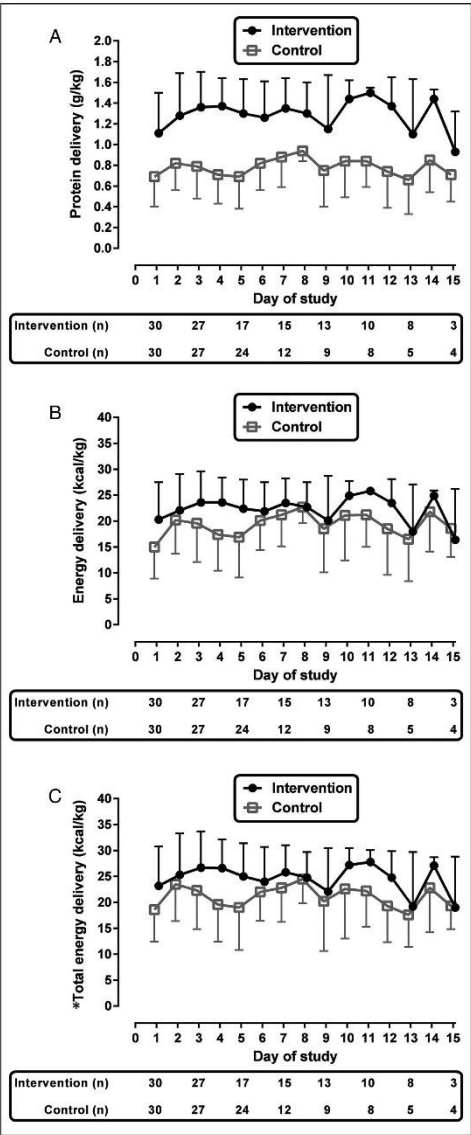


Figure 2. Mean daily protein (A) and energy (B) delivery from nutrition and total energy delivery (C) over the study period according to research group. Error bars represent 1 SD. *Total energy delivery includes energy from nutrition therapy plus calories from dextrose and propofol.

category (Table 4). Greater baseline QMLT was associated with a greater absolute QMLT at discharge, and surgical patients appeared to lose more QMLT compared with medical patients (−0.28 cm [95% CI, −0.44 to −0.01; *P* = .01]).

Physical Assessment Outcomes

Only 6 (20%) participants in the intervention and 16 (53%) participants in the standard care group completed handgrip strength, 7 (23%) and 14 (47%) participants completed medical research council sum-score (MRC-ss) muscle strength measurements, and 8 (27%) and 14 (47%) participants completed physical function tests, respectively. The missed observations were primarily due to participants' inability to complete these assessments based on the de Jonge criteria or participant unavailability as described earlier. In this small patient subgroup, the intervention and control groups showed similar muscle strength, physical function, and clinical outcomes (Table 5).

Discussion

This trial prospectively randomized participants to receive an enteral feeding intervention that resulted in delivery of considerably more protein and energy delivery via nutrition therapy compared with standard care. Importantly, the intervention did not appear to increase adverse events, such as feed intolerance or diarrhea, and the proportion of patients who experienced these issues was consistent with observational literature.^{15,40} Moreover, the intervention was associated with attenuation of QMLT and loss and a reduced proportion of malnourished patients on discharge from ICU, without other signals of harm in terms of other patient-centered outcomes.

In this trial, the intervention resulted in greater protein and energy delivery, which is consistent with previous studies of volume-based feeding.^{16,41} Heyland and colleagues^{16,41} described a novel multimodal approach termed the enhanced protein-energy provision via the enteral route feeding protocol (PEP uP protocol), which incorporated a volume-based enteral feeding regimen. In a single-center sequential period feasibility study, the point estimates of enteral protein and energy delivery were augmented by approximately 10%, with nutrition adequacy improving from a mean of 74% (SD 29%).⁴¹ In a subsequent prospective cluster randomized trial of 18 ICUs, those sites that were allocated to the PEP uP protocol delivered 14% more protein and 12% more calories than the control sites; however, the overall nutrition adequacy with the intervention was a mean of 48% (SD 33%).¹⁶ Subsequently, a single-center randomized control trial used a similar PEP uP style protocol and reported that a volume-based feeding protocol delivered more energy [mean (SD), 93% (17)] compared with a rate-based feeding protocol [81% (19)]

Table 3. Nutrition Outcomes.

Outcomes Variables	Intervention ^a	n	Standard	n	Risk Ratio (95% CI)	P-Value ^b
Patients with feeding intolerance	9 (30)	30	8 (27)	30	1.1 (0.5–2.5)	.77
Patient who had diarrhea	16 (53)	30	16 (53)	30	1.0 (0.58–1.7)	1.0
Malnourished ^c at intensive care unit discharge	2 (6.9)	29	8 (27.6)	29	0.25 (0.06–1.1)	.04

Outcomes Variables	Intervention ^d	n	Standard	n	Mean Difference (95% CI)	P-Value
Cumulative incidence of feeding intolerance, d	0.3 (0.5) 0 [0–1]	30	0.7 (1.5) 0 [0–1]	30	–0.4 (–1.0 to 0.2)	.18 .86
Cumulative incidence of diarrhea, d	1.9 (2.2) 1 [0–3.5]	30	1.3 (1.6) 1 [0–2]	30	0.7 (–0.4 to 1.8)	.23 .57
Weight change admission to discharge, kg	–1.3 (8.5)	22	–2.6 (4.7)	19	1.3 (–3.2 to 5.7)	.57
Mid upper arm circumference change admission to discharge, cm	–1.7 (1.5)	18	–2.0 (1.2)	20	0.3 (–0.6 to 1.2)	.50
Plasma albumin level at discharge, g/L	24 (4.3)	27	24 (5.4)	30	0.5 (–2.6 to 3.7)	.76

^aProportion values represented as n (%).
^bPearson χ^2 P-values.
^cMalnutrition is defined by subjective global assessment category B or C.
^dNormally distributed values are represented as mean (SD); nonnormally distributed data are represented as mean SD (95% CI) with P-values and median [IQR] with P-values.

Table 4. Effect Estimate of Variables on Quadriceps Muscle Layer Thickness (cm) at Intensive Care Unit Discharge Adjusted for Baseline Quadriceps Muscle Layer Thickness (cm).^a

Variables	Effect Estimate Adjusted for Baseline QMLT				Effect Estimate Adjusted for All Covariants			
	Effect	Robust SE	95% CI	P-Value	Effect	Robust SE	95% CI	P-Value
Baseline QMLT, cm	0.61	0.11	0.38–0.83	<.001	0.56	0.11	0.33–0.79	<.001
Intervention	0.22	0.08	0.05–0.39	.01	0.22	0.08	0.06–0.38	.01
APACHE III ^b	0.02	0.02	–0.02 to 0.06	.44	0.01	0.02	–0.03 to 0.05	.70
Age, ^c y	0.02	0.03	–0.03 to 0.08	.44	–0.00	0.02	–0.05 to 0.05	.92
Body mass index, ^d kg/m ²	0.02	0.09	–0.17 to 0.21	.82	0.03	0.08	–0.14 to 0.19	.73
Admission category ^e								
Elective surgery	–0.44	0.07	–0.58 to –0.30	<.001	–0.57	0.08	–0.73 to –0.41	<.001
Surgical	–0.28	0.08	–0.44 to –0.11	<.01	–0.24	0.09	–0.41 to –0.06	.01

APACHE, Acute Physiology and Chronic Health Evaluation; QMLT, quadriceps muscle layer thickness.
^aQMLT at discharge, mean right and left side measurement, has been paired within individuals and adjusted for baseline mean right and left side measurements (n = 92).
^bAPACHE III was centered at 75.
^cAge was centered at 60 (per 10 years).
^dBody mass index was centered at 30 kg/m².
^eAdmission category compared with medical admissions.

in critically ill patients; however, protein delivery was not reported.⁴² Moreover, none of the previously mentioned trials of volume-based regimens incorporated functional effects of nutrition such as muscle mass or strength measures. This current trial also differs from previous trials in that prophylactic gastrokinetic drugs and semi-elemental formulae were not prescribed. In addition, the strategy to aid adherence to the volume target implemented included requesting staff to assess nutrition delivery at a set time point in the day (4:00 pm) rather than at the time of the interruption. Lastly, additional protein was supplemented throughout the study period.

Although there is considerable enthusiasm for, and face validity underlying, greater protein delivery to improve

Table 5. Functional and Other Secondary Outcomes.

Outcome Variables	Intervention ^a	n	Standard	n	Mean Difference (95% CI)	P-Value ^b
Handgrip strength (best), kg	20 (6.1)	6	21 (9.3)	16	−0.34 (−9.0 to 8.3)	.94
Muscle strength (MRC score)	55 (5.9)	7	52 (9.6)	14	2.6 (−5.8 to 11.0)	.53
Physical function ^c	6.8 (3.8)	8	7.9 (3.4)	14	−1.1 (−4.4 to 2.2)	.49
ICU LOS, days	10.6 (8.3)	30	9.1 (5.5)	30	1.5 (−2.2 to 5.1)	.42
	7.8 [5.9–13.4]		7.5 [4.9–12.7]			.52
Hospital LOS, days	27.4 (19.0)	30	18.8 (10.9)	30	8.6 (0.6–16.6)	.04
	22 [9.9–43]		15 [9.9–25]			.14
Length of mechanical ventilation, days	8.7 (7.5)	30	7.0 (5.0)	30	1.7 (−1.6 to 5.0)	.30
	6.2 [4.5–10.8]		5.1 [3.6–8.5]			.32
Outcome Variables	Intervention ^d	n	Standard	n	Risk Ratio (95% CI)	P-Value
ICU-acquired weakness ^e	1 (14)	7	4 (28)	14	0.5 (0.07–3.7)	.47
Renal failure ^f	3 (10)	30	3 (10)	30	1.0 (0.22–4.6)	1.0
Mortality						
28 days	4 (13)	30	5 (17)	30	0.8 (0.24–2.7)	.72
60 days	4 (13)	30	5 (17)	30	0.8 (0.24–2.7)	.72
Discharge to a rehabilitation facility	12 (40)	30	13 (43)	30	0.9 (0.51–1.7)	.77

ICU, intensive care unit; LOS, length of stay; MRC, Medical Research Council.
^aNormally distributed values are represented as mean (SD) 95% CI with P-values; nonnormally distributed values are represented as mean (SD) 95% CI with P-values and median [IQR] with P-values.
^bPearson χ^2 P-values.
^cMeasured using scored Physical Function in Intensive Care Unit Test.
^dPortions are listed as n (%).
^eICU-acquired weakness was defined as MRC score <48.
^fRenal failure was defined using the RIFLE criteria.

patient-centered outcomes,³ there is limited evidence to support this intervention. In a systemic review of all relevant randomized controlled trials,⁴³ increasing protein delivery did not improve patient-centered outcomes, although the authors noted that none of the included studies compared standard protein provision with the current guideline recommendations. Ferrie and colleagues¹³ recently reported the impact of delivering different intravenous (IV) protein doses. In this study of 119 critically ill patients, the augmented protein intervention was associated with improvements in surrogate outcomes including handgrip strength, reduced fatigue, and greater forearm muscle thickness.¹³ Collectively, the results of Ferrie et al¹³ and the current trial provide preliminary single-center trial evidence that early protein delivery within the guideline range may attenuate muscle loss in critically ill patients. This concept is also supported by a number of observational studies^{4,5,8,44-46}, however conflicting data have been reported. In the multicenter UK MUSCLE study, greater loss of quadriceps muscle was associated with more protein delivery.⁴⁷ Furthermore, in rabbits studied after burn injury, administration of amino acids was associated with an increase in muscle vacuolization,⁴⁸ and in a pediatric population, increasing doses of IV protein were associated with inferior patient-centered outcomes.⁴⁹ Accordingly, the point

estimates in this trial favoring improvement in surrogate outcomes (QMLT and SGA) should be interpreted with caution.

Clinical Significance

The intervention achieved treatment separation between the groups, with the increase in protein delivery to be at least 0.33 g/kg/d and as much as 0.56 g/kg/d. Particularly in those patients admitted and exposed to the intervention for longer periods, it is possible that this magnitude of protein supplementation could limit the muscle mass losses, commonly observed in critical care patients, or otherwise improve patient-centered outcomes.

Strengths and Limitations

The strengths of this trial include allocation concealment and randomization to limit selection bias, as well as submission of protocol and planned statistical analysis before completion of the trial.¹⁹ The study aimed to provide 2 different protein targets using EN. The intervention delivered protein within the current guideline recommendations, and the control group received care (protein and energy delivery) representative of routine care in Australia and New Zealand.²²

The limitations of this trial include conduct at a single center without a practical method of blinding the intervention, making further validation in other settings desirable. As a pilot trial with a relatively small cohort, the point estimates for important surrogate outcomes, such as QMLT, must be interpreted with considerable caution and may not represent effects at a population level. Also, the intervention was a volume-based protocol with protein supplementation, meaning energy delivery was also increased, which may confound the observed impact of protein on outcomes. Missing data for some of the secondary and tertiary outcomes, particularly for the functional measurements, makes any estimates of effect provisional.⁵⁰ Lastly, only mechanically ventilated enterally fed critically ill patients were enrolled, and of the participants the majority fell into broad medical or trauma classifications. Accordingly, the present data may not be generalizable to patients who require PN or those with primary gastrointestinal disease.

Conclusions

A high-protein volume-based enteral feeding protocol with supplemental protein delivered greater amounts of protein and energy to critically ill mechanically ventilated patients. This intervention was associated with attenuation of muscle loss and reduced prevalence of malnutrition at ICU discharge. These data support the feasibility and clinical relevance of further investigations using this intervention.

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Statement of Authorship

K. Fetterplace, C. MacIsaac, L. J. Beach, and A. Tierney equally contributed to the conception and design of the research; A. M. Deane, M. Mourtzakis, and A. Forsyth contributed to the design of the research; K. Fetterplace, B. M. T. Gill, T. Rechnitzer, L. J. Beach, and L. D. Knight contributed to the acquisition of the data; K. Fetterplace and J. Presneill contributed to the analysis and interpretation of the data; and K. Fetterplace and A. M. Deane drafted the manuscript. All authors critically revised the manuscript, agree to be fully

accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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The End!