

# **NUTRITION IN SURVIVORS OF CRITICAL ILLNESS**

An exploration of the effect of nutrition therapy on muscle mass,  
nutritional status and clinical outcomes after critical illness with a  
focus on patients with a traumatic brain injury

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## **Abstract:**

Critical illness affects ~130,000 Australians each year, costing the health-care system nearly \$3 billion. For intensive care unit (ICU) survivors, quality of life and functional recovery are compromised, with symptoms persisting five years post-discharge. Patients admitted to ICU with traumatic brain injury (TBI) are at particular risk. Accordingly, interventions that enhance recovery will improve patients' quality of life and are also likely to be cost-effective.

Nutrition therapy, ingested or delivered artificially, is an essential component of clinical practice in ICU and post-ICU. In this thesis I reviewed the extent of nutrition research in a hospitalised TBI population (*Chapter 1*) to establish insufficient data reporting intake post-ICU.

In heterogeneous cohorts of critically ill patients, nutrient delivery during ICU admission is below prescribed targets. From a large international cohort, I determined that energy and protein delivery to ICU patients with TBI is below targets, and deficits in the first 12 days are associated with longer time to discharge alive from ICU and hospital, and prolonged mechanical ventilation (*Chapter 4*).

In a methodologically-rigorous single-centre observational study I established that energy and protein deficits exist in ICU. Perhaps of more concern, these deficits increase post-ICU leading to cumulative deficits throughout hospitalisation (*Chapter 1*). These observations highlighted methodological issues, particularly with weighed food records to measure oral intake of hospitalised individuals (*Chapter 2*). Logistical and attitudinal barriers impede nutrition delivery. Interviews with medical and nursing practitioners provided insight into why these occur (*Chapter 1*). Additionally, TBI patients have marked changes in ultrasound-derived quadriceps muscle thickness. I established that this novel methodology, while challenging, is feasible and may correlate with total lean mass and long-term function (*Chapter 3*).

To provide context beyond the cohort of TBI patients I explored relationships between nutritional intake during critical illness and long-term function. In a blinded pilot trial of critically ill patients, those randomised to augmented enteral nutrition to deliver greater energy, were more likely to return to work after 12-months than those receiving standard nutrition (*Chapter 4*).

In addition, there is considerable interest within the critical care community on the effect of protein delivery on outcomes. I conducted a meta-analysis of randomised controlled trials (RCTs) with greater or lesser amounts of protein delivered to critically ill patients and did not observe any effect of greater protein dose on clinical outcomes. However even the cohort receiving greater protein had amounts lower than recommended in international guidelines.

Lastly, because a frequent criticism of the role of nutritional therapy in the critically ill is the lack of effect on mortality, I undertook a systematic review and identified that nutrition intervention studies in critical care with the primary outcome of mortality have utilised sample size calculations that require a large, and possibly implausible, effect on mortality. The implications are that investigators should incorporate more realistic estimates of effect size in the future and that previous RCTs may have failed to detect an effect on mortality even if there was such an effect (*Chapter 5*).

## **Declaration:**

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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25<sup>th</sup> January 2017

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Professor Lauren Williams was there from the start, initially as my primary supervisor at the University of Canberra, and then as an external supervisor. Despite my lack of research experience and only the beginnings of a very rough plan stemming from my clinical frustrations, Lauren encouraged me in the PhD direction and shaped my plan into an achievable and succinct proposal. As the only non-medical supervisor on my panel, Lauren provided a unique perspective and kept my plans grounded and realistic. I am appreciative of her attention to detail and ongoing support.

Professor Daren Heyland is one of the leading critical care nutrition researchers internationally and I am so fortunate to have had his expert input into this research. Despite the distance, Daren has been a generous and enthusiastic collaborator, and I have valued his intuitive research ideas, insightful comments, forward thinking, and support of novice researchers.

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Finally, I would like to thank the generous and selfless support of the patients and their families for their willingness to be involved in research in what could only be one of the most physically and emotionally challenging situations an individual could experience. I hope that this work, in some way, can improve the care of patients in the future.

## **Rationale for research:**

The purposes of this research program were to:

- 1.) Provide a greater understanding of longitudinal nutrition support practices in critically ill patients, particularly those with a traumatic brain injury, throughout the entire hospitalisation;
- 2.) Detail anthropometric changes that occur during hospitalisation in this population and their relationship to longitudinal functional outcomes;
- 3.) Evaluate novel methodologies to measure nutritional intake and changes in anthropometry, particularly muscle size, in survivors of critical illness and traumatic brain injury; and
- 4.) Evaluate associations between nutritional therapy and clinical outcomes, including mortality, in critically ill patients, particularly those with a traumatic brain injury.

## **Format of thesis:**

This thesis is by publication, supplemented by narrative, as per University of Adelaide guidelines. This thesis comprises two distinct but complementary sections. Section one encompasses three chapters and section two contains two chapters. Each section of this thesis is preceded by a narrative introduction and followed by a conclusion of the major findings and future directions.

In total, the thesis comprises nine manuscripts: three reviews of the literature and six manuscripts resulting from a series of original clinical and observational studies. At the time of submission of this body of work, all nine of these manuscripts have been published or accepted for publication. None of these manuscripts were solicited by the journals. All of these manuscripts were submitted to appropriate nutrition, neurotrauma, or intensive care journals. The nine manuscripts are presented in the style of the publication to which they were submitted, accounting for the variance in manuscript structure. For consistency, manuscripts are presented in UK English and references for the nine publications are combined and included at the end of this thesis.

The format of this thesis is as follows:

### **Section One: Nutritional intake and anthropometry in traumatic brain injured patients during and after intensive care stay**

Section one incorporates three chapters that describe the current nutrition delivery practices and anthropometric measurements in patients admitted to intensive care, with a focus on those patients admitted with a traumatic brain injury.

#### **Chapter 1: Nutrition support practices in critical illness and traumatic brain injury**

Chapter one includes a summary of the literature relevant to nutrition delivery to critically ill patients and three manuscripts.

Manuscript 1<sup>1</sup> is a scoping review of the nutrition and traumatic brain injury (TBI) literature and was published in the *Journal of Neurotrauma*. This provides a broad overview of the extent of nutrition research in a TBI population, including a description of the types of interventions and outcome measures existing in the literature.

Manuscript 2<sup>2</sup> was published in *Clinical Nutrition*. This manuscript is the first of three that resulted from a labour-intensive 12-month prospective observational study that formed a major component of my candidature. Using a rigorous methodology I detailed nutritional intake, and barriers to intake, throughout the entire hospital admission of patients admitted to ICU with a moderate-severe TBI. The novelty of this study is that it is the first study to accurately quantify longitudinal nutrition intake in a patient group initially admitted to the ICU then discharged to the general hospital ward. The study involved quantification of oral nutrition intake as well as liquid nutrient administered via enteral-tube feeding.

Manuscript 3 addresses the views and attitudes on nutrition support of medical and nursing staff working with TBI patients in the critical care and acute care settings. This qualitative study provides context for delivery of care and explores the reasons behind inadequate nutrition support to head injured patients. It was accepted for publication without revisions in the *Journal of Parenteral and Enteral Nutrition*.

## Chapter 2: Methodology and measurement of nutritional intake

This chapter evaluates methodologies used to quantify nutritional intake in a hospitalised population, with a particular focus on the challenges associated with recording accurate oral intake data in those patients discharged from ICU to the general hospital ward.

The manuscript<sup>3</sup> presented in this chapter was published in the *Journal of Human Nutrition and Dietetics*. This methodological paper, using data from the 12-month

observational study described above, contributes to our understanding of how to accurately quantify ingested nutrients in a hospitalised population.

### Chapter 3: Measurement of anthropometric changes over time in critically ill patients admitted with a traumatic brain injury

Chapter three is a summary of anthropometric measurements in critically ill patients. The manuscript in this chapter has been accepted in *Critical Care and Resuscitation*. This manuscript provides a description of the anthropometric changes in patients admitted to ICU with a TBI, including changes in quadriceps muscle thickness using an ultrasonography technique. This paper is the first to report changes in body composition measures in a sub-set of ICU survivors, and provides incremental evidence that the non-invasive technique of ultrasonography is a valid means to measure changes in muscle size in critically ill patients.

## **Section Two: Influence of nutritional intake on outcomes in critical illness and TBI**

Section two encompasses two chapters that explore relationships between nutritional intake in the critically ill, particularly those with TBI, and clinical outcomes.

### Chapter 4: Influence of nutritional intake on mortality and clinical outcomes in intensive care and after traumatic brain injury

This chapter includes three manuscripts. The first of these evaluates the association between energy and protein provision and patient-centred outcomes in a critically ill cohort with TBI. The subsequent manuscripts evaluate the relationship between nutrient provision and outcomes, including mortality, in a general intensive care population. There is considerable controversy regarding the optimal amount of energy and protein to deliver to critically ill patients and the manuscripts that comprise this chapter provide important data that contributes to an improved understanding of patient needs.

The first manuscript that comprises chapter four was published in *Critical Care*<sup>4</sup>. Using international data I was able to identify relationships between calorie and protein intake, nutrition support practices, and clinical outcomes in this group of patients.

The second manuscript is a systematic review and meta-analysis of protein delivery to critically ill patients and has been accepted for publication in *Critical Care and Resuscitation*. All RCTs of nutrition interventions in critically ill patients that reported a difference in protein delivery between the two study arms were included, and a meta-analysis of the effect of protein dose on clinical outcomes was conducted.

The third manuscript<sup>5</sup> is a longitudinal follow-up of patients enrolled in a blinded, randomised controlled trial and was published in *Anaesthesia and Intensive Care*. This study evaluated the impact of augmenting early calorie delivery on patient's quality of life and employment status one year after ICU admission.

While I am listed as second author on the two preceding publications, I contributed substantially to the study design, conduct and data interpretation for these studies and drafting/editing of subsequent manuscripts. Based on my contribution my supervisors are of the opinion that inclusion of these papers in this thesis is justified.

#### Chapter 5: Alternative outcome measures for nutritional studies in intensive care

Chapter five proposes an alternate view to the current orthodoxy when using mortality as the primary outcome in trials of nutrition therapy in the critically ill. This chapter includes a systematic review<sup>6</sup> of randomised controlled trials of nutrition interventions in intensive care with the primary outcome powered for mortality. Specifically, I explored the appropriateness of the sample size calculations presented in these randomised controlled trials and provide suggestions for future directions in my arena of research, i.e. nutritional therapy in the critically ill. The manuscript was published in the *American Journal of*

*Clinical Nutrition* and based on this publication I have been invited to give a presentation at the 2017 Clinical Nutrition Week, the annual meeting of the American Society for Parenteral and Enteral Nutrition (ASPEN), which will be held in Florida, USA.

Publications included in this thesis are as follows, in order of appearance:

**Costello LS**, Lithander FE, Gruen RL, Williams LT. *Nutrition therapy in the optimisation of health outcomes in adult patients with moderate to severe traumatic brain injury: Findings from a scoping review*. *Injury* 2014;45(12):1834-41.

**Chapple LS**, Deane AM, Heyland DK, Lange K, Kranz AJ, Williams LT, Chapman MJ. *Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury*. *Clin Nutr* 2016;35:1315-22.

**Chapple LS**, Deane AM, Williams LT, Strickland R, Schultz C, Lange K, Heyland DK, Chapman MJ. *Longitudinal changes in anthropometry and impact on self-reported physical function following traumatic brain injury*. *Crit Care Resusc* 2017;19:29-36.

**Chapple LS**, Deane AM, Williams LT, Lange K, Kranz A, Heyland DK, Chapman MJ. *Weekend days are not required to accurately measure oral intake in hospitalised patients*. *J Human Nutr Diet* 2016, (E-pub ahead of print, DOI: 10.1111/jhn.12432).

**Chapple LS**, Chapman MJ, Shalit N, Udy A, Deane AM, Williams LT. *Barriers to nutrition intervention for patients with a traumatic brain injury: Views and attitudes of medical and nursing practitioners in the acute care setting*. *JPEN* 2017; (e-pub ahead of print), DOI:10.1177/0148607116687498.



**Chapple LS**, Chapman MJ, Lange K, Deane AM, Heyland DK. *Nutrition support practices in critically ill head-injured patients: A global perspective*. Crit Care 2016;20:6.

Davies M, **Chapple L**, Peake S, Moran J, Chapman M. *Protein delivery and clinical outcomes in the critically ill: A systematic review and meta-analysis*. Crit Care Resusc (in press, accepted Nov 2016).

Reid D, **Chapple L**, O'Connor S, Bellomo R, Buhr H, Chapman M, Davies A, Eastwood G, Ferrie S, Lange K, McIntyre J, Needham D, Peake S, Rai S, Ridley E, Rodgers H, Deane A. *The effect of augmenting early nutritional energy delivery on quality of life and employment status one year after ICU admission*. Anaesth Intensive Care 2016;44(3):406-12.

Summers MJ,\* **Chapple LS\***, McClave SA, Deane AM. *Event-rate and delta inflation when evaluating mortality as a primary outcome from randomized controlled trials of nutritional interventions during critical illness: A systematic review*. AJCN 2016; 103(4): 1083-90. (\*Contributed equally to manuscript).