What happens to nutrition intake in the post-ICU hospitalisation period? An observational cohort study in critically ill adults

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Clinical relevancy statement:

Little information exists regarding the progress of nutrition intake through the hospital admission in patients who have survived critical illness, with the majority of research focussed on the early period of illness. Furthermore, the later period of illness may be an important stage for nutrition rehabilitation, however nutrition interventions to date have not addressed this. We aimed to describe

energy and protein intake and determine the feasibility of measuring energy requirements with indirect calorimetry in the post-ICU hospitalisation period in critically ill adults.

Financial disclosure:

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Conflict of interest statement:

ARD is an employee of Baxter Healthcare Corporation, Australia. This position commenced in September 2015, after the primary trial had been designed and recruitment had begun. There are no conflicts of interest for any other authors.

Disclosure:

EJR has received unrestricted research funding for an independent investigator initiated study from Baxter Healthcare Corporation. RP, CH, AMD, SM and DJC are on the management committee for this study and MB is the study statistician (NCT03292237).

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Abstract:

Background: Little is currently known about nutrition intake and energy requirements in the post-intensive care unit (ICU) hospitalisation period in critically ill patients. We aimed to describe energy and protein intake and determine the feasibility of measuring energy expenditure during the post-ICU hospitalisation period in critically ill adults.

Methods: Nested cohort study within a randomised controlled trial in critically ill patients. After discharge from ICU, energy and protein intake was quantified periodically and indirect calorimetry attempted. Data are presented as n (%), mean (standard deviation (SD)) and median [inter quartile range (IQR)].

Results: Thirty-two patients were studied in the post-ICU hospitalisation period and 12 had indirect calorimetry. Mean age and BMI was 56 (18) years and 30 (8) kg/m² respectively, 75% were male and the median estimated energy and protein requirement 2000 [1650-2550] kcal and 112 [84-129] g, respectively. Oral nutrition either alone (n=124 days, 55%) or in combination with EN (n=96 days, 42%) was the predominant mode. Over 227 total days in the post-ICU hospitalisation period, a median [IQR] of 1238 [869-1813] kcal and 60 [35-89.5] g of protein was received from nutrition therapy. In the 12 patients who had indirect calorimetry, the median measured daily energy requirement was 1982 [1843-2345] kcal and daily energy deficit, -95 [-1050-347] kcal compared to the measured energy requirement.

Conclusion: Energy and protein intake in the post-ICU hospitalisation period was below estimated and measured energy requirements. Oral nutrition provided alone was the most common mode of nutrition therapy.

Clinical Trial registry details: www.clinicaltrials.gov; NCT01847534 (First registered 22nd April 2013, last updated 31st July 2016).

Introduction:

Randomised controlled trials (RCTs) comparing nutritional interventions in the critically ill have frequently failed to prove nutrition interventions positively benefit patients compared to usual care. One plausible explanation is that these trials have predominately focussed on interventions of short duration, applied early during critical illness, while patients are in the acute phase of illness and remain in the intensive care unit (ICU). This approach does not consider the dynamic metabolic response to critical illness and the potential role of nutrition delivery during different phases of hospital stay.

It is plausible that nutritional interventions administered during the post-ICU hospitalisation period may be even more important than those applied early. Early in critical illness, endogenous glucose supplies are high, meaning provision of artificial nutrition during this period may lead to relative overfeeding, which has been associated with deleterious consequences ^{1, 2}. Later in the metabolic response to critical illness, endogenous glucose supplies have been utilised and anabolism takes over

to facilitate recovery². Accordingly, exogenous carbohydrate and protein may be even more important later than in the early phase of critical illness, as patients require and are capable of utilising the nutrition provided. In the few studies that have investigated nutrition intake in the post-ICU hospitalisation period, energy and protein deficits have been thought to continue, or even to accumulate for multiple reasons³⁻⁵. Additionally, there are no data available on energy requirements in critically ill patients during the post- ICU hospitalisation period.

Given the lack of data on nutrition intake and energy requirements in the post-ICU hospitalisation period in critically ill patients, we performed a cohort study nested within an RCT. Our primary aim was to describe energy and protein intake in the post-ICU hospitalisation period in the study cohort. Secondary outcomes were to determine the feasibility of measuring energy expenditure with indirect calorimetry during this period and compare measured versus predicted estimates during this time.

Methods:

We performed a nested cohort study within a phase II, parallel group, open label RCT of a supplemental parenteral nutrition (PN) intervention compared to usual care, in critically ill patients^{6,7}. In brief, 100 patients with at least 1 organ failure were randomized to a supplemental PN or usual care within 48-72 hours of ICU admission, with the intervention provided for 7 days. Two participating sites agreed to participate in this nested study. Consecutive patients from the 2 participating sites were then included during the randomization process. Data collection for this cohort study commenced when the patient was transferred from the ICU to the hospital ward, or commenced oral intake in the ICU, whichever occurred first. The full inclusion and exclusion criteria for the RCT can be viewed in

the supplementary material (S1) and the details of the trial details at www.clinicaltrials.gov; NCT01847534 (First registered 22nd April 2013, last updated 31st July 2016).

Estimated energy and protein requirements

Body weight was standardized in the primary trial at randomisation using 'calculated body weight' (CBW) according to the following schedule:

- CBW was the patient's actual weight if their BMI was deemed to be $<25 \text{ kg/m}^2$
- CBW was set to the ideal weight at a BMI of 23 kg/m^2 if their BMI was $\geq 25 \text{ kg/m}^2$

Once set, the CBW for all calculations was not changed. Energy requirements were determined daily in ICU using a fixed prescription method of 25 kcal/kg CBW or 30 kcal/kg CBW if the patient was receiving renal replacement therapy or extracorporeal membrane oxygenation on that day⁸. Once transferred to the ward, management of nutrition was as per the treating clinicians preference. For the purpose of this analysis, estimated energy and protein requirements were assumed to be constant and extrapolated from the last day of ICU stay.

Calculated Energy Expenditure

Indirect calorimetry was performed by trained staff using the FitMate for non-ventilated patients (manufactured by Cosmed, Rome, Italy). Measurements were attempted twice weekly if it was

expected the patient could breathe through the mouthpiece for at least 10 minutes, using a nose clip supplied by Cosmed and censored at day 28 or hospital discharge, whichever occurred first. The quality of the test was monitored via the FitMate device, which provides an indication of variance during test conduct. When measurements could not be conducted, the explanation was recorded.

Nutritional Intake

Nutrition intake data was censored at day 28 or hospital discharge. Intake was measured second daily (Monday-Friday) in the post-ICU hospitalisation period when there were study personnel available. Commencement of oral intake was defined as the commencement of food or fluid with the intent to provide nourishment (and excluded sips of fluid or tastes of food to assess ability to swallow or tolerate oral intake safely). The post-ICU hospitalisation period was defined as being from either the commencement of oral intake as per defined above (even if the patient remained in ICU) or from the time of transfer from the ICU to a non-ICU hospital ward in the participating hospital, whichever occurred first. On the days assessment occurred, the mode of nutrition was recorded, with one of the following options allowed; EN, PN, oral, combined EN and PN, combined EN and oral or none. Food and oral supplements were both classed as 'oral' in mode, however the energy and protein contribution from food and oral supplements were collected separately. Assessment of oral nutrition intake was conducted using study food record charts (supplemental material, S2). Study dietitians and nursing staff used 24 hour recall methods, medical records, and the assistance of family and ward staff to record nutrition intake. To improve accuracy, study dietitians with knowledge of their usual hospital foodservice assisted with recording of intake and estimated macronutrient intake.

Statistical analysis:

Categorical data are reported as numbers and percentages (%), continuous data as mean (standard deviation (SD)) where normally distributed or as median [interquartile range (IQR)] where not normally distributed. Baseline and outcome variables were compared using Chi-square tests for equal proportion, Student's t-test for normally distributed outcomes and Wilcoxon rank-sum tests otherwise. Bland-Altman analysis was performed between energy requirements measured by indirect calorimetry and the study predictive estimate to assess mean bias and limits of agreement. Mean bias was calculated as the mean difference between the measured energy requirement using indirect calorimetry and the energy requirement from the predictive estimate for each study day where both data points were available. The 95% limits of agreement were calculated as the mean bias $\pm$ 2 standard deviations. The Bland-Altman plots represent the mean of the measured and predicted energy requirement on the x-axis and the difference between the 2 measurements on the Y-axis (measured minus the predicted energy requirement). Missing data was not imputed. Analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata Statistical Software: Release 14.4 (StataCorp LP, College Station, TX) and a two-sided p-value of 0.05 was considered to be statistically significant.

Ethics approval

Ethics approval was obtained from The Alfred Hospital Research and Ethics committee and the Northern A Health and Disability Ethics Committee in New Zealand, as well as the Monash University Research and Ethics Committee. At the time of consent for the main trial, consent for the sub-study was also obtained. As participants were unable to provide consent themselves at the time of enrolment, the patient's legal surrogate, relative/friend or whanau member was approached for

consent or agreement to participate in the study. Patients were approached at a later time if it was appropriate and they regained the capacity to provide consent to continue to participate.

Results:

Fifty-six patients were included in this sub-study; nutritional intake data during the post-ICU hospitalisation period were obtained in 32 patients and 12 patients had indirect calorimetry performed (Figure 1). Demographic data of the study population is provided in Table 1.

Overall in the 32 patients studied, there were 227 total study days in the post-ICU hospitalisation period. The median [IQR] predicted daily energy and protein requirement for these patients was 2000 [1650-2550] kcal and 112 [84-129] g, respectively. A median of 1238 [869-1813] kcal and 60 [35-89.5] g of protein was received from all sources of nutrition therapy on the days assessed. The median overall nutrition adequacy using the predicted energy and protein estimate was 79% [41%-108%] and 73% [44-98%]. Oral nutrition alone was the most common mode of nutrition during this period (n=124 (55%) of study days), followed by oral nutrition in combination with EN (n=96 (42%)), EN alone (n=6 (3%)) and no nutrition (n=1 (0.5%)). PN provided alone, or in combination with EN, was not administered during the post-ICU hospitalisation period. The lowest median proportion of predicted energy and protein requirements was provided on the days oral intake was provided alone without oral supplements (37% [21%-67%] of energy and 48% [13%-63%] of protein requirements) and the highest on the days oral nutrition was combined with EN (104% [66%-132%] of energy and 99% [60%-127%] of protein requirements). Table 2 provides further details about the energy and protein contribution from nutrition sources and modes. Using the predictive energy and protein

estimates, the median daily deficits were -442 [-1323-186] kcal/day for energy and -30 [-69- -1] g/day for protein during the post-ICU hospitalisation period.

In total there were 73 indirect calorimetry measurements attempted during the post ICU period. Of these, 50 (68%) could not be conducted, most commonly because the patient declined (n=13 (26%)) or they were considered confused by staff (n=11 (22%)) (Table 3). In those who had indirect calorimetry (n=12, 23 tests), the median measured energy requirement was 1982 [1843-2345] kcal compared to the median predicted energy requirement of 2000 [1725-2880] kcal in the same group. The median difference between the measured energy requirement on the days performed and predictive study estimate was 16 [-307-520] kcal. In total, a median of 1890 [921-2348] kcal and 85 [35-121] g of protein was received from all sources of nutrition therapy on the days indirect calorimetry was performed. The median daily energy deficit was -161 [-886-150] kcal using a predictive equation and -95 [-1051-347] kcal using the measured requirement as the gold standard.

The mean bias between the measured estimate and the study predictive estimate (95% CI) was -58 kcal (CI -293 to 177) in the Bland-Altman analysis and the limits of agreement, -1.1e+03 to 1028 87 kcal. Bland-Altman plots are shown at Figure 2 and further details on indirect calorimetry measurements in Table 3.

Clinical outcomes are presented in Table 1.

Discussion

This is one of only a few published papers describing nutrition intake in the post-ICU hospitalisation period in critically ill survivors, and the largest in a mixed medical population. It is also the first study that has attempted to measure energy requirements with indirect calorimetry in a critically ill population after ICU stay. It provides important information which was previously unknown about the progress of nutrition intake and the feasibility of indirect calorimetry in critically ill survivors, after discharge from the ICU. Oral nutrition alone was the most common mode of nutrition delivery, and energy and protein intake with this mode was less than estimated and measured expenditure during the post-ICU hospitalisation period. The combination of EN and oral nutrition provided the greatest proportion of energy and protein delivery compared to estimated requirements. There was minimal difference between the measured and predictive energy requirement however; the measurements could infrequently be conducted, and the limits of agreement were wide, indicating significant variability between the measured and predicted energy requirement.

There is limited literature describing nutrition intake in the post-ICU hospitalisation period following critical illness, however that which is available supports our findings; energy and protein intake remains below predicted requirements³⁻⁵. A study conducted in 37 moderate traumatic brain injury patients suggested that energy and protein intake in ICU was lower than on the ward, however energy and protein intake was below predicted requirements during both periods. Additionally, those receiving oral intake had a much greater energy deficit than those receiving tube feeding, which we also observed³. In a study investigating oral nutrition intake 7 days post extubation in 50 critically ill patients, intake did not exceed 55% of predicted requirements on all 7 days assessed⁵.

The reason poor nutrition intake occurs during the post-ICU hospitalisation period in patients who receive oral nutrition alone is likely to be multifactorial. One study followed 17 patients after their ICU admission and performed semi-structured interviews of patients to determine what was impacting on nutrition intake during this period⁹. Factors such as appetite, viewpoint on food and eating, and physical ability to eat were all described⁹. Important system factors also appeared to contribute, specifically, a culture of removing artificial feeding tubes with the view to promoting oral intake (even if oral intake was poor or the quantity not assessed by a dietitian) and the priority of nutrition therapy on the ward^{4,9}. This was further supported by a second study that interviewed medical and nursing professionals working with patients with traumatic brain injury, also highlighting the competing healthcare-related issues and priority of care for each patient and individual preference of and belief regarding the importance of nutrition¹⁰.

Although measurements were few, we observed significant variation in metabolic rate measured by indirect calorimetry and a smaller daily energy requirement than when calculated by the study predictive estimate. The significant variability in measured energy requirements is not a new finding in critical illness and is the reason predictive equation estimates are considered to be at risk of error¹¹. This study provides further evidence to support that variability in metabolic rate continues after ICU and although the mean bias was small in the Bland-Altman analysis, the limits of agreement observed were very wide and the mean difference between the measured estimate and the predictive study estimate highly variable. The wide limits of agreement are partially explained by a small sample size, however also support the significant individual variation observed in measured energy expenditure. It must also be noted that the choice of predictive energy equation may alter the observed agreement when compared to a measured energy estimate using indirect calorimetry, as each predictive equation has different accuracy rates, and these may change over the course of illness.

Implications for future practice and research

There are several important findings in this work that have implications for future nutrition practice and research. In these patients, oral nutrition was the primary mode of nutrition therapy provided, and energy and protein intake remained below both predicted and measured energy targets in the post-ICU hospitalisation period when oral intake was provided alone. Even with the combination of oral supplements, oral nutrition alone may be insufficient to meet nutrition needs in this population. Importantly, when oral intake was combined with EN (occurring in almost half the patients (42%)), energy and protein intake was not deficient, but also frequently provided *more than* the estimated requirements. This may indicate that the combination of EN with oral nutrition may be the best way to meet nutrition needs in the post-ICU hospitalisation period. And in those who received more than their predicted energy and protein requirement with the combination of EN and oral nutrition, it may be hypothesised that perhaps the method or interval used to quantify nutrition intake was inaccurate, or that levels of staffing to review nutrition plans and tailor nutrition delivery may have been inadequate. Furthermore, it is unknown if a period of ‘over-nutrition’ following acute illness is beneficial or harmful in recovery. Indirect calorimetry could infrequently be conducted on the ward, most commonly because the patient refused. This has implications for the utility of this method in practice and research however this should be tested formally with dedicated staff. Therefore, research must now focus on understanding the barriers to adequate oral intake, accurate assessment of nutrition intake and the development of strategies to manage the associated issues in the post-ICU hospitalisation period.

Strengths and limitations:

This study is the largest study investigating nutrition provision in the post ICU hospitalisation period, and therefore provides valuable new information. The conduct within a RCT enabled rigorous data collection and study processes. There were however limitations to this work and these must be considered in the interpretation of our results. Firstly, this study was conducted at only 2 centres with a small cohort, and this limits some of the comparisons and conclusions that can be made. It was a sub-study, and there were not always dedicated research staff at both sites on the post-ICU ward. Fifteen patients were included in the primary trial but who did not provide data for this nested cohort study. There may therefore have been selection bias. Furthermore, the hospital ward environment is unpredictable and not as controlled as in ICU. Despite best attempts by participating sites, this has affected data completeness for both assessment of oral intake and indirect calorimetry measurements. To reduce the burden of data collection with limited resources on the ward, nutrition intake assessment did not occur daily and there are well documented issues with the accuracy of using food record charts to assess oral intake¹². The energy deficit was small when energy intake was compared to measured energy requirements however it must be considered that the interval between nutrition intake and indirect calorimetry assessment, the method to quantify nutrition intake, as well as the limited number of indirect calorimetry measurements available may effect the accuracy of this result. Further, it appears from the Bland-Altman analysis that there may be lower mean bias at lower measured energy requirements compared to measurements that are higher, this should be explored in future research. No information was collected regarding why intake was limited, and while it has been reported that patients received oral nutrition as the greatest proportion, it is unknown if this mode of nutrition was the most appropriate mode for the patient, or what were the contributing issues when intake was inadequate. This is an area for future research. Body weight was adjusted in the parent RCT to prevent overfeeding, and the predictive energy estimate based on this adjusted weight. This

may have led to a lower predictive energy requirement than commonly observed in usual clinical practice, and may influence the mean bias observed between the study predictive estimate and the measured requirements. Furthermore, the last predictive energy and protein requirement in ICU was extrapolated to the ward, and considered the ward requirement. These processes may not accurately reflect clinical practice and may have caused some inaccuracies. Therefore, it must be considered that the method of weight adjustment, and the method to predict energy requirements will influence any assessment of bias and this must be considered in the interpretation of the results. Lastly, this study has primarily focussed on energy intake. Macro and micronutrients provided by nutrition are likely to have a synergistic effect and energy is likely to be only one component which may benefit patients.

Conclusion

Energy and protein intake in the post-ICU hospitalisation period was less than both predicted and measured energy estimates and was most commonly provided by oral nutrition alone. Energy and protein intake was greatest in those who received EN in combination with oral nutrition, and lowest in those who received oral nutrition alone without oral supplements. Indirect calorimetry measurements could infrequently be performed.

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Table 1: Baseline and outcome characteristics

Variable	Whole cohort (n=32)	Indirect calorimetry (n=12)	No indirect calorimetry (n=20)
Age, years, mean (SD)	56 (18)	59 (15)	53 (19)
Sex, male, n (%)	24 (75)	83 (10)	14 (70)
BMI, kg/m ² , mean (SD)	30 (8)	29.5 (6)	30 (9)
Weight, mean (SD)	90 (28)	88 (21)	91 (32)
Calculated body weight, mean (SD)	79 (17)	78.5 (12)	80 (19)
Energy requirement, kcal/kg actual weight, median [IQR]	24.5 [23-27]	23 [22-26]	25 [23-27]
Energy requirement, kcal/kg CBW, median [IQR]	25 [25-30]	25 [25-30]	25 [25-30]
Protein requirement, g/kg actual weight, median [IQR]	1.2 [1.1-1.3]	1.2 [1.1-1.3]	1.2 [1.1-1.4]
Protein requirement, g/kg CBW, median [IQR]	1.3 [1.3-1.5]	1.4 [1.2-1.5]	1.3 [1.3-1.5]
APACHE II score, mean (SD)	18 (7)	18 (8)	17 (5)
APACHE III diagnosis code, n (%)			
Cardiovascular	17 (53)	7 (53)	10 (50)
Trauma	7 (22)	5 (25)	2 (17)
Respiratory	2 (6)	1 (5)	1 (8)

Sepsis	3 (9)	3 (15)	0 (0)
Musculoskeletal	1 (3)	0 (0)	1 (8)
Time from ICU admission to oral intake commencement, days, median [IQR]	13 [4-16]	13 [4-16]	11 [5-15]
ICU LOS, days, mean (SD)	12[6-17]	12 [7-17]	12 [6-17]
Ward LOS, days, median [IQR]	10 [7-18]	13 [6-19]	9 [7-16]
Hospital LOS, days, mean (SD)	24 [18-33]	25 [21-33]	22 [17-34]
Survival, n (%)			
ICU D/C	100% (32)	100% (12)	100% (20)
Hospital D/C	100% (32)	100% (12)	100% (20)

APACHE: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index; CBW: Calculated body weight (see manuscript for definition); D/C: Discharge; ICU: Intensive care unit; IQR: Interquartile range; SD: Standard deviation

Table 2: Energy and protein intake in the post-ICU period on the days intake was assessed (n=227)

Variable	Result
Energy contribution by nutrition source on days assessed, median [IQR], kcal	
EN	893 [480-1996]
Food	648 [272-1207]
Oral supplements	250 [0-600]
Proportion of predictive study energy estimate, median [IQR], %	
EN	58 [21-93]
Food	35 [13-53]
Oral supplements	14 [0-29]
Protein contribution by nutrition source on days assessed, median [IQR], g	
EN	43 [24-84]
Food	31 [9-61]
Oral supplements	12 [0-24]
Proportion of predictive study protein estimate, median [IQR], %	
EN	55 [20.5-88]
Food	31 [9-56]
Oral supplements	11 [0-25]
Energy contribution by combination of nutrition on days assessed, median [IQR], kcal	
EN alone	962 [469-1685]
Oral nutrition	

Oral nutrition (food only, no oral supplements provided)	1443 [803-1923]
Oral nutrition (food and supplements provided)	894 [406-1473]
EN and oral nutrition combined	1562 [1099-1992]
Protein contribution by combination of nutrition on days assessed, median [IQR], g	1921 [1215-2627]
EN alone	
Oral nutrition alone	48.5 [24-84]
Oral nutrition (food only, no oral supplements provided)	68.5 [40-94.5]
Oral nutrition (food and supplements provided)	50 [13.5-73.5]
EN and oral nutrition combined	76 [52-100]
	90 [51-123]
Proportion of predictive study energy estimate provided by combination of nutrition on days assessed, median [IQR], %	
EN alone	62 [21-96]
Oral nutrition alone	66 [38-89]
Oral nutrition (food only, no oral supplements provided)	37 [21-66]
Oral nutrition (food and supplements provided)	73 [51-94]
EN and oral nutrition combined	104 [66-132]
Proportion of predictive study protein estimate provided by combination of nutrition on days assessed, median [IQR], %	
EN alone	59 [20.5-97]
Oral nutrition alone	60 [37-83]
Oral nutrition (food only, no oral supplements provided)	48 [13-63]
Oral nutrition (food and supplements provided)	68 [49-84]

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Table 3: Indirect calorimetry results

Variable	Result (n=23)	Min	Max
Measured RMR, kcal, median [IQR]	1982 [1843-2345]	1705	3306
VO ₂ , ml/L, median [IQR]	284 [264.5-313]	245	475
Test length, mins, median [IQR]	7 [5-9]	1	11
Indirect calorimetry could not be performed, n (%)	50 (60)		
Reason, n (%)	13 (26)		
Patient declined	11 (22)		
Agitated/confused	9 (18)		
Patient unsuitable	4 (8)	n/a	n/a
Nasal oxygen	3 (6)		
Other	1 (2)		
Clinician unavailable	3 (6)		
Patient unavailable	1 (2)		

IQR: Interquartile range; RMR: Resting metabolic rate

Figure 1: Patient flow diagram

ICU: Intensive care unit

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Figure 2: Bland-Altman analysis of agreement between measured energy estimates using indirect calorimetry and the study predictive equation estimate in the post-ICU hospitalisation period.

X axis: Mean energy requirement obtained with indirect calorimetry and the predictive study estimate; Y axis: difference between measured energy requirement and predictive equation estimate.

The upper and lower lines represent the 95% limits of agreement

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