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Original article

Glycaemic variability and its association with enteral and parenteral nutrition in critically ill ventilated patients

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SUMMARY

Background & aims: Extremes of dysglycaemia as well as glycaemic variability are associated with excess mortality in critically ill patients. Glycaemic variability is an increasingly important measure of glucose control in the intensive care unit (ICU) due to this association; however, there is limited data pertaining to the relationship between exogenous glucose from nutrition and glycaemic variability and clinical outcomes. The primary aim of this study was to determine if glycaemic variability is associated with an increase in mortality. Secondary objectives were to investigate any factors affecting glycaemic variability, and to characterise the role nutrition, particularly carbohydrate, plays as a contributing factor to glycaemic variability and other clinical outcomes (duration of ventilation and ICU length of stay).

Methods: Data on patients in a combined medical/surgical tertiary Australian Intensive Care Unit (ICU), ventilated for >24 h and exclusively fed by artificial nutrition support was extracted from a clinical database of prospectively collected information over an 18 month period. Glycaemic variability was defined as the coefficient of variation (GV; standard deviation/mean of blood glucose levels x 100). Statistical analysis was performed using logistic regression, zero-truncated negative binomial and linear regression as appropriate to the distribution of the outcome variable using R software.

Results: Data on up to 759 subjects was available. The average age of the study cohort was 56.9 years with a mean (standard deviation) APACHE III score of 72 (28). 66% of the study subjects were male. Glycaemic variability was associated with an increase in mortality (odds ratio 1.02; 95% CI: 1.00–1.04, $p = 0.03$). Factors associated with glycaemic variability included Acute Physiology and Chronic Health Evaluation III score (0.09, 0.06–0.11, $p < 0.001$), being male (−1.67, −2.97 to −0.38), $p = 0.01$) and mean units of insulin per day (0.08, 0.06–0.09, $p < 0.001$). There was no effect of any nutritional factor on glycaemic variability. Further exploratory analyses though showed that for those patients who required insulin during ICU admission, increased insulin dose was associated with increasing carbohydrate (incidence rate ratio (IRR) 1.003, 1.001–1.005, $p = 0.001$). Mean daily carbohydrate provision (grams) was associated with an increase in ventilation hours (IRR, 95% CI: 1.009, 1.008–1.009, $p < 0.001$) and length of intensive care unit stay (IRR, 95% CI: 1.007, 1.006–1.008, $p < 0.001$).

Conclusion: This study confirms that GV was associated with excess mortality. Furthermore, administration of increasing doses of insulin was associated with increased GV. Increased carbohydrate intake was associated with an increased insulin requirement, as well as increased duration of mechanical ventilation and ICU length of stay. These findings provide important context for further prospective trials investigating the effect of carbohydrate provision in mechanically ventilated critically ill patients requiring artificial nutritional support.

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1. Introduction

Hyperglycaemia, a common surrogate marker of severity of illness [1], is prevalent in critically ill patients with approximately 75% of patients experiencing elevated blood glucose levels (BGL) during their intensive care unit (ICU) admission [2]. While exogenous insulin forms the primary therapy for management of hyperglycaemia, it is a contributor to an increase in hypoglycaemia episodes [3]. Both deviations from the acceptable glucose level range are independently associated with an increase in mortality [1,3–7]. Furthermore, it has emerged that glycaemic variability or fluctuation is associated with an increase in mortality [2,8–11]. This is likely explained by the relationship between fluctuations in blood glucose control and an increase in oxidative stress [12], which subsequently promotes mitochondrial changes and in some instances cell death [13]. The aforementioned mortality effect disappears in patients with pre-existing diabetes [2,14]. It has been speculated that this cohort are potentially pre-conditioned to glycaemic variability and its associated metabolic implications thereby leaving them largely unaffected by fluctuations in their blood glucose control [15].

Current focus for glucose management in ICU is predominantly related to exogenous insulin administration [16–21]. Increasing doses of insulin though are associated with an increase in hypoglycaemia episodes and glycaemic variability [22,23]. As such, it is prudent to explore other factors that may influence glucose control such as nutrition provision. Nutrition support in ICU is a standard aspect of clinical care and usually entails formula fed through a tube or an intravenous infusion in patients who are on ventilator support. A reduction in glycaemic load by using a diabetes specific formula is associated with a reduction in the requirement for exogenous insulin and an improvement in glycaemic variability [24–26]. In addition to this, low carbohydrate formulae were also historically used to assist with management of hypercapnea [27,28]. These applications though do not form part of the international nutrition care guidelines for critically ill patients and hence are not used in routine clinical practise [29–32]. There is impetus for exploration of the effect of standard nutrition provision practises on glycaemic variability.

The primary aim of this study was to determine if glycaemic variability is associated with an increase in mortality. Secondary objectives were to investigate any factors affecting glycaemic variability, and to characterise the role nutrition, particularly carbohydrate, plays as a contributing factor to glycaemic variability and clinical outcomes such as ventilation hours and length of stay in the intensive care.

2. Methods

2.1. Setting and patients

In this cross sectional study we utilised electronic clinical data from patients admitted to the ICU at the Princess Alexandra Hospital (PAH) in Brisbane, Australia over an 18 month period between October 2014 and April 2016. The PAH ICU is a 26 bed combined medical/surgical tertiary unit with over 2300 admissions per year. Patients admitted during the study period who required mechanical ventilation for ≥24 h and exclusive artificial nutrition support, as defined by liquid enteral nutrition formulae or parenteral nutrition, were deemed eligible. Patients under the age of 18 were excluded. Ethical approval (HREC/16/QPAH/254) and a waiver of consent were obtained from the Metro South Human Research Ethics Committee, Brisbane, QLD, Australia.

2.2. Data collection

Clinically relevant data was extracted from the electronic ICU database Metavision® (Vision Software Solutions – an iMDsoft Company, Australia). Measures extracted for the analyses included baseline demographics - age, gender, weight, height, insulin requirement pre-admission and severity of illness score (Acute Physiology And Chronic Health Evaluation (APACHE) III [33]); infusions - exogenous insulin, intravenous (IV) fluids and nutrition; blood glucose levels and clinical outcomes markers such as ventilation hours, length of ICU stay and mortality data. While initially data on steroid use was extracted from the database, it could not be used to inform analyses as many patients formed part of an ongoing blinded clinical trial involving the prescription of steroids vs. placebo drugs.

2.3. Insulin infusion and nutrition protocol

The PAH ICU team uses an insulin infusion protocol to manage blood glucose levels with a target blood glucose range of 4–10 mmol/L. The unit uses a fixed algorithm system for varying insulin sliding scales to achieve this target.

The ICU's standard nutrition protocols were used to determine target rate. Energy and protein targets based on the protocol are outlined in Table 1 below.

2.4. Variable definitions

Many of the variables such as insulin dose, carbohydrate, percentage of protein and energy and glycaemic variability had to be calculated from the data retrieved. Mean daily insulin dose was calculated as the sum of units of insulin administered per day divided by the number of days in ICU. Carbohydrate dose, expressed as mean grams/day, accounted for both carbohydrate content of nutrition formulae and glucose from intravenous fluids averaged over the course of the admission. Energy and protein received were calculated as a percentage of requirements that patients received per day divided by the calculated estimated nutritional requirements (estimated energy requirements = 25 kcal/kg BW and protein requirements = 1.2 g/kg BW [32,34], averaged over the length of stay in ICU. Finally, glycaemic variability was defined as the coefficient of variation (GV; standard deviation/mean of blood glucose levels) x 100) [35] for the purpose of this study. The means and standard deviations of each patient's blood glucose levels were calculated per 24 h period to derive a daily coefficient of variation (GV). The mean daily GV was then averaged over the course of the individual's admission and expressed as a percentage.

2.5. Outcome measures and predictor variables

The primary outcome measure for this study was ICU mortality. Secondary outcome measures included i) GV, ii) duration of ventilation (hours) and iii) length of stay in ICU (days).

Predictor variables considered for mortality included age, disease severity (APACHE III score), GV, gender and mean daily insulin dose. ICU length of stay was excluded from the potential predictive factors in the final model as patients' shorter length of stay was a consequence of death.

Table 1
Approximate energy and protein targets.

	Energy target (per day)	Protein target (per day)
Enteral nutrition	25–30 kcal/kg BW[a]	1.2–1.5 g/kg BW[a]
Parenteral nutrition	30–35 kcal/kg BW[a]	1.2–1.5 g/kg BW[a]

[a] BW = body weight; If body mass index (BMI) > 30 kg per metre squared (kg/m^2), adjusted ideal body weight (AIBW) was used to calculate requirements [43].

Predictor variables considered for GV were age, APACHE III, BMI, gender, insulin dose, percentage of protein and energy requirements met and carbohydrate provision (grams/day).

Further exploratory analysis was undertaken to determine associations between nutrition and significant predictor variables for GV. The outcome measure identified for this analysis was insulin dose. Predictor variables considered were age, APACHE III score and carbohydrate (grams/day).

Predictor variables considered for ventilation hours and length of stay in ICU included age, APACHE III score, BMI, GV, gender, insulin dose, percentage of protein and energy requirements met as well as carbohydrates (grams/day).

2.6. Statistical analysis

Distribution of data (normal or non-normal) was assessed using graphical and numeric methods. Summary statistics are reported as mean (standard deviation) for continuous normally distributed variables or median (interquartile range) for non-normally distributed variables. Categorical variables are reported as frequencies. Comparisons between groups were performed using *t*-tests for normally distributed variables, Wilcoxon Rank Sum tests for non-normally distributed variables and chi-square tests for categorical variables. All analyses were conducted using R: A Language and Environment for Statistical computing [36].

Logistic regression analysis was used to identify factors associated with mortality in ICU.

Multiple linear regression was used to assess factors associated with GV. Logistic regression was used to determine factors associated with need for insulin in ICU. Factors associated with increased doses of insulin in patients who received any during their ICU admission were determined using negative binomial regression.

Duration of ventilation expressed in hours and length of stay in ICU were modelled using zero truncated negative binomial regression using the R package, VGAM [37]. This technique is suitable for analysing data where the outcome variable is weighted towards smaller values, there are no zeros and the data is overdispersed, making Poisson or simple negative binomial regression unsuitable.

For all regression models, univariate analysis was performed and predictors with a p-value of <0.2 entered into an initial multivariate model. Predictor variables with the highest p-values were manually removed in a stepwise fashion until all remaining variables were significant. Statistical significance was set at $p < 0.05$. Estimates of effects from logistic regression effects are reported as the Odds Ratio (OR), from linear regressions as the beta coefficient, and from zero truncated negative binomial regression as the Incidence Rate Ratio (IRR). All estimates are reported with their 95% confidence interval.

3. Results

3.1. Patient characteristics

759 patients were included in the study. Refer to the Patient Flow Diagram (Fig. 1) for exclusions once the initial dataset including 776 patients was retrieved. Patient characteristics, categorised by ICU mortality are outlined in Table 2. Patients on average spent a longer period in ICU (6 days [4–9]) than the Australian site average (1.8 days). A total of 725 patients had recorded data on insulin use prior to admission with 55 (7.6%) of these identified as having insulin dependent diabetes. Patients with diabetes managed with diet or oral hypoglycaemic agents could not be identified through the database. During admission, 311/759 (41%) of the study subjects did not receive any insulin.

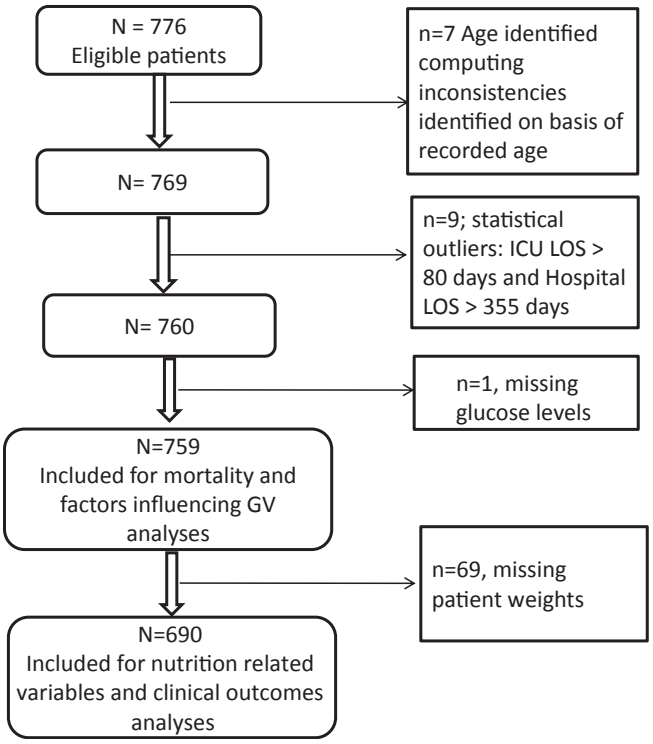

Fig. 1. Patient flow diagram.

3.2. Mortality

Information on age, APACHE III score, carbohydrate provision, GV, gender and mean daily insulin was available for 759 subjects. Predictors remaining in the final logistic regression model for mortality were age ($p = 0.01$), APACHE III score ($p < 0.001$) and GV ($p = 0.03$) all associated with an increase in mortality (Table 3).

3.2.1. Pre-existing insulin dependent diabetes

In the 55 subjects known to have IDDM prior to ICU admission, GV did not persist as a predictor variable for mortality ($n = 55$; $p = 0.32$); however, it continued to be significantly associated with mortality in the group of patients not documented to require insulin pre-admission ($n = 670$; $p < 0.001$).

3.3. Glycaemic variability

APACHE III score, daily insulin dose and being female were associated with increased GV (Table 4). Older age was associated with increased GV in the initial univariate analysis (0.05, 0.01–0.09, $p = 0.01$) but became inversely associated in the final multivariate model which is likely due to its interaction with severity of illness scoring (APACHE III). While higher insulin doses were associated with greater levels of GV, carbohydrate provision was not ($p = 0.7$).

On conducting the exploratory analyses, it was noted that older patients with increased severity of illness scores and carbohydrate doses (grams/day) were more likely to require insulin with OR = 1.017, 1.011–1.023, $p < 0.001$ and OR = 1.006, 1.003–1.008, $p < 0.001$ respectively. In the 448 patients who required insulin of ≥0.1 U/day, adjusted for age and APACHE III score, carbohydrate (grams) provision was associated with increasing doses of insulin (IRR = 1.003, 1.001–1.005, $p = 0.001$).

Table 2
Patient characteristics.

	All patients n = 759	Survived ICU n = 651	Died in ICU n = 108	P-value for survived vs died in ICU
Age (years)	56.9 (43.4–68.2), n = 759	56.2 (41.95–67.05), n = 651	63.5 (54.4–74.0), n = 108	<0.0001
Male n/N (%)	499/759 (66)	430/651 (66)	68/108 (62)	
BMI (kg/m^2)	27 (24–31), n = 690	27.0 (24.0–31.0), n = 591	28.0 (24.0–32.5), n = 99	0.2
APACHE III score	72 (28), n = 759	67.0 (26.1), n = 651	91.0 (29.2), n = 108	<0.0001
On insulin before ICU admission (n/N,%)	55/725 (7.6%)	47/619 (7.6%)	9/106 (8.4%)	0.8
Nutrition requirements met (mean %/day)	65 (44–85), n = 690	65 (45–85), n = 591	62 (39–86), n = 99	0.4
Protein requirements met (mean %/day)	59 (38–80), n = 690	59 (39–80), n = 591	58 (32–80), n = 99	0.4
Carbohydrate (mean grams/day)[a]	134 (89–180), n = 759	134 (88–181), n = 651	124 (79–182), n = 108	0.5
Carbohydrate (mean grams/kg/day)	1.8 (1.2–2.3), n = 690	1.8 (1.2–2.3), n = 591	1.6 (1–2.4), n = 99	0.5
Insulin (mean units/day)	3.9 (0–27), n = 759	2.3 (0–34.3), n = 651	22 (0–51), n = 108	0.0003
Glycaemic variability (GV) - Coefficient of variation (%)	19 (14.3–25.5), n = 759	18.4 (14.1–24.9), n = 651	22.6 (17.9–29.3), n = 108	<0.0001
Duration of ventilation (hours)	107 (57–162), n = 759	108 (55–204), n = 651	104 (65–189), n = 108	0.85
ICU Length of stay (days)	6 (4–9), n = 759	7 (4–11), n = 651	5 (3–9), n = 108	0.0001

BMI: Body mass index; APACHE: Acute Physiology And Chronic Health Evaluation; ICU: Intensive care unit.
[a] Carbohydrate from nutrition and intravenous fluids.

Table 3
Mortality – Logistic regression analysis (n = 759)[a].

	Odds Ratio	95% Confidence interval	P value
Age	1.02	1.0–1.04	0.01
APACHE III	1.02	1.01–1.03	<0.001
Glycaemic variability (GV)	1.02	1.0–1.04	0.03

[a] Refer to Appendix 1 for stepwise regression results.

Table 4
Linear regression analysis for factors influencing GV (n = 759)[a].

GV as a marker of glycaemic variability	Coefficient	Confidence Interval	p value
Age	−0.05	−0.09–−0.01	0.019
APACHE III	0.09	0.06–0.11	<0.001
Insulin (units)	0.08	0.06–0.09	<0.001
Gender (Male – reference category)	−1.67	−2.97–−0.38	0.011

[a] Refer to Appendix 1 for stepwise regression results.

3.4. Nutrition related variables and clinical outcomes

Increasing amounts of carbohydrate (grams/day) were associated with a longer duration of mechanical ventilation and ICU length of stay (Table 5). No other predictor variables remained in the final model aside from the three nutrition related variables – carbohydrate provision, protein and nutrition (energy) provision. A Spearman's correlation matrix yielded a Rho > 0.85 for these variables. As such, carbohydrate provision, being the key nutrition marker of interest for the purpose of this study, was chosen as the nutrition related variable to remain in the final regression analyses.

Table 5
Nutrition related variables and clinical outcomes (mechanical ventilation and ICU length of stay) (n = 690)[b].

	Incidence rate ratio	Confidence Interval	p value
Duration of mechanical ventilation			
Carbohydrate (g)[a]	1.009	1.008–1.009	<0.001
ICU length of stay			
Carbohydrate (g)[a]	1.007	1.006–1.008	<0.001

[a] Carbohydrate provision based on nutrition sources as well as intravenous fluids where appropriate.
[b] Refer to Appendix 1 for stepwise regression results.

4. Discussion

This analysis confirms existing data that GV is associated with excess mortality. This study is the first of its kind in investigating the interplay between GV, nutrition (specifically carbohydrate) and clinical outcomes in a cross sectional ICU cohort receiving routine clinical care. It focussed on identifying and characterising the role nutrition may exert on glucose control. The salient findings of this study are:

- Increased GV, age and APACHE III scores were associated with an increased risk of mortality,
- Increasing dose of insulin, higher APACHE III scores and being female were associated with an increase in GV (Table 4). Increasing dose of insulin was associated with an increased dose in carbohydrate provision.
- Increasing amounts of carbohydrate (grams) was associated with an increase in duration of ventilation and ICU length of stay.

4.1. Patient characteristics

Patients' longer ICU stay as compared to the Australian site average could be attributed to the inclusion criteria specifying patients be ventilated and fed for a minimum of 24 hours thereby encapsulating higher acuity patients within the study cohort. The median GV of this study cohort is similar to the mean/median GV in studies similar to ours [9,10,14,38]. Carbohydrate provision was not excessive, falling well below the maximum glucose oxidation rate of 5–7 g/kg/day [39].

4.2. Mortality

Patients who died in ICU were older, had a higher APACHE III score, required a higher mean insulin dose and had a greater degree of GV than those who survived. Our findings that GV, adjusted for age, APACHE III score and gender, is associated with excess mortality are consistent with findings from other studies [9–11,15,40]. While the pathophysiological process behind this association still remains somewhat unclear, it is becoming increasingly evident that GV should be considered in the context of overall glycaemic management in ICU patients [8]. Results from larger, multi-centre studies [8,9,14,38], have consistently found an association between pre-existing diabetes on admission to ICU and reduced mortality. Our study confirms that GV persists to be significantly associated with mortality in the subset of patients not requiring

insulin pre-admission but not in those who did have a documented pre-admission insulin requirement.

4.3. Glycaemic variability

Based on assessment of the range of methods used to quantify GV [35], the coefficient of variation method was determined to be most appropriate for this patient cohort. Most observational studies exploring GV have placed particular focus on its relationship with mortality, with only one study examining potential contributing factors. Al-Dorzi and colleagues (2010) conducted a nested cohort study of 523 patients within a larger clinical trial randomising patients to intensive insulin therapy or conventional therapy. Age, daily dose of insulin and history of diabetes were found to be predictors of increased glycaemic fluctuation. These findings hold similarities to those of our study with APACHE III score and daily insulin dose found to be significantly associated with GV. Our findings can be explained by the positive association between hyperglycaemia and increasing severity of illness [41]. These more unwell patients tend to require insulin which, when administered, increases the likelihood of peaks and troughs in glucose levels hence contributing to an overall increase in glycaemic variability.

No significant associations were found between GV and any of the parameters of nutrition provision (carbohydrate, percentage of energy and protein requirements). The findings from Al-Dorzi and colleagues were not dissimilar. As described, authors explored the data further which highlighted, not unexpectedly, that in those patients receiving insulin, increasing amounts of carbohydrate was associated with increasing doses of insulin.

4.4. Nutrition related variables and clinical outcomes

Markers of nutrition provision (energy and protein provision as well as grams of carbohydrate) were persisting significant factors associated with both an increase in ventilation hours and ICU length of stay. However, due to their correlation and subsequent interaction in the statistical analyses, they could not be concurrently included in the modelling. Carbohydrate was used as the predictor variable as an objective of this study was to investigate its role on glucose control in this setting. There are two ways that this association can be interpreted. Firstly, ICU patients are often at the peak of their illness on admission to ICU and subsequently tend to have lower rates of nutrition prescribed in this early, acute stress response phase due to a myriad of factors including medical instability and poor tolerance. As admission progresses, patient acuity improves and tolerance of nutrition provision is better thereby increasing the amount of carbohydrate tolerated. Secondly, an alternative explanation relates to studies which have shown an association between carbohydrate and hypercapnea in patients with respiratory issues [27,28,39]. This provides clinical cause for our finding pertaining to increased duration of ventilation. Further prospective investigation is required to tease out this relationship in greater depth.

Duration of ventilation and ICU length of stay are highly correlated (Rho 0.92, $p < 0.001$) in this study and others [42], therefore authors hypothesize that the association found between carbohydrate (grams/day) and ICU length of stay is a surrogate outcome of the relationship between carbohydrate and increased duration of ventilation.

4.5. Clinical implications

This study strengthens previous observations that increased GV is independently associated with excess mortality in critically ill patients [16,18,40]. Findings from our study also confirm that increasing doses of insulin are associated with increased GV. It follows that minimising insulin doses through alternate strategies to meet blood glucose targets may result in lower GV and fewer episodes of hypoglycaemia [25]. In this context, our study provides further new evidence for clinicians to consider lower carbohydrate feeding regimes in critically ill patients. Our data is drawn from actual clinical management and demonstrates associations between carbohydrate provision and increased insulin requirement, duration of mechanical ventilation and length of ICU stay. These findings are strengthened by conclusions of other clinical studies which indicate that reduced carbohydrate formulae improved GV and reduced duration of mechanical ventilation in patients with pre-existing pulmonary disease [24,25,28]. Critical care nutrition guidelines identify the need for more evidence supporting the use of lower or modified carbohydrate feeds [29,31]. The current study potentially strengthens the rationale for this approach as an alternative to intensive insulin regimes that may be associated with harm [18].

The authors suggest that reducing carbohydrate provision may be a plausible and pragmatic strategy to improve glycaemic control and potentially clinical outcomes. These new findings provide further impetus for prospective randomised controlled trials investigating impact on glycaemic control and clinical outcomes, specifically duration of ventilation, in a heterogeneous cohort of critically ill patients.

4.6. Limitations

The key limitation of this study is inherent to retrospective data extraction. Authors were unable to retrieve detailed information on patients pre-existing diabetes status. While able to identify patients on insulin pre-admission, there was no data to identify patients with diabetes who were on diet control measures or on oral hypoglycaemic agents. This prevented a more detailed sub group analyses (between patients with/without diabetes) which has been shown to significantly impact on mortality. Despite this, our study was able to determine similar predictors of mortality and glycaemic variability.

5. Conclusion

This study confirms that increased GV was associated with excess mortality. Furthermore, administration of increasing doses of insulin was associated with increased GV. Increased carbohydrate intake was associated with an increased insulin requirement, as well as increased duration of mechanical ventilation and ICU length of stay.

These findings provide important context for further prospective trials investigating the effect of carbohydrate provision in mechanically ventilated critically ill patients requiring artificial nutritional support.

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Conflicts of interest

The authors have no conflict of interests to declare.

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RD, RH, CF, RG, JF, AT, CJ and DS contributed to study design. CF and RG provided statistical input. RD drafted the manuscript. All

authors critically reviewed the manuscript and agree to be accountable for the accuracy and integrity of the work. Ms. Azmat Ali (Team Leader, Nutrition and Dietetics, Princess Alexandra Hospital) provided input on the unit's nutrition protocols.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.08.001.

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